Title
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Journal
Chemical Reviews, 118(20)

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Publication Date
2018-10-24

DOI
10.1021/acs.chemrev.8b00081

Peer reviewed

HHS Public Access

Author manuscript

Chem Rev. Author manuscript; available in PMC 2019 October 24.

Published in final edited form as:

Chem Rev. 2018 October 24; 118(20): 10049–10293. doi:10.1021/acs.chemrev.8b00081.

Phosphine Organocatalysis

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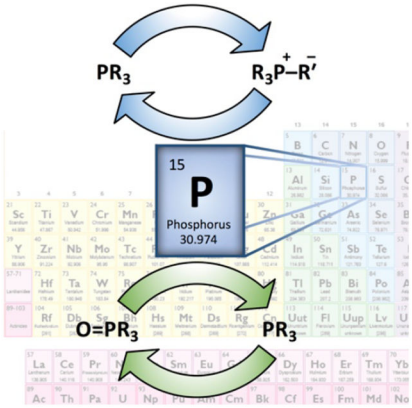
Abstract

The hallmark of nucleophilic phosphine catalysis is the initial nucleophilic addition of a phosphine to an electrophilic starting material, producing a reactive zwitterionic intermediate, generally under mild conditions. In this Review, we classify nucleophilic phosphine catalysis reactions in terms of their electrophilic components. In the majority of cases, these electrophiles possess carbon–carbon multiple bonds: alkenes (section 2), allenes (section 3), alkynes (section 4), and Morita–Baylis–Hillman (MBH) alcohol derivatives (MBHADs; section 5). Within each of these sections, the reactions are compiled based on the nature of the second starting material—nucleophiles, dinucleophiles, electrophiles, and electrophile–nucleophiles. Nucleophilic phosphine catalysis reactions that occur via the initial addition to starting materials that do not possess carbon–carbon multiple bonds are collated in section 6. Although not catalytic in the phosphine, the formation of ylides through the nucleophilic addition of phosphines to carbon–carbon multiple bond–containing compounds is intimately related to the catalysis and is discussed in section 7. Finally, section 8 compiles miscellaneous topics, including annulations of the Hüisgen zwitterion, phosphine-mediated reductions, iminophosphorane organocatalysis, and catalytic variants of classical phosphine oxide–generating reactions.

Graphical Abstract



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The authors declare no competing financial interest.

1. INTRODUCTION

One of the salient features of nucleophilic phosphine catalysis is that reactions are typically initiated by the preferential addition of tertiary phosphines to activated carbon–carbon multiple bonds to form β-phosphonium α-carbanion species. Horner provided the first report of such zwitterionic species. In 1955, he isolated the crystalline zwitterionic adducts **1** formed from triethyl- and triphenylphosphine and ethylenemalononitrile (Scheme 1).[1] The same year, he also noted that acrylonitrile, when treated with triethylphosphine in the presence of water, would polymerize to form head-to-tail polymers of acrylonitrile as phosphonium hydroxide salts. It was only in 1963 that Rauhut and Currier demonstrated the first tributylphosphine-catalyzed dimerization of acrylates to form α-methylene succinates.[2] Contemporarily, Winterfeldt reported the first heterobimolecular phosphine catalysis between dimethyl acetylenedicarboxylate (DMAD) and aldehydes in an annulation event to form butenolides.[3] Two years later, the famed Morita reaction [also known as the Morita–Baylis–Hillman (MBH) reaction] surfaced.[4] In the Morita reaction, a Horner zwitterion adds to an aldehyde to eventually form α-hydroxymethylated acrylates and acrylonitriles after alkoxide-to-enolate proton transfer and β-elimination of the tricyclohexylphosphine catalyst. In 1972, Baylis and Hillman patented their amine-catalyzed Morita reaction.[5]

Once considered a novelty, nucleophilic phosphine catalysis today provides reliable means to prepare synthetic intermediates and products in all areas of Organic Chemistry, including medicinal agents, natural products, ligands for catalysis, and materials.[6–51] While reports of asymmetric variants and the applications of known phosphine-catalyzed reactions grow, the majority of research efforts of late have been dedicated to the development of “new” reactions. To aid active practitioners, as well as the general synthetic chemistry audience, in their understanding of this fast-growing area of research, this Review first categorizes the modes of nucleophilic phosphine catalysis based on the carbon–carbon multiple bond-containing starting materials, namely alkenes (section 2), allenes (section 3), alkynes (section 4), and MBH-alcohol derivatives (MBHADs; section 5). The reactions are then further divided in terms of the second starting materials—nucleophiles, electrophiles, and combinations thereof—that dictate the subsequent reaction pathways.

In addition, section 6 discusses nucleophilic phosphine catalysis processes that occur in the presence of electrophiles other than the aforementioned carbon–carbon multiple bond-containing molecules. Although not catalytic in phosphine, the formation of ylides through nucleophilic addition of phosphines to activated multiple bonds, and their subsequent Wittig reactions, is intimately related to nucleophilic phosphine catalysis. Therefore, section 7 covers the chemistry of ylides that are formed through nucleophilic addition of a phosphine. Phosphorus ylides are particularly relevant with the recent advent of catalytic Wittig reactions, which blur the line between classical phosphine-mediated reactions and phosphine catalysis processes. Finally, section 8 compiles miscellaneous topics, including annulations of Hüisgen zwitterions, phosphine-mediated reductions, iminophosphorane catalysis, and catalytic variants of classical phosphine oxide-generating reactions. Many of these reactions produce enantioenriched products when chiral phosphines are used. Enantioselective variants of each reaction are discussed at the end of each section.

2. NUCLEOPHILIC PHOSPHINE CATALYSIS OF ALKENES

Horner's zwitterionic adduct formed through the conjugate addition of a phosphine to an activated olefin follows multifarious modes of reaction pathways depending on the nature of the second partner of the reaction—whether it is a nucleophile, electrophile, or an electrophile/nucleophile hybrid. In the absence of the second reaction partner, conjugate addition–β-elimination can facilitate isomerization of an alkene.

2.1. Phosphine-Catalyzed Isomerization of Alkenes

In many instances, intramolecular cyclization is an efficient method of making hetero- and carbocyclic systems bearing complex functionalities. Such a strategy fails, however, when an undesired olefin geometry is present in the substrate. In 2012, Hintermann and co-workers came up with a solution, using phosphine conjugate addition, to isomerize the incorrect olefin geometry in situ, allowing intramolecular lactonization to provide functionalized coumarins (Scheme 2).[52] Through this method, substrates bearing the undesired *E*-olefin geometry can be used to generate coumarins bearing various substituents.

In 2016, the Takemoto group developed the asymmetric synthesis of anti-α,β-diamino acid derivatives through tandem orthogonal organocatalysis (Scheme 3).[53] In the sequential reactions, the isomerization, which occurred in the presence of 10 mol % of PPh_3 in CH_2Cl_2 at room temperature, played a key role.

2.2. Phosphine Catalysis of Alkenes with Nucleophiles

2.2.1. Phosphine-Catalyzed Michael Addition.—More than four decades ago, White and Baizer demonstrated the phosphine-triggered general base catalysis between 2-nitropropane and activated olefins;[54] since then, many research groups have expanded the substrate scope of pronucleophiles and olefins, increasing the molecular complexity of the products (Scheme 4). Carbon- and oxygen-centered nucleophiles are suitable for phosphine-catalyzed Michael addition. Many carbon pronucleophiles, including methyl 2-(phenylsulfinyl)-acetate,[55] dimethyl malonate,[56] and β-ketoesters,[57] can undergo efficient Michael additions into activated olefins. α-Benzylketone also has been demonstrated to undergo intramolecular Michael additions in tandem with intramolecular Rauhut–Currier (RC) reactions.[58] In addition to carbon pronucleophiles, Toste and Bergman have observed the incorporation of methanol and water as pronucleophiles when employing trimethylphosphine as the catalyst.[59]

In 1973, White and Baizer reported the first example of Michael additions through phosphine-triggered general base catalysis of 2-nitropropane into activated olefins, employing nucleophilic tertiary phosphines (tributylphosphine, dimethylphenylphosphine, methyldiphenylphosphine, triphenylphosphine) as alternative catalysts to traditional strong bases.[54] Although no strong bases were added, the Horner zwitterion **2** deprotonates the pronucleophile to form the phosphonium–enolate ion pair **3**. Once deprotonated, the pronucleophile undergoes Michael addition into another olefin, resulting in the generation of the enolate **4**. This enolate will further catalyze the reaction by deprotonating another molecule of pronucleophile and furnish the Michael product (Scheme 5). Furthermore, the

notion of general base catalysis is supported through computational analysis [density functional theory (DFT), using the B3LYP level of theory with the 6-31+G(d) basis set], revealing distinct transition states.[60]

White and Baizer reported highly efficient phosphine-catalyzed Michael additions of 2-nitropropane pronucleophile to various activated olefins, including ethyl acrylate, methyl vinyl ketone (MVK), acrylonitrile, and substituted acrylonitriles.[54] From a comparison of the reactivities of phosphine and analogous amine catalysts, they demonstrated that amines did not catalyze the reaction—a situation they attributed to weaker nucleophilicity (Scheme 6).

Methyl phenylsulfinylacetate, an activated carbon-centered pronucleophile, also undergoes efficient Michael addition in the presence of tributylphosphine.[55] Yoshida demonstrated that the reaction of methyl phenylsulfinylacetate with 1-octen-3-one in the presence of tributylphosphine leads to a good yield of the Michael adduct (Scheme 7).

While looking into transition metal catalysts for efficient Michael additions of carbon-centered pronucleophiles, Echavarren and Moreno-Mañas found that ruthenium dihydride [$RuH_2(PPh_3)_4$] and ruthenium dichloride [$RuCl_2(PPh_3)_3$] both promoted the additions of hindered carbon-centered pronucleophiles into electron-deficient olefins.[56,57] While these ruthenium catalysts worked beautifully, a few substrates provided comparable or better yields when the reactions were catalyzed by phosphine catalysts (Scheme 8).

Later in 2003, Bergman and Toste disclosed the efficient Michael additions of alcohol pronucleophiles into activated olefins, including acrylates, acrylonitriles, and MVK, in the presence of trimethylphosphine, a strong nucleophilic phosphine.[59] Primary and secondary alcohols were incorporated in the products with good yields (Scheme 9). Phenol, a less-nucleophilic pronucleophile, also underwent the Michael addition into MVK in moderate yield. Peculiarly, water could also be applied as a pronucleophile, resulting in a good yield of ethyl-3-hydroxybutanoate.

With the great results disclosed by Bergman and Toste, the phosphine-catalyzed Michael addition was quickly adopted by many research groups. The range of pronucleophiles increased to include allyl alcohols,[61] ethanol,[62] oximes,[63] malonates,[64] pyrimidine-2,4-diones,[65] aminoindolizines (Scheme 10),[66] α-fluorinated and α-trifluoromethylated nucleophiles (Scheme 11),[67,68] hydrogen phosphoryl compounds (Scheme 12),[69–71] and various phosphorus-centered nucleophiles (Scheme 12),[72,73] producing an array of functionalized aliphatic cyanides, sulfones, ketones, and esters.

As alternatives to commonly employed triphenylphosphine and tributylphosphine, Bourissou and co-workers tested the feasibility of using phosphine–borane catalysts (“frustrated Lewis pairs”) to promote the classical Michael addition.[74] Although the reactions were not highly efficient, their study served as a proof of concept, granting the possibility of novel reaction modes and providing helpful insights into catalyst development. Moderate yields were obtained when using various phosphine–borane catalysts (Scheme 13). In terms of catalyst structures, the reactions proceeded faster with dimethyl substituents on the phosphorus center. Such reactivity was also observed when switching triphenylphosphine to

trimethylphosphine. While frustrated Lewis pair catalyst systems do work, further developments will be needed to increase their reaction efficiencies.

All the Michael addition examples covered so far have invoked the idea of intermolecular coupling of two starting reactants, generating acyclic adducts. With strategic substrate design, Liao and co-workers demonstrated the syntheses of functionalized pyrrolidines through intramolecular Michael reactions.[75] The 5-endo-trig cyclization produced pyrrolidines bearing various aromatic substituents, ranging from electron-donating *p*-methoxyphenyl to electron-poor *o*-bromophenyl (Scheme 14). Using DFT calculations, Qiao, Wei, and co-workers investigated the mechanism of this intramolecular cyclization. The calculated results indicated that the Gibbs free energy barriers of 5-endo-trig cyclizations are lower than those of 5-exo-trig cyclizations and that the reaction pathway furnishing the *RS*-configured product has the lowest Gibbs free energy barrier, in agreement with the experimental findings.[76]

Interestingly, Hoyle and co-workers prepared thiol-terminated oligomers from phosphine-catalyzed Michael additions between 1,6-hexanedithiol and 1,4-butanediol diacrylate (Scheme 15).[77] Thiol-terminated oligomers were obtained quantitatively in the presence of 0.1 wt % dimethylphenylphosphine (DMPPh) within 10 min at room temperature. After subsequent reactions, the oligomers were polymerized to give polythiourethane elastomers. Hoyle and co-workers also used phosphine-catalyzed Michael reactions between pentaerythritol tetrakis(3-mercaptopropionate) and various alkyl acrylates to prepare mono- and difunctional thiols (Scheme 16).[78] Treatment of pentaerythritol tetrakis(3-mercaptopropionate) with alkyl or hydroxyl alkyl acrylates (1 or 2 equiv) in the presence of DMPPh resulted in functionalized thiols. These functionalized thiols served as monomers in polymerizations that resulted in dense and uniform network structures.

Taton and co-workers developed phosphine-catalyzed group transfer polymerization (GTP) of alkyl(meth)acrylates—a significant application of phosphine-catalyzed Michael reactions in the preparation of polymers (Scheme 17).[79] Inspired by the phosphine-catalyzed Mukaiyama-aldol reactions, Taton elegantly introduced phosphine-catalyzed Mukaiyama–Michael reactions into polymerizations—specifically, to GTP reactions. The strongly nucleophilic and basic phosphine tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) powerfully catalyzed the GTP of methyl methacrylate to provide products with good dispersity in quantitative yields, but a lower yield and level of dispersity resulted when using *tert*-butyl acrylate.

With the use of a chiral phosphine as catalyst, asymmetric Michael addition has also been explored. Lu reported the first enantioselective Michael addition catalyzed by the chiral phosphine **P1** derived from L-valine (Scheme 18).[80] According to ^{31}P NMR spectroscopy, the resting state of the catalyst was identified as a cationic phosphonium species, in agreement with the results reported by Bergman and Toste.[59] A transition state model was proposed involving a nucleophile–phosphonium ion pair effect, with stabilization through hydrogen bonding from the appendant amide group of the catalyst. The well-organized substrate–catalyst complex forced the Michael acceptor to approach from the *Si* face of the complex, due to the protruding 3,5-bistrifluoromethylbenzylamide group. A low reaction

temperature significantly enhanced the enantioselectivity, providing Michael adducts in excellent yields and with excellent enantiomeric excesses. Furthermore, 3-aryl oxindoles reacted with higher product conversions and better enantioselectivities than did 3-alkyl oxindoles.

Zhang, Liu, and co-workers developed the asymmetric intermolecular Michael additions of β-carbonyl esters to β-trifluoromethyl enones and 3-aroyl acrylates, catalyzed by the multifunctional biamide-phosphine catalysts **P2a** and **P2b** in the presence of methyl acrylate and an inorganic base, K_3PO_4, which acted as a proton shuttle that enhanced the reactivity (Scheme 19).[81] With the use of 5 mol % of the catalyst in the presence of methyl acrylate (2 equiv) and K_3PO_4 (30 mol %) in toluene at −20 °C, the Michael adducts were obtained in good to excellent yields (67–99%) with excellent enantioselectivities (84–99% ee). The Michael addition of β-ketoesters also occurred to give the products in moderate to good yields with excellent enantioselectivities (90–98% ee).

Using a different catalytic strategy, Xu and co-workers developed enantioselective Michael additions between aldehydes and maleimides (Scheme 20).[82] In the presence of a dual-component catalyst system (a cinchonidine-derived primary amine and triphenylphosphine), the Michael additions between various aliphatic aldehydes and a wide range of maleimides furnished the corresponding adducts in excellent yields and excellent enantiomeric excesses. Interestingly, the presence of triphenylphosphine as an additive improved the yields tremendously (by up to 2.6 times, compared with the reaction performed in its absence) and increased enantiomeric excesses moderately (by up to 1.2 times). A noncovalent interaction between the amine and triphenylphosphine was proposed to form a supramolecular structure that facilitated the reaction. Evidence for this noncovalent interaction was obtained using a series of tools, including UV–vis, fluorescence emission, NMR, and circular dichroism spectroscopy.

2.2.2. β-Boration of α,β-Unsaturated Carbonyl Compounds.—

In 2012, Fernández and co-workers presented the first organocatalytic β-boration of α,β-unsaturated carbonyl compounds using catalytic amounts of phosphine and alcohol (Scheme 21).[83] No Brönsted base is required to activate the bis(pinacolato)diboron. In the presence of 4 mol% of PCy_3, a series of α,β-unsaturated substrates were treated with B_2pin_2 in MeOH at 70 °C, affording the desired products in moderate to good yields. In the process, the phosphine attacks the most electrophilic carbon of the α,β-unsaturated carbonyl compound to form a zwitterionic phosphonium enolate species, which is protonated by the excess of MeOH. The presence of bis(pinacolato)diboron stabilizes the MeO^- anion, thus forming the Lewis acid–base $[B_2pin_2{\cdot}MeO]^-$ adduct.

2.2.3. Cyanosilylation of Carbonyl Compounds.—

Using a strategy similar to that in the Henry reaction below (section 2.2.4) Tian and co-workers realized phosphine-catalyzed cyanosilylation of carbonyl compounds to furnish cyanohydrin silyl ethers (Schemes 22 and 23).[84] The combination of triphenylphosphine and methyl acrylate proved to be an extremely effective catalytic system for the cyanosilylation of carbonyl compounds. The reaction afforded various cyanohydrin silyl ethers in high yields. A wide scope of

substrates, including aromatic or aliphatic aldehydes and ketones, were compatible with the transformation.

2.2.4. Phosphine-Catalyzed Henry Reaction.—When treating activated alkenes with pronucleophiles in the presence of a phosphine, Michael addition is the dominant pathway operating through general base catalysis. The concept of a general phosphonium zwitterion base can also be adapted in other reactions to initiate nucleophilic attacks. In 2008, the Tian group applied such an idea, reporting a phosphine-catalyzed Henry reaction using a catalytic amount of triphenylphosphine and methyl acrylate to produce a phosphonium zwitterion as a base that could activate various nitroalkanes (Scheme 24).[85] The reaction yielded a collection of functionalized β-nitroalkanols with excellent efficiencies, tolerating various aromatic and aliphatic aldehydes.

2.3. Phosphine Catalysis of Alkenes with Dinucleophiles

Reactions of activated alkenes with simple nucleophiles often do not generate cyclic products because they cannot provide enough atom units to construct a five- or six-membered ring. Riyaz and co-workers reported a rare annulation with isatylidenemalononitrile and cyclohexane-1,3-dione, affording complex spirooxindoles in good yields.[86] The isatylidenemalononitrile was generated through in situ condensation between malononitrile and isatin (Scheme 25). In the presence of triphenylphosphine, conjugate addition produced the zwitterionic species **5**, activating the pronucleophile for subsequent Michael addition. The intermediate **6** then underwent proton transfer, enolizing the carbonyl group and triggering cyclization. After a series of proton transfer events, the spirooxindole **7** was afforded.

Although the scope of the reaction was limited, complex spirooxindoles could be generated rapidly from simple starting materials, tolerating both malononitrile and ethyl cyanoacetate (Scheme 26).

2.4. Phosphine Catalysis of Alkenes with Electrophiles

As mentioned in the Introduction, phosphine-catalyzed reactions of alkenes with other electrophiles are the oldest and most classical examples of nucleophilic phosphine catalysis.

2.4.1. MBH Reactions.—The MBH reaction (Scheme 27) refers to the addition of electron-deficient alkenes to aldehydes in a 1,2-manner when using a Lewis base (e.g., tertiary phosphine or amine) as the catalyst to form allylic alcohol derivatives, so called MBH adducts (MBHADs). Similarly, the reaction involving imines is known as the aza-Baylis–Hillman reaction. Phosphine-catalyzed MBH reactions, aza-Morita–Baylis–Hillman reactions, their enantioselective variants, and their applications have been summarized in a vast range of accounts and reviews,[87–108] especially some recent reviews,[109–111] and, therefore, will not be further discussed herein.

2.4.2. RC Reaction.—The Rauhut–Currier (RC) reaction is one of the most important methods for carbon–carbon bond formation and is significant and synthetically useful, with the ability to construct acyclic and carbo- and heterocyclic compounds and multiple

stereocenters, while tolerating various substrates. In 2009, Miller published a beautiful review on the RC reaction,[14] introducing its history and development. Therefore, herein we discuss only the progress in the RC reaction since 2009.

2.4.2a. Enantioselective Intramolecular RC Reaction.: In 2010, Malachowski and co-workers elegantly used a combination of cross olefin metathesis and the phosphine-catalyzed intramolecular RC reaction to furnish bicarbocyclic structures with all-carbon quaternary stereocenters (Scheme 28).[112] The cross-metathesis products effectively underwent the RC reaction in the presence of a trialkylphosphine (e.g., tributylphosphine, trimethylphosphine), to produce chiral bicarbocyclic structures in good to excellent yields.

In 2011, Wu and co-workers reported a phosphine-catalyzed enantioselective intramolecular RC reaction (Scheme 29).[113] Through catalyst screening, the chiral phosphinothiourea bearing a longest alkyl substituent was identified as the superior catalyst. In the presence of 20 mol % of the phosphine **P3**, a wide range of bis(enones) were applicable to the reaction, forming cyclohexenes in good to excellent yields and with excellent enantiomeric excesses. In a subsequent exploration, Wu and co-workers tested more chiral bifunctional phosphine catalysts.[114] With 10 mol % of the chiral cyclohexane-based thiourea–phosphine **P4**, the intramolecular RC reaction worked well in CH_2Cl_2 at 0 °C to furnish the cyclohexenes in up to 99% yield and with up to 99% ee (Scheme 30). An alkyl bis(enone) was also a suitable substrate for the reaction, giving its acetyl cyclohexene in 76% yield with 86% ee.

In 2012, Sasai, Enders, and co-workers described a chiral phosphine-catalyzed intramolecular RC reaction for the synthesis of α-alkylidene-γ-butyrolactones (Scheme 31).[115] They found that the tosylamide-containing phosphine **P5** was the best catalyst for the reaction, after testing 14 other chiral phosphines and amines. Using 20 mol % of the chiral phosphine **P5**, the annulations of a wide spectrum of dienones bearing aliphatic and aromatic substituents proceeded smoothly in chloroform at 0 °C, providing chiral α-alkylidene-γ-butyrolactones exclusively in good yields and with good to excellent enantioselectivities. Aryl-substituted dienones displayed superior reactivity over alkyl-substituted ones. A reaction mechanism was also proposed (Scheme 31). Later in 2013, Sasai and co-workers further extended the substrate scope of the intramolecular RC reaction to include more dienone enolates, exclusively furnishing α-methylidene-γ-butyrolactones in high yields.[116]

In 2015, Zhang and co-workers prepared a new class of chiral sulfinamide phosphines **P6** (Scheme 32).[117] From 17 chiral sulfinamide phosphines prepared in a facile manner from commercially available starting materials, the chiral phosphines (R,R_S)-**P6** and (S,R_S)-**P6** catalyzed enantioselective intramolecular RC reaction in the presence of phenol to give the annulation products in high to excellent yields and with good to excellent enantioselectivities. In addition, using (R,R_S)-**P6** as the catalyst allowed the kinetic and parallel kinetic resolution of racemic precursors through a phosphine-catalyzed enantioselective intramolecular RC reaction, with excellent yields and enantioselective induction. For example, when the racemic substrate **8** was treated with (R,R_S)-**P6**, a parallel kinetic resolution occurred to produce enantioenriched **9** and **10** in 55% yield/89% ee and 44% yield/99% ee, respectively. The stereochemistry in the parallel kinetic resolutions could

be explained by two possible transition states (Scheme 32). The zwitterion intermediate formed through nucleophilic addition of (R,R_S)-**P6** to the acrylate chain of *rac*-**8** is stabilized through a vital hydrogen bond between the sulfinamide and the enolate. The front site of the enolate is blocked by the bulky TIPS group. The steric repulsion between the TIPS group and the methyl group makes addition to the methyl-substituted olefin much slower than addition to the other olefin, thereby inducing parallel kinetic resolution.

In 2017, the Huang group developed a multifunctional chiral aminophosphine (**P7**)-catalyzed enantioselective intramolecular RC reaction of cyclohexadienones (Scheme 33).[118] Various hydro-2*H*-indole derivatives bearing an all carbon quaternary center were obtained in high yields (up to 94%) with excellent diastereoselectivities (up to >20:1 dr) and moderate to excellent enantioselectivities (up to >99% ee). Notably, with a catalyst loading of 2 mol %, the reaction on a gram scale, using 4 mmol of the substrate, also provided the products in high yields and with excellent stereoselectivities.

In 2012, Shi and Zhang developed a phosphine-catalyzed intramolecular RC reaction to prepare chiral cyclohexene and cyclopentene derivatives (Scheme 34).[119] Under catalysis with the (*R*)-BINOL-derived phosphine **P8**, bis(enones) bearing a wide variety of electron-rich and -deficient aromatic, heteroaromatic, and aliphatic substituents underwent intramolecular RC reactions at room temperature to produce cyclohexene derivatives in good yields and with high levels of enantioselectivity. These intramolecular annulations were, however, quite slow, requiring 2 to 4 days to reach completion. For the preparation of cyclopentenes, the reaction conditions were more severe: a higher catalyst loading (from 20 to 35 mol %) and a lower temperature (from 25 to −15 °C). Under these conditions, the reaction required a long period of time (up to 7 days) to give the cyclopentene derivatives in low to moderate yields and with moderate to excellent enantioselectivities. An increase in the reaction temperature improved the yields but diminished the enantioselectivities dramatically.

In 2015, Grossmann, Spring, and co-workers studied the synthesis of α-methylidene-δ-lactones through RC cyclization of chalcone derivatives (Scheme 35).[120] Using the valine-derived phosphine **P5** or the phenylalanine-isoleucine-derived phosphine Boc-FIP **P9** as the chiral catalyst, chalcone derivatives presenting various substituents underwent the cyclizations to furnish chromanones in moderate to excellent yields and with moderate to excellent enantioselectivities. Shortly thereafter, the Albrecht group reported a similar synthesis of α-methylidene-δ-lactones using a phosphine-catalyzed intramolecular RC reaction (Scheme 36).[121] Under catalysis with 20 mol % of the valine-derived phosphine **P5**, the intramolecular annulation gave α-methylidene-δ-lactones in moderate to good yields and with moderate to good enantioselectivities.

In 2017, the Fan group described a chiral phosphine **P10**-catalyzed intramolecular vinylogous RC reaction of *para*-quinone methides (*p*-QMs) for the construction of functionalized 4-aryl-3,4-dihydrocoumarins and 4-aryl-3,4-dihydroquinolin-2-ones (Scheme 37).[122] Various *p*-QM esters presenting electronically different substituents on the aromatic ring underwent the reaction in dichloromethane at 15 °C to afford 4-aryl hydrocoumarins in high yields (89–99%) and with moderate to excellent enantioselectivities (50–99% ee). The

enantioselectivities decreased for substrates having substituents at the 5-position, due to a steric effect. *p*-QM amides were also suitable substrates, furnishing the desired 4-aryl-3,4-dihydroquinolin-2-ones in high yields (up to 98%) with excellent enantioselectivities (up to 94% ee).

2.4.2b. Enantioselective Intermolecular RC Reaction.: In 2015, Huang and co-workers documented the first multifunctional chiral phosphine-catalyzed enantioselective intermolecular cross RC reaction of diverse electron-deficient olefins (Scheme 38).[123] In the presence of a catalytic amount of **P7** (10 mol %), the enantioselective intermolecular cross RC reactions of 3-aroyl acrylates with aryl vinyl ketones worked smoothly at 16 °C in chloroform, furnishing their cross RC adducts in good yields with excellent enantioselectivities. A range of 3-aroyl acrylates and aryl vinyl ketones, bearing a diverse array of substituents with various electronic properties, were compatible with the reaction. A transition state involving multiple hydrogen bonds was proposed to rationalize the enantioselectivity.

Using the chiral sulfinamide bis(toluenyl)phosphine **P11** as the chiral catalyst, Zhang, Zhao, and co-workers also developed an intermolecular cross-RC reaction of α,β-unsaturated carbonyl compounds (Scheme 39).[124] In the presence of 2.5–10 mol % of **P11**, the intermolecular enantioselective cross-RC reactions of various 3-aroyl acrylates and vinyl ketones proceeded smoothly in chloroform at −20 °C, delivering their cross RC products in good to excellent yields with excellent enantioselectivities. In addition to 3-aroyl acrylates, 2-ene-1,4-diones were also compatible with the reaction, giving comparable results. Moreover, ^{31}P NMR spectroscopic experiments revealed that the more nucleophilic phosphine moiety initialized the reaction.

In 2017, Zhang and co-workers reported the phosphine-catalyzed enantioselective intermolecular cross-vinylogous RC reactions of alkyl vinyl ketones with *para*-quinone methides (Scheme 40).[125] In the presence of the chiral amide-derived phosphine **P12** (10 mol %), a series of para-quinone methides presenting various substituents underwent cross-vinylogous RC reactions smoothly with alkyl vinyl ketones, providing structurally diverse diarylmethines with mostly good yields and excellent enantioselectivities.

In 2016, Zhang, Zhao, and co-workers synthesized a novel type of chiral sulfinamide phosphine containing a bulky aromatic side chain (**P13**) and applied it in highly enantioselective intermolecular cross RC reactions of active alkenes and acrolein (Scheme 41).[126] Using 10 mol % of **P13** as the chiral catalyst, 3-aroyl acrylates having aromatic substituents underwent the reaction in toluene at −20 °C to give the desired products in good yields with good enantioselectivities. Aliphatic substrates were also suitable for the reaction and their products were obtained with good enantioselectivities, albeit requiring a higher catalyst loading and a longer reaction time. In addition, 2-ene-1,4-diones also worked in the reaction at lower temperature (−30 °C), but with a higher catalyst loading (20 mol %).

Using the chiral catalyst (S,R_S)-**P6**, Zhang, Zhao, and co-workers also achieved highly enantioselective cross RC reactions of activated alkenes with vinyl ketones (Scheme 42).[127] The activated alkenes and vinyl ketones underwent the reaction in the presence of 10 mol %

of Xiao-Phos in toluene at −20 °C, furnishing the desired products in good to excellent yields with good to excellent enantioselectivities.

In 2017, the Zhang group studied the phosphine-catalyzed asymmetric cross-RC reactions of vinyl ketones and *β*-perfluoroalkyl-substituted enones, providing enantioenriched multifunctional compounds bearing a *β*-perfluoroalkyl-substituted stereocenter (Scheme 43).[128] Under the optimized conditions [using 10 mol % of 3,5-bis(trifluoromethyl)benzoyl amide phosphine **P14** as the catalyst in chloroform at −50 °C], the reactions of *β*-perfluoroalkyl-substituted enones presenting various substituents worked well to afford their products in good yields and enantioselectivities. In addition, vinyl ketones presenting both aliphatic and aromatic substituents were suitable substrates for the RC reaction.

In 2017, Wu and co-workers reported a nucleophilic phosphine-catalyzed RC-type 1,6-conjugate addition of methyl vinyl ketone to *p*-QMs (Scheme 44).[129] Using 10 mol % of the phosphine **P15** as the chiral catalyst and dichloromethane as the solvent at −20 °C, the asymmetric RC-type 1,6-conjugate additions of *p*-QMs presenting various substituents and MVK provided their products in excellent yields (91–99%) with excellent enantioselectivities (92–98% ee).

Most recently, the Li group studied the mechanism and stereoselectivities of the phosphine-catalyzed RC reaction of *N*-phenylmaleimide and 2-benzoyl acrylate on the basis of calculations (Scheme 45).[130] They investigated the mechanism of the RC reaction both in the absence and presence of benzoic acid, which was found to play roles in both activation and proton transfer. As displayed in Scheme 45, in the presence of benzoic acid, both *N*-phenylmaleimide and 2-benzoyl acrylate were activated through hydrogen bonding. The intramolecular proton transfer occurs through two successive H-shift processes with the assistance of $PhCO_2H$.

In 2018, the Wang group exploited 2-vinylpyridines as a new type of electron-poor system for the asymmetric cross RC reaction (Scheme 46).[131] Using the bifunctional phosphine **P16** as the chiral catalyst, 2-vinylpyridines were chemo- and enantioselectively activated and their reactions with 3-aroyl acrylates or 2-ene-1,4-diones led to highly valued chiral pyridine building blocks in moderate to good yields and with moderate to excellent enantioselectivities.

2.4.3. Phosphine-Catalyzed Intramolecular RC–Aldol Annulation.—

Although this Review does not cover RC and MBH reactions, Thalji and Roush described an intriguing example of a regioselective intramolecular aldol condensation.[132] In their study, reported in 2005, the RC adduct **11** of the bis-enone produced the thermodynamically less favorable cross-conjugated dienone **12** instead of the conjugated dienone **13** (Scheme 47). Under typical base catalysis, the endione **11** generates the thermodynamic conjugated dienone **13**. Thalji and Roush proposed that the *β*-phosphonium **14** is stabilized by the carbonyl oxygen through coordination, thereby increasing the acidity of the methyl ketone for regioselective deprotonation. The stabilized oxaphospholidine enol ether **15** undergoes a regioselective aldol reaction.

This regioselective aldol reaction proceeds smoothly when a shorter tether is used (Scheme 48). Remarkably, only one regioisomeric dienone product is formed out of the four possible products when a non-C_2-symmetric γ-*gem*-dimethyl-substituted bis-enone is employed (entry 2). Nonsymmetric bis-enones with β-substituents also afforded their desired cross-conjugated dienones (entries 3 and 4). Sterically more demanding substrates required higher reaction temperatures.

2.4.4. Phosphine-Catalyzed Stetter Reaction and β-Umpolung Addition into Aldehydes.—When treating activated alkenes and aldehydes with tertiary phosphines, the famous Morita reaction will occur to produce α-hydoxymethylated acrylates. Instead of forming the Morita product, however, in 2002, Kim and co-workers discovered rare examples of phosphine-catalyzed Stetter reactions between acrylamide and arylaldehydes.[133] The reaction commences with nucleophilic addition of tributylphosphine to the arylaldehyde, producing the intermediate ylide **16** after proton transfer (Scheme 49). This ylide then undergoes conjugate addition to acrylamide to produce the intermediate **17**. Proton transfer and elimination of the catalyst generate the γ-ketoamide.

Several γ-ketoamides, featuring various substitution patterns on the aryl ring system, were obtained in moderate yields (Scheme 50). Several substituents, including halogens and alkyl groups, were tolerated under the reaction conditions.

In the same publication, Kim also disclosed another example of rare reactivity: a phosphonium ylide undergoing β-umpolung addition to aldehydes, affording γ-hydroxyacrylamides (Scheme 51). Nucleophilic addition of the phosphine to acrylamide generates the phosphonium ylide after proton transfer. A reversal of polarity allows nucleophilic addition to occur at the β-carbon of acrylamide.

After the initial discovery of phosphine-catalyzed Stetter reactions and β-umpolung additions of acrylamide, the Teng group expanded the reaction scope to various electron-poor arylaldehydes and ethyl acrylate (Scheme 52).[134] Applying tris(*p*-methoxylphenyl)phosphine as the catalyst allowed the preparation of various γ-ketoesters and γ-hydroxyacrylates with greater efficiencies, but the reaction products were mixtures of γ-ketoesters and γ-hydroxyacrylates.

2.4.5. Phosphine-Catalyzed Annulation through Michael-Intervened Aza-MBH Reaction.—Marinetti and co-workers reported a variant of the MBH reaction that leads to functionalized pyrrolines with good efficiencies (Scheme 53).[135] Nucleophilic addition of the phosphine to the conjugated diene readily generates the phosphonium enolate, which is trapped with the tosyl imine to yield the phosphonium amide **18**. This zwitterionic intermediate performs intramolecular addition to yield **19**. After proton transfer, the intermediate **20** eliminates the phosphine catalyst to form the functionalized pyrroline.

The reaction produces a mixture of two diastereoisomers in a 9:1 ratio, favoring the cis-isomer. The diastereoselectivity improves when a substituent with high steric demand is installed on the enone–enoate system (Scheme 54). One striking difference between this reaction and the intramolecular RC reaction of a bis-α,β-unsaturated carbonyl compound is

the opposite regioselectivity for the initial nucleophilic addition of the phosphine catalyst. The traditional intramolecular RC reaction proceeds through phosphine addition at the more electrophilic enone over the enoate, whereas this reaction favors initial addition of the phosphine at the enoate site over the enone. Various aryl imines are applicable in the annulation reaction, but isobutyl imine, a rare electrophile in phosphine catalysis, has also been incorporated to form substituted pyrrolines. In many cases, alkyl imines are not stable in phosphine-catalyzed reactions, due to decomposition through hydrolysis.

In 2011, Marinetti reported the phosphine-catalyzed syntheses of hexahydroisoindol-4-ones.[136] Using a functionalized cyclohexenone and *N*-tosyl imines, several hexahydroisoindol-4-ones were prepared in good to moderate yields (Scheme 55). When a halogenated imine was applied under the optimized conditions, the annulation product was obtained in excellent yield. Interestingly, as in the aforementioned linear enone–enoate system, isobutylidene imine could be employed to give a functionalized hexahydroisoindol-4-one in good yield.

In 2010, Sasai and co-workers reported an efficient route toward functionalized isoindolines through aza-MBH–Micheal annulation.[137] Although somewhat similar, this strategy differs from the aforementioned cyclization events reported by Marinetti (Section 2.4.5). Highly conjugated enone–enoate systems were not used in this case. Instead, the enone portion of the molecule was tethered to an aromatic imine to offer various annulation patterns. Using the chiral phosphine **P17**, isoindoline derivatives were prepared in excellent yields and with high levels of enantiocontrol (Scheme 56). With MVK as a substrate, isoindoline was isolated in excellent yield and with excellent enantiomeric excess (entry 1). A typically difficult substrate, acrolein, also underwent smooth conversion to the annulation product with good enantiocontrol, albeit in a moderate isolated yield (entry 2). A significant drop in yield and selectivity occurred when phenyl acrylate was employed as a substrate, suggesting slight incompatibility with acrylate systems (entry 3).

2.4.6. Phosphine-Catalyzed Annulation through Michael-Intervened RC Reaction.—

Similar to the alkene annulation first disclosed by the Marinetti group in 2009 (Section 2.4.5), phosphine-catalyzed cyclization also occurs between activated dienes and arylidenemalononitriles, leading to functionalized cyclopentenes (Scheme 57). Huang and co-workers used this approach to prepare a collection of highly substituted cyclopentenes.[138] One salient feature of this reaction is the use of a catalytic amount of benzoic acid as an additive to promote the reaction efficiency and decrease the reaction temperature. For this reaction, higher yields were obtained from electron-deficient arylidenemalononitriles (entry 1). A lower yield resulted from a less activated alkene (entry 2). In addition to simple aryl ring systems, a heteroarylidenemalononitrile was also employed to give its cyclopentene product in good yield (entry 4). When using a less-activated 2,4-dienoate as the substrate, however, no reaction was observed (entry 5).

Expanding the reaction to more complex substrates, in 2013 Huang disclosed the syntheses of highly functionalized spirooxindoles from conjugated dienes and activated methyleneindolinones (Scheme 58).[139] Using various 2,4-diones, spirooxindoles were isolated in good yields, favoring the trans-isomers.

As well as testing commonly used electrophiles (e.g., aldimines, arylidenemalononitriles), Chuang used this reaction to functionalize the surface of C_{60} (Scheme 59).[140] In contrast to the previous examples, activated ene-ynes were used instead of the traditional conjugated dienes. The reaction proceeded through the same mechanism, yielding an external olefin unit.

Instead of applying conjugated 2,4-dienes, He and co-workers used cross-conjugated diene systems for the Michael-intervened RC reaction.[141] Employing arylidenemalononitriles and diarylidene acetones to provide one extra carbon unit, formal [4 + 2] annulation events occurred with good efficiencies. Starting with the nucleophilic addition of tributylphosphine into diarylidene acetone, the phosphonium enolate **21** is generated (Scheme 60). By introducing arylidenemalononitrile, an RC-type addition occurs, providing the intermediate **22**. Subsequent Michael addition and enolate tautomerization give the phosphonium enolate **23**, which undergoes elimination of the phosphine to afford the functionalized cyclohexanone **24**.

Reactions of dibenzylidene acetone with various arylidenemalononitriles resulted in good conversions to their products (Scheme 61, entries 1 and 2). Interestingly, a high diastereoselectivity was observed when employing 2-thienylidenemalononitrile (entry 2). Unfortunately, the reaction efficiencies were notably affected once substituents were placed on the diarylidene acetone ring system, leading to lower product yields (entries 3 and 4).

Using the catalyst **P18**, complex spirocyclohexanoneoxindoles were also prepared with high enantiomeric excesses and great diastereoselectivities (Scheme 62).[142] Many cross-conjugated aryldienones, bearing aryl, heteroaryl, and cycloalkyl units, were suitable substrates under the reaction conditions.

2.4.7. Phosphine-Catalyzed RC–Michael Annulation.—In 2004, Couturier disclosed a tandem annulation process, involving an intramolecular RC reaction and subsequent Michael addition, to generate decalin systems.[58] This reaction is initiated by the addition of tricyclohexylphosphine onto the bis-enone to give the phosphonium enolate **25**, which proceeds through an intramolecular RC reaction to produce the enone **26** after elimination of the phosphine (Scheme 63). The subsequent Michael reaction was proposed to proceed via general base catalysis with the mediation of water.

Although only a catalytic amount of the phosphine is required according to the proposed mechanism, a stoichiometric amount is generally employed to expedite the reaction (Scheme 64). Addition of water or alcohol solvent is beneficial, facilitating the proton transfer process. Moderate yields of functionalized decalins are obtained. When isopropanol is used as the solvent, a catalytic amount of tributylphosphine can be employed to achieve comparable results. For more highly substituted bis-enone systems, a greater amount of nucleophilic trimethylphosphine must be applied with an external base, cesium carbonate, to assist efficient deprotonation and provide a good yield of the corresponding decalin.

Multicyclic ring structures can be synthetically challenging and cumbersome to access, especially in enantiomerically pure form. In 2012, Chi and co-workers reported an

enantioselective phosphine-catalyzed intramolecular [2 + 4] annulation generating highly functionalized multicyclic heterocycles with high optical purities.[143] Taking advantage of intramolecular reactivity, elaborated enoate–enimine systems were suitable substrates, providing two heterocyclic rings with adjacent stereocenters (Scheme 65). Using the chiral aminophosphine **P5** as the catalyst, moderate to excellent yields were obtained for various substituent patterns on the aromatic rings, along with high enantioselectivities. An enoate–enimine system bearing a bulky 6-*tert*-butyl group afforded the annulation product in near quantitative yield and with high enantiomeric excess (entry 1). Product yields were lower, however, when altering the electronic properties of the aromatic ring systems (entries 2 and 4).

In contrast to the Michael-intervened RC reaction, the Zhong group observed complete RC additions followed by subsequent intramolecular Michael reactions to generate a series of functionalized tetrahydropyridines (Scheme 66).[144] In this reaction, a catalytic amount of *p*-methoxyphenol was used to facilitate proton transfer. Several tetrahydropyridines were prepared with high yields and diastereoselectivities and complex substitution patterns.

Loh and Zhong demonstrated an enantioselective variant of the above transformation using the catalyst **P19** (Scheme 67).[145] Although the products were produced in moderate yields, excellent diastereoselectivities and good enantioselectivities were obtained, with various aryl groups tolerated. The use of a *p*-methoxyphenylsulfonyl protecting group improved the enantioselectivities of the reactions.

Shi and co-workers expanded the reaction to use the catalyst **P20** to generate a set of functionalized spirotetrahydropyridineoxindoles (Scheme 68).[146] To enhance the enantioselectivity, a highly sterically demanding 2,4,6-triisopropylphenyl group was installed as a protecting group on the oxindole. Under the optimal conditions, the products were isolated in good yields and with high enantiomeric excesses.

In the following year, the Shi group improved the formation of spirotetrahydropyridineoxindoles by using the catalyst **P21** (Scheme 69).[147] In this case, the sterically demanding 2,4,6-triisopropylphenyl group could be replaced by a less hindered tosyl protecting group while maintaining excellent enantioselectivities. The isolated yields of the products were, however, lower than they were in previous examples.

In 2015, Wu and co-workers reported the preparation of a class of multifunctional chiral phosphines and their application in the [4 + 2] annulation (Scheme 70).[148] The chiral phosphine **P22** bearing three stereogenic centers was identified as the optimal catalyst for the enantioselective formal [4 + 2] cycloadditions between α,β-unsaturated imines and methyl vinyl ketone. Nevertheless, only moderate to good enantioselectivities were obtained.

In 2016, with the aim of synthesizing thiazole-containing piperidine derivatives, Bakulev, Fan, and co-workers developed the phosphine-catalyzed [4 + 2] annulation of *N*-sulfonyl-1-aza-1,3-dienes with vinyl ketones (Scheme 71).[149] Benzenesulfonyl-substituted thiazole-containing tetrahydropyridine derivatives were obtained in moderate to good yields with good to excellent diastereoselectivities. Thiazole-containing piperidines were obtained through deprotection and reduction of the [4 + 2] annulation products.

Very recently, Zhang and co-workers developed enantioselective [4 + 2] cycloadditions of electron-deficient *N*-sulfonyl-1-aza-1,3-dienes and vinyl ketones (Scheme 72).[150] In the presence of the chiral phosphine ***P*23** (7.5 mol %), a series of 1-aza-1,3-dienes underwent enantioselective [4 + 2] cycloadditions with aryl vinyl ketones in generally high yields and enantioselectivities. For the reactions of 1-aza-1,3-dienes with alkyl vinyl ketones, however, the chiral phosphine **P14** displayed the best performance, with the corresponding [4 + 2] cycloadducts obtained in moderate to high yields and with high enantioselectivities. Furthermore, the chiral phosphine **P24** proved to be the best for catalyzing the enantioselective [4 + 2] cycloadditions between chalcone-derived imines and methyl vinyl ketone, with the corresponding functionalized tetrahydropyridines obtained in moderate yields and with high enantioselectivities.

The Zhang group also developed a phosphine-catalyzed [4 + 2] annulation of electron-deficient dienes and alkyl vinyl ketones, providing functionalized cyclohexenes under mild reaction conditions (Scheme 73).[151] Using 10 mol % of Ph_2PMe as the catalyst, the reaction of a variety of aryl-substituted electron-deficient dienes with alkyl vinyl ketones worked well in THF at room temperature, affording the corresponding products in moderate to good yields with excellent diastereoselectivities. Unfortunately, no desired products were obtained when using dienes bearing alkyl substituents. The asymmetric reaction has also been studied using Peng-Phos **P25**, which gave the chiral product in 75% ee.

2.4.8. Phosphine-Catalyzed Annulation through Aldol-Intervened RC Reaction.—Although cyclopentenes are highly valued molecular motifs for secondary metabolite syntheses and pharmaceutical development, fused ring systems (e.g., hexahydropentalen-2-one) are equally important. In 2013, the Shi group disclosed a phosphine-catalyzed aldol-intervened RC reaction for the construction of various hexahydropentalen-2-ones.[152] The formation of the hexahydropentalen-2-ones can be controlled when employing dimethylphenylphosphine as the catalyst (Scheme 74). The reaction proceeds through initial nucleophilic addition of the phosphine to bis-cyclopropenone, generating the phosphonium enolate **27**. Intramolecular cyclization events then occur to give the intermediate **28**. The highly strained intermediate **28** undergoes skeletal rearrangement to give the intermediate **29** with the addition of water. Further rearrangement and decarboxylation afford the desired hexahydropentalen-2-one **30**.

Although a catalytic mechanism is invoked, a stoichiometric amount of the phosphine was used to promote reaction efficiencies, giving various hexahydropentalen-2-ones in moderate to good yields (Scheme 75). Under the optimized conditions, the reaction tolerated some functionalization on the aryl and diester motifs, allowing rapid construction of molecular complexity.

2.4.9. Phosphine-Catalyzed RC–Aldol–S_N2' Annulation.—When an activated alkene **32** is employed as the electrophile, instead of an imine, in the phosphine catalysis of ε-oxo-dienoates, tetrahydrocyclopentafurans **36** can be prepared through an RC–aldol–S_N2' cascade pathway (Scheme 76).[153] In the proposed mechanism, the zwitterion **31** adds to methoxycarbonyl vinyl ketone **32** to form the intermediate **33** (Scheme 76). Proton transfer

generates the ylide **34**, which adds to the ketone unit of the α-ketoester to form **35**. Allylic substitution of the phosphine in intermediate **35** provides the cyclopentafuran **36**.

Under the optimized conditions, several tetrahydrocyclopentafuran derivatives were prepared in good yields (Scheme 77). Similar to Marinetti's phosphine-catalyzed aza-MBH–Michael annulation (Section 2.4.5), no reaction occurred when a bis-enoate system was employed.

2.4.10. Phosphine-Catalyzed [2 + 2 + 2] Annulation.—As mentioned above, reactions with activated alkenes will often not produce cyclic products because of the shortage of atom units in each reaction partner. Nevertheless, Huang and Chen demonstrated a unique annulation process, involving two molecules of an acrolein and one unit of an aldimine, for the synthesis of functionalized tetrahydropyridines through [2 + 2 + 2] annulation.[154] In this reaction, (2′-hydroxy-biphenyl-2-yl)diphenylphosphane (LBBA) served an important role in stabilizing the phosphonium zwitterionic intermediates (Scheme 78). First, LBBA adds into acrolein to give the corresponding phosphonium anion **37**, with the OH group of LBBA stabilizing **37** to avoid excessive oligomerization. Addition of **37** into the aldimine yields the intermediate **38**. Subsequent Michael- and aldol-type additions generate the intermediate **39**. Elimination of the phosphine and water, with proton transfer steps, yields the functionalized tetrahydropyridine **40**.

The reaction tolerates substrates bearing various functionalities on the aromatic ring of the aldimine (Scheme 79). Using the bifunctional phosphine catalyst LBBA, several tetrahydropyridines were isolated in moderate yields.

After a few years, Huang and Chen reported another [2 + 2 + 2] annulation.[155] From arylidene cyanoacetates and acrolein, a domino [2 + 2 + 2] reaction occurs to provide functionalized cyclohexenes. Various functionalized cyclohexenes can be synthesized using the bifunctional LBBA catalyst, favoring the cis-diastereoisomer. Arylidene cyanoacetates substituted with both electron-donating and -withdrawing groups are suitable for the reaction with acrolein as the electrophile (Scheme 80). The yields of the reactions of the electron-rich arylidene cyanoacetates are lower than those of their electron-poor counterparts. Polyaromatic and heteroaromatic arylidene cyanoacetates are also applicable. Although the yield was lower, excellent diastereoselectivity was discerned when employing 2-furylidene cyanoacetate (entry 4).

In the same year, He demonstrated an alternative [2 + 2 + 2] process employing arylidene cyanoacetates and MVK (Scheme 81),[156] instead of the acrolein used in Huang and Chen's [2 + 2 + 2] annulation (Scheme 78).[154] The resulting cyclohexane products incorporated two molecules of arylidene cyanoacetate and one of MVK. In the proposed mechanism, the zwitterion **41**, formed through the addition of triphenylphosphine to MVK, undergoes addition to benzylidene cyanoacetate to form the adduct **42** (Scheme 81). Subsequent addition to the second benzylidene cyanoacetate produces compound **43**. Displacement of the phosphine catalyst produces the cyclohexane **44**.

Under the optimized conditions, several functionalized cyclohexanes were synthesized efficiently as single diastereoisomers (Scheme 82). The reaction afforded better yields when using substrates featuring electron-poor aryl groups, as in Huang and Chen's case. A minimal amount of cyclohexane was isolated when a strongly electron-withdrawing benzylidenemalononitrile was applied as a reaction partner.

2.4.11. Phosphine-Catalyzed [2 + 2 + 1] Annulation.—Shi and co-workers were the first to observe the reactivity of a [2 + 2 + 1] annulation, in the context of using aldimines as electrophile partners (Scheme 83).[157] The reaction with an aldimine initially proceeds to generate the intermediate **45**. The ylide **46**, formed upon proton transfer, undergoes direct displacement of the tosylamide group, followed by elimination of tributylphosphine, providing the functionalized dihydropyrrole **47**.

Under the optimized conditions, several functionalized dihydropyrroles, along with fully aromatized pyrroles, can be obtained (Scheme 84). Substituents on the arylaldimine can range from an electron-donating *p*-methoxy group to an electron-poor *p*-fluoro unit. A heteroaryl 2-furaldimine was also tolerated well in the reaction.

In the 2011 Communication, He also reported the formation of derivatized cyclopentenes through the [2 + 2 + 1] annulation route.[156] High yields of cyclopentenes were acquired in the presence of hydroquinone (operating as a polymerization inhibitor) and when employing tributylphosphine as a more nucleophilic catalyst (Scheme 85). In all cases, both electron-donating and -withdrawing substituents were tolerated under the reaction conditions, providing high yields of cyclopentenes. Electron-donating groups provided slightly lower yields. In most cases, the reactions proceeded to completion within minutes.

2.4.12. Phosphine-Catalyzed Alkene–Maleimide/Maleic Anhydride [4 + 1] Annulation.—As described in the previous sections, many activated alkenes can serve as two-carbon synthons in many phosphine-catalyzed reactions. It was not until 2014 that the Shi group disclosed the interesting reactivities of maleimides and maleic anhydrides behaving as one- and three-carbon synthons, respectively.[158] With maleimide and 1,3-butadiene as reaction partners, they synthesized a collection of functionalized spirocyclopentenes through a phosphine-catalyzed [4 + 1] annulation pathway (Scheme 86). Starting from the 1,3-butadiene, the zwitterion **48** is formed readily in the presence of triphenylphosphine. Addition into maleimide produces the intermediate **49**. After a series of proton transfers, followed by intramolecular displacement of the phosphine, the spirocyclopentene **50** is formed, incorporating maleimide serving as one-carbon synthon.

Various 1,3-butadienes bearing different aryl groups are suitable reaction partners in the alkene [4 + 1] annulation, affording highly functionalized spirocyclopentenes in high yields (Scheme 87). Both electron-rich and -poor aryl ring systems are tolerated well, with no erosion in reaction efficiency.

In addition to the [4 + 1] annulation pathway, an unusual [3 + 2] annulation was also disclosed in the same Communication.[158] Through this pathway, maleic anhydride reacted to provide a three-carbon synthon for the annulation (Scheme 88). The initially formed

zwitterion **51** undergoes addition to maleic anhydride to generate the intermediate **52**. This addition causes ring opening of the anhydride, triggering decarboxylation and displacement of the phosphine, yielding the cyclopentenone **53**.

Using tris(*p*-fluorophenyl)phosphine as the catalyst allowed various cyclopentenones to be isolated in good yields (Scheme 89). Similar to the [4 + 1] annulation of spirocyclopentenes, this reaction is also highly efficient and tolerates various aromatic systems as substituents.

At the same time, the group led by He also reported a phosphine-catalyzed [4 + 1] annulation between 1,3-butadienes and maleimides (Scheme 90).[159] In addition, they employed 1,3-azadienes as reaction partners to expand the scope of the reaction, providing access to functionalized spirodihydropyrroles in good yields. Similar to Shi's approach, He's optimized protocol required the presence of catalytic benzoic acid as an additive to facilitate proton transfer and lower the reaction temperature. In both cases, substrates bearing electron-donating and -withdrawing functionalities were tolerated well, giving good yields of their products.

2.4.13. Azomethine Imine–Alkene [3 + 2] Annulation.—Three reaction partners are commonly used in many phosphine-catalyzed reactions with electrophiles: activated alkenes, aldehydes, and aldimines. In 2014, Guo and co-workers introduced azomethine imines as electrophilic partners for many phosphine-catalyzed reactions. For reactions of an activated diphenylsulfone alkene with azomethine imines, they observed efficient [3 + 2] annulations that generated complex tetrahydropyrazolopyrazoles (Scheme 91).[160] The reaction proceeds with nucleophilic phosphine addition to the activated alkene to give the zwitterionic species **54**. In the presence of an azomethine imine, addition occurs to give the intermediate **55**. Displacement of the catalyst provides the tetrahydropyrazolopyrazole **56**.

Employing various azomethine imines allows both functionalized tetrahydropyrazolopyrazoles and hexahydropyrazoloisoquinolines to be prepared in high efficiencies (Scheme 92). The diastereoisomers shown in Scheme 92 were obtained as the major products, while the other alternatives were not observed or were obtained in only an extremely low amount. The reaction is highly tolerant of various substituents on the aromatic ring of the azomethine imine.

In 2017, the Guo group further expanded the scope of this [3 + 2] cycloaddition to nitrones (Scheme 93).[161] Using 20 mol % of PPh_3 or DMAP as the catalyst, various nitrones performed the [3 + 2] cycloaddition with diphenylsulfone alkenes in dichloromethane at room temperature, furnishing a series of 4,5-bis(phenylsulfonyl)isoxazolidine derivatives in moderate to excellent yields. The scaled-up reaction and further transformation of the cycloadducts demonstrated that the reaction could be a practical tool for organic synthesis.

2.4.14. Phosphine-Catalyzed α-Arylation of Enones/Enals.—Krische and co-workers reported a rare example of a phosphine-catalyzed α-arylation when using tributylphosphine and triarylbismuth(V) as the arylation reagent.[162] Taking advantage of the compatibility of phosphines and bismuth(V), the activated enone, in the form of the

zwitterion **57**, reacts with bismuth(V) to give the intermediate **58** (Scheme 94). Aryl group transfer and elimination of the phosphine affords the arylated enone **59**.

Both cyclohexenone and cyclopentenone are suitable substrates for the reaction, giving good yields of their α-arylated products (Scheme 95). Various aryl groups can be installed through this strategy, although strongly π-donating substituents in the p-position greatly diminish the efficiency of the reaction.

This versatile α-arylation has been applied to the synthesis of the antidepressant paroxetine (Scheme 96).[163] Using dihydropyridinone as a reaction partner, efficient α-arylation has been achieved using Bi(p-$FC_6H_4)_3Cl_2$ to provide the intermediate **60**. A few more transformations yielded paroxetine **61**.

2.4.15. Phosphine-Catalyzed Annulation via RC–Michael Addition–Michael Addition.—In 2017, Shi, Wei, and co-workers developed a phosphine-catalyzed [2 + 1 + 2] cycloaddition of isatin-derived electron-deficient alkenes with vinylpyridines (Scheme 97).[164] The phosphorus ylides generated from two types of alkenes and phosphine reacted with electron-deficient alkenes to afford spirocyclopenteneoxindole derivatives containing three stereocenters in moderate to good yields with good diastereoselectivities. According to the proposed mechanism, the phosphine attacks the β-position of the vinylpyridine to generate a zwitterionic intermediate **62**, which reacts with isatin-derived electron-deficient alkenes to form another zwitterionic intermediate **63**. Through proton transfer and a retro-Michael addition, the key intermediate **64** is formed for the annulation reaction.

2.5. Phosphine Catalysis of Alkenes with Electrophile–Nucleophiles

Many of the phosphine-catalyzed reactions with alkenes occur with complex or disordered reactivity patterns. Such complex reactions are often attributable to simple activated alkenes not being able to provide the necessary carbon synthons to trigger an annulation event. To compensate for this deficiency, molecules tethered with both electrophiles and nucleophiles can contribute the carbon synthons necessary for cyclization.

2.5.1. Phosphine-Catalyzed MBH–Michael Reaction.—Substrates containing both electrophilic and nucleophilic functionalities can be used in the phosphine catalysis of alkenes to yield annulation products. Shi and co-workers reported an interesting MBH reaction of salicylaldehyde, followed by intramolecular oxa-Michael addition, leading to products similar to those of the domino oxa-Michael–aldol (DOMA) reaction (Scheme 98).[165]

The phosphonium enolate **65**, formed through the addition of dimethylphenylphosphine to cyclohexenone, was proposed to undergo the Morita reaction, followed by the oxa-Michael addition and dehydration to produce the tetrahydroxanthenone **66**. While the DOMA product **66** was formed when using the phosphine catalyst, no product was generated when employing 1,4-diazabicyclo[2.2.2]octane (DABCO) in acetonitrile as the solvent. For DABCO to facilitate the transformation, water had to be used as the solvent. This observation supports the notion that the *nucleophilicity* of the phosphine is responsible for

catalyzing the reaction leading to the formation of the DOMA product **66**, and not the *basicity* of the phosphine, as in the case of DABCO in water.

Scheme 99 displays the optimized conditions for the phosphine-catalyzed DOMA reaction. 2,3,4,4a-Tetrahydro-1*H*-xanthen-1-one scaffolds were readily synthesized when treating various salicylaldehydes and cyclohexenone with 20 mol % of dimethylphenylphosphine in acetonitrile at 40 °C. Better yields were obtained when using electron-rich salicylaldehydes. The reaction of 5-nitrosalicylaldehyde did not yield its desired product. Salicylaldehyde with a 3-methoxy group provided its product in poor yield, presumably due to steric hindrance. An additional limitation of this reaction is that cyclohexenone is the only viable olefin substrate.

The Huang group explored another annulation reaction occurring through the MBH–Michael pathway for the synthesis of functionalized 4-aminochromans in good yields, tolerating various substituents on the aromatic ring (Scheme 100).[166] This reaction employed the bifunctional phosphine catalyst LBBA to stabilize the intermediate zwitterionic species.

Furthermore, the reactions with the electrophile and nucleophile can also be performed with individual electrophiles and nucleophiles to access functionalized amino alcohols and diamines. Lin and co-workers disclosed the three-component coupling of arylaldehydes/aldimines, acrylates, and phthalimide/tosylamide through the MBH–Michael cascade reaction (Scheme 101).[167–169] When synthesizing amino alcohols, activated arylaldehydes bearing electron-withdrawing substituents were necessary to achieve good efficiencies. The arylaldehydes could be substituted by aldimines to furnish an array of diamines in good efficiencies when a catalytic amount of methyl acrylate was present as an additive.

Replacing the phthalimide/tosylamide with a carbon pronucleophile (e.g., dimethyl malonate) allowed the preparation of functionalized α-hydroxymethylated alkanols (Scheme 102).[170] Similar to the previously reported formation of amino alcohols, strongly electron-deficient arylaldehydes were necessary to achieve good reaction efficiencies.

2.5.2. Phosphine-Catalyzed Michael–Henry Reaction.—

In 2013, Shi and co-workers reported a phosphine-catalyzed annulation involving β-nitroolefins and tethered electrophile–nucleophile systems for the generation of functionalized cyclohexanes (Scheme 103).[171] Although Shi proposed a general base catalysis mechanism for activating the pronucleophile for the Michael reaction followed by intramolecular Henry addition, the process can also occur through the MBH–Michael pathway described in last section. Again, LBBA is used in this reaction to minimize oligomerization of the β-nitroolefins.

Scheme 104 presents a plausible mechanism for the phosphine-catalyzed Michael–Henry reaction. Michael addition of LBBA to the β-nitroolefin affords the zwitterionic enolate **67**, which functions as a base to deprotonate the malononitrile to produce the intermediate **68**. This intermediate then undergoes Michael addition to the β-nitroolefin to form the intermediate **69**. A subsequent intramolecular Henry reaction, followed by proton transfer with the malononitrile, leads to the highly functionalized cyclohexanol and simultaneous regeneration of **68**.

2.5.3. Acylcyanation.—In 2012, the Liao group developed a novel phosphine-promoted intramolecular acylcyanation of γ-substituted activated alkenes, providing unique access to densely functionalized acyclic ketones bearing β-quaternary carbon centers, with the remarkable feature that both the γ- and β-positions of the activated alkene are functionalized (Scheme 105).[172] The reaction may occur though two pathways. In the presence of a Lewis base catalyst, conjugate addition of the Lewis base to the activated terminal alkene moiety of the cyanohydrin, followed by tandem intramolecular condensation with the ester group and elimination, affords a phosphonium salt **70** with a cyanide anion as a counterion. Subsequent S_N2 substitution, through nucleophilic attack of cyanide anion, produces the desired product (Scheme 105, path A). It is also possible that conjugate addition of the cyanide anion generated in situ to the activated terminal alkene triggers a tandem transformation to give the desired product (Scheme 105, path B).

The Liao group also disclosed the phosphine-catalyzed intramolecular acylcyanation of activated alkenes, which were obtained from readily available starting materials.[173] In the presence of 10 mol % of Bu_3P, functionalized Reissert compounds presenting various *N*-acyl substituents underwent this acylcyanation in DMSO at 30 °C to give functionalized nitriles incorporating quaternary carbon centers bearing a pendent N-heterocyclic motif in moderate to good yields (Scheme 106). The reaction occurs with cleavage of a C–N bond.

3. NUCLEOPHILIC PHOSPHINE CATALYSIS OF ALLENES

A plethora of reactions occur when tertiary phosphine catalysts are present in mixtures of electron-deficient allenes and nucleophiles, electrophiles, electrophile–nucleophiles, or dinucleophiles. When nucleophiles are used as the reaction partners of allenes, γ-umpolung and β'-umpolung additions are the dominant reaction pathways. A classical reaction sequence occurring between an allene and a dinucleophile is the domino γ-umpolung–Michael process, although Kwon[174] reported a Michael–Michael reaction between an allene and dinucleophiles. If electrophiles are mixed with activated allenes, annulation processes, such as Lu's [3 + 2][175] and Kwon's [4 + 2][176] reactions, can occur. A different mode of annulation is observed when electrophile–nucleophiles are administered as annulation partners, with initial nucleophilic addition followed by annulation through a second nucleophilic addition. Arguably, allenes display the most diverse modes of reactivity, providing multifarious arrays of phosphine catalysis products.

3.1. Phosphine-Catalyzed Isomerization of Allenes to Dienes

While the internal redox process to convert 2-alkynoates to corresponding 2,4-dienoates has been known since 1992,[177] Lu observed the first isomerization of an allenoate to a conjugated 2,4-dienoate in 1995 while working on the phosphine-catalyzed γ-umpolung addition of 2,3-butadienoates.[178] When using 2,3-pentadienoate as a reaction partner and a catalytic amount of triphenylphosphine, the conjugated 2,4-dienoate was isolated in good yield (Scheme 107).

In 2009, He and co-workers also achieved the isomerization of allenoates to the conjugated 2,4-dienoates. They demonstrated that triphenylphosphine could be used as the catalyst to isomerize γ-benzyl allenoate to the corresponding 2,4-dienoate in good yield.[179]

Mechanistically, the initial addition of the phosphine occurs at the β-position of the γ-benzyl allenoate, resulting in the formation of the phosphonium dienolate **71**. After proton transfer, the vinylogous phosphonium ylide **72** is formed. Further proton transfer and elimination of the catalyst produces the dienoate with good efficiency (Scheme 108).

Stirring the γ-benzyl allenoate with a catalytic amount of triphenylphosphine in dichloromethane (DCM) provided a good yield of the dienoate as a single (*E,E*)-diastereoisomer in 78% yield (Scheme 109).

In 2014, the Tong group reported a phosphine-catalyzed isomerization of δ-hydroxy-2,3-dienoates to generate δ-oxoacrylates (Scheme 110).[180] Under the influence of a phosphine catalyst, the δ-hydroxy-2,3-dienoates isomerized to corresponding δ-hydroxy-2,4-dienoates. After keto–enol tautomerization, functionalized δ-oxoacrylates were generated.

The same year, Harmata and Hampton described the phosphine-catalyzed isomerization of various allenic sulfones to 2-arylsulfonyl dienes (Scheme 111).[181] Using PPh_3 (20 mol %) as the catalyst and PhOH (20 mol %) as the additive in refluxing THF, a variety of allenic sulfones underwent isomerization, furnishing the desired 2-arylsulfonyl dienes in moderate to good yields. In 2015, Harmata and Hampton further found that, in the presence of 20 or 10 mol % of PPh_3 as the catalyst and 20 or 10 mol % of PhOH as a proton shuttle, a few allenic sulfones isomerized in refluxing THF to produce the 2-arylsulfonyl 1,3-dienes in moderate to good yields (Scheme 112).[182]

3.2. Phosphine Catalysis of Allenes with Nucleophiles

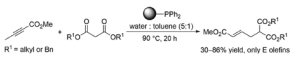
3.2.1. Phosphine-Catalyzed γ-Umpolung Addition.—

While tertiary phosphine catalysts facilitate Michael additions of nucleophiles onto electron-deficient olefins, γ-umpolung reactions occur when electron-deficient allenes react with nucleophiles in the presence of a phosphine catalyst. Cristau, in 1982, was the first to exercise the concept of umpolung addition to activated allenes, but not under catalysis conditions—rather by treating the isolated vinyl phosphonium iodide **74**[183,184] with lithium methoxide in methanol (Scheme 113). Taking 3,4-pentadienone (**73**) as their substrate of interest, triphenylphosphine underwent facile addition into the allenyl double bond. Protecting the ketone as an acetal and counterion exchange with sodium iodide furnished the phosphonium iodide **74**. Treating this salt with methoxide led to γ-umpolung addition. Removal of the acetal protecting group and anion exchange produced the phosphonium salt **75**. The γ-umpolung product **76** was isolated after elimination of the phosphine, using triethylamine as a base.

About a decade later (1994), Trost developed a catalytic variant of the γ-umpolung reaction of 2-alkynoates.[185] Under phosphine catalysis conditions, both 2,3-butadienoate and 2-butynoate are suitable for the reaction, which passes through a common phosphonium dienolate intermediate **77** (Scheme 114). The dienolate **77** activates the pronucleophile through deprotonation to form the ion pair **78**, which undergoes γ-addition to afford the ylide **79**. The phosphonium enolate **80**, formed upon proton transfer, furnishes the γ-umpolung product **81** and the catalyst through β-elimination.

A wide range of pronucleophiles can be applied to the γ-umpolung reaction with allenoates or alkynoates. Oxygen-, nitrogen-, and carbon-centered nucleophiles can be used for such reactions (Scheme 115).

In 1995, Lu documented the γ-umpolung additions of carbon- and oxygen-centered nucleophiles into 2,3-butadienoates, rather than 2-butynoates [first employed by Trost (vide infra)].[178] In their report, dialkyl malonates underwent facile γ-umpolung reactions (Scheme 116). Unlike the reactions employing 2-butynoates, no additives were necessary when employing dialkyl malonates as pronucleophiles. For the reactions of 2,3-butadienoate, the resulting products favored the *E*-geometric configuration (>97:3). The diastereoselectivity decreased when ethyl 2-methyl-2,3-butadienoate was applied (*E*:*Z* = 56:44) in the presence of tributylphosphine. With 2,3-pentadienoate, no γ-umpolung product was produced, due to competing facile isomerization to 2,4-pentadienoate. Benzyl alcohol, a less-acidic pronucleophile, underwent competing Michael addition as well as γ-umpolung addition, due to its higher value of pK_a, leading to inefficient formation of the phosphonium ion pair **78** (Scheme 114). Addition of a substoichiometric amount of acetic acid allowed efficient γ-umpolung addition by facilitating protonation of **77** to form the vinylphosphonium electrophile **78**. In addition to simple malonates, tertiary carbon pronucleophiles can also be used to generate products featuring quaternary centers.[186,187] A polymer-supported triphenylphosphine-catalyzed γ-addition of pronucleophiles to alkynoate was also developed in aqueous media, and the phosphine catalyst was recyclable.[188]



Alvarez-Ibarra reported the additions of carboxylates[189] and α-nitroacetates[190] in γ-umpolung reactions. Functionalized allylic acetates were synthesized when using equivalent amounts of the carboxylic acid and its conjugate base (Scheme 117). The γ-umpolung addition of α-nitropropiolate onto methyl 2-butynoate was facilitated with sodium acetate and acetic acid as additives (entry 2). Upon reduction of the nitro group to an amino group, a synthetically challenging substrate, a γ,δ-didehydrohomoglutamate derivative, was obtained (Scheme 118).

Taran and co-workers reported phosphine-catalyzed γ-additions of phosphorus pronucleophiles to electron-deficient alkynes in the synthesis of 1,3-phosphane oxides (Scheme 119).[191] In the presence of PBu_3 (20 mol %), γ-addition of various phosphorus pronucleophiles to alkynes bearing phosphioyl or phosphinothioyl moieties occurred under microwave irradiation at −150 °C in *i*PrOH for 30 min to give γ-adducts and their isomers in 25–78% yields. Hydrogenation of the γ-adducts with hydrogen gas in EtOH in the presence of Pd/C provided a series of symmetric and nonsymmetric 1,3-phosphane oxides in excellent yields.

In 2006, Virieux and co-workers studied the range of values of pK_a of amine pronucleophiles suitable for γ-umpolung additions to 2,3-butadienoate.[192] They tested several amine-based pronucleophiles, including tetrazole, phthalimide, 1,2,4-triazole, pyrazole, imidazole, indole, and pyrrole (Scheme 120). Pronucleophiles with values of pK_a from 8 to 16 produced γ-umpolung products in moderate to excellent yields, consistent with

Trost's finding.[185] A phosphonium–phenyltetrazolide ion pair was observed, instead of the γ-umpolung addition product, when phenyltetrazole (pK_a = 4.5) was used. Starting at a value of pK_a of 8.5, high yields of γ-umpolung products were isolated as mixtures of *E*- and *Z*-isomers. A significant drop in yield occurred when indole (pK_a = 16.2) was applied as the pronucleophile. A further increase in the pK_a of the pronucleophile, in the case of pyrrole, led only to oligomerization of the 2,3-butadienoate. Based on these observations, the authors concluded that pronucleophiles having values of pK_a of less than 8.5 are not sufficiently nucleophilic to undergo addition, whereas pronucleophiles with values of pK_a greater than 16.2 are not activated through deprotonation because of their lower acidity.

Later in 2012, the Shi group reported an interesting γ-umpolung addition using oximeoxindoles as pronucleophiles (Scheme 121).[193] This reaction proceeds through two γ-umpolung events to give functionalized nitroneoxindoles in good yields, tolerating various substituents on the aromatic ring.

In Trost's studies, functionalized γ-substituted α,β-enoates were attained by reacting methyl 2-butynoate with carbon pronucleophiles, including β-keto esters, α-cyanosulfones, and disulfones. Nitrogen-centered nucleophiles, such as phthalimide, *p*-methylbenzenesulfonamide, and *O*-methylhydroxyamides, were also compatible in the reaction.[194] In addition to intermolecular umpolung additions, an intramolecular variant was also established using a tethered hydroxyl alkynoate (Scheme 122).[195] One similarity in these reactions is the use of a catalytic amount of either triphenylphosphine or bis-(diphenylphosphino)propane (DPPP) with 20 mol % of acetic acid as an additive. Typically, pronucleophiles with values of pK_a of less than 16 are preferred; otherwise the yield is low or no reaction occurs.

In 2012, Kwon disclosed an efficient intramolecular ring closing event to form 2-pyrroline derivatives through phosphine catalysis.[196] This reaction was the first example of intramolecular γ-umpolung addition to yield 2-alkyl-substituted pyrrolines through 5-*endo* cyclization (Scheme 123). Allenoates bearing methyl, isopropyl, and cyclopentyl groups performed well under the reaction conditions to give functionalized 2-alkylpyrrolines in excellent yields (entries 1–3). In addition to alkyl substituents, aryl systems (e.g., *p*-methoxy, *p*-chlorophenyl) were also well suited, giving their products with high efficiencies (entries 4 and 5). Notably, the allenoate presenting a *p*-chlorophenyl group underwent facile γ-umpolung addition in the absence of any additives. This strategy offers an alternative method for generating 2-alkylpyrrolines that cannot be accessed easily through the allene–imine [3 + 2] annulation.

In 2015, Kwon and co-workers reported the stereoselective syntheses of α,β-unsaturated γ-amino esters via phosphine-catalyzed γ-umpolung additions of sulfonamides to γ-substituted allenoates (Scheme 124).[197] With 20 mol % of Ph_3P as the catalyst, a number of sulfonamides with various substituents appended to the benzene ring underwent the addition reaction in Et_2O at room temperature to give the desired products in good to excellent yields (81–98%) with *E*/*Z* stereoselectivities ranging from 89:11 to 99:1. A variety of γ-substituted allenoates were also suitable for the reaction. Nevertheless, branched alkyl groups, or an aryl group, on the allene moiety were not tolerated.

In 2012, Palacios and co-workers reported the phosphine-catalyzed γ-addition of carbon pronucleophiles to allenyl phosphine oxide (Scheme 125).[198] In the presence of PPh_3 (10 mol %) as the catalyst and AcOH as the additive, allenyl phosphine oxide reacted with nitroalkanes or malonate-type pronucleophiles in hot toluene affording γ-functionalized α,β-unsaturated phosphine oxides and isomerized alkynic phosphine oxides in moderate yields and chemoselectivities.

In 2017, the Zhou group developed a phosphine-catalyzed domino reaction of benzofuranones with allenoates that occurred via a β-umpolung/γ-umpolung process (Scheme 126).[199] Using 20 mol % of PPh_3 as the catalyst, allenoates reacted with several substituted benzofuranones in toluene at room temperature to produce a variety of unsymmetrical 3,3-disubstitued benzofuranones in moderate to good yields. The products could be transformed further into other interesting heterocycles.

3.2.1.1. Enantioselective Intermolecular γ-Umpolung Addition.: Asymmetric γ-umpolung additions can also be accomplished, granting access to functionalized acrylate systems with high optical purities. Zhang documented the first example of asymmetric induction in a phosphine-catalyzed γ-umpolung reaction catalyzed by the phosphine **P26** (Scheme 127).[200] As in previous studies, both acetic acid and sodium acetate (50 mol % of each) were used to facilitate proton transfer steps in these γ-umpolung reactions of butynoates and allenoates. Among the various chiral phosphines tested, possessing either axial chirality or a chiral phosphorus center, the best efficiencies were accomplished when using the phosphine **P26**. To probe the scope of the reaction and its limitations, various activating groups were examined on the allene. Unlike [3 + 2] annulations, remote steric influence from the allenyl ester functionality plays little role in terms of enhancing the enantioselectivity of this reaction. The selectivity of the reaction was, however, highly substrate-dependent. Erosion of enantioselectivity occurred when the pronucleophile deviated from a β-keto ester (entries 3 and 4).

After Zhang's first asymmetric γ-umpolung reaction, Pietrusiewicz—while working on enantioselective [3 + 2] annulations—disclosed a short report of the use of the chiral monodentate phosphine **P27** to induce asymmetric γ-umpolung addition (Scheme 128).[201] Moderate yields and chiral inductions are achieved when using either ethyl 2,3-butadienoate or 2-butynoate as the allene.

Pursuing a more efficient asymmetric γ-umpolung pathway, Fu reported several examples of pronucleophiles adding into activated allenes. The reactions of allenamides and a superstoichiometric amount of nitromethane, catalyzed by the chiral phosphinamine **P28**, provided access to acrylate derivatives with high enantiomeric excesses (Scheme 129).[202] Several features in this transformation are noteworthy: (i) the chiral phosphine contains an uncommon phosphinamine group; (ii) a unique Weinreb amide-derived allenamide was the most efficient substrate; and (iii) phenol (10 mol %) was used to assist proton transfer. Accordingly, a variety of optically pure acrylates were generated in high yields with high levels of enantiocontrol (entries 1–4).

Having obtained excellent results in enantioselective γ-umpolung additions with nitromethane, Fu documented an asymmetric variant of the γ-umpolung addition of thiols to γ-alkyl-substituted allenoates.[203] (1*S*,1′*S*,2*R*,2′*R*)-1,1′-Di-*tert*-butyl-2,2′-biphospholane (TangPhos) **P29** induced high levels of enantiocontrol in the γ-umpolung additions of thiols, generating functionalized γ-sulfanyl acrylates (Scheme 130). This catalyst, which had originally been designed by Zhang[204] for use in rhodium-catalyzed asymmetric hydrogenation, was the ideal catalyst for the γ-umpolung additions of thiols. Chen and co-workers performed computational studies using density functional theory to further support the mechanism and understand the efficiency of this transformation.[205] Various γ-substituents (e.g., alkene, alkyne, ether, acetal, ester, and halide groups) on the allenoate are compatible with the reaction conditions. Alkyl thiols bearing aromatic, heteroaromatic, and alkyl substituents are suitable for the transformation. Uniquely, this reaction uses a superstoichiometric amount of the thiol (3 equiv) as well as 2-methyl-2-phenylpropanoic acid (50 mol %) to facilitate the proton transfer process.

To further expand the repertoire of asymmetric thiol γ-umpolung reactions, Fu, in 2011, reported that the chiral phosphepine **P30** generates various functionalized γ-arylsulfanyl acrylates with excellent enantioselectivities (Scheme 131).[206] Unlike the two previous reports, this reaction is conducted at a low temperature (10 °C) for an extended period of time, providing γ-arylsulfanyl acrylates in moderate yields. Notably, a sterically hindered phosphepine is employed, along with, uniquely, pivalic acid (50 mol %) to assist proton transfer.

For many years after the first γ-umpolung addition reported by Zhang and the γ-umpolung reaction of nitromethane, there were no reports of efficient γ-umpolung additions of carbon pronucleophiles until Fu found that the chiral phosphepine **P31** catalyzed the γ-umpolung additions of malonates into allenoates and allenamides asymmetrically with good efficacy (Scheme 132).[207] To achieve high reaction efficiency, a small amount of 2-methoxyphenol (10 mol %) was added to assist proton transfer. Similar to the γ-umpolung reactions of aryl thiols, these reactions were conducted at low temperature to ensure good enantioinduction.

Having had great success in asymmetric γ-umpolung additions, the Fu group explored the possibility of performing enantioselective γ-umpolung additions of nitrogen pronucleophiles. With the spirophosphepine **P32** as the catalyst, they demonstrated the highly effective asymmetric formation of γ-aminoacrylates when using trifluoromethylamide as the pronucleophile (Scheme 133).[208] One of the salient features of this reaction is the absence of any external acidic additives that might promote proton transfer. Presumably, the acidic trifluoromethylamide served as both the pronucleophile and an acidic additive, thereby maintaining efficient proton transfers.

Interestingly, through a synergistic catalytic combination of an achiral phosphine and a chiral squaramide, Mukherjee and Kumar achieved asymmetric γ-addition of α-Angelica lactones to allenoates (Scheme 134).[209] With PPh_3 (20 mol %) and a squaramide derivative (12 mol %) as catalysts and 2,6-di-*tert*-butylphenol (2,6-DTBP, 10 mol %) as an additive, a wide range of allenoates underwent γ-addition with various α-Angelica lactones in mesitylene at −10 °C to provide the products with moderate to excellent yields and

enantioselectivities. A transition state involving hydrogen bonding between the enoate oxygen anion and the squaramide was also proposed.

Almost every example of phosphine-catalyzed γ-umpolung addition in the literature, prior to 2014, used chiral phosphines without additional functionalities that could facilitate hydrogen bonding. Zhao and co-workers reported that the chiral phosphine **P33** can trigger efficient γ-umpolung additions between oxindoles and allenoates to generate functionalized 3,3-disubstituted oxindoles (Scheme 135).[210] Both 3-aryl- and 3-alkyloxindoles are suitable substrates for the reaction, giving their products in excellent yields and with good enantiomeric excesses.

After Zhao's seminal report, Lu and co-workers described a chiral phosphine-catalyzed γ-umpolung addition using oxindoles as the pronucleophiles (Scheme 136).[211] With the phosphine **P34** as the catalyst, the reaction proceeded smoothly, tolerating various alkyl substituents, to give 3-substituted oxindoles in excellent yields and with excellent enantiomeric excesses. Various substituents (e.g., 5-bromo and 5-methoxy groups) on the oxindoles were also tolerated, giving good yields of the products.

In further explorations of the asymmetric γ-addition of allenoates, most studies have focused on expanding the scope of the pronucleophile (Scheme 137).[212] In 2015, the Lu group investigated the γ-addition of 3-fluorooxindoles to 2,3-butadienoates for the construction of oxindoles containing a 3-fluoro quaternary center. Under catalysis with 10 mol % of the L-threonine-derived phosphine-amide **P35**, 3-fluorinated oxindoles presenting various substituents underwent γ-addition to benzyl buta-2,3-dienoate in toluene at room temperature to afford the corresponding products in good to excellent yields (88–95%) and enantioselectivities (83–94% ee).

In 2015, Fu explored the application of 1,3-oxazol-5(4*H*)-ones or 2-amino-3,5-dihydro-4*H*-imidazol-4-ones in asymmetric γ-addition of allenoates (Scheme 138).[213] With the use of the phosphine **P31** as a chiral catalyst and 2-chloro-6-methylphenol or 2-fluoro-6-methylphenol as an additive, diverse 1,3-oxazol-5(4*H*)-ones or racemic 2-amino-3,5-dihydro-4*H*-imidazol-4-ones underwent γ-addition to an array of allenoates in iPr$_2$O at 0 °C, generating their γ-addition products in good yields, diastereoselectivities, and enantioselectivities. Twenty-eight examples were presented. The substituents on the allenoates, 1,3-oxazol-5(4*H*)-ones, and 2-amino-3,5-dihydro-4*H*-imidazol-4-ones had little effect on the reaction efficiency.

Using amino acid-based bifunctional phosphines as chiral catalyst and 5*H*-thiazol-4-ones or 5*H*-oxazol-4-ones as carbon pronucleophiles, Lu, Lan, and co-workers realized a phosphine-catalyzed enantioselective γ-addition to allenoates (Scheme 139).[214] In the presence of the threonine-derived phosphine **P36** (10 mol %), various substituted 5*H*-thiazol-4-ones underwent γ-additions to the allenoates to give γ-functionalized α,β-unsaturated esters in excellent yields and enantioselectivities. Similarly, using the chiral phosphine **P37** as the catalyst and 3 Å MS as an additive, 5*H*-oxazol-4-ones underwent γ-additions to the allenoates to afford their adducts in excellent yields and with good to excellent enantioselectivities. Various substituted 5*H*-thiazol-4-ones and 5*H*-oxazol-4-ones were

compatible reaction partners. The products could be transformed further into enantioenriched tertiary alcohols/thioethers. DFT calculations and the results of control experiments indicated that supramolecular hydrogen bonding interactions between the TsN-H unit and both the carbonyl group in the thiazolone and the bulky silyl group in the phosphine played crucial roles affecting the enantioinduction.

In a further investigation, Lu, Lan, and co-workers achieved regiodivergent C-2- and C-4-selective γ-additions of oxazolones to allenoates (Scheme 140).[215] In the presence of the *O*-TBDPS-L-threonine-based phosphine **P36**, when 2-aryl-4-alkyloxazol-5-(4*H*)-ones were employed as pronucleophiles, γ-addition to *tert*-butyl buta-2,3-dienoate led to C-4-selective γ-addition providing the major products. A variety of oxazolones with alkyl substituents at the 4-position worked well, giving their desired products in good to excellent yields and stereoselectivities, whereas oxazolones with aryl substituents at the 4-position were unsuitable, giving their products with lower values of ee. On the other hand, when using 2-alkyl-4-aryloxazol-5-(4*H*)-ones as pronucleophiles, the chiral phosphine **P38**-catalyzed C-2-selective γ-additions of oxazolones to benzyl buta-2,3-dienoate occurred to give the adducts in excellent yields and with good to excellent enantioselectivities. Further theoretical investigation using DFT calculations revealed that the regioselectivity was determined by the distortion energy resulting from interactions between the nucleophilic oxazolide and the electrophilic phosphonium intermediate.

Using isatin-derived α-(trifluoromethyl)imines as pronucleophiles, Shi and co-workers also achieved enantioselective umpolung γ-additions to allenoates (Scheme 141).[216] In the presence of the thiourea-derived bifunctional chiral phosphine **P39** (20 mol %), a series of isatin-derived α-(trifluoromethyl)imines reacted efficiently with various allenoates to afford their corresponding isatin-derived α-(trifluoromethyl)imine derivatives in good to excellent yields and with moderate to good enantioselectivities.

In 2017, Zhang and Chen also investigated a phosphine-catalyzed asymmetric γ-addition of α-iminoester to allenoates. Using 10 mol % of a chiral phosphine **P40a** as the catalyst, a variety of trifluoromethyl ketimines underwent γ-addition to benzyl buta-2,3-dienoate in toluene at −20 °C, giving the desired products in 64–84% yields and with 90–96% ee (Scheme 142).[217] Interestingly, a three-component reaction involving α-ketoesters was achieved to afford the γ,δ-unsaturated α-amino acid derivatives in 60–77% yields with 90–96% ee.

As an alternative to the use of carbon pronucleophiles, the Jacobsen group developed an efficient γ-umpolung addition to achieve hydroamination of 3-alkynoates, mediated by the catalyst **P41** (Scheme 143).[218] Alkynoates having various substituents at the γ-position were suitable substrates. Notably, 3-alkynoates were used in this case, instead of the traditional 2-alkynoates or allenoates employed in previous examples.

Using alcohols as pronucleophiles, Fu achieved phosphine-catalyzed enantioselective γ-additions to γ-aryl alkynoates (Scheme 144).[219] In the presence of the chiral spirophosphine **P32** (5 mol %), a series of γ-aryl (including heteroaryl) alkynoates reacted with various alcohols to provide the corresponding benzylic ethers in moderate to excellent yields and

with good to excellent enantioselectivities. Furthermore, the author proposed a mechanism for the reaction, involving, as a key step, nucleophilic addition of the alkoxide anion to the γ-position of the typical zwitterionic intermediate.

3.2.1.2. Enantioselective Intramolecular γ-Umpolung Addition.: In 1994, Trost and Li developed the first intramolecular γ-umpolung reaction of ω-hydroxy-2-alkynoates, granting access to functionalized tetrahydrofurans and tetrahydropyrans.[195] Fu developed a highly enantioselective version of this transformation employing the chiral spirophosphepine **P32** (Scheme 145).[220] Two notable features of this reaction are the use of a monodentate phosphine (over the original DPPP catalyst) to prevent alkyne isomerization and the use of benzoic acid (50 mol %) as an acid additive, in lieu of Trost's acetic acid. Various functionalized tetrahydrofurans, tetrahydropyrans, and dihydrobenzopyrans were afforded in high yields and enantiomeric excesses.

After establishing the first examples of asymmetric intramolecular γ-umpolung additions toward tetrahydrofurans and tetrahydropyrans, the same chiral spirophosphepine **P32** was also found to be capable of generating pyrrolidines and 2,3-dihydroindoles with high enantiomeric excesses (Scheme 146).[208] Unlike the intermolecular variant using trifluoromethylamide and no acidic additives, this reaction required either 2,4-dimethoxyphenol or 2-fluoro-6-methoxyphenol as an acidic additive to achieve good reaction yields and enantioselectivities.

3.2.2. Phosphine-Catalyzed β′-Umpolung Addition.—In 2011, Kwon and Shi independently developed a new umpolung reaction of nucleophiles: β′-addition onto α-alkyl allenoates.[221,222] The proposed mechanism begins with the addition of triphenylphosphine onto ethyl 2-methyl-2,3-butadienoate, generating the phosphonium zwitterion **82** (Scheme 147). The β′-proton in the zwitterion **82** is sufficiently acidic to allow equilibrium between **82** and **83**. The vinylogous phosphonium ylide **83** ↔ **84** deprotonates the pronucleophile and furnishes the allylic phosphonium species **85** and the nucleophile pair. Conjugate addition of nucleophiles onto the enoate **85** and subsequent β-elimination of triphenylphosphine results in the formation of the β′-umpolung product **86**.

In Kwon's study, a wide variety of pronucleophiles featuring different nucleophilic atom centers (e.g., oxygen, nitrogen, sulfur, carbon) were used. Phenols with electron-donating or -withdrawing substituents were applicable, with excellent reaction efficiency and diastereoselectivity (Scheme 148). *N*-Tosyl–protected phenylalanine ethyl ester worked well as an amine pronucleophile, giving the functionalized amino acid in excellent yield, although almost equal amounts of the *E*- and *Z*-olefin isomers were isolated (entry 4). Carboxylic acids were also amenable to β′-umpolung addition with either α- or γ-substituted allenoates (entries 5–9). By increasing the size of the substituent on the β′-position of the allene, a *Z*-olefin can be obtained exclusively, due to the steric clash between the methyl group and the β′-substituent (entry 8). Carbon-centered pronucleophiles, such as malononitrile and alkylidene cyanoacetates, are compatible with the β′-umpolung reaction. *E*-Benzaldehyde oxime can also be adapted as an efficient oxygen-centered pronucleophile (entry 12). Although thiols are potent Michael donors in the presence of a phosphine or another base, posing a potential competing pathway against β′-umpolung reaction,

benzenethiol can be implemented in this reaction to give an allylic sulfide favoring the *E*-olefin geometry (entry 13). In addition to allenoates, cyanoallenes also participate in the β'-umpolung reaction to provide allylic ethers of *Z*-olefin geometry in high yields (Scheme 149).

Contemporaneously, Shi also found that phenols and *N*-tosylamides are viable pronucleophiles in the β'-umpolung addition (Scheme 150). In Shi's study, 1,3-diones were employed as carbon-centered nucleophiles. Pronucleophiles containing electron-donating or -withdrawing substituents were suitable for the reaction. For a slow-reacting and less-active pronucleophile (entry 2), triphenylphosphine was used to prevent the facile dimerization of the allene that occurred in the presence of the more strongly nucleophilic tributylphosphine. In general, *E*-isomeric products were favored over their *Z*-isomers. In Shi's tributylphosphine-catalyzed β'-umpolung addition, no β'-umpolung product was observed when benzenethiol was a reaction partner, in contrast to the result for Kwon's triphenylphosphine-catalyzed version. Instead, the Michael addition product was isolated in 94% yield (Scheme 151). Furthermore, only ethyl 2-methyl-2,3-butadienoate was tested as the allene substrate.

3.2.3. Phosphine-Catalyzed Michael Addition.—When reacting allenoates and pronucleophiles in the presence of a phosphine, the most common reaction pathway will be γ-umpolung addition. A few years after Kwon's disclosure of the first Michael addition with an allenoate (vide infra), Huang and co-workers demonstrated a highly chemoselective Michael addition of hydrazones with allenoates to afford functionalized β-amino acrylates (Scheme 152).[223] As displayed in Scheme 153, formation of the product **87** follows the mechanism of β-Michael addition to the allenoate. When the more electron rich PBu_3 is used, the basicity of the zwitterions formed after addition of PBu_3 to the allenoate would be sufficient to deprotonate compound **87** to give the intermediate **90**, which can interconvert with its isomer **91**. Deprotonation of compound **87** by isomer **91** leads to the product **88** and the intermediate **90**, which can further facilitate the β-Michael reaction cycle until the reaction is complete (Scheme 153).

In 2004, the Lu group found that, in the presence of Ph_3P, when treating phenylsulfonyl-1,2-propadiene with 1,3-cyclohexanedione in toluene at 80 °C, the Michael adduct from addition of the enol to the allene was obtained in 49% yield (Scheme 154).[224] Reaction of acetylacetone with phenylsulfonyl-1,2-propadiene was similar to that of the 1,3-cyclohexanedione, but a β-adduct from addition of the carbonion to the allene was obtained in 54% yield.

In 2015, Lu and Gandi reported the phosphine-catalyzed Michael addition of cyanoacetates to allenoates (Scheme 155).[225] When arylcyanoacetates were used as substrates, the β-addition adducts with a quaternary center were obtained as the main products, in excellent yields. In contrast, when benzylcyanoacetates were employed as substrates, the β-selectivity was lost and the γ-adducts dominated.

In 2016, Kwon developed a phosphine-catalyzed intramolecular cyclization of α-nitroethylallenic esters, occurring through β-addition/rearrangement, for the synthesis of

(*Z*)-furan-2(3*H*)-one oxime derivatives (Scheme 156).[226] When using $PMePh_2$ (5 mol %), (*Z*)-furan-2(3*H*)-one oxime derivatives with various substituents were obtained in moderate to excellent yields. A plausible mechanism, involving cyclization of the zwitterionic intermediate followed by intramolecular rearrangement, was proposed.

3.3. Phosphine Catalysis of Allenes with Dinucleophiles

3.3.1. γ-Umpolung–Michael [*n* + 2] Annulation.—

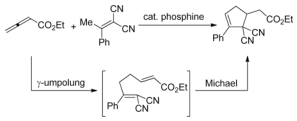
Under phosphine catalysis, a distinctive mode of annulation, through a γ-umpolung–Michael reaction, can occur when reacting dipronucleophiles with activated allenes. Cristau, in 1989, was the first to realize this concept, albeit in a noncatalytic manner.[184] Starting from the phosphonium iodide **79**, γ-umpolung addition occurred readily at the nitrogen center of 2-benylaminoethanol to furnish the intermediate **92** (Scheme 157). Under an acidic environment, tandem acetal removal and elimination of triphenylphosphine triggered Michael addition to give the product morpholine.

It was not until 2002, however, that Lu reported the first catalytic γ-umpolung–Michael reactions involving dipronucleophiles, including cyclohexan-1,3-dione and *N,N*-ditosyl-1,2-ethandiamine (Scheme 158).[227] For this reaction, both activated allenes and alkynes were suitable substrates. The product yields increased and the catalyst loadings decreased when the allene or alkyne was more electron-poor.

In 2002, Liu demonstrated effective thiazoline formation from thioamides and ethyl 2-butynoate in the presence of tributylphosphine, based on the reaction modality of the γ-umpolung–Michael pathway.[228] In this transformation, thioamides acted as good dipronucleophiles to afford thiazolines with excellent regioselectivity (Scheme 159). Comparable reactivity was observed when using heteroaryl thioamides. When an alkyl thioamide was applied, however, the corresponding thiazoline was obtained in significantly lower yield.

In Lu's allene–alkene [3 + 2] annulation (see Section 3.4.1), the allenoate serves as a three-carbon synthon and the electron-deficient olefin provides two carbons for the final five-membered ring product. In 2008, Lu reported the first example of a substituted alkylidenemalononitrile providing three carbons, while the allenoate furnished two carbons, in an unusual [3 + 2] annulation.[229] The reaction was proposed to proceed through initial γ-umpolung addition followed by Michael addition (Scheme 160).

The reaction occurs in relatively high-boiling nonpolar solvents (e.g., xylene), whereas low-boiling polar solvents (acetone, tetrahydrofuran, dichloroethane) render no annulation product (Scheme 161). In general, electron-donating substituents on the arylidenemalononitrile give good yields of the unusual [3 + 2] annulation product. When an electron-withdrawing substituent was placed in the arylidenemalononitrile, no desired product was isolated. The elaborate 2-(chroman-4-ylidene)malononitrile could also be employed, generating a polycyclic structure in moderate yield.



The structure of dihydrofuran resembles many important motifs in secondary metabolites. In 2012, Huang and co-workers disclosed a phosphine-catalyzed annulation to access a series of functionalized dihydrofurans through the γ-umpolung–Michael addition pathway (Scheme 162).[230] Using β-ketoesters bearing different substitutions, the products were isolated in good yields from reactions tolerating alkyl and aryl substituents.

In 2015, Sasai and co-workers developed a domino reaction, initiated by a phosphine-catalyzed γ-addition of allenoates, for the construction of chiral tetrahydrobenzofuranone skeletons (Scheme 163).[231] In the presence of the spirophosphine (*R*)-**P32** (20 mol %), a wide range of prochiral dienones bearing a free hydroxyl group reacted with allenoates to provide a class of highly functionalized tetrahydrobenzofuranones (up to 15 examples) bearing a chiral tetrasubstituted stereogenic center. Moderate to good yields, excellent enantioselectivities, and high *E/Z* ratios (from 1:9 to 1:>20) were obtained. According to the proposed mechanism, the reaction proceeds through a domino sequence of phosphine-catalyzed γ-addition and oxy-Michael reactions (Scheme 164).

3.3.2. Double-Michael [4 + 1] Annulation.—In 2011, Kwon demonstrated a highly efficient double-Michael process to generate functionalized benzimidazolines, benzoxazolines, benzothiazolines, 1,3-benzodioxoles, 1,3-benzoxathioles, and 1,3-benzodithioles.[174] This report provided the first examples of phosphine-mediated double-Michael reactions of dinucleophiles with allenoates to form functionalized heterocyclic scaffolds. The proposed mechanism occurs through phosphine-initiated general base catalysis, starting with the initial generation of the phosphonium dienolate zwitterion **93** (Scheme 165). Deprotonation of the pronucleophile **94** by the phosphonium dienolate **93** produces the ion pair **95**, which is in equilibrium with another vinyl phosphonium species (**96**). At this point, if triphenylphosphine is employed as the catalyst, γ-umpolung–Michael annulation occurs to give the cyclized product **97**. With trimethylphosphine, however, the anionic nucleophile adds to the starting allene to give the intermediate **98**. After γ-protonation, the resulting anion **99** undergoes a second Michael addition to afford the cyclized intermediate **100**, which serves as the base to propagate the reaction, leading to the cyclic double-Michael product **101**.

Under the optimized conditions, six distinct heterocycles—benzimidazoline, benzoxazoline, benzothiazoline, 1,3-benzodioxole, 1,3-benzoxathiole, and 1,3-benzodithiole—were constructed with high efficiency (Scheme 166).

3.3.3. γ-Umpolung–S_N2' [4 + *n*] Annulation.—In 2010, Tong and co-workers documented a novel phosphine-catalyzed γ-umpolung addition with subsequent ring closure to synthesize highly functionalized cyclopentenes.[232] In the proposed [4 + 1] annulation mechanism, triphenylphosphine undergoes nucleophilic addition into the 2-(acetoxymethyl)buta-2,3-dienoate **102** (Scheme 167). Facile elimination of allenylic acetate generates the 2-phosphonium 1,3-diene **103**. Unlike the situation in a typical umpolung

addition, where the phosphonium zwitterion deprotonates the pronucleophiles, an external base is needed in this case to facilitate such deprotonation. The thus-formed anionic nucleophile undergoes γ-umpolung addition to the phosphonium diene **103** to yield the ylide **104**. After proton transfer, the cyclopentene **105** is produced through what amounts to an S_N2' displacement of the phosphine catalyst.

The reaction proceeds smoothly, leading to high yields of cyclopentenes, when a nonpolar solvent, benzene, is employed with triphenylphosphine (20 mol %) as the catalyst. 1,3-Diones, α-cyano ketones, and α-cyano esters are applicable for the reaction, giving good to excellent yields of functionalized cyclopentenes (Scheme 168). When bis-*p*-methylbenzenesulfonylamide is employed, tetrahydropyridazine is prepared in high yield.

In 2016, Liao and co-workers developed a phosphine-catalyzed [4 + 2] annulation of α-aminonitriles with allenoates for the synthesis of diversely substituted tetrahydropyridines bearing quaternary carbon centers (Scheme 169).[233] In this reaction, α-aminonitriles function as *C,N*-bisnucleophilic reaction partners while 2-(acetoxymethyl) buta-2,3-dienoates operate as C4 synthons. In the presence of PPh_3 (20 mol %) and Cs_2CO_3 (130 mol %), α-aminonitriles featuring various *N*-aryl (R^1) groups and R^2 groups were suitable substrates for the reaction, providing their [4 + 2] annulation products in moderate to high yields.

The phosphine-catalyzed [4 + 1] annulation disclosed by Tong and co-workers can also be rendered asymmetric. In 2014, the Fu group employed the chiral phosphepine **P42** to catalyze [4 + 1] annulations between α-cyanocarbonyls and β'-acetoxy allenoates, generating several functionalized cyclopentenes in high yields and enantiomeric excesses (Scheme 170).[234] Various α-cyanoketones and amides were amenable to the reaction conditions. Although an α-cyanoester could also be used, the reaction required a higher catalyst loading to maintain the high yield.

The Lu group took a different approach—using the multifunctional catalyst **P43** derived from L-threonine—to prepare various functionalized spiropyrazolones in excellent efficiencies (Scheme 171).[235] Via a mechanism involving stabilization through hydrogen bonding, complex spiropyrazolones bearing various aryl groups (e.g., phenyl, *p*-nitrophenyl, and 2-furyl rings) were isolated in high yields and with high enantiomeric excesses. Like many multifunctional catalyst systems, the N–H bond in the catalyst **P43** was essential for asymmetric induction.

Fu also developed phosphine-catalyzed [4 + 1] cycloadditions of amines with allenes for the construction of dihydropyrroles (Scheme 172).[236] Using the spirophosphine **P44** (10 mol %) as the catalyst, a wide range of γ-substituted allenoates underwent formal [4 + 1] cycloadditions with various sulfonamides to furnish substituted 2,5-dihydropyrroles in moderate to excellent yields and with excellent enantioselectivities. The resulting dihydropyrroles could be transformed into various useful derivatives, via oxidation or cycloaddition, with good stereocontrol.

3.3.4. α-Umpolung–γ-Umpolung [3 + 3] Annulation.—As mentioned in the previous section, Tong demonstrated a fascinating phosphine-catalyzed [4 + 1] annulation using the α-acetoxymethylated allenoate **102** to generate various cyclopentenes. Following that great discovery, Tong exploited another mode of reactivity: using a δ-acetoxy allenoate to trigger the formation of functionalized 2*H*-pyrans (Scheme 173).[237] The reaction begins with nucleophilic addition of triphenylphosphine to the δ-acetoxy allenoate **106**, generating the zwitterion **107**. Elimination of an acetate ion provided the phosphonium diene **108**. In the presence of a pronucleophile, nucleophilic addition and proton transfer steps occur to give the intermediate **109**. The target 2*H*-pyran **110** is afforded after cyclization and elimination of the catalyst.

Unlike previous examples, no external base was required in this case to activate the pronucleophile (Scheme 174). Various carbon pronucleophiles bearing alkyl and aryl substituents were well suited to the reaction, giving good yields of their products. The reaction failed to provide the desired product, however, when using a highly conjugated allenoate (entry 4).

3.3.5. α-Umpolung–Michael [3 + 2] Annulation.—In the same Communication describing the 2*H*-pyran synthesis, Tong disclosed a novel phosphine-catalyzed pathway involving initial α-umpolung addition followed by a Michael-type addition to generate a functionalized furan (Scheme 175).[237] The first portion of the reaction proceeds as expected, through formation of the phosphonium diene **108** followed by nucleophilic addition. Proton transfer steps lead to the zwitterionic intermediate **111**. After cyclization and elimination of the phosphine, the furan **112** is obtained.

With sodium hydroxide as a basic additive, functionalized furans can be prepared in good yields (Scheme 176). Both α-cyanoketone and 1,3-diones are well suited to this transformation.

3.3.6. δ-Umpolung–γ-Umpolung [3 + 2] Annulation.—Recently, Shi developed the phosphine-catalyzed [3 + 2] spiroannulation of α-substituted secondary β-ketoamides and a δ-acetoxy–modified allenoate (Scheme 177).[238] In this reaction, the β-ketoamides functioned as the bis-nucleophilic partner while the γ,δ-carbons of 5-acetoxypenta-2,3-dienoate acted as a C2 synthon. In the presence of 20 mol % of PPh_3 and 1.0 equiv of $PhCO_2H$, the reactions of various β-ketoamides having different ring sizes and different functional groups proceeded smoothly, giving the desired products with moderate to high diastereoselectivities and in excellent yields. An asymmetric variant of this reaction was also examined, giving the corresponding products with moderate enantioselectivities.

In the same year, employing the cyclic chiral phosphine SITCP as a chiral catalyst, Zhou, Tong, and co-workers successfully developed asymmetric [3 + 2] annulations of δ-acetoxy allenoates with β-carbonyl amides (Scheme 178). Using 10 mol % of (*R*)-**P32** as the catalyst and 1.1 equiv of K_2CO_3 as an additive, various cyclic and acyclic β-carbonyl amides underwent [3 + 2] annulations with allenoates to give β-keto γ-lactams in moderate to good yields and with good to excellent enantioselectivities and diastereoselectivities.[239]

Tong also achieved chiral phosphine–catalyzed asymmetric [3 + 2] annulations of δ-acetoxy allenoates and 2-naphthols (Scheme 179).[240] The δ-carbon of the allentoate reacts with the α-carbon of the 2-naphthol to form a C–C bond, while a C–O bond is formed between the γ-carbon of the allenoate and the hydroxyl group of the 2-naphthol. In the presence of 10 mol % of (*R*)-**P32** as the chiral phosphine and 1.3 equiv of K_2CO_3 as the base, a variety of aryl- and alkyl-substituted allenoates reacted with 2-naphthols presenting different substituents to give their products in good yields and with excellent enantioselectivities. Axially chiral furans were obtained when using DDQ as the oxidant.

3.3.7. β′-Umpolung–Michael–Michael Domino Reactions.—In 2015, Tong disclosed the synthesis of 2-oxabicyclo[3.3.1]nonane and cyclopenta[*a*]pyrrolizine skeletons via phosphine-promoted β′-umpolung–Michael–Michael domino reactions.[241] Treatment of 2-acetoxymethyl-2,3-butadienoate with 2-carbonyl-3-methyl-acrylonitriles bearing aryl or alkyl substituents in the presence of PPh_3 (10 mol %) and Cs_2CO_3 (1.2 equiv) in toluene at room temperature for 12 h generated substituted 2-oxabicyclo[3.3.1]nonanes in 45–88% yield (Scheme 180). The authors postulated a mechanism for these transformations involving β′-umpolung–Michael–Michael reactions. In addition, various 2-carbonyl-3-(2-pyrrole)-acrylonitriles participated in the reactions under similar conditions, delivering cyclopenta[*a*]pyrrolizines in good to excellent yields (Scheme 181). Using Kwon's chiral phosphine *endo*-**P45** as the catalyst, enantioselective variants of these transformations, under otherwise identical conditions, were accomplished to give enantioenriched 2-oxabicyclo[3.3.1]nonanes and cyclopenta[*a*]pyrrolizines in good yields and enantioselectivities (Scheme 182).

3.4. Phosphine Catalysis of Allenes with Electrophiles

While nucleophiles react with allenoates and alkynoates through γ-umpolung addition, β′-umpolung addition, or Michael addition in the presence of a phosphine catalyst, annulations typically occur when electrophiles are involved. Unlike the situation in umpolung reactions, where the β-phosphonium dienolate activates the pronucleophile through deprotonation, the zwitterion functions in this case as a nucleophile to add to the electrophile (e.g., an alkene, imine, ketone/aldehyde, aziridine, or azomethine imine), directly forming a carbon–carbon bond and initiating the annulation processes. Since the first discovery of Lu's allene–alkene [3 + 2] annulation, many other phosphine-catalyzed allene–electrophile annulations have been reported. Among them, Lu's [3 + 2] and Kwon's [4 + 2] annulations are most notable in that (i) each employs three different classes of electrophiles (alkenes, imines, ketones); (ii) each has been applied to the syntheses of natural products and molecules of pharmaceutical value; and (iii) enantioselective versions of each reaction have been developed. Arguably, the allene/electrophile combination provides the most diverse modes of reactivity.

3.4.1. Lu's Allene–Alkene [3 + 2] Annulation.—In 1995, Lu documented a seminal discovery of phosphine-catalyzed [3 + 2] annulation between 2,3-butadienoates or 2-butynoates and electron-deficient olefins, resulting in the formation of functionalized cyclopentenes.[175] A wide variety of olefins, allenoates, alkynoates, and phosphines were implemented to provide functionalized cyclopentenes (Scheme 183).

Being the first example of phosphine-promoted intermolecular annulation of activated allenes, Lu's [3 + 2] reaction has been studied most extensively and has demonstrated its versatility in a multitude of applications. Since its first disclosure, the reaction has been investigated by over 23 different research groups and applied to the syntheses of natural products and molecules of biological significance. Furthermore, many asymmetric variations of the reaction have been reported. Interestingly, Lu's reaction had also been investigated under catalysis of a *polymer*-supported phosphine[242] and under microwave irradiation.[243]

In the mechanism proposed by Lu, both 2-butynoates and 2,3-butadienoates are capable of generating the phosphonium dienolate **77**, which undergoes nucleophilic addition preferably at the carbon α to the electron-deficient olefin, yielding the intermediate **113** (Scheme 184). Upon addition, the electrophilic olefin becomes a transient carbanion that acts as a nucleophile and undergoes addition to the vinylphosphonium portion of the intermediate **113**. After cyclization, proton transfer of the ylide **114** occurs, followed by β-elimination of the phosphine catalyst to afford the cyclopentene **115**. The crucial proton transfer step is assisted by adventitious water.[244–248] Although less favorable, the phosphonium dienolate **77** also undergoes addition to the electron-poor olefin at its γ-carbon to produce the regioisomeric cyclopentene as a minor product. The transition from the zwitterion **77** to the cyclized product **114** was thought to occur through a concerted pathway featuring a single transition state. Through computational analysis, using DFT at the B3LYP/6-31G(d) level, Dudding, Kwon, and Yu revealed that the cyclization occurs instead in a stepwise manner with distinct intermediates.[249–251]

Acrylates and acrylonitriles are amenable to [3 + 2] annulation with 2-butynoates in the presence of catalytic tributylphosphine (Scheme 185). Addition at the α-carbon is greatly favored. Activated olefins (e.g., arylidenemalononitriles) are also viable for Lu's reaction. Catalyzed by a phosphine, benzylidenemalononitrile gives rise to 4,4-dicyano cyclopentenes in great yields, predominately as single regioisomers.[252] The same transformation can be achieved in a one-pot, three-component reaction through in situ condensation of an arylaldehyde and a malononitrile and subsequent [3 + 2] cyclization. When a γ-substituted allenoate is implemented, a highly substituted cyclopentene can be synthesized, albeit in lower yield.[253]

Shi looked into the possibility of performing an allenoate–nitroalkene [3 + 2] reaction and discovered a tandem [3 + 2] annulation with a subsequent γ-umpolung reaction.[254] Under the reaction conditions, the expected [3 + 2] adduct **116** was first generated, presumably undergoing activation through deprotonation by the phosphonium zwitterion. The resulting nitronate anion undergoes the well-precedented γ-umpolung addition (Scheme 186).

Various nitroalkenes are suitable reaction partners when using the mildly nucleophilic tris(*p*-fluorophenyl)phosphine as the catalyst. Nitroalkenes with both electron-donating and -withdrawing functionalities are applicable (Scheme 187). When electron-donating substituents are present, the reaction gives good to high yields of the annulation products. On the other hand, a strongly electron-withdrawing nitro substituent resulted in a low yield of the isolated nitrocyclopentene, but with slightly higher diastereoselectivity. In addition to

functionalized benzene systems, naphthyl, furyl, and propyl groups are also amenable to this reaction.

2-(1-Alkynyl)-2-alken-1-als are special types of alkenes that have also been applied in Lu's [3 + 2] annulation. In the presence of 10 mol % of PPh_3, an array of 2-(1-alkynyl)-2-alken-1-als reacted with allenoates in 1,4-dioxane at room temperature to give various 1-formyl-1-arylethynyl cyclopentenes in good yields and with moderate regioselectivities (Scheme 188).[255]

Several 1,3-dipoles, including diazomethanes, azides, and azomethine ylides, undergo 1,3-dipolar cycloadditions with [60]fullerene. Likewise, annulation products can also be obtained when using [60]fullerene as an electrophile in the [3 + 2] annulation (Scheme 189). Wu[256] and Kroto[257] independently demonstrated a way to generate derivatized [60]fullerenes from reactions with 2,3-butadienoates in the presence of tributylphosphine. Increasing the reaction temperature and switching the catalyst to triphenylphosphine allowed isolation of the annulation products in higher yields.

Fullerenes and their derivatives are versatile components in materials science, electronics, and biomedical science, due to their excellent electronic and structural properties. The derivation of a fullerene can influence these properties tremendously and lead to the preparation of new materials and pharmaceuticals. The phosphine-catalyzed cycloaddition has also been employed in the functionalization of fullerenes. Wu and co-workers prepared a potentially biological active [60]fullerene-podophyllotoxin derivative in a good yield when using the [3 + 2] annulation strategy (Scheme 190).[258]

As mentioned above, Shi and co-workers employed elaborated 1,3-butadienoates and maleimides for the formation of spirocyclopentenes. The same 1,3-butadienoates were also used in reactions with allenoates to generate functionalized cyclopentenes. The 1,3-butadienoates behaved, however, in the same manner as acrylates, providing only two-carbon synthons for the annulation and leaving the other olefin unreactive (Scheme 191).[259] The reactions gave good yields of cyclopentenes bearing various substituents on the aromatic ring, ranging from electron-donating to -withdrawing functionalities.

Around the same time, the He group was also developing novel annulations involving highly conjugated systems, including aza-dienes (Scheme 192).[260] Again, however, they observed a similar reactivity pattern with only one of the olefin units undergoing annulation (i.e., displaying acrylate-type reactivity).

Cyclic chromen-2-one can also be applied in the phosphine-catalyzed [3 + 2] annulation to generate a collection of functionalized dihydrocoumarins (Scheme 193).[261] Under the optimized reaction conditions, functionalized dihydrocoumarins bearing electron-rich and -poor substituents on the benzene ring were obtained with good efficiencies.

Although only a single isolated example was reported, an activated quinolone has also been applied as a reaction partner for the [3 + 2] annulation (Scheme 194).[262]

The phosphine-catalyzed [3 + 2] annulation is a versatile reaction that can be employed to access highly functionalized fused ring systems (Scheme 195).[263] Chromenopyrazoles can be generated in situ and then subjected to the [3 + 2] annulation to give functionalized tetracycles in moderate yields, demonstrating a way to construct molecular complexity rapidly. In addition, this transformation is a rare example of a γ-addition product.

In 2017, Averin and co-workers synthesized a series of N-substituted maleimides bearing an adamantane fragment, through the reaction of maleic anhydride with amines in the presence of 1 equiv of TsOH in refluxing toluene, and then subjected them to 10 mol % triphenylphosphine-catalyzed [3 + 2] cycloaddition with ethyl buta-2,3-dienoate in toluene at room temperature, affording substituted bicyclic succinimides in excellent yields (92–99%) (Scheme 196).[264]

When a cyclic ketone, lactone, or lactam featuring an exocyclic α-methylene group is employed as the alkene component in Lu's allene–alkene [3 + 2] annulation, a functionalized spirocyclopentene can be generated.[265] In 2002, Lu reported the synthesis of spirocyclopentenes from reactions incorporating several exocyclic olefins. These spirocyclic compounds were formed in excellent yields and with good regioselectivities (Scheme 197).

Chen and Xiao reported another spiro-cyclic ring-forming reaction that uses arylideneoxazolones as reaction partners (Scheme 198).[266] They synthesized functionalized spirooxazolones in moderate to good yields through triphenylphosphine-catalyzed [3 + 2] annulation of benzyl 2,3-butadienoate. The reactions furnished higher yields in shorter reaction times when electron-withdrawing arylideneoxazolones were used. Notably, 2-furylideneoxazolone displayed poor regioselectivity.

Pyne employed Lu's [3 + 2] annulation as the key strategy for the syntheses of various spirocyclic L-glutamate analogues (Scheme 199). L-Glutamate is an excitatory neurotransmitter agent in mammalian central nervous systems; studying analogues of L-glutamate can potentially lead to discoveries useful for the treatment of neurodegenerative disorders.[267] When 4-phenyl-2,3-butadienoate was used in the reaction, a single regioisomer of the L-glutamate analogue was isolated.[268] On the other hand, a mixture of regioisomers was observed with moderate yield when employing a 2,3-butadienoate or 2-butynoate as the reaction partner.[269] From (4*S*)-benzyloxazolidinone, the desired product was isolated, favoring one regioisomer, as a single diastereoisomer.[270,271]

In 2016, Miao and co-workers explored the application of 5-arylidene-3-(*tert*-butyl)-2-thioxothiazolidin-4-ones in Lu's [3 + 2] annulation for the synthesis of 5-spiro-cyclopentene-rhodanine skeletons (Scheme 200).[272] In the presence of PBu_3 (20 mol %), the spirocyclic products bearing three contiguous chiral centers were obtained in high to excellent yields and with generally excellent diastereoselectivities. As an extension, they also applied the same reaction conditions to the synthesis of cyclopentene 5-spiro-rhodanine derivatives through one-pot multicomponent reactions. The spirocyclic products were obtained with high to excellent yields and generally as single diastereoisomers. It was proposed that the multi-component coupling reaction proceeds through sequential [3 + 2]/[2 + 3] cycloadditions.

Shi and co-workers used ethyl 2,3-butadienoate and an activated isatin in the preparation of functionalized spirooxindoles.[273] They observed good yields and selectivities from the reaction (Scheme 201). Both electron-donating and -withdrawing substituents were tolerated on the benzene ring of the isatin system, giving good yields. When an electron-donating methoxy group was installed, slightly lower diastereoselectivity was observed for the spirooxindole, albeit formed in good yield (entry 1). Better diastereoselectivity was achieved when an electron-withdrawing bromide functionality was present on the benzene ring of the isatin (entry 2). Notably, a significant erosion in diastereoselectivity occurred when the isatinyl nitrogen was masked with an allyl group, rather than a *tert*-butyl carbonate (Boc) group, presumably due to a steric effect.

Furthermore, Shi and Wei reported the highly diastereoselective formation of spiroxindole structures from isatins and a γ-methyl allenoate.[274] These reactions provided excellent yields of the spiro compounds, with high diastereo- and regioselectivity (Scheme 202). Various halo-substituents could be installed on the benzene ring of the spiroxindole product with excellent efficiency. Using alkynoates and ethyleneindolinones as reaction partners, Miao and co-workers also applied a similar reaction to the synthesis of cyclopentene-fused spiro-oxindole skeletons.[275] Using Kagan's (−)-DIOP ((−)-**P46**) as a chiral catalyst, the enantioenriched spirocyclic product was obtained in 92% yield with >99:1 dr and 58% ee (Scheme 203).

The formation of spirooxindoles continues to be of great interest for many synthesis groups. In 2011, Jia documented the formation of functionalized spirooxindoles from isatinylidenemalononitriles and ethyl 2,3-butadienoate in the presence of triphenylphosphine as the catalyst.[276] In these reactions, although both electron-donating and -withdrawing substituents were tolerated, the former gave slightly lower yields (Scheme 204). Notably, tributylphosphine and triphenylphosphine were employed for the annulations using isatinylidnemalonate and isatinylidenemalononitrile, respectively.

Oxindole-derived electrophiles have become attractive reaction partners in recent years. The Marinetti group also employed arylideneoxindoles to access complex spirocyclopentenes (Scheme 205).[277] The reactions are highly diastereoselective, providing predominantly single diastereoisomers with high efficiencies.

In 2013, Li and co-workers reported an efficient [3 + 2] annulation between ethyl 2,3-butadienoate and benzofuranones, granting access to an array of spirobenzofuranones (Scheme 206).[278] The reaction provides γ-addition [3 + 2] products selectively in high yields and tolerates various aryl groups, including electron-poor *o*-bromophenyl and heteroaryl 2-furyl substituents.

The same year, Pinho e Melo and Santos prepared a series of novel chiral spirocyclopentenyl-β-lactams using Lu's [3 + 2] annulation (Scheme 207).[279] Treatment of allenoates with 6-alkylidenepenicillanates in the presence of PPh_3 gave access to a variety of [3 + 2] adducts with two or three consecutive stereogenic centers, in good yields and diastereoselectivities, albeit with low regioselectivities.

In phosphine catalysis, the most common activating (electron-withdrawing) functional group on the allene has been a carboxylic ester. Although other activating groups (e.g., ketones) can also be used, Wallace demonstrated that aryl and alkyl allenones undergo self-dimerization, rather than the anticipated [3 + 2] annulation, in the presence of cinnamyl phenyl ketone (Scheme 208).[280] That report was the second describing phosphine-catalyzed dimerization of activated allenes. This mode of reactivity is, however, distinct from that in the first reported (by Lu) allenoate dimerization, in which one of the allenes provides three carbons and the other two (the α and β carbons), as in a typical Lu-style allene–olefin [3 + 2] annulation.[175] In Wallace's approach, one allenoate contributed its α-, β-, and carbonyl carbons and carbonyl oxygen, while the second allenone contributed its β- and γ-carbons, producing the pyran **117**. To circumvent this problem, Loh increased the steric bulk of the aryl allenone by installing a trimethylsilyl group at the α-carbon, prohibiting the undesired self-dimerization.[281] With such a trimethylsilyl group in place, aromatic allenones undergo Lu's [3 + 2] annulation in the presence of triphenylphosphine as the catalyst.

Cyclopentenes have been isolated as single isomers in good yields from corresponding aryl trimethylsilyl allenones and electron-deficient olefins in the presence of 20 mol % of triphenylphosphine in toluene at ambient temperature (Scheme 209). High regioselectivity was observed for the [3 + 2] reactions of aromatic allenones, providing exclusively the α-adducts. Furthermore, heteroaromatic allenones could be applied to the reaction conditions to furnish cyclopentenes in comparable yields. In general, the [4 + 2] dimerization products were minimized (to ca. 5%) after installing the trimethylsilyl group.

In 2014, Fan and co-workers expanded the use of aryl allenones to synthesize a collection of cyclopentenes in good yields (Scheme 210).[282] A mixture of both α- and γ-addition products was isolated, consistent with previously reported examples. Only the α-addition product was isolated, however, when using benzyl allenone as the reaction partner.

To solve the regioselectivity issue of Lu's [3 + 2] annulation, Krische designed a series of elaborate tethered enone–ynoate systems that undergo facile intramolecular [3 + 2] annulations to generate functionalized diquinanes.[283] A polar solvent (e.g., ethyl acetate) was beneficial for these transformations, giving good yields of the diquinanes. The reaction proceeded smoothly for aromatic, heteroaromatic, and aliphatic enone–ynoate systems (Scheme 211). It gave a poor result when a less electrophilic enoate–ynoate substrate was tested, providing only a trace amount of the desired product.

Kwon also documented a variant of the intramolecular [3 + 2] annulation to synthesize functionalized coumarins.[284] Tethering the allenoate fragment onto functionalized 2-hydroxycinnamates provided the substrates for the intramolecular allenoate–cinnamate annulations (Scheme 212). Both electron-donating and -withdrawing substituents on the benzene ring of the cinnamate were tolerated, allowing syntheses of cyclopentene-fused dihydrocoumarins. While α,β-unsaturated ethyl esters worked well as electrophilic partners, producing high yields of the corresponding coumarin derivatives (entries 1–3), a nitroalkene required a less-nucleophilic catalyst, triphenylphosphine, in a reaction that proceeded to give a moderate yield of the product (entry 4).

Interestingly, a change in solvent from tetrahydrofuran (THF) to benzene induced an unprecedented phosphine-catalyzed [4 + 2] annulation between a nitroolefin and an allenoate to form the coumarin-fused cyclic nitronate **118** (Scheme 213). The nitronate **118** underwent 1,3-dipolar cycloaddition with both electron-rich and -poor olefinic dipolarophiles, resulting in excellent yields of functionalized nitroso acetals.

Shi introduced the use of 2,3,4-pentatrienoates as three-carbon synthons in the [3 + 2] annulations. Initiated by a catalytic amount of tributylphosphine, 3-diarylidenecyclopentenes and -pyrrolines were formed when 2,3,4-pentatrienoates were reacted with electron-deficient olefins and imines, respectively (Scheme 214).[285] Good to excellent yields of the annulated products were obtained when employing activated olefins and *N*-tosylarylimines.

Unlike other phosphine-catalyzed annulations, Shi's 2,3,4-pentatrienoate annulation requires high catalyst loadings to ensure isolation of functionalized cyclopentenes and pyrrolines in desirable yields. Lower catalyst loadings diminished the reaction yield substantially. Various electron-withdrawing and -donating substituents on the arylidenemalononitrile were tolerated, producing 3-diarylidene-cyclopentenes in high yields. When a less-reactive alkylidenemalononitrile was used, a minimal amount of the annulation product was obtained. For the formation of pyrrolines, both aromatic and heteroaromatic *N*-tosylimines provided good yields. In general, reactions with *N*-tosylimines were lower-yielding than those with arylidenemalononitriles for the formation of 5-diarylidene-cyclopentenes, due to the higher reaction temperature and extended reaction time causing thermal decomposition of the pentatrienoate.

In 2014, Cao and Shi also reacted 2,3,4-pentatrienoates with activated olefins (e.g., vinyl ketones, acrylates) to synthesize functionalized cyclopentenes (Scheme 215).[286] Reminiscent of Shi's work, tributylphosphine was used in larger quantity (50 mol %) under reflux in THF to ensure good reaction efficiencies.

Interestingly, dihydrofurans can also be generated when arylaldehydes are employed instead of activated alkenes (Scheme 216). A variety of arylaldehydes, ranging from those activated with a trifluoromethyl group to heteroaryl groups, can tolerate the reaction conditions.

A total synthesis of (−)-hinesol showcases the utility of Lu's allene–alkene [3 + 2] annulation. In 2003, Lu completed the synthesis of (−)-hinesol with [3 + 2] annulation as the key transformation (Scheme 217).[287] Starting from the enantiomerically pure cyclohexenone **119** and *tert*-butyl 2-butynoate, the spirocyclic ring scaffold **120** was formed using tributylphosphine catalysis. Hydrogenation of the spiroenoate **120** provided the spiroketones **121** and **122** in good yield. Carrying the spiroketone **121** forward, transesterification and modified Oshima olefination resulted in a 76% yield of **123** over two steps. Isomerization of the olefin under an acidic environment, followed by methyl Grignard addition, elaborated **123** into (−)-hinesol **124** in high yield.

Krische also applied his intramolecular enone–ynoate [3 + 2] annulation to the total synthesis of (±)-hirsutene (Scheme 218).[288] Starting from the alcohol **125**, reaction with *p*-methylbenzenesulfonyl chloride followed by displacement of the tosylate with lithium acetylide gave rise to the enyne **126**, which was then deprotonated and treated with methyl

chloroformate to deliver the alkynoate **127** in high yield. Oxidative cleavage of the terminal olefin with ozone and Horner–Wadsworth–Emmons olefination of the resulting aldehyde **128** furnished the precursor enone–ynoate **129**. Employing (*E*)-**129**, intramolecular [3 + 2] annulation proceeded smoothly to provide the desired diquinane **135** in 86% yield. Further elaboration of the diquinane **130**, through catalytic hydrogenation with palladium and lithium aluminum hydride–mediated reduction, gave the diol **131**. Swern oxidation followed by intramolecular aldol condensation led to the known intermediate **132** being obtained in good yield.

In addition to the total synthesis of hirsutene, Krische completed a total synthesis of (+)-geniposide featuring Lu's [3 + 2] annulation (Scheme 219).[289] The synthesis began with [3 + 2] annulation of ethyl 2,3-butadienoate and the enantiomerically pure enone (*S*)-**133**, leading to a moderate yield of the cycloadduct **134**. Addition of cyanide into the cycloadduct **134**, followed by dehydration, generated the vinyl nitrile **135**. Selective reduction of the ethyl ester using diisobutylaluminum hydride afforded the corresponding allylic alcohol **136**. Hydration of the nitrile **136** to the primary amide **137** was completed using the Ghaffer–Parkins catalyst. Nitrosation and hydrolysis of **137**, followed by ester formation, provided the allylic acetate **138** in good yield. In the presence of Otera's catalyst, the acetate was removed and the pivaloyl group was transferred to the primary alcohol to furnish the allylic pivalate **139**. Glycosidation of the hemiacetal **139** with trichloroacetimidate **140** provided the β-glycoside **141** as a single diastereoisomer. Global deprotection of the acetyl and pivaloyl groups was accomplished using lithium hydroxide. Finally, reaction with trimethylsilyldiazomethane reinstalled the methyl ester group to afford (+)-geniposide.

In 2013, Wallace and co-workers applied the [3 + 2] annulation strategy to the synthesis of **144**, a selective estrogen receptor modulator (Scheme 220).[290] After initial enone formation with the ketone **142**, the crude product was subjected to [3 + 2] annulation to give a good yield of the cyclopentene **143**. Subsequent functional group transformations provided the modulator **144**.

3.4.1.1. Enantioselective Allene–Alkene [3 + 2] Annulation using Monofunctional Chiral Phosphines.: Asymmetric catalysis remains an important aspect of organic chemistry, generating enantiomerically pure compounds, especially for natural products synthesis and therapeutic practices. Asymmetric variants of several phosphine catalysis processes with different chiral phosphine architectures (chiral mono- and bifunctional phosphines) have been reported to give good yields and enantioselectivities. The first class of asymmetric phosphine catalysis of allenes to be described was the [3 + 2] annulation generating enantiomerically pure, densely functionalized cyclopentenes. Several chiral phosphines have been developed, with distinct molecular complexities, ranging from phosphines with axial chirality to chirality on the phosphorus center, to induce efficient asymmetric transformations of various substrates (Scheme 221).

The first asymmetric phosphine-catalyzed Lu [3 + 2] annulation was accomplished by Zhang in 1997 when employing the chiral phosphines **P26** and **P53**.[291] Among the various catalysts screened, none of the others provided yields and enantioselectivities similar to those of **P26** and **P53**. Because the rigid bridged phosphines with isopropyl groups on the bicyclic

phosphabicyclo[2.2.1]heptane shielded one face of the phosphonium dienolate, a high degree of asymmetric induction could be achieved when using the phosphine **P53**, with excellent regioselectivity (Scheme 222). The enantioselectivity was heavily influenced by the steric demand of the alkene substrate. The reaction of isobutyl acrylate proceeded with high enantioselectivity (entry 4). Furthermore, the enantioselectivity improved when the reaction with the catalyst **P53** was performed at lower temperature in toluene (entry 5).

Employing a phosphine featuring a bicyclic ring system, in 2004 Pietrusiewicz communicated the asymmetric [3 + 2] annulations between ethyl 2,3-butadienoate and activated olefins.[201] The chiral phosphine **P27** was the catalyst of choice. Unfortunately, the reaction is very limited in substrate scope and gives only moderate yields of the annulation products with minimal asymmetric induction (Scheme 223).

About a decade after Zhang's first report of phosphine-catalyzed asymmetric [3 + 2] annulation, Fu demonstrated high enantioselectivities for [3 + 2] annulations performed using ethyl 2,3-butadienoate and chalcones as electrophiles in the presence of Gladiali's phosphepine (*R*)-**P48** (entries 1–4).[292] Notably, γ-addition products were isolated exclusively, presumably because of steric interference between the ester group of ethyl 2,3-butadienoate and the β-substituents of the chalcones or enones (Scheme 224). For a chalcone bearing a *p*-methoxyphenyl group, 2 equiv of the allenoate were required in the reaction, albeit affording a slightly lower yield of product than those of the reactions of electron-withdrawing chalcones (entry 2).

Using Boc-amino-substituted chalcones as substrates, Guo and Xiao also reported highly enantioselective chiral phosphine–catalyzed [3 + 2] annulations of allenoates that afforded biologically important functionalized cyclopentenes (Scheme 225).[293] In the presence of 20 mol % of (*R*)-**P32**, Boc-amino-substituted chalcone derivatives bearing various substituents reacted with cyclohexyl buta-2,3-dienoate to give a series of 1,4,5-trisubstituted cyclopentenes as single diastereoisomers in good to excellent yields (69–98%) and with excellent regioselectivities (>20:1) and enantioselectivities (94–98% ee).

In 2011, Fu described another efficient process for generating cyclopentenes containing heteroatom quaternary stereocenters.[294] That report was the first documentation of asymmetric [3 + 2] annulation involving the formation of heteroatom quaternary stereocenters. Employing olefins featuring nitrogen, phosphorus, oxygen, and sulfur substituents in conjunction with the chiral phosphepine **P52**, functionalized cyclopentenes were obtained in high yields and enantioselectivities (Scheme 226). Similar to the previous example, high regioselectivities were accomplished through substrate control, with γ-substituted 2,3-butadienoates undergoing complete α-addition.

In 2008, Marinetti synthesized the chiral phosphine **P47**, featuring a ferrocene backbone, and reported its use for inducing high levels of enantioselectivity in [3 + 2] annulations of chalcones (Scheme 227).[295,296] Low regioselectivity ensued when an acrylate was used as the electrophilic partner. To achieve higher regioselectivity, substrate control was required. Thus, chalcones were employed to induce steric bias at the β-position, favoring γ-additions.

These reactions proceeded to form γ-addition products in moderate to good yields and with excellent enantioselectivities.

In 2017, the Zhang group developed phosphine-catalyzed enantioselective [3 + 2] annulations of γ-substituted allenoates with β-perfluoralkyl α,β-enones for the construction of cyclopentene derivatives with three contiguous chiral stereocenters (Scheme 228).[297] When using 10 mol % of (*R,R*)-DPAMP **P49** as the catalyst, the reactions of a wide range of β-trifluoromethyl substituted enones with γ-aryl allenoates worked well to give their products in good yields and with good enantioselectivities. In the case of γ-alkyl allenoates, the multifunctional phosphine ***P*23** was identified as an efficient catalyst. Control experiments revealed that the reaction proceeded through a "deracemization" process when using (*R,R*)-DPAMP as the catalyst, whereas a kinetic resolution reaction occurred when using the multifunctional phosphine as the catalyst.

Asymmetric phosphine catalysis can also be applied to the surface functionalization of fullerenes (Scheme 229).[298] Martín and co-workers employed the chiral (*S,S*)-*f*-binaphane **P54** to derivatize C_{60} through the formation of bridged cyclopentenes. Although the yields were low, the enantioselectivities were excellent.

Further exploring the area of asymmetric allene–alkene [3 + 2] annulation, Marinetti expanded the scope of the electrophiles to include furylidenemalononitrile and a derivatized isatin (Scheme 230). With these sterically demanding alkenes, excellent regioselectivities and enantioselectivities were accomplished when using Gladiali's phosphepine (*S*)-**P48** as the catalyst, providing a functionalized cyclopentene and a spirooxindole.[299–301]

Expanding the applicability of the chiral FerroPHANE, Marinetti demonstrated the efficient asymmetric formation of functionalized spiro[4.5]decanones from ethyl 2,3-butadienoate and 2,6-diaryidene-4-*tert*-butyl-cyclohexanones.[302] Using the chiral FerroPHANE **P47**, high levels of enantio- and regioselectivity were achieved for the spiro[4.5]decanones (Scheme 231, entries 1–3). A higher yield of the spiro[4.5]decanone was obtained when a *p*-methoxyphenyl group was present on the 2,6-diaryidene-4-*tert*-butyl-cyclohexanone, but the reaction required a longer period of time to reach completion (entry 1). With a *p*-chlorophenyl substituent, the yield and enantioselectivity were slightly lower (entry 2). Interestingly, significantly lower yield and diastereoselectivity were obtained from the reaction of 2,6-di-2-furylidene-4-*tert*-butyl-cyclohexanone (entry 3).

The chiral FerroPHANE **P47** can also be used to construct functionalized spirothianones and spiropiperidones, which possess structural integrity similar to that of spiro[4.5]decanones.[303] Reacting 3,5-diarylidene-4-thianones and 4-piperidone with 2,3-butadienoates gave good conversions to spirothianones and spiropiperidones, respectively, along with high enantiomeric excesses (Scheme 232). An excellent yield and enantiocontrol resulted from the reaction of the sterically demanding 3,5-di-9-phenanthrylidene-4-thianone (entry 1). While most substrates provided high enantioselectivities, 3,5-di-*p*-nitrophenylidene-4-thianone formed its product almost exclusively as a single diastereoisomer (entry 3). A spiropiperidone was also prepared in good yield with high selectivity (entry 5).

In the initial report from Chen and Xiao, the formation of spirooxazolones could be conducted asymmetrically using the spirocyclic chiral phosphine (*R*)-**P32**. The poor regioselectivities in the original study were also overcome by Shi to provide a single regio- and enantioisomer (Scheme 233).[304] With optimization, *m*-bromobenzylideneoxazolone provided a superb yield of the corresponding spirooxazolone with high levels of enantio- and diastereocontrol (entry 1). Although efficiencies were modest, arylideneoxazolones bearing strongly electron-withdrawing *p*-nitrophenyl or strongly electron-donating *p*-methoxyphenyl groups led to products with excellent enantioselectivities (entries 2 and 3). In addition to aryl substituents, 2-furylidene and isopropylideneoxazolone were also amenable, although they provided products with lower yields and selectivities (entries 4 and 5). Interestingly, no significant erosion of yield or enantioselectivity occurred when switching to isopropyl 2,3-butadienoate, suggesting minimal steric contribution from the ester group (entry 6).

In 2015, Wei, Shi, Zhou, and co-workers studied the chiral phosphine-catalyzed [3 + 2] annulations of allenoates with benzofuranone-derived olefins and observed substrate-dependent regioselectivities.[305] The enantioselective [3 + 2] cycloadditions in the γ- or α-addition modes were dependent on the substitution pattern of the allenic substrate. In the presence of (*R*)-**P32** (10 mol %) and 4 Å MS, the allenoates underwent γ-addition [3 + 2] cycloadditions with various benzofuranone-derived olefins in toluene/dichloromethane (1:1) at room temperature to produce a series of spirobenzofuranones in moderate to excellent yields and with high regioselectivities and enantioselectivities (Scheme 234). In contrast, γ-substituted allenoates underwent α-addition [3 + 2] cycloadditions with various benzofuranone-derived olefins in toluene at room temperature to provide corresponding spirobenzofuranones in moderate to excellent yields, along with high regioselectivities and enantioselectivities. The divergent regioselectivity was rationalized by consideration of two plausible transition states, based on DFT calculations.

In 2012, Jørgensen realized the generation of functionalized amino acids through asymmetric [3 + 2] annulations using benzylideneoxazolones.[306] Gladiali's phosphepine (*S*)-**P48** mediated these efficient one-pot asymmetric phosphine-catalyzed [3 + 2] annulations, with subsequent opening of the oxazolones yielding amino acids bearing quaternary stereocenters (Scheme 235). Although the diastereoselectivities and conversions to amino acids were moderate, the products were isolated with high enantioselectivities. A better ratio of diastereoisomers was obtained from the reaction of *o*-bromobenzylideneoxazolone, albeit with lowered enantiocontrol (entry 3).

Adding to the repertoire of asymmetric phosphine catalysis using the chiral FerroPHANE **P47**, Marinetti provided access to enantiomerically enriched and functionalized bicyclo[4.3.0]chroman-2-ones through reactions with allenoates and coumarin derivatives (Scheme 236).[307] Good degrees of enantiocontrol and good yields of the bicyclo[4.3.0]chroman-2-ones were observed, along with moderate regioselectivities. Notably, a drastic drop in enantioselectivity was discerned when cyclohexyl 2,3-butadienoate was employed as the substrate, presumably because of steric collision between the cyclohexyl group of the allenoate and the benzene motif of the coumarin.

After exploring various electrophiles for these reactions with the chiral FerroPHANE **P47**, Marinetti examined the use of reacting motifs other than ethyl 2,3-butadienoate. She reported that an allenylphosphonate undergoes asymmetric annulation with chalcone derivatives, creating cyclopentenes in good yields and with high enantiocontrol (Scheme 237).[308] In all cases, the degree of steric hindrance at the R^2 position had a dramatic effect on the level of enantioselectivity. With a methyl substituent, the enantiocontrol remained mediocre (entry 4).

In an attempt to generate enantiomerically pure spirocyclopentenes, in 2007 Wallace communicated an asymmetric [3 + 2] annulation using the chiral phosphine (−)-**P46** (Scheme 238).[280] Although enantioenriched spirocyclopentenes were obtained in moderate yields and enantioselectivities when reacting 3,4-pentadien-2-one with indanone derivatives, good regiocontrol was achieved across various substrates, favoring α-addition products (entries 1–3).

While working with TMS-protected allenones, Loh extended his study to demonstrate that asymmetric induction could be performed using Duphos **P55** to give optically active cyclopentenes (Scheme 239).[281] In these reactions, good enantioselectivities were achieved from the reactions of 2-furyl allenones with chalcones, accompanied by low yields (entries 2 and 3). Nevertheless, the functionalized cyclopentenes were isolated as exclusive γ-addition products, owing to the effect of the α-TMS group of the allenones.

Further advancing the field of asymmetric phosphine catalysis, Loh employed 1,2-bis[(2-methoxyphenyl)(phenyl)-phospino]ethane [(*R,R*)-DIPAMP] **P49** to generate functionalized cyclopentenes from 3-butynoates with high efficiency (Scheme 240).[309] This contribution to asymmetric [3 + 2] annulations differed from Fu's and Marinetti's approaches because (i) it featured a bidentate phosphine, (ii) the three-carbon synthon was generated from derivatized 3-butynoates rather than allenoates, and (iii) α-addition products were isolated exclusively despite the use of 1,3-diarylprop-2-en-1-one systems.

Although it did not employ chiral induction from an optically active phosphine catalyst, an asymmetric variant of Lu's [3 + 2] annulation has been developed by Martín and Ruano using a chiral sulfinyl group as an auxiliary directing chiral induction (Scheme 241).[310,311] Excellent chiral induction was achieved in the synthesis of functionalized 5,5-fused bicyclic systems. In contrast to the asymmetric process, a stoichiometric amount of chiral auxiliary was required. Nonetheless, the chiral auxiliary could be removed easily and, thus, retain the product's chirality.

In 2015, Voituriez, Marinetti, and co-workers synthesized a series of chiral phosphahelicenes and established their applicability in [3 + 2] annulations of γ-substituted allenes and electron-poor olefins (Scheme 242).[312] In the presence of the chiral phosphine catalyst **P56**, [3 + 2] annulation between various γ-substituted allenes and a broad range of arylidene- or alkylidenemalononitriles proceeded smoothly, giving the corresponding cyclopentenes in moderate to excellent yields and with good to excellent diastereoselectivities and enantioselectivities. In addition to various γ-substituted allenes, γ-substituted buta-2,3-

dienenitriles were also compatible in the reactions, albeit with lower yields and enantioselectivities.

In 2015, Fu reported the first phosphine-catalyzed enantioselective intramolecular [3 + 2] cycloadditions of allenic olefins (Scheme 243).[313] Using an appropriate spirophosphine as the catalyst, a wide range of substituted 5-allenic olefins underwent enantioselective intramolecular allene–olefin [3 + 2] cycloadditions in toluene at room temperature, furnishing the corresponding cycloadducts in moderate to excellent yields along with excellent enantioselectivities. Similarly, various substituted 6-allenic olefins underwent [3 + 2] cycloaddition in the presence of **P57** (20 mol %) in toluene at room temperature to provide quinolin-2-one derivatives in 82–91% yields along with 66–90% ee. This protocol features the formation of two new bonds and the generation of two or three new stereogenic centers, including at least one quaternary carbon center, in one step.

3.4.1.2. Enantioselective Allene–Alkene [3 + 2] Annulation using Multifunctional Chiral Phosphines.: In contrast to axial, planar, and phosphorus chiral catalysts that induce asymmetry through steric interactions, in 2007 Miller reported that the bifunctional catalyst **P58** derived from amino acids could generate high degrees of chiral induction through intramolecular hydrogen bonding.[314] In this reaction, relatively sterically demanding benzyl 2,3-budienoate was employed to enhance the yield and enantioselectivity (Scheme 244). Tetralone derivatives are well suited for this transformation, providing high yields, excellent levels of regiocontrol, and good enantioselectivity (entries 1 and 2). The reaction of a heteroaromatic tetralone occurred with diminished yield and enantiocontrol (entry 3). Switching from tetralones to chalcones led to sluggish regioselectivities. To enhance the regiocontrol, benzyl-2,3-pentadienoate was employed (to favor α-addition) along with a stoichiometric amount of the catalyst **P58**, giving the annulation product as a single regio- and enantioisomer (entry 4). In 2016, using dispersion-corrected DFT, Houk elucidated the origin of the stereoselectivity in this reaction.[315] An intermolecular hydrogen bond between the amide vicinal to the phosphonium ion was the key interaction in both the major and minor enantiodetermining transition states. Additional stabilization arose from intermolecular hydrogen bonding between acidic positions of the catalyst and the substrate. Enantioselectivity occurs because the reactant must undergo significant distortion in the transition state leading to the minor enantiomer.

In 2010, Zhao reported another amino acid-derived chiral phosphine catalyst, **P59**, that promotes highly efficient asymmetric [3 + 2] annulations with arylidenemalononitriles to generate various functionalized cyclopentenes.[316] Reminiscent of Miller's aminophosphine, the chiral catalyst **P59** enhances the enantioselectivity as a result of intramolecular hydrogen bonding stabilizing the transition state. In this reaction, the product yield is affected by the amount of chiral catalyst; a lower product yield resulted when the reaction was performed at higher loading. Furthermore, no significant improvements occurred when the reaction was conducted at 0 °C, which led to a longer reaction time and lower yield. In this reaction, arylidenemalononitriles carrying ortho-substituents afforded their products with excellent yields and enantioselectivities (Scheme 245, entries 2–4). The presence of an electron-withdrawing functional group resulted in high enantioselectivity, whereas slightly lower selectivity occurred with electron-donating functional groups. While the yields obtained

from arylidenemalononitriles were excellent, arylidenecyanoacetates provided slightly lower yields after longer reaction times (entries 4 and 5). Regardless of the yields, both arylidenemalononitriles and arylidenecyanoacetates provided exclusive α-addition products with excellent enantiocontrol.

Further expanding the use of aminophosphines derived from natural amino acids led to the generation of a dipeptide-based aminophosphine library. In 2011, Lu and co-workers published an asymmetric version of the [3 + 2] annulation between 2,3-butadienoates and acrylates, using the chiral phosphine **P38**, derived from L-threonine, as the catalyst.[317] To favor the enantioselectivity and regioselectivity, they employed relatively sterically demanding phenanthryl acrylate derivatives as substrates. For example, *tert*-butyl 2,3-butadienoate reacted with excellent regioselectivity and gave the α-addition product exclusively (Scheme 246). After establishing the reactivity of the catalyst, various phenanthryl acrylates were tested to determine the scope of the reaction. Excellent yields and selectivities were obtained when electron-withdrawing aryl groups were present on the acrylate, with rapid formation of the annulation products (entries 2 and 3). Lower yields and longer reaction times were observed when electron-donating aryl groups were attached to the acrylate (entry 4). While aryl acrylates provided good conversions and highly enantioselective reactions, an alkyl acrylate produced a high product yield with a significant erosion of the enantioselectivity (entry 5).

The use of acrylamides in phosphine-catalyzed [3 + 2] annulations had not been reported until 2011 when Lu employed the D-threonine-L-*tert*-leucine-based chiral phosphine **P38** to induce asymmetric allene–acrylamide [3 + 2] annulations, affording cyclopentene derivatives in high yields and with moderate enantioselectivities.[318] Although the levels of enantiocontrol remained moderate, various cyclopentenes bearing a quaternary center were prepared (Scheme 247). Analogous to the [3 + 2] annulations with acrylates, sterically demanding acrylamides and *tert*-butyl 2,3-butadienoate were used to maximize the regio- and enantioselectivities. The reactions of α-aryl acrylamides provided products with high conversions (entries 1–3). Switching to α-methyl acrylamide, however, slowed the reaction and decreased the product yield and enantiocontrol (entry 4).

Using the same catalyst, **P38**, Shi and Lu demonstrated an efficient [3 + 2] annulation of allenoates and maleimides that granted access to functionalized bicyclic cyclopentenes with excellent levels of enantioselectivity (Scheme 248).[319] The reaction was suitable for alkyl-substituted maleimides, giving high yields and high enantiocontrol (entries 1–3). Although using a bulky allenoate is a common strategy for enhancing enantiocontrol, it is noteworthy that increasing the steric bulk of the allenoate in this case led to a drop in enantioselectivity (entry 4). A lower enantiomeric excess was also observed from the reaction of *N*-*p*-methoxyphenyl maleimide (entry 5). Furthermore, only a trace amount of product was detected when using unprotected maleimide, consistent with the notion that an acidic proton is detrimental to phosphine-catalyzed annulations (entry 6).

Employing Zhao's catalyst **P59**, Waldmann and co-workers demonstrated the asymmetric synthesis of functionalized bicyclic cyclopentenes from cyclopentenones and ethyl allenoate (Scheme 249).[320] Under the optimized conditions, various cyclopentenones, bearing such

substituents as phenyl, *p*-phenylphenyl, and isopropyl groups, were well suited to the reaction, giving their products in good yields and with excellent enantioselectivities.

Using amino acid-derived phosphines as catalyst, Lu, Lan, and Ullah developed a highly enantioselective intramolecular [3 + 2] annulation of chalcones bearing an allene moiety (Scheme 250).[321] In the presence of 10 mol % of the L-threonine-based phosphine **P60** and 10 mol % of benzoic acid as an additive, chalcones bearing various aryl substituents afforded dihydrocoumarin architectures in high yields (84–92% yield) and with near-perfect enantioselectivities (95–99.5% ee) and diastereoselectivities. Unfortunately, reactions of a methyl-substituted chalcone and a γ-methyl-substituted allenoate did not lead to their desired products. Theoretical studies (DFT calculations) revealed that a hydrogen bonding network introduced by the achiral Brønsted acid additive led to the enhanced enantioselectivity.

In the same year, Lu, Ullah, and Lan developed a catalyst-controlled regiodivergent [3 + 2] annulation of aurones and allenoates (Scheme 251).[322] The [3 + 2] annulation catalyzed by the L-Thr-D-Thr-based chiral phosphine **P61** in ether afforded the α-isomer predominantly in up to 13:1 ratio, whereas the reaction promoted by the L-Thr-L-Thr-derived chiral phosphine **P62** in CH_2Cl_2 led to the selective formation of the γ-isomer predominantly in up to 7:1 ratio. The scope of the α- and γ-selective [3 + 2] annulations was probed using aurones featuring various aryl or alkyl substituents, affording the α- and γ-adducts, respectively, in good yields and with excellent enantioselectivities. As presented in Scheme 252, Lu and co-workers proposed α- and γ-annulation pathways for this bifunctional phosphine-catalyzed [3 + 2] annulation. The mechanism underpinning the regioselectivity of the reaction is relatively complicated. According to DFT calculations of the catalyst-controlled regioselectivity, the difference in hydrogen bonding resulting from the L,D-dipeptide moiety and that from the L,L-dipeptide moiety in the phosphonium enolate intermediate accounts for the observed regioselectivity in the annulation reaction.

On the basis of He's work, Lu developed enantioselective [3 + 2] annulations of α,β-unsaturated imines with allenoates (Scheme 253).[323] In the presence of the chiral difunctional phosphine **P63** (20 mol%), highly functionalized cyclopentenes, each bearing an all-carbon quaternary center, were obtained in moderate to good yields and with good to excellent enantioselectivities.

In 2017, Zhong and co-workers reported the use of *N*-methylidene-succinimides in the phosphine-catalyzed [3 + 2] cycloaddition (Scheme 254).[324] Using 10 mol% of PPh_3 as the catalyst, [3 + 2] annulations of *N*-aryl and alkyl succinimides with γ-aryl-substituted allenoates proceeded smoothly to afford their corresponding products in moderate to excellent yields (50–96%) and with high diastereoselectivities (dr >99:1). *N*-Aryl succinimides containing ortho-monosubstituted groups on the benzene rings gave their cycloadducts with a 1:1 dr. Using the bifunctional chiral ferrocenylphosphine **P64** as the catalyst, asymmetric [3 + 2] cycloadducts were also obtained in moderate yield and ee.

3.4.2. Lu's Allene–Imine [3 + 2] Annulation.—

In contrast to the formation of cyclopentenes, functionalized pyrrolines are obtained as single regioisomers when *N*-tosyl

imines are used as reaction partners in phosphine-catalyzed [3 + 2] reactions of allenes.[325] Excellent yields of pyrrolines were obtained from the reactions of methyl-2,3-butadienoate with aryl *N*-tosyl or *N*-2-trimethylsilylethanesulfonyl (SES) imines when using triphenylphosphine as the catalyst (Scheme 255).[326] Only a trace of the annulation product was isolated when an alkyl imine was administered. When less-reactive butynoates were employed instead of allenoates, a more nucleophilic catalyst, tributylphosphine, was required to form the target pyrrolines (entries 4 and 5).

Kwon and Shi independently described the synthesis of tetrasubstituted pyrrolines by implementing γ-substituted allenoates as reaction partners (Scheme 256).[327–329] In both cases, tertiary phosphines that are more nucleophilic than triphenylphosphine were required. The 2,5-*cis*-isomers were invariably the major products, especially when a sterically demanding γ-substituent was present. While the reaction afforded excellent yields of pyrrolines in benzene, [3 + 2] annulation resulted in lower yields and diastereoselectivities in DCM. For electron-rich imines, the yields of the pyrrolines was improved when the reaction was performed in THF. Xue reported a similar transformation when reacting aromatic alkynones in toluene.[330] As is the case for most phosphine-catalyzed annulations, no reaction was observed when an alkyl imine was applied.

In 2007, He and co-workers reported the applicability of 1,3,5-triaza-7-phosphaadamantane (PTA) in [3 + 2] cycloadditions of 4-substituted 2,3-butadienoates with *N*-tosyl aryl aldimines, thereby delivering functionalized pyrrolines in good to excellent yields (Scheme 257).[331]

In addition to *N*-sulfonylimines, He found that *N*-thiophosphorylimines readily underwent Lu's [3 + 2] annulation with 2,3-butadienoates and γ-substituted allenoates to provide highly functionalized pyrrolines (Scheme 258).[332] Tetrasubstituted pyrrolines were obtained in good yields in the presence of triphenylphosphine or PTA. Triphenylphosphine was used when more-reactive 2,3-butadienoates were employed as the reaction partner, while sterically more demanding γ-substituted allenoates required PTA, which is more nucleophilic, to achieve satisfactory results. When reacting *N*-thiophosphorylimines, deprotection of the thiophosphoryl group was readily achieved in methanol under acidic conditions.

In 2017, Wu and co-workers employed Lu's [3 + 2] cycloaddition to synthesize *N*-aryl-2-fluorinated-pyrrolines or pyrroles (Scheme 259).[333] Under the optimal reaction conditions (using 20 mol % of PCy_3 as catalyst in toluene at 60 °C), *N*-aryl fluorinated imines presenting electron-withdrawing substituents (e.g., bromo, chloro, iodo, trifluoromethyl) on the benzene ring provide their cycloadducts in moderate to high yields. The product 3-pyrrolines were transformed to pyrroles in the presence of DDQ in toluene at 100 °C.

Other than acyclic imines, Ye and co-workers were the first to use cyclic imines to prepare functionalized pyrrolines with good efficacies (Scheme 260).[334] A good yield of the pyrroline was obtained from the imine bearing a *m*-cyanophenyl group (entry 1). Switching to a *p*-tolyl substituent led to a slight decrease in reaction efficiency (entry 2). While ethyl 2,3-butadienoate offers good conversions to its annulation products, sterically demanding

tert-butyl and cyclohexyl 2,3-butadienoates were also well suited, without noticeable drops in yield (entries 3 and 4).

Following Ye's success at using cyclic imines to generate a class of functionalized dihydropyrroles, both Guo and Wang independently disclosed the use of sulfamate-derived cyclic imines as [3 + 2] annulation partners (Scheme 261).[335,336] In the presence of a catalytic amount of a phosphine, they obtained various functionalized cyclic sulfamidates in excellent yields from reactions tolerating various substitution patterns.

In addition to the reactions of cyclic imines reported by Ye, Wang, and Guo, Ma disclosed a special double [3 + 2] annulation event between an allenoate and cyclic quinazolin-5-ones that provided, with high efficiencies, complex polycyclic heterocycles (Scheme 262).[337] Various substituents were tolerated on the aromatic ring of the ketimine.

With further optimization, Ma and co-workers demonstrated a selective [3 + 2] annulation using cyclic quinazolin-5-ones (Scheme 263).[338] Unlike the case in their previous report, here only one [3 + 2] annulation event occurred when employing triphenylphosphine as the catalyst. They synthesized a variety of functionalized dihydropyrroloquinazolin-5-ones in good yields.

In 2011, Loh reported an elegant, highly efficient route toward functionalized 2-alkyl-substituted pyrrolines from *N*-sulfonyl alkylimines.[339] *N*-Sulfonyl alkylimines can be difficult to handle because they readily decompose through hydrolysis, hampering their applicability in many phosphine-catalyzed reactions. In the presence of trimethylphosphine, Loh demonstrated the in situ isomerization of 3-butynoates to 2,3-butadienoates and subsequent incorporation of *N*-sulfonyl alkylimines through [3 + 2] annulations to afford functionalized pyrrolines in good yields (Scheme 264).

In 2011, Kinderman and co-workers reported the use of rare 2,3-pentadienenitriles—instead of the commonly employed 2,3-butadienoates or 2,3-pentadienoates—in Lu's allene–imine [3 + 2] annulation (Scheme 265).[340] They prepared several pyrroline derivatives bearing a cyano group from these rare allenenitriles. Analogous to the reactivities of allenoates, the transformations of 2,3-butadienenitriles can be catalyzed by triphenylphosphine, providing 2-substituted pyrrolines in good yields (entries 1 and 2). With 2,3-pentadienenitriles as reaction partners, tributylphosphine, a more nucleophilic catalyst, was needed to afford annulation products (entries 3 and 4).

Applying the newly developed method for generating 2-alkyl–substituted pyrrolines (Scheme 266), Loh completed a formal synthesis of (±)-allosecurinine featuring a step involving the formation of the 2,5-dialkylpyrroline **145** in 82% yield (Scheme 266). Subsequent reduction of the ethyl ester afforded the allylic alcohol **146**. Epoxidation using *m*-chloroperoxybenzoic acid furnished the epoxide **147**, which, upon DIBAL-mediated reduction, provided the triol **148** in moderate yield. The 1,2-diol unit was selectively protected to form the acetal **149**, which was converted to the primary iodide **150** using molecular iodine and triphenylphosphine. Dehydroiodination and dissolving metal reduction of the tosyl group yielded the intermediate **151**. Finally, deprotection of the acetonide group

and *tert*-butyloxycarbonyl (Boc) protection of the pyrrolidine amine furnished a known intermediate (**152**) en route to the total synthesis of (±)-allosecurinine.

Lu reported, in 2012, another formal synthesis applying allene–imine [3 + 2] annulation and featuring the amino acid–derived chiral phosphine **P65** (vide infra).[341] This short formal synthesis demonstrated the potential applicability of the key [3 + 2] annulation in natural products synthesis (Scheme 267). Several functional group manipulations were subsequently performed to remove the phosphoryl and silyl protecting groups. Sulfonation of the free pyrroline with *p*tolylsulfonyl chloride provided a formal synthetic target (**153**) toward (+)-trachelanthamidine.

3.4.2.1. Enantioselective Allene–Imine [3 + 2] Annulation Using Monofunctional Chiral Phosphines.: Relative to the formation of cyclopentenes through enantioselective [3 + 2] annulations, reports of asymmetric allene–imine [3 + 2] annulations are rarer. Fewer studies have been reported regarding [3 + 2] annulations of electron-deficient imines for the formation of functionalized pyrrolines. Many challenges remain in the area of asymmetric formation of pyrrolines, and the field requires greater investigation.

In 2006, Gladysz reported the use of the rhenium-backbone phosphine **P66** to catalyze Lu's [3 + 2] annulation between ethyl 2,3-butadienoate and *N*-tosyl imines (Scheme 268).[342] With this catalyst, the desired pyrrolines were isolated in high yields and moderate enantioselectivities. Employing the *p*-methoxybenzaldimine and the *p*-nitrobenzaldimine as substrates afforded corresponding pyrrolines in excellent yields, but with no appreciable degrees of selectivity (entries 2 and 3). Although enantioselectivities were poor in this case when using the monofunctional phosphine **P66**, excellent enantioselectivities were accomplished when applying a bifunctional chiral phosphine (vide infra).[343]

Marinetti was among the forerunners in the discipline of chiral pyrroline construction, reporting numerous studies of various chiral phosphine catalysts and their abilities to generate asymmetric induction.[344] Among the many readily available chiral phosphines with axial chirality and planar chirality that were tested, several induced the asymmetric formation of pyrrolines, albeit with low yields and moderate selectivity (Scheme 269). The less sterically hindered *N*-tosyl benzaldimine was less affected by the steric influence of the chiral catalyst, leading to lower enantioselectivities, whereas the more sterically demanding *N*-tosyl naphthaldimine appeared to be the substrate of choice for observing asymmetric induction. Many phosphines, listed in Scheme 269, produced moderate yields of pyrrolines, but with minimal asymmetric induction. Although the preliminary screening revealed that several phosphine catalysts produced moderate levels of chiral induction, the low yields of these reactions suggested little synthetic utility.

After an extensive search for the ideal catalyst for asymmetric formation of pyrrolines, Marinetti found that Gladiali's phosphepine (*S*)-**P48** functioned with moderate enantiocontrol (Scheme 270).[345–347] Pyrrolines were synthesized in moderate yields across substrates presenting different activating groups of various steric influence, albeit with moderate enantioselectivities (entries 1–4). Slightly better selectivity was observed when employing a sterically demanding *N*-diphenylphosphinamide-protected napthaldimine (entry

4). At present, there have been no reports of highly efficient asymmetric allene–imine [3 + 2] annulations using chiral monophosphines.

Reports of efficient asymmetric allene–imine [3 + 2] annulations remain scarce. Currently, there are only two examples, using multifunctional chiral phosphines, from Jacobsen and Lu, of asymmetric phosphine-catalyzed syntheses of dihydropyrroles with enantioselectivities greater than 90% (vide infra). As previously mentioned, enantioselective synthesis of dihydropyrroles using P-chiral phosphines is challenging, occurring with low yields and selectivities. In 2014, Kwon and co-workers demonstrated a highly efficient enantioselective phosphine-catalyzed allene–imine [3 + 2] annulation for the synthesis of various functionalized dihydropyrroles (Scheme 271).[348] Employing the P-chiral bicyclo[2.2.1]phosphines *exo*-**P45** and *endo*-**P45**, both derived from *trans*-4-hydroxy-L-proline, excellent enantiomeric excesses were achieved from reactions tolerating many substitution patterns. When a sterically demanding *tert*-butyl group was present on the allenoate, the enantioselectivities were greatly enhanced.

Furthermore, *endo*-**P45**, the pseudoenantiomer of *exo*-**P45**, catalyzed the formation of the dihydropyrrole antipodes in excellent yields and enantioselectivities (Scheme 272). In addition, such excellent enantioselectivities were observed with *endo*-**P45** even in the absence of a sterically demanding *tert*-butyl group (entry 2). Like many commercially available chiral phosphines, both *exo*-**P45** and *endo*-**P45**, along with 10 other analogues, are sold by Sigma–Aldrich.

Andrews and Kwon demonstrated the first enantioselective total synthesis of (+)-ibophyllidine featuring an asymmetric [3 + 2] annulation using a novel *trans*-L-4-hydroxyproline-derived chiral phosphine.[349] This achievement also marked the first non-formal total synthesis of a complex natural product employing a phosphine-catalyzed allene–imine [3 + 2] annulation. Starting from the *N*-Boc-indole-3-carboxaldehyde **154**, they prepared the imine **155** in the presence of titanium(IV) chloride (Scheme 273). With the imine **155** in hand, the key transformation—the asymmetric [3 + 2] annulation—was catalyzed by the P-chiral [2.2.1]bicyclic phosphine *endo*-**P45**. The reaction proceeded exceedingly well, affording the pyrroline **156** in 93% yield and 99% enantiomeric excess on a multigram scale. This powerful phosphinecatalyzed asymmetric [3 + 2] annulation set two of the stereocenters in ibophyllidine with excellent efficiency. Hydrogenation with Raney nickel yielded the pyrrolidine **157** and established another stereocenter in the natural product. Treating the intermediate **157** with lithium aluminum hydride reduced the ester portion of the molecule, followed by reductive cleavage of the tosyl group using magnesium powder under sonication; the resulting crude pyrrolidine was acylated with chloroacetyl chloride to provide **158**. Oxidation under Swern conditions and subsequent olefination furnished the indole **159**. Removal of the Boc group was achieved under reflux in the presence of silica. The crude mixture was subjected directly to Finkelstein conditions to generate the iodide **160**. Cyclization of the haloamide was accomplished in the presence of silver trifluoromethanesulfonate, with the following, and final, ring closure occurring through a trimethylphosphine-mediated intramolecular Morita reaction to yield the intermediate **161**. The total synthesis of (+)-ibophyllidine **162** was completed by treating **161** sequentially with Lawesson’s reagent, Raney nickel, and the Dess–Martin periodinane.

In 2016, Kwon et al. described a chiral phosphine catalyzed [3 + 2] cycloaddition of benzyl allenoate and the *N*-(*o*-nitrobenzenesulfonyl) (*o*-nosyl) imine to construct a pyrolindine intermediate for the total synthesis of (−)-actinophyllic acid (Scheme 274).[350] Initially, PPh_3 proved to be a capable catalyst for the reaction, and the chiral [2.2.1] bicyclic phosphine *endo*-**P67** was the optimal catalyst for the chiral version of the cycloaddition, with 99% yield and 91% ee for the cycloadduct. Lowering the temperature did not improve the enantioselectivity. They envisioned that hydrogen bond donors would benefit the results. After screening several hydrogen bond donors, they found that phenol or biphenol greatly accelerated the reaction, while (*S*)- or (*R*)-BINOL could both accelerate the reaction and improve the enantioselectivity. They applied this [3 + 2] cycloaddition to the total synthesis of a biologically active natural product, (−)-actinophyllic acid hydrochloride, in 13 steps.

In 2016, Kumar reported the cyclic chiral phosphine-catalyzed enantioselective [3 + 2] cycloaddition of isatin-derived ketimines with α-substituted allenoates (Scheme 275).[351] In the presence of (*R*)-**P32** (20 mol%), the isatin-derived ketimines underwent enantioselective [3 + 2] cycloaddictions with α-substituted allenoates to afford highly substituted 3,2′-pyrrolidinyl spirooxindoles with consecutive chiral centers in moderate to high yields (31–88%) and excellent enantioselectivities (92.1–99.9% ee).

3.4.2.2. Enantioselective Allene–Imine [3 + 2] Annulation Using Multifunctional Chiral Phosphines.: While the formation of optically pure cyclopentenes through asymmetric allene–alkene [3 + 2] annulations has been studied extensively for many years, the development of corresponding allene–imine [3 + 2] annulations has remained challenging. It was not until 2008 that Jacobsen demonstrated several elegant examples of asymmetric phosphine catalysis generating functionalized pyrrolines, mediated by the chiral phosphinothiourea catalyst **P68**.[343] For this reaction, a relatively sterically demanding imine, *N*-diphenylphosphinoyl imine, was employed to enhance the chiral induction from the catalyst, while maintaining high yields and enantioselectivities (Scheme 276). The reaction tolerated both electron-donating and -withdrawing imines and heteroaromatic imines. A lower catalyst loading was required for electron-withdrawing imines, whereas electron-donating imines required higher loadings of the catalyst. Water and triethylamine also appeared to be important additives for increasing the rate of the reaction and suppressing undesired byproducts. The effect of adding water to increase the reaction efficiency was studied computationally by Yu[244] and Dudding and Kwon.[245]

After Loh's [3 + 2] annulation with alkyl imines was developed, there were no asymmetric reports of such transformations until 2011, when Lu and co-workers described an elegant process for asymmetric induction using the amino acid-derived chiral phosphine **P65**.[341] Reminiscent of Jacobsen's approach, they used sterically demanding diphenylphosphinoyl imines to achieve high enantiocontrol (Scheme 277). Alkyl imines with substituents varying from isobutyl to cyclohexyl provided high conversions to products with excellent degrees of enantioselectivity (entries 1–3). Interestingly, a simple diphenylphosphinoyl acetyl imine underwent the transformation smoothly with only a minor loss in yield (entry 4). Aside from alkyl imines, aryl imines also afforded their functionalized pyrrolines with great efficiencies and enantiomeric excesses (entries 5 and 6). With Jacobsen's and Lu's systems, both enantioisomers of 2-pyrrolines can be accessed for synthetic applications.

Although many multifunctional catalysts have been derived from amino acids, Zhao's chiral phosphine **P59** is especially popular. In 2013, the Guo group demonstrated the formation of functionalized polycyclic sulfamidates catalyzed by **P59** (Scheme 278).[335] The reaction proceeded to give products bearing electron-donating substituents, such as 8-methoxy and 8-methyl groups, in high yields and with high enantiomeric excesses. Lower enantioselectivity was observed, however, when a 6-bromo group was present.

Although the concept of using amino acid-derived phosphines has been well received, achieving high enantioselectivities has remained a great challenge in many cases. In 2014, Toffano and Vo-Thanh reported several proline-derived chiral phosphines containing a thiourea group.[352] The reaction, however, yielded the dihydropyrrole, in low ee, only when using the catalyst **P69a** (Scheme 279).

In 2016, with the use of a bifunctional chiral phosphine as the chiral catalyst, Lu successfully developed enantioselective [3 + 2] annulations of isatin-derived ketimines with both allenoates and γ-substituted allenoates (Scheme 280).[353] In the presence of **P70** (10 mol %), unsubstituted allenoates reacted smoothly with isatin-derived ketimines to give the corresponding spirocyclic cycloadducts in good yields and with excellent enantioselectivities. In addition, the γ-substituted allenoates were also suitable partners for the reaction, providing their cycloadducts with moderate to good diastereoselectivities and excellent enantioselectivities. Using another bifunctional chiral phosphine, **P59**, as the catalyst, Kumar obtained similar results (Scheme 281).[354]

3.4.3. Allene–Ketone [3 + 2] Annulation.—In an effort to apply Lu's allene–electrophile [3 + 2] annulation to the preparation of 2,3-dihydrofurans, Ye and Miller employed aryl trifluoromethyl ketones as electrophiles.[355, 356] Through this strategy, they could prepare functionalized dihydrofurans in moderate to good yields (Scheme 282). Not surprisingly, the reactions of electron-deficient aryl trifluoromethyl ketones had better efficiencies than those of electron-rich counterparts.

3.4.4. Azomethine Imine-Allene [3 + 2] Annulation.—In a typical example of Lu's allene–electrophile [3 + 2] annulation for the formation of a five-membered ring, the activated allene provides its three unsaturated carbon atoms while the alkene, imine, or trifluoromethyl ketone provides two. Nevertheless, in 2011 Guo, Kwon, and Goddard reported an unusual [3 + 2] annulation between an α-alkylallenoate and an azomethine imine under the influence of catalytic phosphine.[357] Each step of the proposed mechanism is quite straightforward, based on the previous observations. The β-phosphonium dienolate intermediate **163**, as formed also in Kwon's [4 + 2] annulation, adds to the azomethine imine **164** at its γ-carbon to avoid steric congestion at the α-carbon (Scheme 283). The resulting amide anion in **165** undergoes conjugate addition to the β-phosphonium enoate portion of the molecule to form the zwitterion **166**, which, upon elimination of the phosphine catalyst, furnishes the tetrahydropyrazolopyrazolone **167**.

The azomethine arylimine–α-methylallenoate [3 + 2] annulation was readily facilitated by tributylphosphine and provided tetrahydropyrazolopyrazolones in excellent yields (Scheme 284, entries 1–4). Even azomethine alkylimines underwent this annulation, albeit in

diminished yield (entry 5). α-Alkylallenoates with other than α-methyl substituents typically required a higher loading of trimethylphosphine for the equally excellent production of the tetrahydropyrazolopyrazolones. Using a spirocyclic chiral phosphine, an asymmetric version of this reaction has also been achieved (Scheme 285).

After the great success of using azomethine imines in phosphine-catalyzed [3 + 2] annulations, Guo and co-workers expanded the scope of the reaction by using ethyl butynoate as a reaction partner, instead of the α-methylallenoate (Scheme 286).[358] From these reactions, they isolated a variety of tetrahydropyrazolopyrazolones **168a**, along with minor isomers **168b**, in good yields. A proposed mechanism explained the formation of the minor isomer, the [3 + 3] annulation product **168b** (Scheme 287).

In 2012, Chen, Wu, and co-workers reported a tandem intramolecular cyclization-intermolecular [3 + 2] annulation sequence (Scheme 288).[359] The Ag-catalyzed intramolecular 6-endo cyclization of *N*-(2-alkynylbenzylidene)hydrazides led to the in situ formation of azomethine imines, which subsequently underwent [3 + 2] annulations with allenoates under catalysis of PPh_3. In the presence of 10 mol % of silver triflate and 20 mol % of PPh_3, a variety of *N*-(2-alkynylbenzylidene)hydrazides and allenoates were compatible with the reaction conditions, furnishing *H*-pyrazolo[5,1-*a*]isoquinolines in moderate to good yields.

Polycyclic pyrazolines were formed by Shi and co-workers when using (*S*)-Me-f-KetalPhos **P72** in a δ-addition–γ-umpolung pathway (Scheme 289).[360] Azomethine imines bearing various substituents (e.g., fluoro, bromo, methyl groups) were tolerated in this reaction, giving their products in good yields and enantioselectivities.

Waldmann and Antonchick extended the methodology to other 1,3-dioples and developed phosphine-catalyzed regioselective dearomatizing [3 + 2] annulation of isoquinolinium methylides with allenes (Scheme 290).[361] The PBu_3-catalyzed [3 + 2] cycloaddition, followed by reduction in one pot, led to the isolation of pyrroloisoquinolines in moderate to good yields (51–95%). α-Trimethylsilyl-substituted aryl allenones were also substrates for this reaction, furnishing their products in yields of 64–91% and with *E*/*Z* ratios from 78:22 to 95:5. Using the bifunctional phosphine catalyst **P59**, up to 37% ee was obtained.

In 2016, Guo reported a phosphine-catalyzed [3 + 2] cycloaddition of phthalazinium dicyanomethanides with α-substituted allenoates (Scheme 291).[362] In the presence of PMe_3 (20 mol %), 1,2,3,10*b*-tetrahydropyrrolo[2,1-*a*]-phthalazine derivatives were obtained with high to excellent yields. They also examined an enantioselective version of the reaction; after screening several chiral phosphines, the model reaction, under the catalysis of **P59**, afforded the final product in 92% yield with up to 55% ee.

In 2017, Zhou reported the regio- and stereoselective phosphine-catalyzed [3 + 2] cycloadditions of allenoates and *o*-hydroxyaryl azomethine ylides for the synthesis of functionalized pyrrolidine derivatives (Scheme 292).[363] Under catalysis with 20 mol % of PPh_3, a wide range of substituted *o*-hydorxyaryl azomethine ylides reacted with allenoates featuring various straight-chain ester units and bulky ester groups, as well as γ-substituted allenoates, to give the corresponding products in good yields with excellent

stereoselectivities. No desired products were formed when α-substituted allenoates were applied in the reaction.

3.4.5. Allene–Phenyl Isothiocyanate [3 + 2] Annulation.—As an alternative to the alkenes and imines commonly used as electrophiles for the [3 + 2] annulation, Virieux and Cristau reported the first example of applying phenyl isothiocyanate for thiophene formation through phosphine catalysis.[364] They generated a few functionalized thiophenes through the mechanism proposed in Scheme 293. Using triphenylphosphine as the catalyst, initial addition into the allene provides the active phosphonium dienolate **169**. In the presence of phenyl isothiocyanate, nucleophilic addition occurs, followed by intramolecular umpolung addition, leading to the ylide **170**. After proton transfer and elimination of triphenylphosphine, the thiophene **171** is produced.

Although the efficiencies were poor, this transformation served as a proof of concept demonstrating that phenyl isothiocyanate could be employed in phosphine catalysis to provide thiophene derivatives (Scheme 294).

After Virieux's initial report of thiophene formation, no further developments occurred in the field until 2011. Rather than employing 2,3-butadienoates, Shi demonstrated that the phosphine-mediated reactions of 2-methyl-2,3-butadienoate and isothiocyanates triggered a novel decarboxylation event leading to functionalized 2-aminothiophenes.[365] Following formation of the phosphonium dienoate **172**, addition into the isothiocyanate at the γ-position gives the intermediate **173** (Scheme 295). Intramolecular α-umpolung addition advances to provide the ylide **174**. A unique proton transfer shifts the anion to the methyl group on the catalyst, setting up the decarboxylation process. After removal of the carbonyl group, re-aromatization of **175** affords the intermediate **176**. At this point, a step-wise alkylation occurs, furnishing the functionalized 2-aminothiophene **177**.

Although various substituents can be installed, these reactions provide 2-aminothiophene derivatives in only modest yields (Scheme 296). *p*-Methoxyphenyl isothiocyanate and benzyl isothiocyanate both provided their functionalized 2-aminothiophenes in moderate yields (entries 1 and 2). Allenoates with various ester groups were tolerated, but lower efficiency was observed when a benzyl ester was the activating group (entry 4). Further development in the area of thiophene synthesis through phosphine catalysis would be needed to provide, with high efficiencies, thiophene motifs bearing diverse functionalities.

3.4.6. Unusual Allene–1,2-Dione [3 + 2] Annulation.—Nair and co-workers reported the use of 1,2-diones as dielectrophilic reaction partners to generate various γ-hydroxybutenolides.[366] In the proposed mechanism, the zwitterion **178** is generated in the presence of a phosphine (Scheme 297). Addition to the dielectrophile then gives the intermediate **179**. Although Nair proposed the addition of water to give a quaternary phosphonium species, it is more likely that an addition/elimination sequence occurs, giving the intermediate **180**. After an intramolecular aldol-type cyclization, the reaction yields the desired γ-hydroxybutenolide **181**.

Although the reaction was proposed to be catalytic in nature, a stoichiometric amount of the phosphine was used to ensure high efficiencies (Scheme 298). Substrates bearing electron-rich and -poor aryl rings (e.g., *p*-fluorophenyl, *p*-methoxylphenyl) reacted to give their products in high yields. A heteroaryl (2-furyl) ring was also compatible with the reaction conditions, albeit giving a lower yield of its product.

3.4.7. Unusual α-Chloroketone–Allene [3 + 2] Annulation.—In 2014, Fan and co-workers examined the use of unconventional 2-chloroacetoacetates as reaction partners (Scheme 299).[367] Here, once the zwitterion **182** is generated, alkylation occurs at the γ-position to provide the intermediate **183**. After deprotonation from an external base, keto–enol tautomerism ensues, followed by cyclization, to give the intermediate **184**. Aromatization affords the furan **185**.

The reaction was best suited for allenones bearing an electron-rich group (e.g., *p*methoxylphenyl, benzyl), resulting in good yields of the desired furans (Scheme 300). Electron-withdrawing functionalities and heteroaryl groups could also be used, but with some erosion of the yield.

3.4.8. Allene–Imine [4 + 2] Annulation.—The versatile reactivity of allenes in combination with electrophiles under phosphine catalysis conditions was further illustrated by Zhu and Kwon's report of allene–imine [4 + 2] annulation.[176] As with Lu's allene–electrophile [3 + 2] annulation,[175] here imines, alkenes, and trifluoromethyl ketone electrophiles can all combine with α-alkylallenoates to form tetrahydropyridines, cyclohexenes, and dihydropyrans, respectively.[368–371] The proposed mechanism begins with nucleophilic addition of tributylphosphine into the 2-substituted-2,3-butadienoate **186**, generating the phosphonium dienolate **187** (Scheme 301). Nucleophilic addition of the zwitterion **187** into the *N*-tosyl imine **188** occurs at its γ-carbon to afford the intermediate **189**. Through proton transfer, the intermediate **189** equilibrates with the vinylogous phosphonium ylide **190↔191**. Another proton transfer furnishes the intermediate **192**. Conjugate addition of the sulfonamide anion to the α,β-enoate and subsequent β-elimination of tributylphosphine provides the tetrahydropyridine **193**. This proposed mechanism has been supported by Qiao and Han's theoretical calculations.[372]

When reacting 2-substituted 2,3-butadienoates and *N*-tosyl imines in the presence of tributylphosphine, Kwon's [4 + 2] annulation proceeded to afford tetrahydropyridines with high efficiency and in high diastereoselectivity (Scheme 302). Specifically, ethyl α-methylallenoate underwent the [4 + 2] annulation with a variety of *N*-tosyl arylimines to provide tetrahydropyridines, typically in over 90% isolated yield. The only exception was observed when the *N*-tosyl arylimine featured a nitrobenzene ring (entry 3). The reaction proceeded even with an *N*-tosyl *tert*-butylimine in the presence of 3 equivalents of sodium carbonate as an additive. The reactions of 2-arylmethyl-2,3-butadienoates and *N*-tosyl arylimines provided 2,6-diaryl tetrahydropyridines in almost quantitative yield, with excellent diastereoselectivity favoring the cis-isomer. Similar to the case with 2-methyl-2,3-butadienoate, marginal erosion of the product yield was detected, while maintaining excellent diastereoselectivity, when strongly electron-deficient arylimines were employed. Both the reaction yield and the diastereoselectivity were slightly compromised, however,

when an ortho-substituted aryl group was present. Nevertheless, the allene–imine [4 + 2] annulation is a robust process, with the large-scale preparation of tetrahydropyridines having been reported.[373]

While 2-methyl-2,3-butadienoate undergoes efficient [4 + 2] annulations with *N*-tosyl imines, 3-methyl-3,4-pentadienone experiences an unusual cascade event, incorporating two molecules of the imine in the process. Shi reported that cinnamyl tetrahydropyridyl ketone can be prepared from 3-methyl-3,4-pentadienone and *N*-tosyl imines in the presence of tributylphosphine (Scheme 303).[368] This reaction proceeds to generate the phosphoniumamide zwitterion **194**, as displayed in Scheme 296 (cf. **192**). Conjugate addition of the sulfonamide anion to the enone portion of the molecule forms the phosphonium enolate **195**. Surprisingly, equilibration to an alternative enolate **196** and subsequent addition to the imine is competitive, producing the intermediate **197**. Conversion to the β-phosphonium enolate **198** and elimination of the phosphine catalyst furnishes **199**, which, upon loss of tosylamine, provides the cinnamyl tetrahydropyridyl ketone **200**.

Under the optimized conditions, several cinnamyl tetrahydropyridyl ketones were generated in moderate yields (Scheme 304). Both electron-rich and -poor arylimines were suitable as reaction partners, with lower product yields obtained when employing electron-rich imines.

As mentioned above for the [3 + 2] annulations, Ye and co-workers developed the use of cyclic imines for annulation, allowing rapid access to polycyclic products. The same cyclic imines could also be employed in [4 + 2] annulations to prepare a variety of functionalized polycyclic tetrahydropyridines (Scheme 305).[374] The reaction produced polycyclic tetrahydropyridines in good yields and tolerated a range of substitution patterns.

Guo and co-workers expanded the use of their sulfamate-derived cyclic imines to phosphinecatalyzed [4 + 2] annulations to prepare functionalized tetrahydropyridines (Scheme 306).[375] The reactions yielded various tetrahydropyridines bearing electron-donating and -withdrawing substituents, with excellent efficiencies.

To explore new annulations involving the γ'-carbon of α-substituted allenoates, the Guo group synthesized tetrahydrobenzofuranone-derived allenoates and applied them in phosphinecatalyzed [4 + 2] cycloadditions with sulfamate-derived cyclic imines for the synthesis of biologically significant multicyclic heterocycles (Scheme 307).[376] Using 20 mol % of Bn_2PPh as the catalyst, various sulfamate-derived cyclic imines reacted with cyclic allenoates to produce their [4 + 2] cycloadducts in good to excellent yields. These reactions were the first phosphinecatalyzed [4 + 2] annulations involving the γ'-carbon of α-substituted allenoates.

Taking advantage of the highly efficient allene–imine [4 + 2] annulation, Kwon applied this methodology in the formal synthesis of (±)-alstonerine (Scheme 308).[377] Starting from diethyl 2-vinylidenesuccinate **201** and the *ortho*-nosyl-protected indole imine **202**, [4 + 2] annulation occurred to produce the tetrahydropyridine **203** in good yield. Subsequent Friedel–Crafts acylation in an acidic medium provided the tetracycle **204**. The nosyl protecting group was removed under Fukuyama's conditions, using benzenethiol, to afford the tetracycle **205** in near-quantitative yield. Methylation of the amine was performed using

the Eschweiler–Clarke method to give the tertiary amine **206**. Reductive deoxygenation, performed in the presence of sodium cyanoborohydride and zinc(II) iodide, led to the amine–borane complex **207**. Release of the tertiary amine from the cyanoborane was accomplished under reflux in ethanol, generating the tertiary amine **208**. Selective diisobutylaluminum hydride-mediated 1,2-reduction of the ethyl ester completed the preparation of the known allylic alcohol **209** in excellent yield.

Later, Barcan and Kwon demonstrated the concise preparation of the skeletal framework of reserpine (**211**, Scheme 309).[378] The allene–imine [4 + 2] annulation was well suited for the construction of the D-ring of reserpine, along with introducing both the A- and B-rings. The key [4 + 2] annulation granted rapid access to the intermediate **210**, allowing the formation of the C-ring and subsequent 6π-electrocyclization to the E-ring, completing the skeletal framework of reserpine.

The methodology also allowed Kwon and co-workers to complete the synthesis of (±)-hirsutine (**213**), starting from readily available materials (Scheme 310).[379] The key intermediate **212** was obtained in good yield through initial imine formation followed by [4 + 2] annulation with the crude imine. Notably, the [4 + 2] annulation gave a high yield of the tetrahydropyridine **212** when using the crude imine as the coupling partner, demonstrating the robustness of this reaction. Finally, formation of the C-ring and functional group manipulations completed the sysnthesis of (±)-hirsutine with good efficiency.

With Lu's [3 + 2] and Kwon's [4 + 2] annulations being well established, small-molecule chemical library approaches for the discovery of enzyme inhibitors and receptor ligands have been developed. In 2007, Kwon disclosed the first example of phosphine catalysis with polystyrene-bound allenoates for a combinatorial library approach toward the identification of potent inhibitors of protein geranylgeranyltransferase type I (GGTase-I) and Rab geranylgeranyltransferase as potential anticancer therapeutics.[380,381] Using SynPhase lanterns grafted with Wang resin, allenoic acids were coupled to the benzyl alcohol units of the Wang linker to install resin-bound allenoates (Scheme 311). Through the split-and-pool strategy, extensive arrays of allenoic acid, imine, and thiol building blocks were incorporated, leading to the production of 4288 compounds comprising a vast variety of functionalized tetrahydropyridines, pyrrolines, pyrrolidines, and piperidines. In vitro assays revealed that the pyrroline **214** and the tetrahydropyridine **215** both displayed submicromolar IC_{50} values against GGTase-I. A derivative of the pyrroline **214** displayed in vivo efficacy against solid pancreatic tumor and lung cancer models in mice, hinting at the possibility of developing novel anticancer therapeutic leads in the future.[382–385]

The pyrrolines and tetrahydropyridines generated from phosphine catalysis of imines and allenoates possess α,β-unsaturated carboxylic ester moieties and, therefore, can be further elaborated into more elaborate multicyclic scaffolds. For instance, through Tebbe olefination, the enoate motifs of pyrrolines and tetrahydropyridines can be transformed into dienol ethers that are suitable for subsequent Diels–Alder reactions (Scheme 312). In the presence of maleimide, triazolindione, tetracyanoethylene, benzoquinone, and imine dienophiles, the 1-ethoxyethenyl pyrroline and tetrahydropyridine underwent their Diels–Alder reactions with, in most cases, exclusive diastereoselectivity, providing densely

functionalized polyheterocyclic compounds. Indeed, Kwon documented the diversity-oriented synthesis of a chemical library comprising 91 polyheterocyclic compounds with 16 distinct scaffolds.[386–388] Gratifyingly, compounds **216**, **217**, and **218** exhibited subtoxic antimigratory activity against MDA-MB-231 human breast cancer cells. With these preliminary data, further development and optimization based on the active compounds might bring forth a better understanding of cell migration and possible therapeutic compounds.

Shortly after the identification of compounds with promising antimigratory activities from the diversity-oriented library of 91 polyheterocyclic compounds with 16 distinct scaffolds, Kwon and Cruz demonstrated a class of octahydro-1,6-naphthyridin-4-ones possessing potent activity in mediating endothelial cell-triggered induction of innate immune response, similar to interferon gamma (IFNγ).[389] This first report of small molecule-induced endothelial activation could potentially lead to the eradication of infections and cancers. Taking advantage of the facile preparation of the Wang resin-bound tetrahydropyridines,[380] a library of octahydro-1,6-naphthyridin-4-ones was built through split/pool synthesis on a solid phase. Again, allenoic acids were coupled to the Wang resin, followed by [4 + 2] annulations with imines in the presence of tributylphosphine (Scheme 313). The resulting tetrahydropyridine carboxylate esters **219** were treated with Tebbe reagent and then subjected to Diels–Alder reactions with imines. Notably, the same imine building blocks were used in both the phosphine catalysis and the Diels–Alder reaction. Highly diastereoselective hydrolysis of the octahydronaphthyridines **220** was facilitated upon simple treatment with trifluoroacetic acid (TFA), releasing the naphthyridinones **221**.

Among the 96 naphthyridinones, five distinctive octahydro-1,6-naphthyridin-4-ones displayed excellent activation of endothelial cell triggered induction of innate immune response (Scheme 314). These studies nicely illustrated the potential utility of the products of phosphine catalysis. The ready translation of the original phosphine catalysis reactions to solid phase processes enables the facile preparation of analogues through split-and-pool combinatorial synthesis—a crucial aspect of modern chemical biological studies.

Enantioselective Allene–Imine [4 + 2] Annulation.: While many asymmetric [3 + 2] annulations have been investigated and reported, only a few asymmetric versions of Kwon's allene–imine [4 + 2] annulation have appeared. In 2005, Fu demonstrated an elegant example of the asymmetric [4 + 2] reaction, generating functionalized tetrahydropyridines when employing Gladiali's phosphepine (*R*)-**P48** (Scheme 315).[390] The reactions provide functionalized *cis*-tetrahydropyridines in almost quantitative yields and with excellent enantioselectivities (entries 1 and 2). Under the catalysis conditions, a vinylidenesuccinate—namely, α-ethoxycarbonylmethylallenoate—was applied to ensure high selectivity. The reaction of the *p*-methoxybenzaldimine afforded its tetrahydropyridine in low yield while maintaining excellent enantioselectivity (entry 3). Moreover, the *o*-chlorobenzaldimine provided a slightly lower product yield with significant erosions of enantioselectivity and regioselectivity, possibly because of steric hindrance (entry 4).

Several years after Fu's first reported asymmetric allene–imine [4 + 2] annulation, Sasai and co-workers published an enantioselective synthesis of polycyclic tetrahydropyridines from

cyclic imines (Scheme 316).[391] Using (*R*)-**P32** as the catalyst, the polycyclic tetrahydropyridines were obtained in good yields and enantiomeric excesses from reactions tolerating various aryl groups. Although a heteroaryl 2-pyridinyl group was also compatible, its product was obtained in lower yield and enantioselectivity.

In 2011, Zhao published the second report on asymmetric allene–imine [4 + 2] annulation using an amino acid–derived chiral phosphine.[392] Coincidentally, this reaction gave high enantioselectivities and yields of tetrahydropyridine derivatives when employing the same amino phosphine (**P59**) that they had used in their first study of the enantioselective allene–alkene [3 + 2] annulation (see Section 3.4.1). Similar to Fu's example, a vinylidenesuccinate was required to ensure high efficiency (Scheme 317). In contrast to Fu's report, an excellent yield of the tetrahydropyridine was isolated with high enantioexcess from *p*-methoxybenzaldimine (entry 1). With *o*-chlorobenzaldimine as the substrate, a minor drop in yield occurred—a consistent trend in allene–imine [4 + 2] annulation (entry 2). While benzaldimine derivatives were well suited in the reaction, 2-thiophenecarboxaldimine could also be used with only a slight erosion in enantioselectivity (entry 4). Using this method, the low-yielding tetrahydropyridines in Fu's system were accessible with high efficiency.

The aforementioned polycyclic tetrahydropyridines could also be formed asymmetrically using the catalyst **P73** (Scheme 318).[375] Guo and co-workers synthesized tetrahydropyridines with various substitution patterns in good yields and with good enantiomeric excesses.

3.4.9. Allene–Alkene [4 + 2] Annulation.—Tran and Kwon further expanded the phosphinecatalyzed [4 + 2] annulation to examine the combination of 2-alkyl-2,3-butadienoates and electron-withdrawing olefins to synthesize functionalized cyclohexenes.[369, 370] Furthermore, they observed that two distinct cyclohexene regioisomers could form selectively, depending on the electronic nature of the phosphine catalyst. Explicitly, γ-addition ensued when employing hexamethylphosphorous triamide (HMPT), a strongly nucleophilic phosphine, leading to the formation of the cyclohexene **222** (Scheme 319). Conversely, use of a weakly nucleophilic triarylphosphine, such as tris(*p*-fluorophenyl)phosphine, led to the phosphonium dienolate isomerizing into the vinylogous ylide and β'-addition occurring to provide the alternative regioisomer **223**. Wang and co-workers provided support for the proposed mechanism through theoretical computations with the M05-2X/6-31G* basis set.[393]

The α-alkylallenoate–alkene [4 + 2] annulation afforded cyclohexenes as two distinct regioisomers, in excellent yields and diastereoselectivities, when treated with HMPT or tris(*p*-fluorophenyl)phosphine in refluxing benzene (Scheme 320). In the presence of HMPT, both electron-withdrawing and -donating arylidenemalononitriles gave excellent yields of the cyclohexenes **224**. When employing tris(*p*-fluorophenyl)phosphine, the alternative regioisomers **225** were obtained with high efficiency. Furthermore, high diastereoselectivities had been reported when the alkyl group in the 2-alkyl-2,3-butadienoates was larger than a methyl group.

In 2014, Fan and co-workers published a short Communication expanding Kwon's allene–alkene [4 + 2] annulation to allow the use of various arylallenones (Scheme 321).[282] These reactions employed triphenylphosphine as the catalyst, rather than tris(*p*-fluorophenyl)phosphine. Various cyclohexenes bearing electron-donating and -withdrawing functionalities on the aryl ring systems were obtained with good efficiencies.

In 2011, Kumar reported a short Communication on the formation of tricylic benzopyrones. Employing the method of [4 + 2] annulation, functionalized tricyclic benzopyrones were prepared from activated chromenones and various allenes, including vinylidenesuccinate, 2-benzyl-2,3-butadienoate, and 2-methyl-2,3-butadienoate (Scheme 322).[394] High yields of the functionalized tricyclic benzopyrones were obtained from vinylidenesuccinate and 2-benzyl-2,3-butadienoate. In contrast, a significantly lower yield was observed when a brominated chromenone was employed. A similar low efficiency was discerned when using 2-methyl-2,3-butadienoate in the reaction.

He, Chen, et al. explored the phosphine-catalyzed [4 + 2] annulations of α-substituted allenoates with oxindoles and indan-1,3-diones presenting exocyclic alkene moieties (Scheme 323).[395] With 20 mol % of PPh_3 as the catalyst, they examined the scope of the [4 + 2] annulations of the allenoates with isatin-derived alkenes or indan-1,3-dione-derived alkenes in toluene at 80 °C, obtaining a series of spirooxindole- or spiroindan-1,3-dione-cyclohexenes in moderate to excellent yields and regioselectivity.

Miao and co-workers developed a bisphosphine-catalyzed sequential [4 + 2]/[4 + 2] annulation of 4-benzylidene-5-methyl-2-phenyl-2,4-dihydropyrazolone with a γ-benzyl-substituted allenoate (Scheme 324).[396] Using 25 mol % of 1,4-bis(diphenylphosphino)butane (dppb) as a catalyst, pyrazolone derivatives featuring various aryl substituents reacted with the γ-benzyl-substituted allenonate to furnish their sequential [4 + 2]/[4 + 2] annulation products as major products and their single [4 + 2] annulation products as minor products.

Enantioselective Allene–Alkene [4 + 2] Annulation.: Asymmetric induction in this system remained a challenge until 2012 when Lu took a step forward, demonstrating an elegant enantioselective [4 + 2] annulation of vinylidenesuccinate and arylidenemalononitriles mediated by the amino acid-based chiral phosphine **P74** (Scheme 325).[397] *tert*-Butyl vinylidenesuccinate was used to enhance the diastereoselectivities. Under the optimal conditions, arylidenemalononitriles featuring *p*-methoxyphenyl and *m*-chlorophenyl substituents were suitable substrates, providing their products in excellent yields and with excellent enantiomeric excesses (Scheme 320, entries 1 and 2). While heteroarylidenemalononitriles reacted highly efficiently, 2-furylidenemalononitrile yielded its corresponding cyclohexenes with lower diastereoselectivity (entry 3). Nonetheless, this study was the first foray in the field of asymmetric catalysis of Kwon's allene–alkene [4 + 2] annulation.

In the same report, Lu extended the asymmetric [4 + 2] annulation to the formation of 3-spirocyclohexene-2-oxindoles mediated by the phosphine **P65**—the same catalyst that had been used for enantioselective [3 + 2] annulations of alkyl imines. Excellent yields of

functionalized 3-spirocyclohexene-2-oxindoles were achieved with high enantiomeric excesses and superb diastereocontrol (Scheme 326). Notably, 4 Å molecular sieves further enhanced the yield and enantiocontrol of the reaction.

Around the same time as Lu's publication, Zhao demonstrated an efficient pathway toward cyclohexenes, with excellent yields and enantioselectivities.[398] Using the chiral phosphine **P59b**, cyclohexene derivatives having the all-syn configuration were prepared from vinylidenesuccinate and arylidenecyanoacetates. The chiral catalyst **P59b** provided excellent asymmetric induction in the generation of functionalized cyclohexenes (Scheme 327). At relatively low temperature, arylidenecyanoacetates containing *p*-chlorophenyl and *p*-methoxyphenyl units reacted with high efficiencies (entries 2 and 3). In addition to traditional aryl and heteroaryl systems, isopropylidenecyanoacetate was well suited to this protocol, providing the first example of an aliphatic substrate undergoing the allene–alkene [4 + 2] annulation (entry 5).

In 2015, Guo developed a new method for the preparation of spiropyrazolones via phosphine-catalyzed [4 + 2] cycloadditions of unsaturated pyrazolones with allenoates (Scheme 328).[399] In the presence of $MePPh_2$ (20 mol %), a wide range of unsaturated pyrazolones bearing electron-rich and -deficient substituents underwent [4 + 2] cycloadditions with various allenoates to deliver spiropyrazolones in moderate to excellent yields and with moderate to good diastereoselectivities. Using the chiral thiourea-based bifunctional phosphine **P73** as the catalyst, the enantioselective [4 + 2] annulations between unsaturated pyrazolones and allenoates provided various chiral spiropyrazolones in moderate to excellent yields, with excellent enantioselectivities, and with moderate to excellent diastereoselectivities.

In 2016, Kumar and co-workers described the chiral difunctional phosphine-catalyzed [4 + 2] cycloadditions of α-substituted allenoates with 3-cyano-chromones to construct polycyclic benzopyrans (Scheme 329).[400] In the presence of the amino acid-derived bifunctional chiral phosphine **P75** (10 mol %), diverse functionalized polycyclic benzopyrans were obtained in high yields, with excellent enantioselectivities, and with moderate to high diastereoselectivities. They proposed transition states to rationalize the selectivity.

In 2016, Guo, Zhou, and co-workers developed chiral phosphine-catalyzed [4 + 2] cycloadditions of barbiturate-derived alkenes and α-substituted allenoates to construct spirobarbiturate-cyclohexene skeletons (Scheme 330).[401] In the presence of the spirocyclic chiral phosphine (*R*)-**P50b** (20 mol %), various α-substituted allenoates and barbiturate-derived alkenes underwent the reaction to provide their spirobarbiturate-cyclohexene derivatives in moderate to excellent yields and with excellent enantioselectivities. In previous chiral phosphine-catalyzed [4 + 2] annulations, only α-alkoxycarbonyl-substituted allenoates had been tolerated in most cases. In this current reaction, however, the scope of the α-substituted allenoates was quite wide.

3.4.10. Allene–Ketone [4 + 2] Annulation.—A report by Ye further expanded the generality of the phosphine-catalyzed allene–electrophile [4 + 2] annulation to the formation

of dihydropyrans from 2-arylmethyl-2,3-butadienoates and aryl trifluoromethyl ketones.[371] Under the optimized conditions, both electron-donating and -withdrawing substituents were tolerated on both aryl rings, furnishing functionalized dihydropyrans in good yields (Scheme 331). In addition to substituted phenyl trifluoromethyl ketones, a heteroaryl trifluoromethyl ketone also worked as expected, generating the corresponding dihydropyran, albeit in lower yield (entry 4). In contrast to the cases in the allene–imine and allene–alkene [4 + 2] annulations, 2-methyl-2,3-butadienoate provided no reaction under Ye's conditions (entry 5). With diethyl 2-vinylidenesuccinate as a partner, the reaction yielded only a trace amount of the annulation product (entry 6).

3.4.11. Allene–Aldehyde Annulation.—In many classical carbon–carbon bond-forming reactions (e.g., aldol, Mannich, and Michael reactions), aldehydes, along with imines and electron-deficient olefins, function as electrophiles against carbanionic nucleophiles. It was, therefore, expected that aldehydes would function as electrophilic reaction partners against the β-phosphonium dienolate zwitterion **77** (see Scheme 184) in Lu's [3 + 2] annulation to provide dihydrofurans. Instead, Kwon demonstrated that the reactions between allenoates and aldehydes produced oxygen-containing heterocycles, including dioxanes,[402] 2-pyrones,[403] and dihydro-2-pyrones,[404,405] depending on the choice of the phosphine catalyst and the reaction conditions (Scheme 332). According to Scheme 327, implementing the sterically less demanding trimethylphosphine favors the *Z*-phosphonium dienolate, which upon addition to an aldehyde forms an intermediate **226**. Instead of undergoing 5-*endo*-trig cyclization, as in Lu's [3 + 2] reaction, the alkoxide **226** incorporates another molecule of aldehyde and provides the dioxanylidene **227** after conjugate addition and β-elimination of trimethylphosphine. The electrostatic interaction between the phosphonium center and the enolate oxygen is overridden when using the sterically demanding tricyclopentylphosphine, forming the *E*-phosphonium dienolate. Addition of the *E*-phosphonium dienolate zwitterion to an aldehyde forms an intermediate **228**, in which the alkoxide is in close proximity to the carboxylic ester. Intramolecular lactonization and eventual loss of tylphosphine after a series of proton transfer steps furnished the 2-pyrone **229**. In addition to the use of a sterically demanding phosphine catalyst, the addition of a solvent capable of hydrogen bonding (e.g., an alcohol) also overrides the phosphonium–alkoxide electrostatic interaction and favors the formation of the *E*-phosphonium dienolate. The addition of the *E*-phosphonium dienolate zwitterion to an aldehyde again provided the intermediate **230**, which readily lactonized. Unlike the case in the 2-pyrone synthesis when using a bulky phosphine, the alkoxide generated upon lactonization can add conjugatively to the β-phosphonium enoate **231** to form the 4-alkoxy-2-pyrone **232** after elimination of trimethylphosphine. The conjugate addition of the alkoxide is further facilitated by the addition of an alkoxide to the reaction mixture. In all cases, the β-phosphonium dienolate zwitterion undergoes addition to an aldehyde at its γ-carbon, due to the favorable electrostatic interaction between the phosphonium center and the developing negative dipole at the aldehyde oxygen.

The formation of dioxanes proceeds to generate the 2,6-*cis*-isomer exclusively and produced higher yields when electron-deficient arylaldehydes were used in excess (Scheme 333). The reaction also provided higher yields when employing sterically demanding, electron-

donating isopropyl 2,3-butadienoate. When synthesizing 2-pyrones, ethyl 2,3-butadienoate was preferred over other 2,3-butadienoates to provide greater yields. At elevated temperature, both electron-rich and -poor aromatic aldehydes produced 6-aryl-2-pyrones in good yields. Whereas aliphatic aldehydes could not be used for the dioxane and dihydro-2-pyrone syntheses, alkylaldehydes could be applied in the syntheses of 2-pyrones, albeit with moderate efficiency. When a methanol/methoxide mixture was used in conjunction with trimethylphosphine, functionalized dihydro-2-pyrones were formed. Similar to the formation of dioxanes and pyrones, higher efficiency was observed when the reaction was performed with electron-deficient aromatic aldehydes.

In 2013, He and co-workers expanded the formation of dioxanes to the use of 2,3-pentadienoates (Scheme 334).[406] Similar to previous findings, the initial nucleophilic addition occurred away from the α-carbon. Under the reaction conditions, arylaldehydes bearing electron-withdrawing substituents underwent cyclization to give their functionalized dioxanes in good yields.

As with simple allenoates, aldehydes do not undergo Kwon's [4 + 2] annulation when mixed with α-alkylallenoates in the presence of a phosphine. Instead, a rare phosphine-mediated vinylogous aldol reaction occurs between the α-methylallenoate and the aldehyde, followed by incorporation of an aryl substituent from the phosphine.[407] This unusual transformation is reasoned to occur through the mechanism displayed in Scheme 335. The ubiquitous phosphonium dienolate **233** undergoes nucleophilic addition into the aldehyde at its γ-carbon to form the intermediate **234**. Following proton transfer, 1,2-phenyl migration occurs with the hydroxyl group sequestering the phosphorus center to give the intermediate **235**. Upon workup, the vinylogous aldol **236** is produced. Khong and Kwon monitored the reaction using NMR spectroscopy to establish the existence of the phosphinite intermediate **235**.

The reaction generated the vinylogous aldol/aryl migration product in mediocre yield when using either triphenylphosphine or tri(p-tolyl)phosphine in conjunction with p-cyanobenzaldehyde (Scheme 336).

Ye and Kwon found that reacting allenes with aldehydes in the presence of a phosphine catalyst could lead to the formation of dihydrofurans,[355] dioxanes,[402] pyrones,[403] and dihydropyrones.[404,405] Adding to the repertoire of phosphine-catalyzed syntheses of oxygen-containing heterocycles, He and Huang reported the formation of functionalized tetrahydrofurans from 2,3-pentadienoates and aromatic aldehydes in the presence of tris(p-fluorophenyl)phosphine.[408,409] The [3 + 2] annulation with aromatic aldehydes was best performed in a nonpolar solvent (e.g., xylene) at elevated temperature to optimize the yields (Scheme 337). Electron-withdrawing aromatic aldehydes reacted in higher yields over shorter reaction times (entry 1), whereas electron-donating substituents hindered the reaction rate and lowered the product yields (entry 2). The regioselectivities were excellent when o-trifluoromethylbenzaldehyde and 3-pyridinecarboxyaldehyde served as reaction partners (entries 3 and 4). Reminiscent of their behavior in phosphine-catalyzed annulations, aliphatic aldehydes were not applicable in this reaction. The reaction of 2-methyl-2,3-pentadienoate was performed in ethanol and gave a lower yield of the corresponding

tetrahydrofuran (entry 5). When the γ-substituent deviated from a methyl group, the reaction afforded the isomerized diene product with only a trace of the tetrahydrofuran. Once more, sterically hindered groups (e.g., phenyl, *tert*-butyl) at the δ-carbon led to no detectable desired annulation products.

Zhao and co-workers expanded the range of accessible tetrahydrofurans by employing electron-poor trifluoromethyl ketones (Scheme 338).[410] When they used aryl ketones bearing electron-deficient substituents, the reactions were more highly efficient. In addition to the formation of tetrahydrofurans, the Zhao group also noted the isolation of functionalized 2,4-dienoates when using tributylphosphine as the catalyst (Scheme 339). Here, the reaction was interrupted at the initial stage of δ-addition, with subsequent elimination of the phosphine generating good yields of various 2,4-dienoates.

3.4.12. α,β-Unsaturated Carbonyl Compound–Allene [4 + 2] Annulation.—In 2015, Lu and co-workers developed phosphine-catalyzed [4 + 2] cycloadditions of allenones to β,γ-unsaturated α-keto esters to prepare enantiopure 3,4-dihydropyrans (Scheme 340).[411] Using the L-threonine dipeptide aminophosphine **P62** (10 mol %) as a chiral catalyst, treatment of allenones with a wide range of β,γ-unsaturated α-keto esters in diethyl ether at room temperature for 48 h led to the generation of optically pure 3,4-dihydropyrans in good to excellent yields and with excellent enantioselectivities. In this reaction, the allenones served as two-carbon synthons and the oxa-dienes acted as four-carbon synthons.

In 2016, Lu and co-workers applied the above methodology further to the chiral bifunctional phosphine–catalyzed [4 + 2] cycloadditions of 3-aroylcoumarins (Scheme 341).[412] In the presence of the dipeptide-based bifunctional chiral phosphine **P62** (10 mol %), enantioselective [4 + 2] cycloadditions of a diverse array of substituted 3-aroylcoumarins with α-substituted allene ketones proceeded smoothly, providing their dihydrocoumarin-fused dihydropyrans in good yields and with mostly high enantioselectivities.

Lu and co-workers also reported the amino acid-derived bifunctional phosphine-catalyzed [4 + 2] cycloadditions between oxadienes and allenones to prepare chiral dihydropyran derivatives (Scheme 342).[413] Under catalysis of the chiral bifunctional phosphine **P1** (10 mol %), a diverse set of cyano-activated oxadienes reacted with a series of α-substituted allenones to afford various functionalized dihydropyran derivatives in good to excellent yields along with good to excellent enantioselectivities.

In 2017, Lu, Wang and co-workers first examined the application of *ortho*-quinone methides in phosphine-catalyzed annulations of allene esters and ketones (Scheme 343).[414] In the presence of a dipeptide phosphine catalyst, biologically interesting chromane derivatives were obtained in good yields with nearly perfect enantioselectivities.

In 2017, Lu, Wang, and co-workers documented a novel enantioselective phosphine-catalyzed [4 + 2] annulation between allene ketones and 1-azadienes for the construction of tetrahydropyridines (Scheme 344).[415] In the presence of the L-Val-derived phosphine **P1**, [4 + 2] cycloadditions of azadienes featuring various aryl/alkyl substituents and allene ketones occurred in dichloromethane at room temperature to afford their desired annulation products

in moderate to excellent yields (32–92%) and with excellent enantioselectivity (from 93 to >99% ee). In contrast, γ-substituted allenones and α-methylallenoates were unsuitable substrates.

Guo and Xiao have described the phosphine-catalyzed [4 + 2] cycloadditions of thiazolone-derived alkenes and α-substituted allenoates used to construct dihydropyran-fused thiazole skeletons (Scheme 345).[416] In the presence of PMe_2Ph (10 mol %), a series of thiazolone-derived alkenes reacted with a diverse array of α-substituted allenoates to give 6,7-dihydro-5*H*-pyrano[2,3-*d*]thiazole derivatives in high to excellent yields. Using the Kwon phosphine **P77** as the chiral catalyst, the enantioselective version of the reaction was successful, affording the corresponding chiral products in high yields and with excellent enantioselectivities. Very recently, Guo and co-workers disclosed another similar enantioselective [4 + 2] cycloaddition of (*E*)-1-benzyl-4-olefinicpyrrolidine-2,3-diones with α-substituted allenoates (Scheme 345).[417] Under catalysis of the dipeptide-based bifunctional chiral phosphine **P65** (20 mol %), various pyrrolidine-2,3-dione-derived olefins reacted with a diverse set of α-substituted allenoates to produce pyrrolidin-2-one-fused dihydropyran derivatives in moderate to good yields and with excellent enantioselectivities.

In 2017, the Zhang group also developed ferrocene-derived bifunctional phosphine-catalyzed asymmetric oxa-[4 + 2] cycloadditions of α-substituted allenoates with enones (Scheme 346).[418] When using 5 mol % of the chiral ferrocene-derived phosphine as the catalyst, various β-perfluoroalkylated α,β-enones underwent [4 + 2] cycloadditions with a series of allenones to provide a broad range of dihydropyrans in moderate to excellent yields and with excellent enantioselectivities. 1,1,1-Trifluorobut-3-en-2-ones and the indolinone-substituted α,β-enones bearing a CF_3 or Ph group were also suitable substrates for the reaction, affording chiral cyclic products in good yields and with excellent enantioselectivities.

3.4.13. Unusual Allene–Alkene [4 + 2] Annulation via δ-Addition–α-Umpolung Reaction.—In 2013, Huang and co-workers reported an interesting reactivity of γ-benzylallenoates in a novel [4 + 2] annulation (Scheme 347).[419] The reaction of the γ-benzylallenoate **237** and triphenylphosphine generates the zwitterion **238**. After a series of proton transfers and the introduction of the activated alkene, the intermediate **239** is produced through a δ-addition pathway. The desired spirocyclohexene **240** is afforded after proton transfers and α-umpolung addition.

This reaction gave excellent yields of various spirocyclohexenes bearing *p*-tolyl, *o*-bromophenyl, and *p*-nitrophenyl groups (Scheme 348). In addition, the transformation was robust, tolerating a good range of arylideneindane-1,3-diones.

At the same time, Marinetti and co-workers also reported the formation of functionalized spirocyclohexenes from arylideneoxindoles and ethyl γ-benzylallenoate (Scheme 349).[420] Reminiscent of Huang's findings, the reaction of ethyl γ-benzylallenoate occurred exclusively through δ-addition. Good yields were afforded of spirocyclohexenes bearing various substituents.

3.4.14. Unusual Diene/Enone–Allene [4 + 2] Annulation via δ-Addition–γ-Umpolung Reaction.—In 2013, the Huang group demonstrated the synthesis of an array of biaryl compounds through the δ-addition–γ-umpolung addition pathway (Scheme 350).[421] This reaction proceeds through initial phosphine addition to the γ-methylallenoate, generating the zwitterion **241**. Proton transfers and addition to the diene lead to the intermediate **242**. Cyclization through the γ-umpolung addition pathway, followed by regeneration of the catalyst, provides the intermediate **243** along with loss of a benzenesulfonyl group. A mixture of the biaryl compounds **244a** and **244b** was obtained through aromatization.

The reaction was most compatible with aryldienes bearing electron-withdrawing substituents, including *p*-bromo and *m*-fluoro groups (Scheme 351). Although a *p*-methoxy group was also tolerated, the reaction afforded its product in low yield, albeit with excellent selectivity toward the elimination product **244b**.

Huang and co-workers also applied this phosphine-catalyzed [4 + 2] annulation strategy to build highly substituted dihydropyrans using the δ-addition–γ-umpolung reaction (Scheme 352).[422] Treatment of α-cyano-α,β-unsaturated ketones with γ-ethyl allenoates in the presence of PPh_3 (20 mol %) in 1,2-dichloroethane (DCE) at 70 °C provided completely substituted dihydropyrans in moderate to good yields, albeit with low diastereoselectivities.

3.4.15. Unusual Allene–Enone/Enimine [2 + 3]/[3 + 2] Domino Reaction.—The use of activated dienes as electrophiles for phosphine-catalyzed reactions has increased in the recent years. In 2014, Huang and co-workers showcased an efficient domino reaction between γ-benzylallenoate and activated dienes to generate a collection of bicyclo[3.3.0]octenes.[423] Similar to the mechanisms of earlier examples, the zwitterion **245** is generated when the γ-benzylallenoate is treated with a phosphine (Scheme 353). Exclusive α-addition occurs to give the intermediate **246**. Proton transfers and a cyclization lead to the intermediate **247**. Subsequent annulation, through α-umpolung addition, and catalyst regeneration afford the bicyclo[3.3.0]octane **248**.

The reaction was very efficient at building molecular complexity rapidly (Scheme 354). With tributylphosphine as the catalyst, activated dienes bearing a range of aryl groups were well suited to the reaction, producing various bicyclo[3.3.0]octenes in high yields.

Leading the field in domino reactions with conjugated electrophiles, the Huang group reported another domino process involving the use of a γ-benzylallenoate and activated enones (Scheme 355).[424] In contrast to their approach presented in Scheme 354,[423] this reaction employed triphenylphosphine as the catalyst and a higher reaction temperature to produce functionalized oxa-bicyclo[3.3.0]octenes in good yields. Here, electron-poor enones improved the efficiencies of the reactions.

Activated enimines could also be used in the domino annulations, as demonstrated by Huang and co-workers in the construction of functionalized aza-bicyclo[3.3.0]octenes (Scheme 356).[425] The reactions were more efficient when using electron-poor enimines. In contrast to

the behavior in the previous examples, an enimine presenting a 2-thienyl group led to only a moderate yield of its product.

In 2016, using a chiral difunctional phosphine as catalyst, Huang developed an enantioselective sequential [3 + 2]/[3 + 2] cycloaddition of γ-substituted allenoates and saccharin-derived ketimines to construct polyheterocyclic products having four contiguous stereogenic centers (Scheme 357).[426] In the presence of **P79** (20 mol %), the reactions of γ-substituted allenoates and saccharin-derived ketimines provided their corresponding products in moderate to excellent yields and with good to excellent enantioselectivities.

3.4.16. Tropone–Allene [8 + 2] Annulation.—In a short Communication, Ishar reported an unusual annulation of tropone.[427] This [8 + 2] annulation occurred when tropone was reacted as the electrophilic partner with an activated allene in the presence of triphenylphosphine (Scheme 358). In this specific transformation, only tropone could be used as the electrophilic reaction partner, although other allenoates and allenones were applicable and gave comparable yields of their [8 + 2] adducts.

3.4.17. Chromone/Diene–Allene [4 + 3] Annulation.—Furthermore, Ishar revealed that chromone could be used as an electrophile for [3 + 2] annulation, with subsequent deformylation furnishing functionalized chromans.[428] In addition, a rare tandem [4 + 3] annulation with rearrangement was encountered when 3-(*N*-arylimino)chromone was the electrophilic partner, giving a functionalized azepine (Scheme 359). Various substituents could be installed on the chromone benzene ring system, providing derivatized azepines in moderate yields.

Huang and co-workers reported an interesting variant of the [4 + 3] annulation that generated an array of functionalized bicyclo[3.2.0]heptenes (Scheme 360).[429] In contrast to the [4 + 2] annulation described above, this reaction proceeded with a further intramolecular cyclization to give complex bicyclic ring systems. Although the products were prepared in moderate yields, the reaction tolerated a variety of dienes featuring electron-donating and -withdrawing aryl rings.

3.4.18. Allene–Aziridine [3 + 3] Annulation.—In 2009, Guo and Kwon reported a novel [3 + 3] annulation of 2-vinylidenesuccinate with *N*-(*p*-nitrobenzenesulfonyl)aziridine that generated derivatized tetrahydropyridines (Scheme 361).[430] In the proposed mechanism, the familiar phosphonium dienolate zwitterion **249** is readily transformed into the vinylogous phosphonium ylide **250** through proton transfer, presumably because of the increased acidity of the β'-proton. Addition to the aziridine forms the intermediate **251**. Another proton transfer converts the phosphonium amide **251** to the β-phosphonium dienolate **252**, which undergoes desulfonylative intramolecular nucleophilic aromatic substitution. The resulting amide **253** affords the functionalized tetrahydropyridine after conjugate addition and elimination of the triphenylphosphine catalyst.

The yield of the reaction was greatly enhanced when employing a stoichiometric amount of the phosphine catalyst (Scheme 362). This strategy tolerated aryl aziridines bearing electron-rich and -poor functionalities, giving high yields and diastereoselectivities. With aryl

aziridines, the formation of *trans*-tetrahydropyridines was favored. A reversal in diastereoselectivity occurred when *N*-nosyl-2-methylaziridine was subjected to the reaction. Unlike substituted aziridines, *N*-nosylaziridine gave a poor yield of its product, possibly because of phosphine-mediated ring opening of the unsubstituted aziridine.

3.4.19. Allene–Azomethine Imine [3 + 2 + 3] Annulation.—Whereas treating azomethine imines and α-alkylallenoates with trimethylphosphine gave rise to tetrahydropyrazolopyrazolones (Scheme 363), a different mode of reactivity was discovered when 2,3-butadienoates were used in the reaction.[357] Ethyl 2,3-butadienoate and tricyclohexylphosphine reacted to give a dimeric phosphonium dienolate intermediate that led to the formation of functionalized tetrahydropyrazolodiazocinones in high yields. This transformation was the first example of a dimeric phosphonium species undergoing an annulation event with electrophiles. The speculated mechanism begins with formation of the conventional phosphonium dienolate **254**, which dimerizes with another molecule of 2,3-butadienoate to afford the intermediate **255**. Annulation with the azomethine imine **164** occurs readily to give the ylide **256**. Proton transfer and elimination of the catalyst, accompanied by olefin isomerization, provided a mixture of the tetrahydropyrazolodiazocinones **257** and **257′**.

Under the optimized conditions, a naphthyl imine and an aryl azomethine imine presenting an electron-donating substituent provided their desired products in good yields (Scheme 364, entries 2 and 5). Higher reaction efficiency was achieved when employing an *o*-haloaryl azomethine imine (entry 3).

One year after Kwon and Guo's publication of the phosphine-catalyzed [3 + 2 + 3] annulation, Ma and co-workers also disclosed the formation of tetrahydropyrazolodiazocinones (Scheme 365).[431] This reaction gave its products in higher yields from strongly electron-withdrawing arylazomethine imines. Furthermore, the mechanism proposed by Kwon and Guo was supported well by the theoretical calculations performed by Ma.

3.4.20. Phosphine-Catalyzed Cyclic-Oligomerization of Allenes.—While working on the formation of tetrahydropyrazolodiazocinones, Ma and co-workers also studied the phosphine-catalyzed oligomerization of allenoates in detail (Scheme 366).[431] They demonstrated that changing the number of equivalents of the allenoate allowed control to be exerted over the oligomerization process. The process of oligomerization was also studied computationally, supporting a mechanism involving a cascade of an RC reaction followed by γ-umpolung cyclization.

3.4.21. Allene–Azomethine Imine [4 + 3] Annulation.—In 2012, Guo and Kwon reported that various trialkyl phosphines could be used to fine-tune the reaction pathways, furnishing both hexahydropyrazoloisoquinoline and hexahydrodiazepinoisoquinoline derivatives with high efficiencies.[432] Compared with the initial report, the efficiency for the [4 + 3] process was improved greatly, suggesting immense synthetic utility. The reaction proceeds with addition of tributylphosphine into the allenoate in the presence of the azomethine imine, providing the phosphonium zwitterion **258** (Scheme 367). Proton transfer

and equilibration lead to the ylide **259**. After further transferring of a proton, an endocyclization occurs, accompanied by loss of the catalyst, affording the hexahydrodiazepinoisoquinoline **260**.

Several functionalized hexahydrodiazepinoisoquinolines had been prepared through this strategy, resulting in high conversions to the products (Scheme 368). High yields of the hexahydrodiazepinoisoquinoline derivatives were isolated when various aryl substituents were present at the β'-position (entries 1–3). Adjusting the substituent pattern on the azomethine imine led to a minor erosion in reaction efficiency (entries 4 and 5).

In a further exploration, Guo applied various *C,N*-cyclic aromatic azomethine imines, including *N*-acetyliminoisoquinolinium betaine, *N*-acetyliminoquinolinium betaine, and *N*-acetyliminophenanthridinium betaine, in phosphine-catalyzed [4 + 3] cycloadditions with allenoates, obtaining dinitrogen-fused heterocyclic compounds in moderate to excellent yields (Scheme 369).[433]

Recently, using a Kwon phosphine as the chiral catalyst, Guo developed the first phosphine-catalyzed enantioselective [4 + 3] cycloaddition of allenoates with azomethine imines (Scheme 370).[434] In the presence of the chiral phosphine *endo*-**P45** (20 mol %), α-substituted allenoates underwent [4 + 3] cycloadditions with quinazoline-based azomethine-imines to provide their corresponding chiral tricyclic heterocycles in high to excellent yields, with high to excellent enantioselectivities, and with mostly excellent diastereoselectivities.

3.4.22. Allene–Enimine [4 + 4] Annulation.—Most recently, Lu, Ullah, and co-workers reported the first phosphine-catalyzed enantioselective [4 + 4] annulation for the synthesis of eight-membered compounds (Scheme 371).[435] Use of 5 mol % of the L-Thr-L-Thr-derived phosphine gave eight-membered ring-fused heterocycles, including benzofuran- and indole-fused azocines, in moderate to excellent yields and with high to excellent enantioselectivities.

3.4.23. Allene–Imine Azadiene Synthesis.—In addition to studying ring-forming events in the category of allenes reacting with electrophiles, Shi also demonstrated the transformations of 2,3-butadienoate into functionalized azadienes under phosphine catalysis.[436] In the proposed mechanism of this process, the phosphonium zwitterion **261** is first generated (Scheme 372). Unlike the case in the formation of pyrrolines (Section 3.4.2, Scheme 251), the zwitterion **261** does not cyclize, due to the lower nucleophilicity on the nitrogen center (Boc-protected). Alternatively, a series of proton transfers occurs, followed by a hydride shift, to give the ylide **262**. After elimination of the phosphine, the reaction arrives at the derivatized azadiene **263**.

Mediocre yields were obtained for aryl imines carrying electron-donating and -withdrawing functional groups (Scheme 373). The reaction efficiency improved when using *N*-Boc-*p*-methylbenzaldimine as the reaction partner. A particularly superb yield of the azadiene was isolated when *N*-Boc-2-furaldimine was subjected to the reaction.

3.4.24. Allene–*o*-Quinone Methide [4 + 1] Annulation.—

Recently, using α-substituted allenoates as C_1-synthons, Waser and co-workers developed the [4 + 1] annulation of *o*-quinone methides (Scheme 374).[437] In the presence of Ph_3P (1 equiv), the reaction proceeded in CH_2Cl_2 at room temperature, providing highly functionalized dihydrobenzofurans with excellent diastereoselectivities in yields of 31–90%. In some cases, a small amount of the [4 + 3] annulation product was observed. According to the proposed mechanism, nucleophilic addition of the phosphine to the β-position of the allenoate leads to the intermediate **264**. Its resonance structure **264′** undergoes proton transfer to yield the β'-carbanionic zwitterion **265**. Addition of **265** to the in situ-formed *o*-QM results in the betaine **266**. Subsequent rapid proton transfer/double bond migration gives the intermediate **267**, which undergoes a 5-exo-trig cyclization and eliminates the phosphine to afford the [4 + 1] annulation product (Scheme 375). The intermediate **266** undergoes intramolecular conjugate addition to produce the [4 + 3] annulation product.

3.5. Phosphine Catalysis of Allenes with Electrophile–Nucleophiles

3.5.1. γ-Umpolung–Aldol [4 + 2] Annulation.—

While many research groups were searching for different pronucleophiles for γ-umpolung additions with allenes, Virieux introduced the idea of combining both pronucleophiles and electrophiles in the same molecule through carbon tethers.[192] The concept flourished, giving rise to a new type of annulation process yielding indolizines from corresponding pyrrole-2-carboxaldehydes. The proposed reaction sequence advances through initial γ-umpolung addition with pyrrole, followed by intramolecular Morita reaction, dehydration, and rearomatization to give the indolizine. Moderate yields of indolizines were obtained from the reactions of ethyl 2,3-butadienoate and methyl 2-butynoate under the optimized conditions (Scheme 376).

3.5.2. Allene–Salicylaldehyde/Imine Annulation.—

Although the vast majority of phosphine catalysis processes have involved conventional pronucleophiles and electrophiles as reaction partners for activated allenes, recent examples have demonstrated that compounds possessing both electrophilic and nucleophilic moieties can be employed to render novel annulation pathways. For example, Huang and Chen documented the formation of functionalized 2,3-dihydrobenzofurans and aminochromans when reacting 2,3-butadienoates and 2,3-pentadienoates with salicyl *N*-thiophosphinylimines in the presence of a phosphine catalyst (Scheme 377).[409,438] Meanwhile, He found that a similar transformation could be achieved using variants of salicylaldehydes, instead of salicyl *N*-thiophosphinylimines, to form derivatized hydroxychromans.[439] Furthermore, Shi demonstrated that both aminochromans and hydroxychromans could be synthesized when using 2,3-butadienoate as a reaction partner.[440] Interestingly, incorporation of the γ- and δ-carbons occurs when 2,3-pentadienoate is used in the reaction. In the case of 2,3-butadienoate, the β- and γ-carbons of the allenoate participate in the reaction to afford chroman products. Phosphine catalysis allows these diverse dihydrobenzofurans and chromans to be accessed quickly, serving as important synthetic intermediates toward more structurally complex natural products.

For the formation of dihydrobenzofurans, LBBA-1 can be used as a doubly activating phosphine catalyst: it both promotes the reaction and stabilizes the anionic intermediate

(Scheme 378). In this process, salicyl *N*-thiophosphinylimines bearing alkyl and halo substituents are suitable reaction partners, furnishing their dihydrobenzofurans in good to high yields. These dihydrobenzofurans are formed selectively as cis-isomers. When using electron-rich imines, the reaction proceeds to completion within a shorter period of time and gives higher yields of its products. In contrast, electron-deficient imines require longer reaction times at elevated temperatures and give lower product yields.

For the formation of aminochromans, the reaction tolerates *N*-thiophosphinylimines containing either electron-donating or -withdrawing substituents and provides its products as mixtures of cis- and trans-isomers (Scheme 379). When the aryl imines present electron-donating substituents, the reactions reach completion within shorter periods of time (entry 1). Interestingly, better diastereoselectivity was observed when employing electron-withdrawing imines (entry 2). Nevertheless, an overly strong electron-withdrawing nitro group terminates the reaction altogether (entry 3).

When salicylaldehyde is used as a reaction partner, strongly nucleophilic phosphines are not suitable for the formation of hydroxychromans; here, the less-nucleophilic tris(*p*-chlorophenyl)phosphine is a suitable catalyst (Scheme 380). Similar to the results described by Huang and Chen,[438] the product is formed exclusively with the *E*-configuration of its olefinic bonds. Reminiscent of the situation for the formation of dihydrobenzofurans and aminochromans, salicylaldehydes presenting electron-donating substituents react faster and give higher yields of their hydroxychromans (entry 1). Salicylaldehydes bearing electron-donating and -withdrawing substituents both produce mixtures of diastereoisomers, slightly favoring the trans-isomers. As in the formation of aminochromans, only a trace of product was isolated from the reaction of 5-nitrosalicylaldehyde (entry 3).

In the absence of the bifunctional catalyst LBBA-1, both amino and hydroxychromans can also be synthesized when reacting 2,3-butadienoate in the presence of tributylphosphine. When *N*-thiophosphinylimine was the reaction partner, a mixture of aminochromans was obtained, favoring the *E*-geometric isomer (Scheme 381). With hydroxychroman, *E*-isomers were produced exclusively when salicylaldehydes were used as reaction partners. In this transformation, the yield was highly dependent on the substituents and the position of the substituents. When an electron-donating group was positioned ortho or para to the phenolic OH group, the yields were better. Electron-withdrawing groups situated ortho or para to the phenolic OH group disfavored conjugate addition, leading to lower yields. In addition, an electron-donating group para to the imino unit hindered initial nucleophilic addition and afforded a lower product yield.

In addition to using salicylaldehydes to generate hydroxychromans, Shi expanded this reaction to include 2-(2-hydroxyphenyl)-2-oxoacetates as electrophilic partners (Scheme 382).[441] Various 2-(2-hydroxyphenyl)-2-oxoacetates were well suited to this reaction, providing their hydroxychromans in good yields, although the *E/Z* products were obtained in almost equal amounts.

Rather than using allenoates, Kumara Swamy and co-workers employed allenylphosphonates as reaction partners for the formation of aminochromans (Scheme 383).

[442] Unlike the situation in Shi's case, elevated temperatures were required to ensure good yields.

Switching the protecting group of the salicylaldimine from a thiophosphinyl to a tosyl group, Huang and co-workers disclosed an interesting twist to the reaction: generating a collection of functionalized benzoxazepines in good yields (Scheme 384).[443] The mechanism involves initial generation of the aminochromans, followed by intramolecular Michael addition to give benzoxazepines bearing various substituents on the benzene ring.

3.5.3. Michael Addition–γ-Umpolung [4 + 1] Annulation.—In 2015, Guo and Xiao disclosed a novel protocol for synthesis of *trans*-2,3-disubstituted indoline backbones via phosphine catalyzed [4 + 1] annulation of 2-tosylaminochalcones with allenoates (Scheme 385).[444] Using PBu_3 (30 mol %) as the catalyst and benzoic acid (20 mol %) as the additive, a wide range of *N*-Ts-substituted chalcones underwent [4 + 1] annulation with a diverse array of allenoates to deliver *trans*-2,3-disubstituted indolines in moderate to good yields and with excellent diastereoselectivities.

3.5.4. *N*-Hydroxyphthalimide–Allene [3 + 2] Annulation via Michael Addition–MBH Reaction.—The Zhou group developed a phosphine-catalyzed domino reaction of *N*-hydroxyphthalimides with allenoates (Scheme 386).[445] Using 10–50 mol % of triphenylphosphine as the catalyst, [3 + 2] annulations of allenoates with various ester groups and several *N*-hydroxyimides gave the corresponding products in moderate to good yields.

3.5.5. [4 + 2] Annulation via δ-Addition–MBH Reaction.—In 2017, aiming to synthesize 1,3-cyclohexadienes from readily available starting materials, Tong developed the phosphine-catalyzed [4 + 2] annulation of δ-acetoxy allenoates with ketones (Scheme 387).[446] With the use of 20 mol % of PPh_2Me in the presence of 1.2 equiv of iPr$_2$NEt, 2-substituted cyclopentane-1,3-diones reacted with δ-alkyl–substituted allenoates to give functional group-rich and structurally complex 1,3-cyclohexadienes in moderate to good yields. The reactions of δ-phenyl-substituted allenoates with diketones were very complicated. When using 20 mol % of PPh_3 in the presence of 1.2 equiv of K_2CO_3, the cyclic β-carbonyl amides reacted with δ-aryl-substituted allenoates, furnishing their tricyclic products in moderate to excellent yields through a process of [4 + 2] annulation/cyclic imide formation.

4. NUCLEOPHILIC PHOSPHINE CATALYSIS OF ACETYLENES

A wide variety of reactions occur when activated alkynes encounter nucleophilic phosphine catalysts. These reactions can be triggered by the phosphine interacting with the activated alkyne alone, resulting in rapid isomerization to the diene. In the presence of a nucleophile, the two major reaction pathways are Michael addition and α-umpolung addition. Ring-forming reactions take place to generate a diverse array of carbo- and heterocycles when dinucleophiles, electrophiles, or nucleophile–electrophiles are incorporated.

4.1. Phosphine-Catalyzed Isomerization of Alkynes to Dienes

As one of the pioneers in using phosphines as catalysts to initiate alkyne isomerization, Trost documented the first detailed study of such transformations.[177] The alkyne **268** undergoes facile nucleophilic addition in the presence of triphenylphosphine to create the vinyl phosphonium enoate **269** (Scheme 388). After proton transfer, the intermediate **270** exists in resonance with the anion **271**, which generates the vinylogous phosphonium ylide **272** through another proton transfer. This vinylogous phosphonium ylide equilibrates with the ylide **273**, leading to the intermediate **274** after proton transfer, with subsequent elimination of the phosphine affording the diene **275**. Yu and Salin's theoretical DFT calculations at the B3LYP level of theory with the 6-31+G(d) basis set support this proposed mechanism, suggesting that intermolecular proton transfers are favored because of the high energy barriers for the intramolecular proton transfer steps.[244,247,248,447] For the purposes of this Review, here we cover only selected literature reports. For more comprehensive coverage, Toy's detailed review regarding alkyne–diene isomerization should be consulted.[11]

Trost found that alkynes activated by ketone functional groups are more reactive than esters, followed by amides. Efficient isomerizations of alkynes of lower reactivity require elevated temperatures and acidic additives (Scheme 389). When both an alkynone and an alkynamide are present, selective isomerization of the former can be accomplished in the absence of acetic acid, leaving the latter undisturbed. In this reaction, the use of triphenylphosphine, a relatively less nucleophilic catalyst, is crucial because the more nucleophilic tributylphosphine produces more oligomeric product.

In the following year (1993), Guo and Lu also reported the isomerizations of alkynes, specifically less-reactive alkynoates and alkynamides (Scheme 390).[448] Instead of introducing an acidic additive, they used tributylphosphine, a more nucleophilic catalyst. Under their conditions, less-reactive yne–enones, alkynoates, and alkynamides were converted to the desired dienes in good yields, while avoiding the use of acetic acid, thereby making this process amenable to compounds carrying acid-sensitive functionalities.

Soon after Lu's report, Rychnovsky identified mild isomerization conditions, featuring phenol as an additive, that greatly decreased the reaction temperature and time for such transformations.[449] When phenol is used to facilitate the proton transfer steps, alkynoates can be isomerized to corresponding trienes in good yields without hydrolyzing any silyloxy or acetal groups. Although not catalytic, this reaction tolerates a variety of alkynoates featuring acid-sensitive groups, allowing them to undergo successful isomerizations while leaving their functionalities unperturbed (Scheme 391).

In 2011, Toy and co-workers reported the use of different types of phosphine catalysts for alkyne isomerizations (Scheme 392).[450,451] Instead of traditional triphenylphosphine or tributylphosphine, they employed solid-supported phosphines. Under the reaction conditions, various alkynoates and alkynones were isomerized to their desired dienoates and dienones in high yields. A notable advantage of using solid-supported phosphines is the ease of separation of the product from the catalyst during purification.

In 2005, Jiang and co-workers reported polymer-supported triphenylphosphine (PS-TPP)-catalyzed isomerizations of 2-ynones to (*E,E*)-2,4-dienones (Scheme 393).[452] In the presence of PS-TPP (20 mol %), various aryl or aliphatic 2-ynones underwent isomerization in toluene at 80 °C to generate (*E,E*)-2,4-dienones in moderate to good yields. PS-TPP could be recycled several times. In 2016, Toy, Kirschning, and co-workers prepared a bifunctional polymer bearing phosphine and phenol groups and applied it to the isomerization of activated alkynes to (*E,E*)-dienes in a flow process (Scheme 394).[453]

In 2015, Trost and Biannic reported a new method for the synthesis of 1,2-dihydropyridine derivatives via phosphine-catalyzed cycloisomerizations of propargylidenecarbamates (Scheme 395).[454] Using the bidentate phosphine DPPP (30 mol %) as the catalyst, a variety of propargylidenecarbamates underwent the alkyne isomerization/electrocyclization sequence to provide 2,6-disubstituted 1,2-dihydropyridines in yields ranging from 44 to 87% (Scheme 396). They demonstrated that the resulting 1,2-dihydropyridines could be transformed into a broad spectrum of useful derivatives, including piperidine, pyridine, or noncyclic carbamates.

4.2. Phosphine Catalysis of Alkynes with Nucleophiles

4.2.1. Phosphine-Catalyzed Michael Addition of Alkynes.—

After White and Baizer's first disclosure of Michael additions to alkenes through phosphine-initiated general base catalysis,[54] several research groups applied the concept to activated alkyne systems. Various pronucleophiles—from alcohols to oximes to thiols—are promising candidates, granting access to functionalized acrylate scaffolds. Carbon pronucleophiles having appropriate values of pK_a (e.g., substituted malonates) are also suitable partners for such alkyne Michael additions (Scheme 397).

Although White and Baizer reported the first phosphine-catalyzed alkene Michael addition around four decades ago,[54] it was not until 1993 that Inanaga disclosed the first phosphine-catalyzed alkyne Michael additions involving alcohol pronucleophiles and methyl propiolate.[455] The mechanistic pathway was believed to involve general base catalysis, similar to that for the Michael additions of alkenes initiated by a phosphine (Scheme 5). McIndoe's mechanistic study suggested that the resting state of the catalyst was a phosphonium species, with no free phosphine detectable.[456] Such evidence is consistent with the proposal of general base catalysis.

In Inanaga's study, primary alcohols reacted well, giving excellent yields of the Michael adducts exclusively in the *E*-geometry; a dramatic drop in yield occurred, however, when 2-octanol was used (Scheme 398). Further increasing the steric bulk to a tertiary alcohol resulted in no product formation. Relative to alcohols, thiols react with comparable efficiencies but with shorter reaction times.

In addition to simple alcohols and thiols, a large range of other pronucleophiles can be employed in these phosphine-catalyzed Michael additions. A survey of the literature reveals that α-hydroxyenones,[457,458] haloalcohols,[459] salicylaldehydes,[460,461] phthalimides,[462] pyrazoles,[463] and hydroxypyridines[464] can all undergo phosphine-catalyzed Michael additions.

Gladysz and co-workers reported a particularly interesting variation of the phosphine-catalyzed Michael addition employing a fluorous phosphine for ready catalyst recovery and easier purification (Scheme 399).[465] Using this approach, they obtained several different Michael adducts in good yields. Furthermore, the catalyst precipitated upon cooling the reaction mixture, simplifying catalyst recovery and separation.

Expanding the scope of the pronucleophiles, Yavari and Trofimov both independently described alkyne Michael additions using oximes (Scheme 400).[466,467] The oxygen center of the oxime motif serves as a good pronucleophile for phosphine-catalyzed Michael additions with mono- or disubstituted alkynes, leading to good yields.

When Inanaga first disclosed the alkyne Michael addition in 1993, the reaction was suitable only for primary and secondary alcohols. Ten years after Inanaga's report, Grossman demonstrated the efficient Michael additions of carbon pronucleophiles under phosphine catalysis.[468] HMPA, a strongly nucleophilic phosphine, was the choice of the promoter for these reactions (Scheme 401). When 3-butyn-2-one was employed as the electrophile, high yields were obtained of the Michael adducts, favoring the *Z*-isomers (entry 1). Intriguingly, the regioselectivity of the reaction can be altered, to select the *E*-isomer, when using ethyl propiolate as the Michael acceptor (entry 2). While the reaction proceeds smoothly, no addition product was observed when an alkylmalonate was invoked as the pronucleophile. Further studies revealed that the Michael addition of the alkylmalonate was significantly slower than the self-oligomerization of 3-butyn-2-one (entry 3). Furthermore, the reaction can be performed under solvent-free conditions, providing comparable yields and selectivities (entry 4).

Murafuji and co-workers developed a method for two-directional carbon chain elongation through phosphine-catalyzed reactions of allyl malononitrile with alkynoates (Scheme 402).[469] Allyl malononitrile and a diverse array of substituted alkynoates were treated with PCy_3 (20 mol %) and then heated under microwave irradiation at 180 °C for 1 h. The corresponding dienes presenting various substituents were obtained in moderate to good yields.

Mohtat and co-workers reported another Michael addition using carbon pronucleophiles, demonstrating an efficient method for preparing functionalized fumarates (Scheme 403).[470] Unlike most Michael additions, quinolinol underwent addition at the *o*-carbon, followed by rearomatization, to give the functionalized fumarates.

In addition to simple thiol pronucleophiles, Baharfar and Ramazani independently disclosed efficient Michael additions using 3-mercapto-2-butanone and 2-napthalenethiol (Scheme 404).[471,472] Although the reaction is catalytic, stoichiometric amounts of triphenylphosphine were used to ensure good yields of the functionalized *β*-mercaptoacrylates.

Further expanding on the alkyne Michael additions of thiols, Zhou and Lu reported, in a short Communication, the efficient phosphine-catalyzed Michael additions of ethanethiol with disubstituted alkynones to furnish functionalized mercaptochalcone derivatives.[473] Unlike the situation in Inanaga's reactions, the resulting mercapto Michael products favored the *Z*-olefinic geometry when aryl alkynones were used instead of methyl propiolate. Aryl

alkynones possessing either electron-withdrawing fluoride or electron-donating methoxy groups reacted well, giving their desired Michael adducts in excellent yields (Scheme 405). Notably, the reaction reached completion within a shorter period of time when an electron-withdrawing substituent was installed on the aryl ring system.

In 2014, Zhang and Li described phosphine-catalyzed regio- and stereoselective additions of various O-based nucleophiles (e.g., acetic acid, arylcarboxylic acids, phenols, 2-iodophenol) to yne-enones for the synthesis of highly functionalized 1,3-butadienes derivatives (Scheme 406).[474] Various yne-enones, including aromatic enones and aliphatic enones, underwent the reaction to furnish their corresponding products in moderate to good yields. An enyne with a formyl group and (*E*)-methyl 3-benzylidene-2-oxopent-4-ynoate were also suitable substrates.

In all of the previous examples, one molecule of pronucleophile reacted with one molecule of activated alkyne to furnish a bimolecular reaction product. In contrast, Endo designed a mild and efficient polymerization occurring through phosphine-catalyzed alkyne Michael addition using dinucleophile and dipropiolate systems to produce polymers in excellent yields (Scheme 407).[475–478] While a diol polymerized smoothly without regioselectivity issues, a dithiol produced a mixture of *E*- and *Z*-isomers, favoring the latter. The tributylphosphine-catalyzed dual Michael reactions between activated terminal acetylenes and dithiols afforded various dithioacetals in good yields. Notably, this method was applicable to the preparation of novel polymers containing dithioacetal units in their main chains.

4.2.2. Phosphine-Catalyzed Michael-Lactonization.—No annulations had been observed when employing mononucleophiles in alkyne Michael additions until Yavari reported the Michael-lactonization process in 1998. Although not catalytic, electrophilic aromatic substitution (formal Michael addition) of phenols occurs across the acetylenic bond in dimethyl acetylenedicarboxylate (DMAD), followed by intramolecular lactonization; such transformations remain unique and rare (Scheme 408).[479–481]

In 2011, Xue conducted a study of the reactions between alkynones and β-ketoesters and reported a phosphine-catalyzed Michael–lactonization as a means of preparing 2-pyrone derivatives.[482] In the presence of triphenylphosphine and potassium *tert*-butoxide, various pyrones were prepared in good yields (Scheme 409). With ethyl acetoacetate and ethyl *p*-bromobenzoylacetate as substrates, high yields of the target pyrones were obtained (entries 1 and 2). Sterically congested ethyl pivaloylacetate also underwent a smooth transformation to its pyrone, with only a minor loss in yield (entry 3). In contrast, a dramatic drop in reaction efficiency occurred when using diethyl malonate (entry 4).

4.2.3. Phosphine-Catalyzed Michael–Heck Annulation.—Over the years, chemists have been seeking simple and rapid transformations for converting simple starting materials into complex molecular architectures. Toward this end, Fan and Kwon demonstrated an efficient annulation strategy for generating highly functionalized alkylidene phthalans through Michael–Heck reactions.[483] Unlike many other single-step phosphine-catalyzed reactions, the Michael–Heck reaction is a two-step single-flask operation. Notably,

triphenylphosphine displays dual-reactivity in this reaction: first acting as a nucleophilic catalyst and then as a ligand for palladium. Under the optimized conditions, *o*-iodobenzyl alcohols and activated alkynes furnished various alkylidene phthalans in good to high yields (Scheme 410). With 2-iodo-3-methyl benzyl alcohol as the reaction partner, an excellent conversion to the product was observed with good stereoselectivity (entry 3). Sterically demanding *o*-iodobenzyl alcohol bearing a benzylic cyclopropyl group also underwent a smooth transformation to its desired phthalan (entry 4). Interestingly, aside from carbonyl groups as activators, a sulfone was also well suited to the reaction conditions, providing its sulfonated phthalan in moderate yield (entry 7).

Further demonstrating the utility of these versatile Michael–Heck reactions, Fan and Kwon completed the syntheses of a group of rare fungal metabolites isolated from the genus *Cladosporium* sp.: 3-deoxyisoochracinic acid (**277**), isoochracinic acid (**278**), and isoochracinol (**279**) (Scheme 411). Starting from the phthalan **276**, global debenzylation and olefin hydrogenation yielded the natural metabolite 3-deoxyisoochracinic acid (**277**) in quantitative yield. Subsequently, benzylic oxidation of 3-deoxyisoochracinic acid (**277**) with acetic acid and chromium trioxide suspended in dichloromethane provided isoochracinic acid (**278**). Reduction of the carboxylic acid moiety, through chemoselective reduction with borane–tetrahydrofuran complex, delivered isoochracinol (**279**).

In 2015, Kwon and Fan further extended their methodology to prepare alkylidene indane and indanone derivatives (Scheme 412).[484] In the presence of PPh_3 (20 mol %), a wide range of 2-iodobenzylmalonates or 2-iodobenzoylacetates underwent Michael additions to electron-deficient alkynes, and then the reaction mixtures were treated with $Pd(OAc)_2$ to generate the alkylidene indane and indanone derivatives in moderate to excellent yields and with good stereoselectivities. The reaction tolerated an array of substrates and led to the generation of more than 20 compounds. The synthetic utility of this Michael addition–Heck cyclization sequence was demonstrated in the preparation of sulindac, a nonsteroidal anti-inflammatory drug (Scheme 413).

4.2.4. Phosphine-Catalyzed *α*-Umpolung Addition.—Over the years, a popular strategy to generate complex acrylate motifs has been alkyne Michael addition through phosphine-initiated general base catalysis. Analogous to phosphine catalysis of allenes with nucleophiles, *α*-umpolung reactions are also dominant pathways for gaining access to functionalized acrylates. In this realm, various pronucleophiles can be used in *α*-umpolung additions (Scheme 414).

When treating activated acetylenes with pronucleophiles in the presence of a phosphine in an acetic acid buffer, nucleophilic *α*-umpolung addition occurs. As one of the pioneers of allene *γ*-umpolung reactions, Trost documented the first alkyne *α*-umpolung addition in 1997 when using phthalimide and sulfonamides as pronucleophiles, providing access to *α*-dehydroamino acids.[485] Reminiscent of the additive used in allene *γ*-umpolung additions, an unusual mixture of sodium acetate and acetic acid was also implemented to facilitate efficient addition. When ethyl propiolate was used for preliminary screening, an equal ratio of the Michael product and the *α*-umpolung product was observed (Scheme 415). The competing Michael addition was averted when using *β*-substituted propiolates. In addition to

phthalimides, alkyl and aryl sulfonamides are tolerated in these reactions, albeit providing their products in lower yields.

Yavari and co-workers prepared 2-(2-oxopyridin-1(2*H*)-yl)but-2-enedioates through triphenylphosphine-catalyzed addition of 2-hydroxypyridine to dialkyl acetylenedicarboxylates in refluxing chloroform (Scheme 416).[486] High yields and moderate regioselectivities were accomplished.

In the same year, Yavari and co-workers studied the phosphine-promoted addition reactions between ethyl propiolate and acetanilides or arylsulfonylanilides (Scheme 417).[487] Treatment of ethyl propiolate with various acetanilides in the presence of PPh_3 (10 mol %) gave α-substituted acrylates and β-substituted acrylates as the major and minor products, respectively, in excellent yields and with moderate regioselectivities. In addition, under otherwise identical conditions, the reactions of arylsulfonylanilides led only to β-substituted acrylates (Michael addition products) in excellent yields.

Taran and Xue independently found that activated carbon and oxygen pronucleophiles are also applicable in α-umpolung reactions. 1,3-Dicarbonyl compounds can be used to generate functionalized acrylates through the α-umpolung strategy (Scheme 418).[488–490] When employing the relatively less reactive diethyl malonate, a greater amount of phosphine catalyst was required to expedite the reaction (entry 2). Although good yields of α-umpolung products were obtained using ethyl propiolate in combination with 1,3-dicarbonyl compounds, prolonged reaction times were required when applying disubstituted alkynes (entry 3). Intramolecular α-umpolung addition was explored after tethering oxygen pronucleophiles to activated alkynes; annulations occurred to generate derivatized tetrahydrofuran-3-ones.[491,492] An excellent yield of the annulation product was isolated when a phenyl group served as a steric block at the β-position of the alkynone (entry 4). In the absence of the phenyl group, the efficiency of the reaction plummeted, possibly because of intramolecular Michael addition (entry 5). Notably, α-umpolung addition occurred (5-*exo*-dig) with phosphine catalysis to give cyclic five-membered ring systems (entry 4 and 5), whereas gold catalysis provided six-membered rings (6-*endo*-dig).

Xue and co-workers also investigated phosphine-catalyzed additions of *o*-hydroxyacylphenols to terminal alkynoates for the synthesis of functionalized 1,4-pentadienes (Scheme 419).[493] In the presence of 50 mol % of PPh_3, a variety of *o*-hydroxyacetophenones were employed in the α-addition reaction with terminal alkynoates, providing functionalized 1,4-pentadidenes in moderate yields. When the methyl group of the ketone was replaced by a longer alkyl group, single α-addition products were obtained in moderate yields under the standard conditions.

A polymer-supported tertiary phosphine has also been prepared for the α-additions of carbon nucleophiles to α,β-unsaturated compounds (Scheme 420).[494] When using the phosphine **JJ-TPP** (10 or 8 mol %) as the catalyst, various carbon nucleophiles (e.g., 1,3-dicarbonyl compounds, acetoacetates, malonates) reacted with α,β-unsaturated compounds (e.g., ynones, Michael acceptors) at room temperature under solvent-free conditions,

delivering their corresponding *E*-isomeric α-adducts in isolated yields of 18–90%. The catalyst could be recycled and reused several times, retaining its good activity.

Li and co-workers reported a phosphine-catalyzed intramolecular α-umpolung addition.[495] Under catalysis with 10 mol % of PPh_3, various propiolamides underwent the intramolecular addition to give β-lactams in moderate to excellent yields. α-Amino esters, α-amino ketones, and α-amino nitrile were suitable substrates (Scheme 421). In addition, 4,4-disubstituted products could also be synthesized.

In 2016, Ramasastry and co-workers investigated the intramolecular α-umpolung additions of ynones for the synthesis of a broad range of cyclopent[*b*]annulated heteroarenes (Scheme 422).[496] In the presence of 10 mol % of PCy_3, ynones tethered to indole derivatives gave their corresponding products in moderate to good yields and with excellent *E/Z* selectivities. In addition, ynones tethered to 2-methyl benzothiophenes and benzofurans were also appropriate substrates, affording their desired products in moderate to excellent yields and with good *E/Z* selectivities.

Taran and co-workers reported an efficient α-umpolung addition of cyanide anions to alkynoates (Scheme 423).[497] The reactions proceeded with in situ release of the cyanide anion from a cyanohydrin and gave good yields of functionalized α-cyanoacrylates.

Asghari and co-workers reported another interesting α-umpolung addition, using kojic acid as the pronucleophile (Scheme 424).[498] Under the reaction conditions, addition occurred at the α-position, generating vinylated kojic acids in good yields.

In 2016, Jia and Xie developed the phosphine-catalyzed α-addition of o-carborane to alkynoates to prepare a series of 1-alkenyl-o-carboranes (Scheme 425).[499] Under catalysis with $P(4\text{-}MeOC_6H_4)_3$ (10 mol %), o-carborane underwent α-additions to a series of alkynoates, thereby providing functionalized o-carboranes in low to excellent yields.

In addition to carbon and oxygen pronucleophiles, phosphorus[500–502] and nitrogen[503,504] pronucleophiles are also suitable agents for phosphine-catalyzed α-umpolung additions (Scheme 426). The use of diethyl phosphonate as the pronucleophile for the α-umpolung reactions generated bisphosphonate or phosphonate compounds. Furthermore, Yavari[503] and Hekmatshor[504] independently showcased the use of heterocycles and amides as suitable pronucleophiles for the reaction.

In 2012, an intramolecular α-umpolung pathway was revealed for constructing various 3-oxanones and 3-oxepanones.[505] Peczuh and co-workers demonstrated the use of intramolecular α-umpolung addition of alkynyl hemiketals through nucleophilic catalysis with a phosphine, adding a novel pathway to the repertoire of phosphine-mediated reactions. In this transformation, nucleophilic attack occurs upon opening of the alkynyl hemiketal (Scheme 427). Nucleophilic addition into the *seco*-alkynyl hemiketal, followed by deprotonation, generates the zwitterionic species **280**. Subsequent intramolecular α-umpolung addition and elimination of the phosphine catalyst affords the functionalized 3-oxanone **281**.

For efficient intramolecular α-umpolung addition to occur, a sterically demanding substituent must be positioned at the alkyne terminus (Scheme 428). Good yields of the 3-oxanones were isolated from densely oxygenated substituents (entries 1 and 2). The reaction can be extended to the formation of larger ring systems, giving a 3-oxepanone with good efficiency (entry 3).

In the absence of the sterically hindering phenyl substituent at the terminus of the alkyne, dimerization of the 3-oxanone occurs through a hetero-Diels–Alder reaction, delivering a higher level of molecular complexity (Scheme 429). Here highly functionalized spiroketals were obtained in good yields under mild reaction settings (entries 1–3).

Similar to alkyne Michael additions, this annulation process seldom occurs with mononucleophiles. On the other hand, Xue reported that 1-(2-hydroxyaryl)-3-arylpropane-1,3-dione undergoes α-umpolung addition as a pronucleophile into alkyl propiolates, the products of which then cyclize to give functionalized chromones or open up to give vinyl esters.[506] The formation of both a vinyl ester and a chromone suggests that the initial addition of triphenylphosphine into ethyl propiolate gives a vinyl phosphonium enoate that activates the 1-(2-hydroxyaryl)-3-arylpropane-1,3-dione to form the ion pair **282** (Scheme 430). A sequence of α-umpolung addition, proton transfer, and intramolecular cyclization generates the intermediate **283**. At this point, elimination of the phosphine and water occurs if an alkyl substituent is present in the system, affording the functionalized chromone **284**. If an aryl substituent is installed, then acyl transfer occurs to yield the vinyl ester **285**.

Aryl systems with methoxy groups installed at the meta- and para-positions afforded their products in better yield (Scheme 431, entry 1). The reverse trend was observed when 1-(2-hydroxyphenyl)-3-*p*-fluorophenylpropane-1,3-dione was subjected to the reaction conditions (entry 2). Other propiolates (e.g., methyl and benzyl propiolates) provided their vinyl esters in mediocre yields (entries 3 and 4).

Looking at the formation of the chromones, the reaction efficiency remained low across various alkyl substituents (Scheme 432). Once the substituent deviated from a hydrogen or a methyl group, the yield of the chromone dropped dramatically (entries 2–4). Moreover, the substitution pattern tolerated very few variations and limited the diversity of the chromones.

4.2.5. Phosphine-Catalyzed *anti*-Carboboration.—

In 2014, Sawamura and co-workers disclosed an *anti*-carboboration of alkynoates catalyzed by a phosphine (Scheme 433).[507] Treating an alkynoate with tributylphosphine generates the phosphonium enoate **286**. In the presence of borane, complexation and intramolecular α-umpolung addition occur to give the intermediate **287**. Release of the phosphine catalyst affords the β-borylacrylate **288**.

Various arylalkynoates and boranes are well suited to the reaction, providing a range of functionalized β-borylacrylates (Scheme 434). Both alkyl and aryl boranes gave good yields of their products. Providing synthetic leverage, the products can be functionalized further through transition metal–catalyzed cross-coupling reactions.

Under phosphine catalysis, *anti*-selective vicinal silaboration and diboration of the C–C triple bonds of alkynoates also occurred to afford β-boryl-α-silyl acrylates and α,β-diboryl acrylates, respectively (Scheme 435).[508] Phosphine-catalyzed addition of B_2pin_2 to terminal alkynes was also investigated under photoirradiation (Scheme 436).[509] The light source and solvent had remarkable influences on the yields and trans/cis ratios. Unfortunately, aromatic alkynes (e.g., phenylacetylene) did not react under either of these two conditions.

4.3. Phosphine Catalysis of Alkynes with Dinucleophiles

Annulation is uncommon in both alkyne Michael and α-umpolung additions with monopronucleophiles, unless they occur in an intramolecular manner. Using dipronucleophiles, however, many pathways are possible, granting access to various heterocyclic compounds. The major pathways in this category are double-Michael and α-umpolung-lactonization reactions. Many dinucleophiles, activating groups, and phosphines participate well in this domain of phosphine catalysis (Scheme 437).

4.3.1. Phosphine-Catalyzed Double-Michael Annulation.—

In 1999, Grossman, one of the leaders in the area of Michael addition, was the first to demonstrate the concept of annulation through a double-Michael reaction.[510] His studies inspired other research groups to examine this novel phosphine-catalyzed annulation process, providing access to carbocyclic and heterocyclic ring systems. Employing ethyl 2,6-dicyano-5-oxoheptanoates as carbon dinucleophiles and 3-butyn-2-ones as Michael acceptors, good yields of cyclohexanones were isolated after the double-Michael addition sequence (Scheme 438). The formation of functionalized cyclopentanones was also viable from ethyl 2,5-dicyano-4-oxohexanoate, albeit in moderate yields.

Seven years after Grossman's first report, Yavari described a heterocyclic variant of the double-Michael reaction, using catechol as the dinucleophile.[511] As a proof of concept, a benzodioxole was prepared in low yield when using a stoichiometric amount of triphenylphosphine (Scheme 439). Unfortunately, the reaction was very inefficient, giving a low yield of product and displaying limited substrate variance; therefore, it does not possess great synthetic utility.

It was not until 2007 that Kwon documented a versatile annulation strategy using the concept of double-Michael addition with mixed dinucleophiles to generate 10 distinct heterocyclic compounds with excellent efficiency.[512–514] Many heterocyclic ring structures can be constructed from dinucleophiles reacting through a double-Michael pathway. Employing amino acid-derived dinucleophiles, enantiomerically pure oxazolidines, thiazolidines, and pyrrolidines were formed with excellent yields and diastereoselectivity (Scheme 440). Switching to aromatic dinucleophiles, this mixed double-Michael strategy could also be used to synthesize indolines, dihydropyrrolopyridines, benzimidazolines, tetrahydroquinolines, tetrahydroisoquinolines, dihydrobenzo-1,4-oxazines, and dihydrobenzo-3,1-oxaines. In this reaction, the use of DPPP is crucial to ensure high yields, presumably because of the beneficial anchimeric assistance from the bisphosphine in stabilizing phosphonium ions. The reactions of aromatic dinucleophiles are facilitated when introducing acetic acid and sodium acetate as additives to expedite efficient proton transfers.

The mixed double-Michael reaction appears to be the most versatile annulation process for generating heterocyclic compounds in the realm of phosphine catalysis with activated alkynes and dinucleophiles.

Although Lu and co-workers had reported asymmetric phosphine-catalyzed Michael additions, enantioselective double-Michael reactions remained elusive. Khong and Kwon synthesized several proline-derived chiral phosphines as potential catalysts for an asymmetric double-Michael reaction (Scheme 441).[515] Nevertheless, they observed low enantioselectivities, with the chiral phosphine **P80** being one of the better catalysts.

In 2017, Hooper, Lupton et al. reported a [5 + 1] annulation of ynone/Michael acceptors with sulfonamides, affording isoquinolones, pyrrolidinones, and pyrrolopiperazines (Scheme 442).[516] Variations of the sulfonamide partner, the β-substituent of the ynone, the Michael acceptor, and the linker could be tolerated, with the desired products obtained in moderate to good yields and with good Z/E ratios. Nevertheless, use of an aliphatic linker and a pyrrole linker resulted in moderate yields. In addition to ester moieties, the Michael acceptor could also be modified with nitrile units. The asymmetric variant was viable when using a chiral phosphine, but the enantioselectivity was poor.

4.3.2. α-Umpolung–Michael [*n* + 2] Annulation.—

While looking into the γ-umpolung–Michael annulation, Liu discovered a competing reaction pathway giving a different regioisomer of thiazoline.[228] After extensive structural elucidation, this regioisomer of thiazoline appeared to have formed through a α-umpolung–Michael pathway (Scheme 443). The proposed reaction mechanism involves initial α-umpolung addition followed by Michael addition to release the phosphine catalyst, affording the corresponding thiazoline in moderate yield.

Analogous to Liu's formation of the thiazoline, in the same year Lu disclosed the formation of piperazines and 1,4-diazepanes through α-umpolung–Michael annulation pathways.[227] With nitrogen dinucleophiles, functionalized piperazines and 1,4-diazepanes were afforded in high yields (Scheme 444). Under the optimized conditions, both alkynoates and alkynones are suitable reaction partners, rendering piperazines and 1,4-diazepanes with high efficiency (entries 1–3). In all cases, the reactions were complete within 24 h, with the exception that the 1,4-diazepane required a prolonged reaction time.

In addition to thioamides and diamines, Yavari and co-workers demonstrated that α-nitroacetates could be used as dinucleophiles for the formation of functionalized isoxazoles (Scheme 445).[517] The in situ-generated zwitterion **289** activates the pronucleophile for subsequent α-umpolung addition, generating the intermediate **290**. Proton transfers, elimination of the catalyst, and aromatization led to the isoxazole **291**.

Although various isoxazoles were isolated in good yields, the scope of the reaction was very limited, requiring the use of DMAD-type substrates featuring alkyl esters (Scheme 446).

4.3.3. S_N2'/S_N2–Michael Annulation.—

One of the rare occurrences in phosphine catalysis is the formation of functionalized furans. In 2011, Tong reported the first example of phosphine-catalyzed furan synthesis from an alkynoate and a carbon pronucleophile.[518]

In Tong's proposed mechanism, addition of triphenylphosphine generates the familiar vinyl phosphonium enoate **292**, which further activates the pronucleophile **293** through deprotonation (Scheme 447). Subsequent net α-umpolung addition, accompanied by the loss of acetate, gives the intermediate **294**. Formation of the phosphonium dienolate **295** is achieved through deprotonation of **294** by an acetate anion. With anion equilibration, the dienolate **296** is generated from **295**. Through subsequent Michael addition, the dienolate **296** provides a gateway to the functionalized furan **297**.

Under the optimized conditions, high yields of derivatized furans were obtained from various carbon pronucleophiles, including α-cyanoacetophenone and acetylacetone (Scheme 448). The best results were achieved when electron-withdrawing α-cyano ketones were employed (entries 1 and 2). The relatively less activated acetylacetone provided a substantially lower yield (entry 3). When using γ-disubstituted alkynoates, various alkyl groups could be placed on the furan system, albeit in lower yield (entry 4).

Adding to the repertoire of phosphine-catalyzed furan syntheses, an alternative reaction pathway was observed when employing methyl 4-bromo-2-butynoate as a reaction partner. Tong demonstrated that functionalized trisubstituted furans could be constructed through an alternative route (Scheme 449).[518] From methyl 4-bromo-2-butynoate, similar activation of the carbon pronucleophile occurs to generate the ion pair **298**. Upon coordination with a silver salt, formal γ-umpolung addition occurs to afford the intermediate **299**. Keto/enol tautomerization and Michael addition regenerate the phosphine catalyst, giving the intermediate **300**. After rearomatization, the trisubstituted furan **301** is obtained through a formal γ-umpolung–Michael process.

A variety of trisubstituted furans can be accessed with good efficiencies under the optimized conditions. Similar to the aforementioned pathway (Scheme 447), electron-withdrawing α-cyano ketones provided better conversion to their products (Scheme 450). Once the pronucleophile was switched to acetylacetone, the yield decreased significantly. Fused ring systems could also be obtained from cyclohexan-1,3-dione, albeit with decreased efficiency.

4.3.4. α-Umpolung–Lactonization/Lactamization.—

In addition to the double-Michael and α-umpolung–Michael annulation pathways described above, Yavari reported the successful formation of benzoxazines from 2-hydroxyanilines as dinucleophiles when using a stoichiometric amount of a phosphine, in a process occurring through an α-umpolung–lactonization pathway.[511] Later, Taran expanded the scope and the utility of α-umpolung–lactonization using diols, catechols, mercapto alcohols, thioureas, and dithiocarbamates as effective dinucleophiles, granting access to a series of heterocyclic compounds with high efficiency (Scheme 451).[519, 520] As depicted in Scheme 444, various dinucleophiles afforded their desired heterocyclic compounds in good yields. With relatively less-nucleophilic catechol as the dinucleophile, refluxing was required to generate the benzodioxane in a yield slightly lower than that of the product formed from butane-1,3-diol (entries 2 and 3). When employing thioureas, elevated reaction temperatures were needed, especially in the case of *N*,*N*-diphenylthiourea (entries 5 and 6). Dithiocarbamate, generated in situ, resulted in a good yield of the corresponding thiazolidinone (entry 7).

Further expanding the scope of the α-umpolung–lactamization with thioureas, Taran disclosed a method for preparing functionalized thiohydantoins in good yields.[521] In the reactions of unsymmetrical thioureas, various thiohydantoins were prepared from ethyl propiolate bearing a phenyl substituent at the alkyne terminus, preventing potential undesired Michael addition. With *N*-methyl-*N*′-methylthiourea and *N*-methyl-*N*′-methylthiourea as reaction partners, good conversions to the corresponding thiohydantoins occurred, forming single regioisomers (Scheme 452, entries 1 and 2). Interestingly, a mixture of thiohydantoins **302**/**303** was isolated when employing *N*-methyl-*N*′-*p*-methoxybenzylthiourea (entry 3). The regioselectivity was more pronounced in the case of a thiourea derivative bearing an aromatic substituent (entry 4). Although a mixture of regioisomers was observed, the selectivity could be tuned to select for the other isomer when using an aromatic thiourea carrying a bulky cyclohexyl group (entry 5).

As alternatives to the use of thioureas as dinucleophiles, Alizadeh and Taran independently disclosed the formation of functionalized hydantoins[522] and imidazolones[523] (Scheme 453). Alizadeh and co-workers took the approach of employing in situ-generated ureas as dipronucleophiles for the annulation, with stoichiometric phosphine to ensure high efficiencies. Taran also used various ureas as substrates to generate a collection of functionalized imidazolones, tolerating various aryl substituents, in high yields.

Although limited in substrate scope, Nasiri and co-workers employed vinylogous amides as potential carbon–nitrogen di-pronucleophiles to generate tetrahydroindole-2,4-diones (Scheme 454).[524] They achieved moderate yields from vinylogous amides with minimal functionalization.

4.4. Phosphine Catalysis of Alkynes with Electrophiles

4.4.1. Phosphine-Catalyzed DMAD–Aldehyde/Ketone γ-Butenolide Synthesis.—

Many annulations of electrophiles occur in the presence of nucleophilic phosphine. In 1966, Winterfeldt documented the first example, using DMAD in combination with benzaldehyde, of a functionalized butenolide formed by means of phosphine catalysis.[3] His proposed mechanism proceeds with nucleophilic addition of triphenylphosphine into DMAD (**304**) to generate the vinyl phosphonium enoate **305**; Johnson and Tebby had discovered such zwitterionic species back in the early 1960s (Scheme 455).[525,526] Addition of the enolate **305** into benzaldehyde (**306**) induces the formation of the allylic phosphonium alkoxide **307**, which undergoes intramolecular lactonization, followed by methoxide incorporation and elimination of the phosphine catalyst, to afford the butenolide **308**.

Since Winterfeldt's isolated example in 1966, no major developments were reported for several years in the field of phosphine catalysis of alkynes with electrophiles. It was not until 1996 that Nozaki and Takaya broadened the scope of DMAD annulations with the use of aryl α-keto esters.[527] These highly activated aryl α-keto esters promoted the formation of functionalized butenolides, expanding the reaction to incorporate electrophiles other than benzaldehyde (Scheme 456). In this transformation, an electron-withdrawing *p*-nitrophenyl substituent grants good reaction efficiency, giving a high yield of the target butenolide (entry 1). Switching the aryl portion to a less-activating phenyl group, the yield of the reaction diminished dramatically (entry 2). When benzoyl cyanide was applied as the electrophile, an

electron-donating methoxy group could be implemented without significantly affecting the efficiency, providing appreciable yields (entries 3 and 4). In addition to α-keto esters and benzoyl cyanides, trifluoromethyl ketone was also applicable under the reaction conditions, giving a good yield of its annulation product (entry 5).

More recently, Shi and Bayat independently disclosed the formation of functionalized γ-butenolides from DMAD and arylaldehydes (Scheme 457).[528,529] Although both electron-poor and -rich arylaldehydes underwent this reaction, only moderate yields were obtained with limited substrate scope.

In contrast to the traditional Winterfeldt reaction, Lu and co-workers employed arylaldimines as their electrophiles, forming functionalized pyrrolin-2-ones in excellent yields (Scheme 458).[326]

Further expanding the scope of the Winterfeldt reaction, in 1997 Nair introduced the concept of using 1,2-diketones as electrophiles to generate derivatized butenolides.[530–532] They demonstrated that polyaromatic 1,2-diketones were suitable for this transformation, giving good yields of their corresponding butenolides (Scheme 459). Unfortunately, the reaction proceeds with poor regioselectivity, providing an equal mixture of two regioisomers, when naphthalene-1,2-dione is a reaction partner (entry 2). To ensure better conversion, symmetrical diketones can be used to avoid regioselectivity issues. In addition to 1,2-diketones, benzoquinone—a conjugated 1,4-diketone—also served as a good reaction candidate, affording the spirobutenolide in high yield (entry 3).

The Winterfeldt reaction can also be performed using benzofuran-2,3-diones and phthalic anhydrides as electrophile partners (Scheme 460).[533, 534] Esmaili and Bayat demonstrated the synthesis of spirobenzofuran-2-ones and spirophthalans with good efficiencies and tolerance for various substituents on the benzene ring system.

4.4.2. Phosphine-Catalyzed DMAD–Ketone Oxetene Synthesis.—Asghari and Zhu independently disclosed the formation of functionalized oxetenes through phosphine catalysis between alkynoates and ketones (Scheme 461).[535,536] Although Asghari was the first to report the reaction, Zhu greatly improved its scope and reaction efficiency. Under the optimized conditions, various arylaldehydes were suitable for the reaction, providing good yields of their products. The reaction is proposed to be catalytic, but a stoichiometric amount of phosphine was used to ensure good efficiencies.

4.4.3. Phosphine Catalysis of DMAD and Isobenzothiazoline to Form Benzothiazepine.—The electrophiles used frequently for annulation are aryl aldehydes, α-keto esters, benzoyl cyanides, trifluoromethyl ketones, and 1,2-diketones. Rarely, however, have sulfenamides been used as electrophiles in phosphine catalysis. In 2009, Reboul demonstrated the nucleophilic ring opening of a sulfonamide with the phosphonium zwitterion generated from triphenylphosphine and DMAD.[537] According to his mechanism, nucleophilic addition occurs across the activated triple bond to produce the phosphonium zwitterion **305** (Scheme 462). This zwitterion undergoes addition into the electron-deficient sulfur center of the sulfonamide **309**, leading to a ring opening event. Upon sulfur–nitrogen

bond incision, the anion **310** proceeds to afford the functionalized benzothiazepine **311** by means of Michael addition.

Although the scope of this transformation was limited, the study demonstrated the possibility of sulfenamides behaving as electrophiles in phosphine-catalyzed annulations. To promote the efficiency of this reaction, a stoichiometric amount of triphenylphosphine was administered, resulting in a good yield of the target benzothiazepine (Scheme 463, entry 1). While the reaction operates through phosphine catalysis, better results were discerned when using a catalytic amount of cesium fluoride. In addition to DMAD, dicyanoacetylene also formed its desired product comparably (entry 2). In contrast, no reaction occurred when employing the relatively less activated di-*tert*-butylsulfonylacetylene (entry 3).

4.4.4. Phosphine-Catalyzed DMAD–Imine Benzo[*g*][1,2,3]oxathiazocine Synthesis.—Similar to the synthesis of oxetenes, dihydroazetes can be formed when using arylaldimines in place of arylaldehydes. In 2014, Guo and co-workers reacted cyclic sulfamate-derived imines with alkynoates in the presence of a phosphine. Interestingly, the expected dihydroazetes underwent formal retro-[2 + 2] ring opening to give functionalized benzo[*g*][1,2,3]oxathiazocines (Scheme 464).[538] The reaction is highly efficient, tolerating cyclic imines with various substitution patterns.

4.4.5. Phosphine-Catalyzed α'-Addition–α-Umpolung Annulation.—While working on phosphine-catalyzed polymerizations of dinucleophiles and di-propiolates, Tomita and Endo disclosed the serendipitous discovery of bisalkynones undergoing intramolecular annulation, through phosphine-catalyzed α'-aldol additions and subsequent α-umpolung reactions, to give functionalized bicyclic furanones in good yields (Scheme 465).[539] This tandem α'-addition–α-umpolung addition reaction, known as the Tomita zipper cyclization, has since been applied to a variety of electrophiles, including ketones, α,β-unsaturated carbonyl compounds, imines, and azomethine imines.

Reacting various bisalkynones with tributylphosphine generates bicyclic furanone systems in good yields (Scheme 466). The reaction proceeds with complete stereocontrol, forming bicyclic ketones as single diastereoisomers (*Z*-olefin geometry with cis-ring juncture). Although both 5,5-and 5,6-fused systems can be formed through this pathway, the product was no longer obtained when the tether length was increased further.

In contrast to the reactions reported in the previous sections (Sections 4.4.1–4.4.4.), a novel alkyne–isatin [3 + 2] annulation occurs when switching DMAD to 3-butyn-2-one.[540] In this reaction, the highly activated DMAD is not required to trigger the annulation event. In 2012, Shi reported the formation of 3-spirotetrahydrofuran-3-one-2-oxindole derivatives when treating 3-butyn-2-one and isatins with methyldiphenylphosphine. In the proposed mechanism, methyldiphenylphosphine undergoes nucleophilic addition to 3-butyn-2-one, providing the vinyl phosphonium anion **312** (Scheme 467). After proton transfer, annulation occurs with isatin to give the intermediate **313**. Upon elimination of the catalyst, the 3-spirotetrahydrofuran-3-one-2-oxindole **314** is afforded.

Under a suitable environment, 3-spirotetrahydrofuran-3-one-2-oxindole derivatives can be prepared in high yield (Scheme 468). An isatin derivative bearing a 5-methoxy group reacted smoothly to give an excellent yield of its product, whereas a lower yield of product was isolated from the isatin presenting a 7-bromo substituent (entries 1 and 2). Replacing the benzyl protecting group on the isatin with an electron-withdrawing Boc group resulted in high reaction efficiency (entry 3). While no significant deviation in yield occurred when varying the protecting group, a sterically demanding trityl group did hinder the conversion to product (entry 4).

In the same year as the original disclosure, Shi and co-workers also reported an asymmetric variant of the aldol–α-umpolung annulation (Scheme 469).[541] Unlike the racemic reactions, however, these transformations employed (+)-DIOP ((+)-**P46**) to produce spirooxindoles in moderate yields and enantioselectivities. Furthermore, a highly sterically demanding anthracenylmethyl group was required, along with reduced temperatures, to ensure these moderate selectivities.

Around the same time, Huang and co-workers also disclosed an efficient method for synthesizing functionalized spirooxindoles from alkynones and isatins (Scheme 470).[542] In contrast to Shi's approach, they added benzoic acid into the reaction mixture to increase the yields. Accordingly, spirooxindoles bearing various substituents (e.g., *p*-methylphenyl and *p*-fluorophenyl groups) were obtained in high yields.

Recognizing Tomita's work in 2003, Fu saw the potential synthetic utility of the transformation in forming functionalized diquinanes.[543] Designed after Tomita's yne-dione system, here a [3 + 2] annulation event occurred involving sequential Michael and α-umpolung additions (Scheme 471). In Fu's proposed mechanism, initial nucleophilic addition provides the enolate **315**, which undergoes Michael addition and then α-umpolung addition to give the ylide **316**. Elimination of the catalyst generates the diquinane derivative **317**.

With tributylphosphine as the catalyst, functionalized diquinanes and hydrindanes can be synthesized readily with good efficiencies (Scheme 472). Phenyl propargyl ketone is well suited to the reaction conditions, giving a high conversion to the product diquinane (entry 1). Furthermore, a sterically demanding cyclohexyl substituent on the terminal alkyne had no major effect on the reaction efficiency (entry 2). Although a slight drop in yield was observed, a hydrindane motif was isolated after elongating the carbon tether (entry 4).

In 2013, Zhou and co-workers demonstrated the synthesis of functionalized spirooxindoles from an alkynone and enynes derived from isatins (Scheme 473).[544] Similar to the previous examples, this reaction involves annulation without participation of the extra unit of unsaturation. Regardless of the structure of the inert acetylene unit, the reaction gave good yields of the spirooxindoles.

In the same year, Ramachary and co-workers prepared a variety of cyclopentone-fused spirooxindoles through phosphine-catalyzed formal [3 + 2] cycloadditions (Scheme 474).[545] Treatment of isatin-derived activated olefins with various ynones in the presence of an appropriate tertiary phosphine [Ph_3P, (p-$FC_6H_4)_3P$, or (p-$MeOC_6H_4)_3P$, 20 mol%] in

dichloroethane (DCE) generated the corresponding cyclopentone-fused spirooxindoles in moderate to good yields with moderate to excellent diastereoselectivities.

To further expand the area of Michael–*α*-umpolung annulation, the Huang group used arylideneindan-1,3-diones as reaction partners to produce a collection of functionalized spiroindan-1,3-diones in good yields (Scheme 475).[546] The reaction tolerates arylideneindan-1,3-diones bearing various substituents (e.g., *m*-bromophenyl, *o*-tolyl, and *p*-nitrophenyl groups) while maintaining good efficiencies. With a strongly electron-withdrawing nitro group, however, the yield decreased slightly.

In 2017, Guo and co-workers developed a $MePPh_2$-catalyzed [3 + 2] annulation of ynones and barbiturate-derived alkenes (Scheme 476).[547] Several functionalized spirobarbituratecyclopentanones were obtained through these [3 + 2] annulations, with the assistance of a weak acid (PhOH), in moderate to excellent yields and with excellent *E*/*Z* stereoselectivity. Many aryl-substitued ynones and barbiturate-derived alkenes with aryl and heteroaryl substituents were suitable substrates.

During the exploration of the annulations of ynones with barbiturate-derived alkenes, Guo found that an unprecedented phosphine-catalyzed [4 + 2] annulation of ynones with barbiturate-derived alkenes occurred in the presence of an inorganic base, affording biologically interesting 1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione derivatives (Scheme 477).[547]

In 2016, Ramachary and co-workers studied the phosphine-catalyzed intermolecular Tomita zipper cyclization of ynones with cyclic *N*-sulfonyl *α*-iminoesters (Scheme 478).[548] In the presence of 20 mol% of PPh_3 and 20 mol % of acetic acid, ynones and *N*-sulfonyl *α*-iminoesters underwent the [3 + 2] annulation to give functionalized cyclopentanone-fused benzosultams in good yields (78–95%) with moderate to excellent stereoselectivities (*E*/*Z* = 1.3:1–11.1:1).

The same year, Guo and co-workers presented the first example of a phosphine-catalyzed [3 + 3] annulation of C,N-cyclic azomethine imines with ynones through the Tomita zipper cyclization. Using 20 mol % of Ph_3P as the catalyst and 20 mol % phenol as the additive, the reaction provided tricyclic heterocyclic compounds in high yields (67–94%) and with moderate to excellent stereoselectivities (*Z*/*E* = 1:1–>20:1) (Scheme 479).[549] An asymmetric variant of this phosphine-catalyzed [3 + 3] annulation of *C,N*-cyclic azomethine imines with ynones was also investigated. Amino acid-based bifunctional chiral phosphines exhibited moderate enantioselective catalytic capability.

Around the same time, using *N,N*-cyclic azomethine imines as substrates, Huang and co-workers reported a similar [3 + 3] annulation of ynones.[550] In the presence of PPh_3 (30 mol %), several ynones reacted with various azomethine imines in a mixed solvent (*n*BuOH/$CHCl_3$, 1:1) at 30 °C to afford functionalized hydropyridazine derivatives in moderate to good yields.

Recently, Ramachary and co-workers reported phosphine-catalyzed [3 + 2] annulative dimerization of ynones. Two molecules of ynones acted as C2 and C3 synthons, respectively,

to furnish 5-alkylidene-2-cyclopentenones (Scheme 480).[551] When using 20 mol% of PPh_3 as the catalyst and 10 mol % of (±)-BINOL as the cocatalyst, ynones presenting various aryl substituents reacted well to afford their cycloadducts in moderate yields.

4.4.6. Phosphine-Catalyzed [*n* + 2] Annulation Through a Michael Addition Cascade.—With 3-formylchromones and alkynes as reaction partners, Waldmann and Kumar demonstrated that phosphine catalysts promote a Michael addition cascade that results in cyclization.[552,553] Such reactivity results in ring formation at the α- and β-carbons of the alkyne (Scheme 481).

Subsequently, Waldmann, Kumar, and co-workers reported the preparation of novel electron-deficient chromone-fused dienes through phosphine-catalyzed [4 + 2] cycloaddition and subsequent acidic ring-opening rearrangement (Scheme 482).[554] Treatment of α-chromonyl ketoester with various 2-alkynoates in the presence of triphenylphosphine (20 mol %) in toluene at 60 °C for 10–30 min gave substituted tricyclic benzopyrones in good yields. When treated with 10% trifluoroacetic acid (TFA) in dichloromethane, these substituted tricyclic benzopyrones were converted to target electron-deficient chromone-fused dienes, which are promising precursors of important natural products.

Employing the highly versatile enimines generated between propiolates and imines (vide infra), Tong reported an annulation process for elaborating enimines and propiolates into functionalized dihydropyridines.[555] The reaction proceeds with nucleophilic addition of triphenylphosphine into the activated alkyne, generating the vinyl phosphonium enoate **318** (Scheme 483). In the presence of the enimine **319**, this enoate undergoes addition to produce the intermediate **320**. Subsequent conjugate addition prompts elimination of the phosphine catalyst, furnishing the dihydropyridine **321** after a [1,3]-hydride shift.

Under the optimized conditions, a moderate yield of the dihydropyridine was obtained (Scheme 484, entry 1). With superstoichiometric amounts of activated alkynes, the corresponding enimines could be generated in situ, followed by annulation to provide functionalized dihydropyridines with good efficiency (entries 2 and 3). When *p*-methoxybenzaldimine was administered, the dihydropyridine was obtained in high yield (entry 2). In contrast, a lower yield of product was discerned when *p*-chlorobenzaldimine was subjected to the reaction conditions (entry 3).

Tong demonstrated that such an annulation event is also viable when using α-cyano enones, providing functionalized dihydropyrans with good efficacy.[556] The reactivity was similar to that of the annulations with enimines, with α-cyano enones bearing aryl substituents giving higher reaction yields (Scheme 485, entries 1 and 2). Although both alkynones and alkynoates can be used in this transformation to afford functionalized dihydropyrans, reactions with alkynoates require elevated temperatures to ensure better conversions, due to their relatively lower reactivity (entries 2 and 3).

In 2012, MacKay and co-workers reported the synthesis of functionalized 2-cyanocyclopentenes through the α–addition–Michael addition pathway of enynes (Scheme

486).[557] The reactions gave 2-cyanocyclopentenes in good yields from substrates featuring various electron-withdrawing groups (i.e., ester, nitrile, and sulfone).

In 2015, Lee and co-workers developed the phosphine-catalyzed [3 + 2] annulations of activated 1,4-naphthoquinones and acetylenecarboxylates as a facile and efficient method for preparing a variety of biologically interesting and novel naphtho[1,2-*b*]furan derivatives (Scheme 487).[558] When using 40 mol % of TPP as the catalyst, various 1,4-naphthoquinones presenting different ester moieties reacted with several acetylenecarboxylates to give their corresponding products in moderate to good yields. Nevertheless, 2-acetylnaphthalene-1,4-dione, naphthalene-1,4-dione, and 2-methoxynaphthalene-1,4-dione did not react under the standard conditions.

4.4.7. Phosphine-Catalyzed Synthesis of 5-Membered Oxacycle from γ-Hydroxybutynoate.—Williamson and Marinetti developed an interesting Michael addition cascade, forming both tetrahydrofurans and oxazolidines through reactions between activated propargyl alcohols and electron-deficient alkenes and imines. Independently, Williamson disclosed the formation of functionalized tetrahydrofurans from activated alkenes, followed by Marinetti's report of the formation of oxazolidines from imines (Scheme 488).[559, 560] In the proposed pathway, nucleophilic addition of the phosphine activates the propargyl alcohol for attack across the olefin, followed by Michael addition and regeneration of the phosphine catalyst.

In these reactions, both alkylidenes and arylidenemalonates are amenable substrates, providing functionalized tetrahydrofurans in high yields (Scheme 489). With sterically hindered alkylidenemalonates, the reaction proceeds smoothly under solvent-free conditions. When arylidenemalonates are applied, use of toluene as a solvent at elevated temperatures facilitates efficient conversions, due to the relatively low reactivity of arylidenemalonates. For the formation of oxazolidines from *N*-tosylimines, an analogous reaction pathway is followed. Although an excellent yield of the oxazolidine was obtained when *p*-nitrobenzaldimine was employed in this transformation, *p*-methoxybenzaldimine afforded only a minute amount of its product.

Published one year after the unique γ-hydroxybutynoate annulation reported by Williamson (Scheme 490), Tejedor disclosed an interesting Michael addition cascade, forming 5,5-fused bicyclic ring systems, in 2009.[561] The functionalized bicyclic system was attributed to a proposed Michael–Michael addition followed by a second Michael–Michael addition (Scheme 490). In this mechanism, nucleophilic addition of tributylphosphine occurs to generate the vinyl phosphonium enoate **322**, activating the tethered alcohol via proton transfer and triggering intramolecular Michael addition with methyl propiolate (**323**), forming the intermediate **324**. Subsequent conjugate addition results in the dihydrofuran **325**. A second Michael–Michael event occurs to construct the 5,5-fused system **326**.

Although the substrate scope for the reaction was restricted, this Michael addition cascade is impressive and worthy of note (Scheme 491). Using tributylphosphine as the catalyst, complex bicyclic systems can be generated from simple propargyl alcohols and methyl propiolate, affording products as mixtures of *E*- and *Z*-isomers.

4.4.8. Phosphine-Catalyzed Conversion of Propiolates to α-Substituted Acrylates.—

In addition to ring-forming events, acylic enimines can also be prepared through phosphine catalysis between alkynes and imines. In the lexicon of synthetic chemistry, enimines are valuable molecular puzzle pieces that lead to the generation of more complex molecular architectures. In 2010, Tong disclosed several reports of the syntheses of functionalized enimines and their further use in phosphine-catalyzed annulations.[562] According to Tong's proposal, triphenylphosphine undergoes nucleophilic addition into methyl propiolate, giving the vinyl phosphonium enoate **318** (Scheme 492). Addition into an *N*-tosyl imine produces the intermediate **327**. After proton transfer, the vinylogous phosphonium ylide **328** exists in resonance with the ylide **329**. Proton transfer allows the phosphonium enamine **330** to eliminate the catalyst, affording the enimine **331**.

For the generation of enimines, *p*-methoxybenzaldimine is well suited to the reaction conditions, providing high yields (Scheme 493 entries 1 and 3). In contrast, a severely lower yield was discerned from the reaction of *p*-chlorobenzaldimine (entry 2). No enimine was observed after switching to the strongly electron-withdrawing *p*-nitrobenzaldimine, suggesting the importance of tuning the electronic properties of the benzaldimines (entry 4).

Prior to Tong's report, Xue and co-workers observed (in 2005) similar reactivity when treating alkynones with arylaldehydes, generating various α-ketoenones (Scheme 494).[563] In combination with 1,3-diones, conjugate addition occurs upon formation of the α-ketoenones, producing functionalized 2,4-diketopentane-1,5-diones in moderate yields. Strongly electron-withdrawing *p*-nitrobenzaldehyde was employed to ensure good efficiencies.

While enimines can be generated when propiolates are treated with a phosphine catalyst in the presence of *N*-tosyl imines, the use of aldehydes in place of the imines does not lead to the formation of enones. Instead, complex vinyl esters are generated. In 2008, Xue reported the use of triphenylphosphine as a catalyst to trigger the formation of vinyl esters from electron-deficient aldehydes.[564] According to the proposed route, phosphine-catalyzed dimerization of the propiolate produces the intermediate **332** (Scheme 495). After incorporation of the aldehyde, the alkoxide **333** is formed. The intermediate **334** is generated after proton transfer and isomerization. Another proton transfer and incorporation of the aldehyde afford the alkoxide **335**, which undergoes an intramolecular hydride shift to furnish the vinyl ester **336**.

Under the optimized conditions, higher efficiency was obtained when using *p*-bromobenzaldehyde and *m*,*m*-dibromobenzaldehyde as reaction partners (Scheme 496). The reaction is very sensitive to the electronic properties of the substrate, giving a low yield of the vinyl ester from the relatively less activated benzaldehyde. No product was afforded from strongly electron-donating *p*-methoxybenzaldehyde.

Similar to enimines, functionalized 1,3-butadienes are of great interest to the synthetic community as useful synthetic building blocks in the total syntheses of natural products. In 2011, Wang reported a novel synthetic route, through phosphine catalysis, toward functionalized 1,3-butadienes from propiolates and arylidenemalononitriles.[565] In his

proposed mechanism, nucleophilic addition of triphenylphosphine into the propiolate provides the familiar vinyl phosphonium enoate **337** (Scheme 497). This enoate undergoes addition into the arylidenemalononitrile **338**, creating the intermediate **339**. After a series of proton transfer events, triphenylphosphine is ejected to afford the functionalized 1,3-butadiene **340**.

The reactions of aryl-, polyaryl-, and heteroarylidenemalononitriles provided functionalized 1,3-butadienes in good yields (Scheme 498, entries 1–4). While a high yield of the product was obtained when using 2-furylidenemalononitrile (entry 4), a mediocre conversion to the product was noted when employing *p*-bromobenzylidenemalononitrile (entry 3).

4.4.9. Phosphine Catalysis of Butynoates and Aroylformates to Form Cyclopentenes.—In 2014, Miller and co-workers disclosed a phosphine-catalyzed annulation between butynoates and aroylformates as a means of generating various cyclopentenes (Scheme 499).[566] The reaction proceeds through phosphine-catalyzed dimerization of the butynoate, giving the zwitterion **341** after proton transfer. In the presence of an aroylformate, nucleophilic addition and olefin isomerization occur to generate the intermediate **342**. Skeletal rearrangement and proton transfer steps lead to the intermediate **343**. Lactone formation and olefin transposition give the lactone **344**. The desired bicyclic product **345** is generated after ring closure and elimination of the phosphine.

Although the reaction is catalytic, using tricyclohexylphosphine in stoichiometric amounts provided better efficiencies (Scheme 500). Moderate yields of the bicyclic cyclopentenes were obtained from various aroylformates. At a lower catalyst loading and with subsequent methanolysis, functionalized cyclopentenes were afforded in good yields.

4.4.10. Phosphine-Catalyzed *δ*-Addition of Alkynones to Ketones/Imines.—In 2016, Shi and co-workers developed the first phosphine-catalyzed nucleophilic addition of the *δ*-carbon of alkynones to electron-deficient carbonyl-containing compounds (Scheme 501).[567] In the presence of $P(4\text{-}FC_6H_4)_3$ (20 mol %), the hex-3-yn-2-one reacted with a variety of trifluoroacetyl compounds, *α*-keto-carboxylate esters, or isatin derivatives to furnish the corresponding substituted 3,5-dien-2-one derivatives in moderate to excellent yields. Deuterium labeling experiments, control experiments, and NMR spectra indicated that the final products were formed through a *δ*-carbon addition of the zwitterionic intermediate, followed by isomerization.

In a further study, Shi, Wei, and Sun explored the application of ketimines in this addition reaction.[568] Using $P(4\text{-}FC_6H_4)_3$ (20 mol %) as the catalyst and 4 Å MS as the additive, alkynones underwent nucleophilic addition to several cyclic trifluoromethyl ketimines to give their corresponding products in moderate to excellent yields (Scheme 502). Under the standard conditions, isatin-derived *N*-Boc ketimines bearing various substituents also reacted with 3-hex-2-one, affording their products in moderate to excellent yields.

Shi and Wei also reported phosphine-catalyzed tetrahydrofuran/tetrahydrofuranone formation from 2-amidophenones and alkynones. Unlike the examples described above, the 2-amido group of the phenone facilitated intramolecular conjugate addition of the alcohols

that resulted from the δ-addition. Through subtle adjusting of the substituent of the 2-amidophenones, addition of water, and changing the reaction temperature, two kinds of highly regioselective cycloaddition products were obtained in moderate to excellent yields (Scheme 503).[569] In the presence of P(4-FC_6H_4)$_3$ (20 mol %) as the catalyst in toluene, β,δ-cycloaddition products were obtained as major products at 65 °C, whereas α,α'-cycloaddition products were achieved as major products at 10 °C.

4.4.11. Phosphine-Catalyzed Butynone–Alkene [3 + 2] Annulation.—Similar to Lu's allene–alkene [3 + 2] annulation, Cui, Xie, and co-workers developed a microwave-assisted phosphinecatalyzed [3 + 2] cyclization of dicyanomethylideneoxindoles and ynones (Scheme 504).[570] Unlike the allene–alkene [3 + 2] annulation, the ynone–alkylidene malononitrile combination demonstrated a preference for the cyclization initiated through a reaction at the γ-carbon of alkynone. In the presence of 60 mol % of PPh_3 and 30 mol % of BINOL as an additive, several spirooxindoles were obtained in moderate to good yields and with moderate to excellent diastereoselectivities.

4.4.12. Unusual [3 + 2] Annulation of Conjugated Enynoates.—Chuang and co-workers studied the phosphine-catalyzed [3 + 2] cycloaddition of enynoates with [60]fullerene (Scheme 505).[571] Using 40 mol % of PCy_3, various enynoates reacted with [60]fullerene to afford cyclopentenofullerenes in yields of 20–43%. Quite different from most reactions of allenes and alkynes involving a phosphine, here the phosphine underwent α-addition toward the enynoates to generate reactive 1,3-dipole species, which reacted with [60]fullerene to give the annulation products.

4.4.13. Dimerization of Conjugated Enynones.—Recently, Shi and co-workers developed a phosphine-catalyzed dimerization of conjugated ene-yne ketones to deliver 4,5-dihydrobenzofurans (Scheme 506).[572] The reaction of ene-yne ketones with a wide range of aryl and alkyl substituents on the alkyne moiety proceeded well to furnish their corresponding products in high yields. Nevertheless, the ene-yne ketone substituted with a sterically bulky 1-naphthyl group did not give its desired product under the standard conditions. Substrates with various electron-withdrawing groups (ketone, ester, benzenesulfonyl, NO_2) were also suitable for this reaction, affording their corresponding products in moderate to good yields. Using a xyl-BINAP **P81** as the chiral catalyst, the asymmetric variant of this reaction gave its desired products in 75–94% ee, albeit with moderate yields.

4.5. Phosphine Catalysis of Alkynes with Nucleophile–Electrophiles

In this section, we describe various tethered reaction partners, bearing both electrophilic and nucleophilic functionalities, that have been used in annulations with activated alkynes. As mentioned above, activated alkynes are similar to activated alkenes in that their annulations can be difficult to achieve if they cannot contribute enough atom units to ensure ring formation. To compensate for such deficiencies, tethered electrophile–nucleophile systems can contribute the necessary number of atom units for annulation.

4.5.1. Phosphine-Catalyzed Pyrrole Synthesis.—Yamamoto and co-workers used an α-isocyanoester and alkynoates to trigger a phosphine-catalyzed pyrrole synthesis (Scheme 507).[573,574] Initial formation of the zwitterion **346** activates the pronucleophile for cyclization, forming the intermediate **347**. Proton transfers, elimination of the catalyst, and aromatization lead to formation of the pyrrole **348**.

Both alkyl- and arylalkynoates were applicable under the reaction conditions, providing good yields of their corresponding pyrroles (Scheme 508). The use of DPPP enhanced the reaction yields. In general, alkynoates bearing electron-rich substituents (e.g., alkyl and *p*-methoxylphenyl groups) gave higher product yields.

4.5.2. Phosphine-Catalyzed Quinoline Synthesis.—Recalling the cyclization reactions of alkenes and allenes with salicylaldehyde derivatives, annulation also occurs between activated alkynes and salicylaldehyde analogues in the presence of phosphines. In 2012, Khong and Kwon demonstrated the formation of functionalized quinolines from *o*-tosylamidobenzaldehydes and *o*-tosylamidophenones (Scheme 509).[575] The tandem cyclization sequence was speculated to involve Michael addition followed by intramolecular aldol reaction to give a hydroxyquinoline. Acidic workup facilitated dehydration, providing the quinoline derivatives. Quinolines featuring various substitution patterns around the aromatic ring system were obtained in high yields.

4.5.3. Phosphine-Catalyzed Quinolone Synthesis.—Changing the substrate to *o*-tosylamidobenzothioates, Khong and Kwon demonstrated an efficient method to access functionalized quinolones in good yields (Scheme 510).[576] Although various substituents could be employed in this reaction, strongly electron-donating dimethoxy groups lowered the product yield (entry 4).

4.5.4. Phosphine-Catalyzed α-Amino-γ-ketoester Synthesis.—Oe and co-workers disclosed the synthesis of functionalized α-amino-γ-ketoesters from a propiolate, phthalimide, and arylaldehydes (Scheme 511).[577] The reaction was proposed to involve initial α-umpolung addition with phthalimide, followed by a second addition to the arylaldehyde to give the intermediate **349**. Proton transfers and catalyst regeneration resulted in the α-amino-γ-ketoester **350**.

Using arylaldehydes as both the reactant and solvent, the reactions proceeded to give the α-amino-γ-ketoesters in good yields (Scheme 512). Although both electron-rich and -poor arylaldehydes could be used while maintaining good efficiencies, the reaction performed in 2-furaldehyde gave a lower product yield.

4.5.5. Phosphine-Catalyzed Annulation via Michael Addition–α-Addition.—In 2013, Zhou and Lu reported a phosphine-catalyzed annulation involving *N*-hydroxyphthalimide and propiolates (Schem 513).[578] The reaction is believed to proceed through initial phosphine-catalyzed Michael addition, followed by an intramolecular MBH reaction to produce various hydroxyisoxazoloisooxindoles. Various ester moieties on the propiolate were tolerated without erosion of the yield.

More recently, Zhou and Lu extended the Michael addition–α-addition further to the combination of *N*-tosylaminophthalimides and alkynoates or alkynyl ketones (Schem 514).[579] In the presence of PPh_3 (20 mol %), *N*-(1,3-dioxoisoindolin-2-yl)-4-methylbenzenesulfonamide reacted smoothly with several types of alkynoates or alkynyl ketones in *N*,*N*-dimethylformamide (DMF) at room temperature, affording 3-hydroxy-1*H*-pyrazolo[5,1-*a*]isoindol-8(3a*H*)-ones in moderate to excellent yields.

The Michael addition–α-addition product formed between an isatin-derived sulfonylhydrazone and an alkynone can further rearrange to form a pyrazoloquinazoline product. Zhou and Lu also reported the PBu_3-catalyzed cycloadditions of sulfonylhydrazones and alkynones, occurring via a domino process (Scheme 515).[580] Under catalysis with PBu_3 (30 mol %), the reactions of a series of alkynones bearing different substituents with several sulfonylhydrazones provided acyl-substituted pyrazoloquinazoline derivatives in acceptable yields. They proposed two plausible pathways—involving sequential isomerization–aromatization and 1,5-sigmatropic rearrangement, respectively—for the reaction.

4.5.6. Acylcyanation.—In 2016, Ohmiya and Sawamura disclosed the highly stereoselective phosphine-catalyzed acylcyanation of alkynoates with acyl cyanides (Schem 516).[581] In the presence of $PPhMe_2$ (10 mol %), a series of acyl cyanides reacted with different types of alkynoates to provide trifunctionalized alkenes with mostly high yields and good anti/syn selectivities. In addition, they proposed a plausible mechanism. The zwitterionic intermediate formed from addition of the phosphine to the alkynoate undergoes nucleophilic substitution with ab acylcyanide, followed by conjugate addition of a cyanide ion, with elimination of the catalyst giving the final product. In 2017, Wei, Qiao, and co-workers used DFT to further study the mechanism of the $PPhMe_2$- and PBu_3-catalyzed selective vicinal acylcyanations of alkynoates.[582]

5. NUCLEOPHILIC PHOSPHINE CATALYSIS OF MBH-ALCOHOL DERIVATIVES (MBHADs)

A new emerging field in phosphine catalysis involves the reactions of Morita–Baylis–Hillman alcohol derivatives (MBHADs). By installing a leaving functionality at the β′-position of the acrylate, a novel phosphonium species is formed, opening the door to new reaction pathways. Similar to phosphine catalysis of alkenes, allenes, and alkynes, the reactions of MBHADs can be divided into several categories: with nucleophiles, with dinucleophiles, with electrophiles, and with electrophile–nucleophiles.

5.1. Phosphine Catalysis of MBHADs with Nucleophiles

When pronucleophiles are used in combination with MBHADs, allylic alkylation and amination are the dominating reaction pathways. Employing the novel MBHADs discovered by Lu (vide infra),[583] Krische reported allylic alkylations and allylic aminations from the reactions of trimethylsilyloxyfuran and phthalimide, respectively, generating functionalized γ-butenolides and β′-amino acrylates, respectively.[584–586] In his proposed mechanism, the reaction proceeds through an S_N2'–S_N2' process (Scheme 517). Starting from the MBHAD

351 discovered by Lu, nucleophilic addition of the phosphine occurs, displacing the allylic acetate through an S_N2' pathway to generate the phosphonium species **352**. The in situ-formed acetate anion activates the pronucleophile to undergo a second S_N2' process, regenerating the phosphine catalyst and producing the allylic alkylation product **353**.

MBHADs bearing either aryl or alkyl substituents could be invoked in this reaction. For allylic alkylation, 2-trimethylsilyloxyfuran was used in a superstoichiometric amount, providing derivatized γ-butenolides in good to high yields (Scheme 518). The reaction proceeded with high diastereoselectivity to give the cis isomer as the major product, except when the MBHAD carried a methyl ester as an activating group and low diastereoinduction was observed. Changing the pronucleophile to a phthalimide allowed allylic amination to occur. In addition to acrylates and enones, vinyl phosphonates were also suitable substrates for allylic amination, albeit requiring elevated reaction temperatures.

Enantioselective Phosphine Catalysis of MBHADs with Nucleophiles.—Similar to γ-umpolung additions, reactions of MBHADs with nucleophiles can also be conducted asymmetrically. Shi used the chiral binaphthyl phosphine **P82** to promote effective asymmetric addition of 2-trimethylsilyloxyfuran into MBHADs to afford functionalized γ-butenolides.[587] The reaction encompassed a wide substrate scope, with both electron-donating and -withdrawing substituents on the MBHAD providing high yields and excellent enantioselectivities (Scheme 519). The yield and enantioselectivity both decreased when an *n*-propyl substituent was placed on the MBHAD (entry 3). Furthermore, the yield of γ-butenolide plummeted when the activating ketone group was replaced by an ester functionality, although the reaction retained its high enantioselectivity. Prolonged reaction times were needed for full conversion to the γ-butenolide when the MBHAD bore an alkyl substituent or an ester activating group. In all cases, a superstoichiometric amount of water was added to ensure good efficiency. That water is a beneficial assistant for proton transfer in this process was discerned by Yu, Dudding, and Kwon in 2007.[244–248]

Further expanding the repertoire of 2-trimethylsilyloxyfuran additions to MBHADs, Shi appended a modified L-proline unit to his binaphthyl-backbone chiral phosphine to improve the efficiency of the addition.[588] Use of the chiral phosphine **P83** led to significant rate enhancements across various substrates (Scheme 520). Notably, the reaction of the MBHAD bearing a *p*-nitrophenyl unit reached completion within 5 h, compared with 24 h for the original reaction. Significant increases in the reaction rate and yield were also observed in the case of the MBHAD presenting a *m*-chlorophenyl substituent (entry 2). In contrast, the reaction time was longer and the yield lower in the case of the *p*-tolyl-appended MBHAD (entry 4).

Aside from 2-trimethylsilyloxyfuran as the pronucleophile, Shi demonstrated that oxazolone derivatives could also be used efficiently as pronucleophiles undergoing asymmetric addition in MBHADs.[589] Among various screened catalysts, the chiral phosphine **P84**, featuring a thiourea group, was the best in terms of conversions, diastereoselectivities, and enantioselectivities (Scheme 521). Excellent yields were achieved for substrates having various types of substitution, in addition to excellent enantioselectivities (entries 1–5). When

a strongly activating *p*-nitrophenyl or ethyl group was present in the MBHAD, the diastereoselectivity decreased significantly (entries 1 and 4).

In 2007, Hou employed the planar chiral [2.2]-paracyclophane monophosphine (*R*)-**P85** as an organocatalyst to developed asymmetric allylic aminations of MBH acetates (Scheme 522).[590] Although various MBH adducts, including VMK- and acrylate-derived ones bearing aromatic or aliphatic substituents, were good substrates for this reaction, the enantioselectivities were not very satisfactory. The acrylate-derived MBH adducts presenting aromatic substituents provided higher yields and better enantioselectivities than did those having aliphatic substituents. Notably, in addition to commonly used MBH acetates, MBH *tert*-butyloxycarbonates were also converted into their products in good yields and with low to moderate enantioselectivities.

From a screen of several bifunctional chiral phosphines, Shi identified the thiourea-containing bifunctional phosphine catalyst **P86** as being most suitable for asymmetric amination (Scheme 523).[591] Under the optimized conditions, both electron-donating *p*-tolyl and strongly electron-withdrawing *p*-nitrophenyl substituents gave high yields of their amination products (entries 1 and 2). When employing a *p*-cyano-substituted MBHAD, an exceptionally high yield of the desired product was isolated with good enantioselectivity (entry 3). Curiously, a significant drop in reaction efficiency occurred when a *p*-trifluoromethyl substituent was present (entry 4). While both electron-donating and -withdrawing substituents were amenable to the transformation, prolonged reaction times were necessary when employing MBHADs bearing non-activating aryl groups (entries 2 and 5).

Similar to the reactivity of the bifunctional thiourea catalyst **P86**, the L-proline-tethered catalyst **P83** facilitated the addition of phthalimide into MBHADs in good yields.[592] Although good efficiencies were obtained, the levels of asymmetric induction remained low (Scheme 524). With reaction times prolonged to hours, good yields of aminovinyl ketones were obtainable, albeit with poor enantiocontrol.

In 2015, Wu, Sha, and co-workers synthesized and applied the chiral thiourea-phosphine **P87** to the allylic amination of MBH acetates with phthalimide[593] but obtained only moderate to good enantioselectivities (Scheme 525).

Expanding upon Shi's pioneering work, Lu and co-workers developed, in 2012, an efficient synthesis, mediated by the chiral dipeptide phosphine **P88**, of acrylates bearing a 3,3-disubstiuted phthalide moiety, with high degrees of enantioselection (Scheme 526).[594] The polarity of the solvent significantly influenced the regioselectivity of the reaction. In a nonpolar solvent (e.g., toluene), the γ-product was obtained exclusively. The crucial hydrogen bonding interaction was disrupted when conducting the reaction in DMSO, leading to isolation of the α-adduct as the major product. High conversions and good levels of enantiocontrol were observed across various 3,3-disubstiuted phthalides having different substitution patterns. Remarkably, alkyl MBHADs also gave their products in good yields and with excellent enantiomeric excesses, in contrast to previous reports of sluggish behavior.[587,589]

Shi and co-workers disclosed a similar transformation, involving 3-arylbenzofuran-2-ones as pronucleophiles producing functionalized 3,3-disubstituted benzofuran-2-ones (Scheme 527).[595] Various aryl-substituted MBHADs were suitable substrates under the reaction conditions, giving their products in high yields and with high enantiomeric excesses when using the catalyst **P89**. The functionalized acrylates were obtained, however, as mixtures of two diastereoisomers, favoring the syn isomer.

In 2017, using a simple chiral sulfinamide phosphine catalyst, Zhang, Wu, and co-workers developed a highly efficient and regio-/enanotioselective allylic alkylation of indenes with MBH carbonates for the synthesis of enantioenriched 1,1,3-trisubstituted (trifluoromethyl)indene derivatives bearing a quaternary stereogenic carbon center (Scheme 528).[596] The chiral sulfinamide phosphine **P90** (10 mol %) catalyzed the conversion of a mixture of 1-aryl-3-(trifluoromethyl)-1*H*-indenes and 3-phenyl-1-(trifluoromethyl)-1*H*-indene to afford the desired products in 76–98% yields and with 90–97% ee.

In 2007, Hou applied the chiral phosphine (*R*)-**P85** in an attempt at asymmetric allylic alkylation, producing an isomer of a γ-butenolide in good yield and with excellent diastereoselectivity, albeit with relatively low enantiomeric excess (Scheme 529).[590]

In 2015, Wu, Sha, and co-workers developed a highly enantioselective allylic alkylation of MBH carbonates with β,γ-butenolides, catalyzed by a chiral squaramide-phosphine.[597] Using 10 mol % of the squaramide-phosphine **P91**, the reaction proceeded efficiently to afford its corresponding products in yields of 55–98% and with good to excellent dr's and excellent enantioselectivities (Scheme 530). This reaction was very sensitive to the electronic and steric properties of the substituents. Alkyl MBH carbonates were unreactive substrates under the typical reaction conditions.

In 2012, Shi and Deng introduced diphenyl phosphite and diphenylphosphane oxide as pronucleophiles to develop an asymmetric allylic substitution for the synthesis of chiral allylic phosphites and phosphane oxides.[598] They prepared a series of chiral binaphthyl–derived phosphine catalysts and found that the multifunctional thiourea-phosphane **P92** demonstrated excellent catalytic capability. In the presence of 20 mol % of **P92**, various MBH adducts reacted with diphenyl phosphite or diphenylphosphane oxide to provide enantioenriched allylic phosphites and phosphane oxides in 70–99% yields and with 90–97% ee (Scheme 531).

In 2016, Vo-Thanh and Toffano reported the use of bifunctional chiral phosphine-thiourea organocatalysts, derived from L-proline, in the asymmetric allylic substitution of MBH adducts with alkyl thiols resulting in C–S bond formation. These reactions were the first examples of phosphine-catalyzed allylic substitutions for C–S bond formation (Scheme 532).[599] The nonasymmetric reaction of the MBH carbonate with alkylthiols was performed using 20 mol % of triphenylphosphine. The asymmetric versions were explored using five different chiral phosphine-thioureas (**P69a**–**e**) as organocatalysts, affording α-methylene-β-mercapto esters in moderate to excellent yields and with moderate to excellent enantioselectivities. The scope of the MBH carbonate was, however, very narrow. In most cases, enantioselectivities were bad.

In 2016, Zhang and co-workers disclosed the phosphine-catalyzed enantioselective umpolung addition of trifluoromethyl ketimines to MBH carbonates (Scheme 533).[600] In the presence of the chiral bifunctional phosphine **P40a** (10 mol %), a series of trifluoromethyl ketimines having various electronic properties underwent Michael additions to MBH carbonates bearing various substituents to afford enantioenriched trifluoromethyl amines featuring a tertiary chiral stereocenter, in high yields and with excellent enantioselectivities. Substitution without polarity inversion (umpolung) was observed, however, when substituted MBH carbonates were used. In addition, an induction model was proposed to rationalize the good enantioselectivity.

5.2. Phosphine Catalysis of MBHADs with Dinucleophiles

Reminiscent of earlier studies, a three-carbon synthon from an alkylidenemalononitrile can be obtained to afford cyclohexenes through [3 + 3] annulation. The reactivity holds true even with the use of MBHADs. In 2009, Lu reported the formation of functionalized cyclohexenes from MBHADs and alkylidenemalononitriles in the presence of triphenylphosphine.[601] In the reaction pathway, the activated alkylidenemalononitrile acts as a dinucleophile that undergoes initial addition and elimination processes to generate the intermediate **354** (Scheme 534). Further activation prompts a subsequent Michael addition, furnishing the functionalized cyclohexene.

Derivatized cyclohexenes had been prepared in high yields with fair diastereoselectivities (Scheme 535, entries 1–4). The MBHAD bearing a *p*-nitrophenyl substituent provided a slightly lower product yield but better diastereoselectivity (entry 2). Switching to the MBHAD presenting a methyl substituent, high levels of diastereoselectivity were preserved across reactions with various aryl- and alkylidenemalononitriles (entries 3 and 4). Notably, a near-quantitative amount of the cyclohexene was obtained when the arylidenemalononitrile bore a *p*-bromo group (entry 3).

A few years later, He and co-workers expanded the reaction with dinucleophiles by employing various aminoalcohols, aminothiols, and diamines as four-atom synthons, generating a collection of seven-membered ring systems, including 1,4-oxazepanes, 1,4-thiazepanes, and 1,4-diazepanes (Scheme 536).[602] These products were obtained in high yields and with good diastereoselectivities.

5.3. Phosphine Catalysis of MBHADs with Electrophiles

5.3.1. MBHAD–Alkene [3 + 2] Annulation.—Lu, one of the pioneers in the field of phosphine catalysis, discovered another novel active phosphonium species, **357**, that opened the door to several new annulation reactions (Scheme 537).[583,603] By installing a β'-leaving group, the phosphonium species **356** is generated from the MBHAD **355** through an S_N2' or S_N2 process. Unlike the reactions of the phosphonium dienolate **77** and the vinyl phosphonium enoate **356**, the use of an external base is required (when acetate or bromide is the leaving group) to activate and generate the vinyl phosphonium ylide **357**. The resulting ylide **357** undergoes nucleophilic addition across the activated olefin **358**, followed by addition and elimination of the phosphine catalyst to afford the two possible regioisomers **359** and **360**.

Reactions of MBHADs with methylenemalonates and 3-keto-2-methyleneesters as electrophiles would involve initial bond formation predominately at the α-position, producing α-addition products. On the other hand, reactions of 2-methyleneindanone, α,β-unsaturated ketones, and aryl-/alkylidenemalononitriles as activated olefins afford their γ-addition products exclusively. Despite the fact that both α- and γ-cyclopentenes can be accessed selectively, most [3 + 2] annulations with MBHADs favor the formation of γ-products, with only sporadic examples leading to α-cyclopentenes.

The novel MBHADs had broad substrate scope, similar to phosphine-catalyzed [3 + 2] annulations with allenoates and alkynoates, when generating cyclopentenes with excellent regioselectivity (Scheme 538). When a Boc group was installed, the reaction proceeded with efficiency comparable with those of allenoates and alkynoates, requiring no external base because it generated *tert*-butoxide in situ (entries 2 and 3). Both alkyl and aryl substituents on the MBHAD were tolerated, giving functionalized cyclopentenes in excellent yields. The regiochemistry was high when using alkyl- or arylidenemalononitriles, with annulation occurring from the β' position of the MBHAD.

Soon after Lu's novel discovery, He reported a viable transformation between Boc-protected MBHADs and chalcones, producing functionalized cyclopentenes.[604] With tributylphosphine as the catalyst in chloroform, good yields of cyclopentenes were obtained (Scheme 539). Like Lu's [3 + 2] annulation, the reaction efficiency was affected by the electronic properties of the electrophile. A better yield was observed when the chalcone bore an electron-withdrawing *p*-nitrophenyl substituent; switching to an electron-donating substrate, the reaction afforded the product with lower conversion.

While working on the formation of functionalized cyclohexenes, He also discovered a unique phosphine-catalyzed cascade reaction giving highly substituted cyclopentenes.[604] The cascade [3 + 2] cyclization–allylic alkylation went through initial [3 + 2] annulation, followed by alkylation of the ring system prior to elimination of the phosphine catalyst (Scheme 540).

Although the reaction proceeds with good efficacy, an extended amount of time was required to reach completion (Scheme 541, entries 1–4). With chalcones bearing fluoride, chloride, and nitro substituents, good yields of the cyclopentenes were obtained with good diastereoselectivities (entries 1–3). On the other hand, the alkylated cyclopentene was obtained in moderate yield when a *p*-methoxylphenyl substituent was installed (entry 4).

Envisioning the formation of multiple rings, Tang disclosed the intramolecular [3 + 2] annulations of MBHADs to form functionalized bicyclic and tricyclic ring systems with high efficiency.[605–607] Tethering the MBHAD to an activated olefin, the reaction produced both bicyclic and tricyclic skeletons with high levels of diastereoselectivity (Scheme 542, entries 1–4). A minor degree of olefin isomerization was observed in the reaction, but it could be suppressed through the addition of a catalytic amount of titanium(IV) isopropoxide (entry 2). Moreover, electron-deficient trisubstituted olefins could also be employed to generate tricyclic ring systems featuring quaternary carbon centers (entry 4).

Derivatives of isatins are often used as electrophiles in phosphine catalysis because they are activated olefins. Nonetheless, for many years no reports appeared describing the use of isatins to generate phosphonium zwitterions. In 2010, Shanmugam derived MBHADs from isatins and used them in [3 + 2] annulations to generate functionalized spirocyclopenteneoxindoles in fair yields.[608] Although derivatized spirocyclopenteneoxindoles could be prepared, the substrate scope was limited (Scheme 543). Although, in general, MBHAD-derived ylides added at the γ-position to the phosphonium species, in this example, due to the steric congestion at the γ-carbon, addition occured at the α-carbon.

Limited substrate scope and efficiency were observed when the MBHADs were derived from isatins. To increase the generality and the efficiency of this reaction, Shi reported a phosphinecatalyzed [3 + 2] annulation occurring with high conversions, giving functionalized spirocyclopenteneoxindoles when using activated isatins as electrophiles.[609] Extremely high degrees of diastereoselectivity observed with the MBHADs presented *p*-nitrophenyl and *p*-cyanophenyl substituents (Scheme 544, entries 1 and 2). Switching to less-activated MBHADs, 1,4-bis(diphenylphosphino)butane (dppb) was required as the catalyst to provide comparable yields, albeit with lower diastereoselectivities (entries 3–5).

In addition to traditional MBHADs, Miao and co-workers disclosed in 2014 a highly efficient [3 + 2] annulation involving MBHADs activated by a phosphonate group (Scheme 545).[610] MBHADs and isatylidenemalononitriles bearing various electron-donating substituents (e.g., methoxy, methyl groups) were well suited to the reaction conditions, generating their products in excellent yields and with good diastereoselectivity. Furthermore, this reaction was unique in providing α-products exclusively.

N-Phenylpyrazolone-derived alkenes have also been employed as substrates in phosphinecatalyzed [3 + 2] annulations of MBH carbonates for the synthesis of chiral spiropyrazolones featuring a quaternary stereogenic center (Scheme 546).[611] Under catalysis with PBu_3, a variety of chiral spiropyrazolone derivatives afforded their products in good yields (84–97%) and with good diastereoselectivities.

In 2014, the He group described the use of 2-nitroallylic acetates as C3 synthons in the phosphine-catalyzed [3 + 2] annulation/allylic alkylation reactions of electron-deficient alkenes (Scheme 547).[612] With $PhPMe_2$ (20 mol %) as the catalyst, the [3 + 2] annulation/allylic alkylation of aromatic nitroallylic acetates and enones with aryl substituents occurred to give cyclopentenes in moderate to good yields and with good diastereoselectivity. Isatin-derived alkenes were also suitable substrates for this reaction, affording spirocyclopenteneoxindoles in moderate yields and with high diastereoselectivity. 2-Nitroallylic acetates also underwent a [3 + 3] annulation with 1,1-dicyanoalkenes to give cyclohexenes under the catalysis of 4-dimethylaminopyridine (20 mol %).

Enantioselective MBHAD–Alkene [3 + 2] Annulation.: Tang and Zhou disclosed an intramolecular [3 + 2] annulation of MBHADs with alkenes, catalyzed by the chiral phosphine (*S*)-**P50a** featuring a spirocyclic backbone (Scheme 548).[613] This spirophosphine catalyzed the formation of the desired tricyclic skeletons in excellent yields and with high

enantioselectivities (Scheme 541, entries 1–3). A common problem in this MBHAD–allene intramolecular [3 + 2] annulation was olefin isomerization of the products. Similar to previous examples, titanium(IV) isopropoxide prohibited the isomerization and greatly improved the selectivity of the reaction (entries 2 and 3).

Spirocyclopentaneoxindole structures are present in many natural products, including notoamide A, (–)-paraherquamide A, and cyclopiamine B. In 2011, Barbas took a step forward in advancing the realm of asymmetric phosphine catalysis by documenting the asymmetric formation of spirocyclopenteneoxindoles catalyzed by 1,2-bis-[(2*S*,5*S*)-2,5-diphenylphospholan-1-yl]ethane [(+)-Ph-BPE, **P51**].[614] Functionalized spirocyclopenteneoxindoles were synthesized in high yields and with good enantioselectivity from Boc-protected MBHADs and 3-alkylidene-2,3-dihydroindol-2-ones (Scheme 549). Here, the chiral induction and enhanced yields arose from aromatic π-stacking between the substrates and the catalyst. A drop in yield and enantioselectivity was observed when using 1,2-bis[(2*S*,5*S*)-2,5-diethylphospholan-1-yl]ethane [(+)-Et-BPE], consistent with the lack of aromatic π-stacking. Also, it was noteworthy that a low product yield and low enantiocontrol were discerned from an acetaldehyde-derived MBHAD (entry 3). A further increase in reaction efficiency occurred when an amide protecting group was employed to rigidify the alkylidenedihydroindolone substrate, presumably the result of a six-membered ring featuring an intramolecular hydrogen bond. In addition to the amide protecting group, a Boc-protected alkylidenedihydroindolone was a suitable substrate for the reaction at lower temperature, with a higher catalyst loading required to maintain the same degree of efficiency and enantioselectivity (entry 4).

With its wonderful success in generating various spirooxindoles enantioselectively, Barbas and co-workers expanded the use of the chiral catalyst **P51** to synthesize spirobenzofuranones (Scheme 550).[615] Similar to previous examples, these reactions yielded, with excellent efficiencies, spirobenzofuranones bearing various substitution patterns. The use of aryl MBHADs was important because alkyl-substituted MBHADs led to products in lower yields and enantiomeric excesses.

At almost the same time in 2012, employing Me-DuPhos as the chiral catalyst, Liu and co-workers studied a similar [3 + 2] cycloaddition (Scheme 551).[616] Treatment of a variety of MBH carbonates of isatins and *N*-phenylmaleimide in the presence of **P93** (30 mol %) in toluene at room temperature generated the corresponding spirocyclopentaneoxindoles with excellent diastereoselectivities and enantioselectivities and in moderate to good yields.

In 2015, Zhong prepared a series of novel chiral ferrocenylphosphines and applied them in asymmetric [3 + 2] cycloadditions of MBH carbonates with maleimides (Scheme 552).[617] Using 10 mol % of the (R,S_{FC})-ferrocenylphosphine **P64b**, a variety of MBH carbonates underwent [3 + 2] annulations with maleimides to afford their corresponding bicyclic imides in yields of 67–99% and with 84–99% ee. Nevertheless, an *o*-nitro-substituted MBH carbonate could not give its corresponding product, due to steric hindrance. No products were detected from the reactions of alkyl MBH carbonates.

Having made excellent progress in asymmetric [3 + 2] annulations with catalysts based on L-threonine, Lu demonstrated another elegant protocol—using another L-threonine–based chiral phosphine—for the preparation of functionalized spirocyclopenteneoxindoles in excellent yields and enantioselectivities (**P88**, Scheme 553).[618] The reaction tolerated MBHADs bearing *p*-tolyl, 2-thienyl, and *p*-cyanophenyl substituents, providing high reaction yields and enantiocontrol (entries 2, 3, and 5). Although 2-naphthyl and 2-thienyl systems were formed, equal amounts of the regioisomers were obtained when a 2-thienyl substituent was installed (entry 5).

In 2012, Shi reported the use of the chiral thiourea phosphine **P94** in catalyzing [3 + 2] annulations between MBHADs and trifluoromethylidene malonates.[619] Unlike the reaction reported by Barbas (Section 5.3.1), here a multifunctional chiral catalyst was used instead of a bidentate phosphine. Under the optimal reaction conditions, cyclopentene derivatives—valuable synthetic intermediates—were acquired in high efficacy and with excellent enantioselectivities (Scheme 554). The MBHAD bearing a highly electron-withdrawing *p*-nitrophenyl substituent provided the target cyclopentene in almost quantitative yield and with good enantiocontrol (entry 1). A less activated phenyl substituent provided a lower conversion to its product (entry 3). While the reactions proceeded well across various MBHADs, only a trace amount of product was detected when a chalcone-type system was administered (entry 5).

Among the pioneers in using dipeptide-derived chiral phosphines, Lu and co-workers demonstrated an efficient [3 + 2] annulation between MBHADs and maleimides, generating bicyclic imides with excellent enantiomeric excesses (Scheme 555).[620] Employing the catalyst **P95**, they isolated various cyclic imides in excellent yields and with excellent diastereo- and enantioselectivities. In addition, alkyl-substituted MBHADs were also compatible with the reaction conditions.

Also working on the same transformation, Shi's group reported that the chiral phosphine **P94** could induce good yields and high enantioselectivities when generating functionalized cyclic imides (Scheme 556).[621] Compared with Lu's examples, these reactions afforded their products in slightly lower yields. Nevertheless, cyclic imides bearing various substitution patterns were obtained with high enantiomeric excesses. Notably, the product was isolated in lower yield when the electron-donating *p*-methoxylphenyl-substituted MBHAD was the substrate (entry 3).

In a separate report published in the same year, Shi and co-workers demonstrated the formation of spiroindan-1,3-diones when using the same chiral catalyst, **P94** (Scheme 557).[622] Although high enantiomeric excesses could be achieved from these reactions, the products were isolated in only moderate yields. Furthermore, the substrate scope was limited to highly activated arylideneindan-1,3-diones and aryl-substituted MBHADs bearing electron-poor ring systems.

In 2016, Chen studied the asymmetric annulations of MBH carbonates derived from isatins and 2-alkylidene-1*H*-indene-1,3(2*H*)-diones (Scheme 558).[623] Using the Kwon phosphine *exo*-**P45** as a chiral catalyst, the [3 + 2] annulations generated bisspirocyclic oxindoles. With

the use of 10 mol % of the bifunctional phosphine **P96**, the [3 + 2] cycloadducts from the MBH carbonates and 2-alkylidene-1*H*-indene-1,3(2*H*)-diones were obtained in high yields (80–96%) and with excellent enantioselectivities (79–94% ee).

In the same year, Guo developed an asymmetric [3 + 2] cycloaddition of MBH adducts with barbiturate-derived alkenes, catalyzed by the chiral difunctional phosphine **P59** (Scheme 559).[624] In the presence of **P59** (20 mol %), a series of barbiturate-derived alkenes reacted with various MBH adducts to give spirocyclic barbiturate-cyclopentenes in generally high yields and with high to excellent enantioselectivities (81–99% ee). Using the same chiral phosphine, **P59**, Guo also realized enantioselective [3 + 2] cycloadditions of MBH cycloadducts with cyclic 1-azadienes (Scheme 560).[625] Various MBH adducts underwent the reactions with cyclic 1-azadienes, generating enantioenriched cyclopentenes bearing three consecutive chiral centers in moderate to excellent yields and with mostly excellent enantioselectivities.

In 2018, Guo offered a new approach to biologically significant chiral hexahydropentalene derivatives through multifunctional chiral phosphine-catalyzed asymmetric [3 + 2] annulations of 5-arylmethylenecyclopent-2-enones and MBH carbonates (Scheme 561).[626] A variety of aromatic MBH carbonates and aromatic cyclopent-2-enone derivatives gave their cycloadducts in moderate to good yields and with excellent enantioselectivities. Unfortunately, neither alkyl-substituted MBH carbonates nor alkyl-substituted cyclopent-2-enone derivatives underwent the reaction.

5.3.2. MBHAD–Imine [3 + 2] Annulation.—Reminiscent of his [3 + 2] annulation between allenoates and *N*-tosyl imines (Scheme 254), Lu reported that derivatized pyrrolines could be synthesized from MBHADs and *N*-tosyl imines.[627] In this reaction, the *p*-chlorobenzaldimine produced an excellent yield of the functionalized pyrroline, exclusively as the cis isomer (Scheme 562). Like Lu's allene [3 + 2] annulation, 3-furaldimine was also compatible with this process, giving a high yield of its annulation product. On the other hand, a significant drop in reaction efficiency occurred when the *p*-methoxybenzaldimine or the MBHAD bearing an *n*-propyl group was employed.

As an extension of the MBHAD–imine [3 + 2] annulations disclosed by Lu, Guo and co-workers employed cyclic sulfamate-derived imines in the synthesis of various sulfamidates (Scheme 563).[628] The reactions gave annulation products in good yields, tolerating various aryl MBHADs and imines. Unlike other examples, the reactions yielded 2,3-dihydropyrroles, instead of the typical 2,5-dihydropyrroles, favoring conjugation with benzene rings.

In 2013, Ma and co-workers developed a novel method to prepare *N*-fused tricyclic products through phosphine-catalyzed [3 + 2] cycloadditions between MBH carbonates and cyclic *N*-acyl-substituted ketimines (Scheme 564).[629] Using Bu_3P (10 mol %) as the catalyst, many *N*-fused tricyclic 2-pyrrolines (32 examples) were furnished in excellent yields and diastereoselectivities from the [3 + 2] cycloaddition. In contrast, without the nitrogen protecting group (R^2 = H), the yield was only 18%. They demonstrated that the prominent

efficiency was dependent on the presence of di- or trifluoromethyl and *N*-protection groups in the cyclic *N*-acyl ketimines.

5.3.3. MBHAD–Azo Compound [3 + 2] Annulation.—In addition to olefins and imines, aryl azo compounds are also suitable substrates for phosphine-catalyzed [3 + 2] cycloadditions with MBH adducts. In 2015, Meng, Wang, and co-workers documented the first phosphine-catalyzed [3 + 2] cycloadditions of MBH carbonates with arylazosulfones for the construction of pyrazole skeletons (Scheme 565).[630] Using PBu_3 (20 mol %) as the catalyst, a wide range of MBH adducts underwent [3 + 2] cycloadditions with various arylazosulfones, furnishing various substituted pyrazoles (28 examples) in 65–99% yields. Various MBH adducts and diverse arylazosulfones were compatible with the reactions.

5.3.4. MBHAD–Ketone [3 + 2] Annulation.—Ketones also act as electrophiles that undergo [3 + 2] cycloadditions with MBH carbonates (Scheme 566).[631] In the presence of 50 mol % of PBu3, the reactions of CF_3-activated ketones (bearing an electron-donating, -neutral, or -withdrawing substituent at the 4- or 3-position of the aryl group) with the nonsubstituted methyl vinyl ketone-derived MBH carbonate afforded a series of CF_3-containing 2,3-dihydrofurans in moderate to high yields (47–70%) and with excellent chemo- and regioselectivities.

5.3.5. Tropone–MBHAD [6 + 3] Annulation.—After the discovery of MBHADs and understanding their reactivities, Lu reported an annulation event involving tropone as the electrophile, generating a [4.3.1]-bicyclic structure.[632] In the proposed mechanism, nucleophilic addition occurs producing the phosphonium species **356** from the MBHAD **355** (Scheme 567). Activation of **356** through deprotonation gives the active phosphonium ylide **357**. With the introduction of tropone (**361**), bond formation across the conjugated system occurs to generate the intermediate **362**, with subsequent cyclization and elimination of the phosphine catalyst giving rise to the target [4.3.1]-bicyclic structure **363**.

Compared with the tropone–allene [8 + 2] annulation reported by Ishar (see Scheme 358),[427] the reactivity was different when MBHADs were used, giving high yields of [6 + 2] adducts (Scheme 568). Similar to the process mentioned above, no external base was required to facilitate the reaction when a Boc-protected MBHAD was employed (entry 1). Furthermore, MBHADs bearing either ester or ketone activating groups were well suited to the reaction, giving comparable yields of their products (entries 1–3). When more electron-withdrawing ketones were used as activating groups, the reactions were completed within shorter periods of time (entries 2 and 3).

5.3.6. MBHAD–Azomethine Imine [3 + 3] Annulation.—In 2015, Guo and co-workers developed the phosphine-catalyzed enantioselective [3 + 3] cycloaddition of MBH carbonates with *C,N*-cyclic azomethine imines (Scheme 569).[633, 634] Prior to this report, they had intensively studied phosphine-catalyzed enantioselective [3 + 3] cycloadditions between *C,N*-cyclic azomethine imines and electron-deficient acetylenes or allenoates, but obtained only low yields and low chemoselectivities. In contrast, the MBH carbonates were superior reaction partners of *C,N*-cyclic azomethine imines in the presence of an appropriate phosphine. Using the spirophosphine (*R*)-**P32** (20 mol %) as the catalyst, K_2CO_3 (1.5 equiv)

as the base, and 4 Å MS, various MBH carbonates underwent [3 + 3] cycloadditions with a diverse array of *C,N*-cyclic azomethine imines to afford a wide range of enantiomerically pure 4,6,7,11*b*-tetrahydro-1*H*-pyridazino[6,1-*a*]isoquinoline derivatives (36 examples). The electronic and steric properties of the MBH carbonates and *C,N*-cyclic azomethine imines had no effects on the enantioselectivities but had a slight impact on the synthetic yields.

Aiming to synthesize biologically active quinazoline-based small molecules, Guo further applied quinazoline-based azomethine imines for the chiral phosphine-catalyzed enantioselective [3 + 3] cycloadditions of MBH carbonates (Scheme 570).[635] Using 20 mol % of the Kwon phosphine, the reaction proceeded smoothly in dichloromethane at −10 °C to afford various optically active quinazoline-fused heterocycles in high yields (75–98%) and with excellent diastereoselectivities (dr > 20:1) and good to excellent enantioselectivities (82->99% ee).

In 2017, Wei presented a theoretical investigation of the detailed mechanism and stereoselectivity of phosphine-catalyzed annulation of MBH carbonates with *C,N*-cyclic azomethine imines (Scheme 571).[636] In general, there are six steps in the catalytic cycle. The reaction begins with nucleophilic addition of the chiral phosphine to the MBH carbonate. Next, cleavage of the C–O bond is accompanied by dissociation of the *t*-$BuOCO_2^-$ group. The phosphonium enolate is then formed, along with the decomposition of *t*-$BuOCO_2H$. In the following step, nucleophilic addition to the other reactant, the *C,N*-cyclic azomethine imine, generates the C–C bond. Subsequent ring-closure, followed by regeneration of the phosphine, affords the final product. The computational results revealed that the C–C bond formation process is the stereoselectivity-determining step, with advantageous hydrogen bonds and less steric hindrance in the *R,R*-configuration of the transition state for C–C bond formation determining that the P(*R,R*) product predominated.

5.3.7. Pyrone–MBHAD [4 + 3] Annulation.—In addition to alkenes, imines, and tropone, the prevalent Diels–Alder reagent, pyrone, can also be used in phosphine catalysis with MBHADs. Lu disclosed that reactions of MBHADs with pyrone in the presence of triphenylphosphine provide functionalized bicylo[3.2.2]nonadienes (Scheme 572).[637] According to his mechanism, triphenylphosphine reacts with the MBHAD **364** to form the phosphonium ylide **365** (Scheme 565). In the presence of the pyrone **366**, nucleophilic addition occurs at the β'-position, providing the intermediate **367**. After ring closure and elimination of the catalyst, the bicylo[3.2.2]nonadiene **368** is obtained.

Interestingly, the lactone motif in pyrone persist to afford a bicylo[3.2.2]nonadiene, rather than generating carbon dioxide through a retro-Diels–Alder reaction (Scheme 573). The reaction tolerated MBHADs presenting either electron-donating or -withdrawing substituents. When the MBHAD featured an electron-donating *p*-methoxyphenyl group, a good yield (86%) of the functionalized bicylo[3.2.2]nonadiene was isolated. A moderate yield (62%) was obtained when using an MBHAD containing an electron-withdrawing functionality. As an alternative to using an ester as the activation functionality, a ketone could also be used with comparable efficiency (74% yield).

In 2015, Chen developed the $(4\text{-}FC_6H_4)_3P$-catalyzed [4 + 3] cycloadditions between bromo-substituted MBH adducts derived from isatins and aza-oQMs, performed in the presence of Cs_2CO_3 and 4 Å MS,[638] providing their corresponding products having an azaspirocycloheptane oxindole scaffold in moderate to good yields (Scheme 574). This unprecedented protocol was very challenging, as both reactants must be generated in situ from multifunctional starting materials.

In 2017, Huang and Chen developed a phosphine-catalyzed intermolecular sequential [4 + 3] domino annulation/allylic alkylation of *N*-tosyl azadienes and MBH carbonates, which served as 1,2,3-C3 and C1 synthons, respectively (Scheme 575).[639] With catalysis of 25 mol % of $P(p\text{-}CH_3OPh)_3$ in the presence of 25 mol % of $PhCO_2H$, the reaction afforded a wide range of benzofuran-fused seven-membered nitrogen heterocycles in good to excellent yields. Two C–C bonds, one C–N bond, and one quaternary center were formed in this reaction.

5.3.8. Enone/Enimine/Diene–MBHAD [4 + 1] Annulation.—Generally, MBHADs undergo transformations similar to those of allenes, serving as three-carbon synthons in annulations. In 2010, Zhang disclosed a rare annulation pathway for MBHADs: reacting as one-carbon synthons with functionalized enynes, furnishing dihydrofurans through [4 + 1] annulation (Scheme 576).[640] In the proposed mechanism, the MBHAD **369** undergoes decarbonylation in situ, generating *tert*-butoxide and the phosphonium species **370**. Upon deprotonation by *tert*-butoxide, the vinyl phosphonium ylide **371** is formed, in resonance with the vinylogous ylide **372**. The ylide **372** undergoes nucleophilic addition across the olefin in the enyne **373**, providing the zwitterionic species **374**. After olefin isomerization, addition and elimination of the catalyst provide the dihydrofuran **375**.

In this reaction, the majority of the substrate reacts to form the dihydrofuran with good diastereoselectivity (Scheme 577). Aryl groups were tolerated in the reaction, giving good yields of their annulation products (entry 1). While alkyl substituents could also be used, a higher catalyst loading was required and significantly lower yields were obtained (entry 2). In addition to enyne substrates, benzylidene ethyl acetoacetate could also be implemented, but tetrahydrofuran was required as the solvent to provide a good yield (entry 3).

Employing activated enones, Huang and co-workers also prepared a collection of functionalized dihydrofurans (Scheme 578).[641] Enones bearing either electron-donating *p*-tolyl or electron-withdrawing *p*-nitrophenyl rings were amenable to the reaction conditions, providing their dihydrofurans in good yields. Furthermore, these dihydrofurans could be derivatized into functionalized 2*H*-pyrans through amine catalysis.[642]

Expanding the scope of the enone substrates, the Shi group employed chromenones as electrophilic partners in reactions with MBHADs, yielding functionalized chromenone-fused dihydrofurans (Scheme 579).[643] Chromenones with various substitution patterns were tolerated in the reaction, producing fused dihydrofurans with good efficiencies.

Similar to Zhang's [4 + 1] annulations with enones, He and co-workers demonstrated that enimines react with MBHADs, granting access to functionalized 2-pyrrolines through an

analogous mechanism.[644] The reaction proceeded with initial conjugate addition into the enimine, followed by intramolecular aza-Michael addition to afford functionalized 2-pyrrolines in excellent yields and diastereoselectivities (Scheme 580, entries 1–4). Enimines with *p*-methoxyphenyl or *p*-trifluoromethylphenyl substituents were tolerated well, giving high conversions to their products (entries 2 and 3).

A highly enantio- and diastereoselective [4 + 1] annulation of α,β-unsaturated imines and allylic carbonates, with the catalysis of a novel hybrid P-chiral phosphine oxide-phosphine, was realized by the He group in 2017 (Scheme 581).[645] This type of new P-chiral phosphine oxide-phosphine **P97**, featuring a sole unit of P(O)-chirality in the molecule, had been synthesized for the first time. Several enantioenriched polysubstituted 2-pyrrolines were obtained in good to excellent yields and with up to 99% ee with >20:1 dr through the reactions between aryl-substituted α,β-unsaturated imines and allylic carbonate when using 15 mol % of the catalyst.

In 2015, Shi and Xu disclosed an interesting Ph_2PMe-catalyzed regio- and diastereoselective [4 + 1] annulation of MBH carbonates with oxindole-derived α,β-unsaturated imines, furnishing functionalized 1′,2′-(dihydrospiro[indoline-3,3′-pyrrol]-2′-yl)acrylates in moderate to good yields and with good diastereoselectivity (Scheme 582).[646] The asymmetric [4 + 1] annulation was also examined using an amino acid-derived chiral phosphine catalyst **P98**, delivering the chiral cycloadduct in 78% yield and with 7:1 dr and 61% ee.

Further expanding the scope of [4 + 1] annulation, He and co-workers demonstrated that activated dienes could also be employed in the reaction to generate functionalized cyclopentenes (Scheme 583).[647] The reactivity of activated dienes was similar to that of activated alkenes, with the reactions giving high yields of cyclopentenes bearing various aryl groups, including *p*-methoxyphenyl, *p*-chlorophenyl, and 2-thienyl. Interestingly, acetate-protected MBHADs gave higher yields of their products in this reaction than did Boc-protected MBHADs.

As alternative to enones, enimines, and dienes, He and co-workers examined the use of nitroolefins as reaction partners (Scheme 584).[648] As expected, the reaction proceeded to give functionalized cyclic nitronates in good yields and diastereoselectivities. With unsubstituted MBHADs, the reaction produced cyclic nitronates, predominately as trans isomers (entries 1 and 2). When aryl MBHADs were used, *cis*-cyclic nitronates were obtained as major products.

Shi and co-workers also achieved the [4 + 1] annulation between dienes and asymmetric MBHADs when using their pioneering thiourea-containing phosphines. Employing the catalyst **P99**, they prepared various dicyanocyclopentenes in good yields and enantiomeric excesses (Scheme 585).[649] Notably, high reaction efficiencies resulted from MBHADs bearing an electron-withdrawing aryl ring (e.g., *p*-nitrophenyl).

Expanding the area of asymmetric [4 + 1] annulation, the Shi group later reported an efficient method, using the catalyst **P100**, for constructing spirooxindoles (Scheme 586).[650]

Similar to previous examples, aryl MBHADs bearing electron-poor aryl rings were well suited to the reaction, giving spirooxindoles in high yields and enantioselectivities.

In 2017, Li developed a chiral phosphine–catalyzed enantioselective [4 + 1] annulation of MBH carbonates with enones, providing optically active 2,3-dihydrofurans with two chiral stereogenic centers bearing functionalized groups (Scheme 587).[651] An interesting monoxide of DuPhos **P101** was used as the chiral catalyst. Several cycloadducts were formed in moderate to good yields and with excellent enantioselectivities (94->99% ee) and diastereoselectivities (>20:1 dr).

In 2016, He described the phosphine-catalyzed [4 + 1] annulations of MBH adducts with *o*-hydroxylphenyl or *o*-aminophenyl ketones (Scheme 588).[652] In the presence of PPh_3 (20 mol %), a series of MBH adducts underwent cycloadditions with *o*-hydroxylphenyl or *o*-aminophenyl ketones, affording *syn*-selective dihydrobenzofurans and dihydrobenzoindolines in moderate to high yields, with mostly excellent diastereoselectivities for the *o*-hydroxylphenyl ketones and decreased diastereoselectivities for the *o*-aminophenyl ketones.

5.3.9. Phosphine-Catalyzed MBHAD–Diene Bicyclo[4.1.0]heptane Synthesis.—As mentioned in previous sections, Huang and co-workers were the first to use 1,3-bis(sulfonyl)butadienes in various annulations. In 2014, another novel synthetic strategy was disclosed by the Huang group, further demonstrating the versatility of 1,3-bis(sulfonyl)butadienes in the preparation of functionalized bicyclo[4.1.0]heptenes (Scheme 589).[653] Under phosphine catalysis, the zwitterion **376** is generated from the MBHAD. Nucleophilic addition between the diene and the zwitterion **376** produces the intermediate **377**. After cyclization, proton transfers, and catalyst displacement, the functionalized bicyclo[4.1.0]heptene **378** is obtained.

The reactions of 1,3-bis(sulfonyl)butadienes bearing various substituents (e.g., *p*-tolyl, *p*-*N*,*N*-dimethylaminophenyl, 2-furyl, and isopropyl groups) provided a range of functionalized bicyclo[4.1.0]heptenes, isolated in high yields (Scheme 590). The reaction was, however, sensitive to steric effects, tolerating only unsubstituted MBHADs. No product was formed when a β'-methylated MBHAD was employed.

5.3.10. Enone–MBHAD [2 + 2 + 1] Annulation.—He documented the construction of elaborated cyclopentanes while working on the cyclization–allylic alkylation reaction, in which the MBHAD again served as a one-carbon synthon.[604] Notably, a rare dimerization of the chalcone occurred to provide the four-carbon fragment, while the MBHAD acted as the one-carbon synthon. In the proposed mechanism, the vinylogous ylide **379** is formed immediately in the presence of tributylphosphine (Scheme 591). Initial addition onto the chalcone, followed by a second incorporation of chalcone, produces the intermediate **380**. After olefin isomerization, addition and elimination of tributylphosphine bring forth the cyclopentane **381**.

Moderate yields of cyclopentanes were isolated when the reactions were performed for 3 days (Scheme 592). To generate appreciable yields of cyclopentanes, a highly activated

chalcone bearing a *p*-nitro group was employed to improve the conversions. In addition to the *n*-butyl ester, the sterically hindered *tert*-butyl ester was also capable of producing its functionalized cyclopentane in reasonable yield.

5.4. Phosphine Catalysis of MBHADs with Electrophile–Nucleophiles

Pioneers in the use of electrophile–nucleophiles in phosphine catalysis, Huang and Chen demonstrated the compatibility between MBHADs and salicyl *N*-thiophosphinylimines in the formation of functionalized dihydrobenzofurans catalyzed by triphenylphosphine.[654] The reaction operates through initial addition of the vinylogous ylide into the *N*-thiophosphinylimine and a subsequent S_N2' reaction to regenerate the catalyst (Scheme 593).

Various alkyl and nitro substituents on the *N*-thiophosphinylimine were amenable to the reaction conditions, producing dihydrobenzofurans in high to excellent yields and with good diastereoselectivities for the trans-isomers (Scheme 594, entries 1–4). A highly sterically demanding substrate also underwent a smooth conversion to the annulation product (entry 2). With a *p*-tolyl substituent on the MBHAD, the product was obtained with complete diastereocontrol (entry 4), whereas lower diastereoselectivity was observed from an *N*-thiophosphinylimine bearing a *p*-nitro functionality (entry 3).

6. MISCELLANEOUS PHOSPHINE CATALYSIS

While the majority of nucleophilic phosphine catalysis reactions are initiated by the addition of phosphine to activated carbon–carbon multiple bonds, electrophiles other than alkenes, allenes, alkynes, and MBHDs also undergo an array of catalysis processes in the presence of phosphines. This section compiles those miscellaneous nucleophilic phosphine catalysis reactions.

6.1. Acylation of Alcohols

The acylation of alcohols (e.g., esterification) is a crucial reaction because its products (e.g., esters) exist in many biological materials and are widely utilized, for example, in the fragrance industry. In 1993, Vedejs and co-workers developed the first nonenzymatic esterification method: tributylphosphine-catalyzed esterification of alcohols with anhydrides.[655] Treatment of tertiary alcohols or phenols with 1.3–1.5 equiv of an anhydride in the presence of 5–15 mol % of a phosphine and 1.5 equiv of triethylamine at room temperature provided the corresponding esters in good to excellent yields (Scheme 595). ^{1}H, ^{31}P, and ^{13}C NMR spectra provided evidence for the reaction mechanisms: nucleophilic attack of the anhydride by the phosphine to form ion pairs as intermediates. This protocol worked effectively on a gram scale and in a rapid manner. Nevertheless, the substances were restricted to bulky tertiary alcohols or phenols. Shortly thereafter, they further explored this method and expanded the reaction scope.[656] The electron density of the phosphine played the decisive role affecting the catalytic activity: the more nucleophilic the phosphine, the higher the catalytic activity. Furthermore, the reactivity was partly affected by the counterions of the phosphonium intermediates. Various alcohols and carboxylic acid derivatives, including cyclic anhydrides and diketene, were also compatible with the reaction

(Scheme 596). Notably, the Bu_3P-catalyzed esterification was inert toward the byproduct carboxylic acids and functioned under mild and neutral reaction conditions.

Subsequently, Vedejs and co-workers developed an asymmetric variant of the phosphine-catalyzed esterification. They observed the enantioselective acylation of alcohols by anhydrides with high enantioselectivity when applying chiral phosphines under mild conditions (Scheme 597).[657] Various alcohols and anhydrides were compatible with the reaction. For example, in the presence of 5–8 mol % of the chiral phosphine **P102**, 1,2-cyclohexanediol was converted to the corresponding monoacetate with up to 67% ee; 1-phenyl-2,2-dimethylpropan-1-ol was acylated to the corresponding ester in up to 81% ee, albeit in only low yield and after a long reaction time (ca. 2 weeks).

Vedejs and co-workers significantly increased the reaction rate for the acylation of alcohols, by up to 2 orders of magnitude, when using novel bicyclic phospholanes (Scheme 598).[658] The bicyclic phospholane **P103** catalyzed the acylation of 1-(*α*-naphthyl)ethanol to the corresponding benzoate ester with excellent enantioselectivity (up to $s = 28$) and high improvements in the rate of the reaction (up to 1200 times). This improvement of reactivity resulted from the conformationally favored geometry of bicyclic phospholanes to destabilize the ground state, determined from both single crystal information and computational modeling.

In 2004, Vedejs and co-workers demonstrated the asymmetric acylation of *meso*-hydrobenzoin with improved enantioselectivities when employing their novel phosphines and phosphabicyclooctanes (Scheme 599).[659] Interestingly, catalysis using the phosphines **P104** and the phosphabicyclooctanes **P105** led to different products.

Inspired by Fu's elegant method of protecting trialkylphosphines via trialkylphosphonium salts,[660] Vedejs and co-workers prepared appropriate trialkylphosphonium salts to replace the sensitive trialkylphosphines in the enantioselective acylation of alcohols.[661] The trialkylphosphonium salts, prepared from inexpensive starting materials, effectively promoted the enantioselective esterification of alcohols after in situ deprotonation using triethylamine for values of s of less than 30, matching the activity of corresponding free phosphines. For the cases where s was greater then 30, the activity of the trialkylphosphonium salts **P106**/NEt_3 was inferior to that of the corresponding phosphines **P105**, presumably because of perturbation arising from the presence of triethylamine or ammonium tetrafluoroborate (Scheme 600).

To further probe the relationship between the structures of the catalysts and their reactivity, Vedejs and co-workers synthesized three novel chiral cyclophospholanes and tested their catalytic activity toward the acylation of alcohols (Scheme 601).[662] Among them, the chiral tricyclic phospholane **P109** catalyzed the isobutyroylation and benzoylation of alcohols, generating corresponding esters, with rapid rates and good enantioselectivity.

In 2009, the Erdik group used tri-*n*-butylphosphine as a catalyst to effectively promote the acylation of *n*-alkyl phenylzincs, providing an atom-economical method for the preparation of various *n*-alkyl arylketones generated in moderate to excellent yields within an hour (Scheme 602).[663]

In 2006, Takata and co-workers introduced phosphine-catalyzed acylation of alcohols to supramolecular chemistry for the construction of [2]rotaxanes (Scheme 603).[664] They used tributylphosphine as the catalyst to promote the condensations of pseudo[2]rotaxanes, featuring a hydroxyl group terminus, with bulky anhydrides, furnishing [2]rotaxanes in high yield, even when performed on a gram scale. Functionalization of the crown ether component of the pseudo[2]rotaxane had only a marginal effect on the tributylphosphine-catalyzed capping. Relative to catalysis using N-containing bases, the greatest advantage of this method was that the weak basicity of the phosphines had an insignificant effect on the hydrogen bonding in the pseudo[2]rotaxanes, maintaining their structures for the building of the [2]rotaxanes.

Subsequently, Takata et al. developed an asymmetric version of this method: treatment of a hydroxyl-terminated dialkylammonium salt and a dibenzo[24]crown-8 derivative with a bulky anhydride (3,5-dimethylbenzoic anhydride) in the presence of a chiral phosphine (**P110** or **P111**) resulted in low yields of planar chiral [2]rotaxanes (Scheme 604).[665] These chiral phosphines were less reactive than tributylphosphine in the acylation of alcohols but provided enantioselectivities of up to 4.4% ee for the planar chiral [2]rotaxanes.

Hedrick and co-workers examined the applicability of a series of tertiary phosphines in the controlled ring-opening polymerization of lactides (Scheme 605).[666] Using an initiator (e.g., an alcohol), PBu_3, $PhPMe_2$, Ph_2PMe, PPh_3, and related phosphines effectively promoted the ring-opening polymerization of lactides through esterification, thereby furnishing polylactides with good polydispersities and predictable molecular weights. The polydispersity index could be finely tuned by varying the tertiary phosphine.

6.2. Ring-Opening Reactions of Aziridines/Epoxides

In 2002, Hou reported the phosphine-catalyzed ring-opening reactions of aziridines.[667] Using PBu_3 (10 mol %) as the catalyst in refluxing toluene, various aziridines reacted with a wide range of nucleophiles (e.g., phenols, thionols, amines) to furnish *anti*-1,2-bifunctional products in good to excellent yields in most cases. The mechanism involved the phosphonium zwitterion, obtained from the nucleophilic addition of tributylphosphine to the aziridine, behaving as a general base, deprotonating the pronucleophiles to form nucleophiles, which then attacked the aziridines to form their ring-opened intermediates. These ring-opening intermediates accepted a proton from another pronucleophile, furnishing the final product and generating another nucleophile (Scheme 606).

Shortly thereafter, in 2003, Hou further expanded the substrate scope for these reactions to include epoxides and found that water was a suitable solvent for the phosphine-catalyzed ring-opening reactions of epoxides and aziridines (Scheme 607).[668] As analogues of aziridines, various epoxides reacted with a wide range of nucleophiles when using tributylphosphine (10 mol %) as the catalyst in water at 25–40 °C, furnishing *anti*-products in good yields (with regioselectivities from 67:33 to >95:5 for unsymmetrical substrates). Similarly, the reactions of aziridines under otherwise identical conditions led to the formation of their ring-opened *anti*-products in excellent yields in most cases. Notably, water was a superior solvent to acetonitrile for these two classes of reactions, in terms of reaction efficiencies and rates.

Hou also employed acetic anhydride in the phosphine-catalyzed ring-opening reactions of aziridines and epoxides to prepare esters of β-amino alcohols and 1,2-diols (Scheme 608).[669] Treatment of an array of symmetrical or unsymmetrical *N*-tosyl aziridines with acetic anhydride in the presence of Bu_3P (10 mol %) in refluxing toluene afforded the ring-opened *anti*-products in good yields (with regioselectivities from 65:35 to >95:5 for unsymmetrical *N*-tosyl aziridines). Similarly, various epoxides formed, under otherwise identical conditions, *anti*-1,2-diol esters in excellent yields.

In 2004, Hou and co-workers further applied the P-ylides formed from the nucleophilic addition of a phosphine to aziridines or epoxides to the construction of conjugated dienes (Scheme 609).[670] Treatment of aziridines or epoxides with ketones or aldehydes in the presence of a stoichiometric amount of tributylphosphine (1.2 equiv) in refluxing *tert*-butanol gave conjugated dienes in moderate to good yields and with moderate stereoselectivities. The major product had the (*E*,*E*)-configuration. Based on the results of control experiments, they proposed a mechanism involving a retro-vinyl triphenylphosphonium bromide (VTB) salt reaction.

In 2007, Zhang and co-workers studied the phosphine-mediated ring-opening reactions of aziridines and epoxides with diphenyl diselenide (Scheme 610).[671] Treatment of various aziridines and epoxides with diphenyl diselenide in the presence of a stoichiometric amount of PBu_3 (1.0 equiv) in acetonitrile furnished β-amino and β-hydroxy selenides, respectively, in moderate to excellent yields. They postulated that the tributylphosphine served as a reducing agent during these transformations.

In 2008, Hou reported the phosphine-facilitated formal [3 + 2] cycloaddition of aziridines with carbon disulfide, or isothiocyanates, to synthesize 1,3-thiazolidine derivatives (Scheme 611).[672] In the presence of PBu_3 (10 mol %), various aziridines reacted with carbon disulfide and various isothiocyanates in refluxing acetonitrile or *tert*-butanol to afford substituted 1,3-thiazolidines in moderate to good yields. Steric hindrance effects considerably impacted the reaction efficiency. Epoxides were also suitable substrates for these reactions.

In 2009, Matsukawa and Tsukamoto documented a facile method for the synthesis of β-functionalized sulfonamides, through phosphine-catalyzed ring-opening reactions of aziridines with silylated nucleophiles (Scheme 612).[673] With the use of TTMPP (5–10 mol %) as the catalyst, the reactions of a wide range of mono- and disubstituted *N*-tosyl aziridines with silylated nucleophiles (Me_3SiCN, Me_3SiCl, Me_3SiN_3) provided β-functionalized sulfonamides as single stereoisomers in good to excellent yields. For the mechanism, they postulated that the reactions began with the formation of an activated hexa- or pentacoordinated silicon intermediate from the addition of the phosphine to the silylated nucleophile, followed by the nucleophilic addition of the intermediate to the aziridine and subsequent N-silylation, giving the final products and regenerating the phosphine.

In 2010, Endo and co-workers studied the anionic alternating copolymerization of a bis(lactone) and an epoxide, using various tertiary phosphines as initiators (Scheme 613).[674] Several tertiary phosphines, including PPh_3, PBu_3, and PCy_3, acted powerfully as initiators

to promote the anionic alternating copolymerization of a bicyclic bis(γ-lactone) and a glycidyl phenyl ether, furnishing linear alternating copolymers identical to those formed using *t*BuOK, with comparative molecular weight distributions. Notably, the reaction rates of the tertiary phosphines were considerably enhanced relative to those obtained using *t*BuOK. They proposed two plausible mechanisms for the polymerization, in which the phosphine reacted with either the bis(lactone) or the epoxide through nucleophilic addition.

6.3. Ring-Opening Reactions of Cyclopropenones/Cyclobutenones

A novel reaction of cyclopropenones with alcoholic nucleophiles, catalyzed by a Lewis base, was reported by the Shi group in 2015 (Scheme 614).[675] They used this kind of reaction to synthesize allenic esters under mild conditions and observed an interesting dynamic kinetic asymmetric transformation (DYKAT) of racemic cyclopropenones catalyzed by a multifunctional chiral phosphine, proven through NMR spectroscopic tracing experiments, mass spectrometry, and DFT calculations. Using 20 mol % of DABCO, 10 mol % of PPh_3 (or 20 mol % of PBu_3), and 4 Å MS as an additive in THF at room temperature, a variety of cyclopropenone derivatives reacted with various nucleophiles (phenols, alcohols) to afford the allenic esters in good yields. With the amino acid-derived phosphine **P112a** as a chiral catalyst, the asymmetric reactions of aromatic cyclopropenones with various alcohols led to their desired products in 64–84% yields and with 75–83% ee.

In 1993, Cammers-Goodwin reported the first phosphine-catalyzed ring-opening reactions of substituted cyclobutenones (Scheme 615).[676] Cyclobutenones reacted powerfully with methanol in the presence of tributylphosphine (5 or 17 mol %) at elevated temperature to give β,γ-unsaturated esters as major products in good yields, along with β,γ-unsaturated esters as minor products. Cammers-Goodwin proposed a mechanism involving a zwitterionic phosphonium species, obtained from the Michael addition of PBu_3 to a cyclobutenone, behaving as a general base to deprotonate methanol. Nucleophilic addition of methoxide to the carbonyl moiety and a following Grob fragmentation led to the product.

In 2015, Zhang and co-workers reported the phosphine-catalyzed enantioselective [4 + 2] cycloaddition of cyclobutenones with isatylidenemalononitriles (Scheme 616).[677] Among a series of amino acid-derived and other amino-containing phosphines, they identified the phenylalanine-derived thioureidophosphine **P112b**, which has a structure similar to that of **P112a**, as the most potent promoter for the annulation. Using **P112b** as the catalyst in the presence of NaI and 4 Å MS as additives in toluene at 50 °C, the cyclobutenones, acting as 1,4-dipoles, reacted with the isatylidenemalononitriles to provide enantioenriched spirocyclooxindole scaffolds in good to excellent yields and with good enantioselectivities. A plausible transition state was proposed to rationalize the asymmetric induction.

6.4. Cyanosilylation of Carbonyl Compounds

In 2009, Matsukawa and co-workers established a methodology to construct cyanohydrin silyl ethers and cyanohydrin carbonates through phosphine-catalyzed cyanosilylation and cyanocarbonation.[678] Using tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP, 5 mol %) as the catalyst (Scheme 618), when aliphatic ketones were employed as substrates, cyanohydrin silyl ethers were generated in high yields. In the case of aromatic ketones, an elevated

temperature (50 °C) was required to achieve excellent yields (Scheme 617). Aliphatic and aromatic aldehydes, as well as aliphatic ketones, were competent substrates for the cyanocarbonation of aldehydes and ketones. Aromatic ketones were much less reactive, even when treated at elevated temperatures for extended periods of time.

To improve the cyanosilylation of ketones substantially, Vaccaro, Lanari, and co-workers applied a polymer-supported triphenylphosphine (PS-TPP) under solvent-free reaction conditions.[679] Among a series of polystyrene-supported Lewis bases, they found that a polystyrene-supported triphenylphosphine was the most effective catalyst. Using PS-TPP (5 or 2 mol %) and trimethylsilyl cyanide (1.2 or 1.1 equiv) at 60 °C under solvent-free reaction conditions, the cyanosilylations of α,β-unsaturated or saturated ketones proceeded well to give their products not only in good yields (72–99%) but also with low environmental factors (5–10; environmental factor = kg of waste/kg of desired product) (Scheme 619). Notably, the environmental factor for the PS-TPP-mediated cyanosilylation of acetophenone decreased dramatically in a cyclic-mode flow or a continuous flow reactor, from 0.47 to 0.16, respectively (Scheme 620).

6.5. Aldol and Alkynylation Reactions of Aldehydes

The aldol reaction is a powerful tool for the construction of C–C bonds, furnishing various medicinal and bioactive δ-hydroxy carbonyl compounds or derivatives.[680–684] The products exist in a wide range of medicinal agents and complicated natural products. Phosphines, due to their good nucleophilicity, were also reported, by Imamoto et al., as being applicable to accelerate Mukaiyama aldol reactions in good yield.[685] After catalyst screening, the bulkiest phosphine, TTMPP, was identified as the most effective catalyst. Treatment of trimethylsilyl enol ethers with aldehydes, including aromatic and aliphatic aldehydes, in the presence of 20 mol % of TTMPP generated their corresponding products in good yields (Scheme 621). They briefly examined the reaction of phenyltrimethylsilyl acetylene with benzaldehyde in the presence of TTMPP and found that the transformation occurred effectively in DMF in good yield (up to 85%), furnishing 3-phenyl-2-propyn-1-phenyl-1-ol.

Following Imamoto's preliminary exploration of the reaction of phenyltrimethylsilyl acetylene with benzaldehyde catalyzed by TTMPP, Sekine and Matsukawa intensively studied the alkynylation of aldehydes using trimethylsilylacetylene.[686] The catalytic activity of TTMPP improved significantly upon increasing the temperature. In the presence of 10 mol % of TTMPP as the catalyst, various aldehydes, including aliphatic and electron-rich or -deficient aromatic ones, reacted with trimethylsilylacetylene in DMF at 100 °C, leading to 3-phenyl-2-propyn-1-phenyl-1-ol and its derivatives in excellent yields (Scheme 622).

The phosphine-catalyzed aldol reaction was updated by Mino and co-workers to an asymmetric version through the use of a chiral phosphine.[687] Treatment of electron-deficient aromatic aldehydes with cycloketones in the presence of 30 mol % of the chiral phosphine **P113**, and 10 mol % of TFA as an additive, in DMF at 0 °C, led to chiral β-hydroxy ketones in 58–100% yield and with high diastereoselectivities (up to 98:2, dr) and enantioselectivities (60–97% ee) (Scheme 623). The reaction was sensitive to the electronic properties of the aromatic aldehydes and the structural properties of the ketones. For

example, the yields and diastereoselectivities decreased greatly for the reactions performed using 4-nitrobenzaldehyde and cyclopentanones as substrates.

In 2014, Matsukawa and co-workers reported the efficient Mukaiyama aldol reactions between silyl enol ethers and aldehydes, with catalysis by a readily accessible, user-friendly, and reusable polymer-supported phosphine, PS–PPh_3 (Scheme 624).[688] Using 5 mol % of PS–PPh_3, aromatic aldehydes with either electron-withdrawing or -donating groups furnished their products in high yields (85–95%). The reactions of aliphatic aldehydes also gave their corresponding products in high yields but required longer reaction times. Heteroaromatic aldehydes were also suitable substrates for the reaction. In addition, 10 mol % of PS–PPh_3 could catalyze the Mannich reactions of silyl enol ethers with various imines.

Chisholm and Weeden further expanded the phosphine-catalyzed aldol reactions to include nitroaldol (Henry) reactions (Scheme 625).[689] Trialkyl phosphines and electron-rich tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) dramatically accelerated the nitroaldol reactions between aldehydes/diketones and nitromethane to give moderate to good yields of their products, even with a catalyst loading as low as 0.05 mol %. They proposed a catalytic mechanism in which the phosphine serves as a base to deprotonate nitromethane and initialize the transformation, based on (1) the relationship between the electronic properties and the reactivity of the catalyst and (2) the complete deactivation of the catalyst by an acidic substrate. This report reminded the chemical community that they should be careful when studying transition metal-catalyzed nitroaldol reactions featuring phosphines as ligands.

Shortly thereafter, Hayashi and Hirata demonstrated a quite similar result for phosphinecatalyzed nitroaldol reactions—to be exact, the same phosphine (TTMPP) for an almost identical reaction (Scheme 626).[690] Furthermore, they introduced nitroethane to the nitroaldol reaction and reported that electron-deficient aromatic aldehydes were more reactive than electron-rich ones. In addition, they established that nitroethane furnished β-nitro alcohols with low to moderate diastereoselectivities.

6.6. Unusual Addition Reactions of Enones and Aldehydes

Although Lewis bases, such as $Ph_3P{=}O$ and HMPA, could catalyze the 1,4-reduction of α,β-unsaturated ketones with trichlorosilane, the 1,2-reduction of aldehydes hardly occurs under the same conditions, thereby allowing a one-pot reductive aldol reaction of α,β-unsaturated ketones with aldehydes (Scheme 627).[691–693] On the basis of this strategy, in 2008, Nakajima and co-workers achieved Lewis base (e.g., $Ph_3P{=}O$ and HMPA)-catalyzed reductive aldol reactions of α,β-unsaturated ketones with aldehydes (Scheme 628).[691] In the presence of a Lewis-basic catalyst, three-component reaction of enones, aldehydes, and trichlorosilane proceeded smoothly to afford the corresponding aldol products in satisfactory yields. Reactions of chalcone with electron-donating and -withdrawing benzaldehyde derivatives gave their products in high yields, but the reaction of an aliphatic aldehyde led to a low yield of its product. For the reaction of chalcone with benzaldehyde, the catalytic activity of $Ph_3P{=}O$ was better than that of HMPA. In 2010, using the chiral Lewis base (*S*)-Binapo as a chiral catalyst, the Nakajima group further demonstrated that the asymmetric reductive aldol reactions of enones, aldehydes, and trichlorosilane was workable, affording

optically active β-hydroxy ketones with good to high diastereo- and enantioselectivities (Scheme 628).[692] Recently, the Schindler group extended the scope of the enones to include lactones, lactams, and morpholine amides having α,α-disubstituted and α,α,β-trisubstituted alkene moieties. The β-hydroxylactones, lactams, and morpholine amides bearing α-quaternary carbon centers were constructed in up to 85% yield and 50:1 dr (Scheme 629).[693]

In a process very different from the above reductive aldol reaction of enones, aldehydes, and trichlorosilane, in 2009 Zhang and co-workers presented the phosphine-dependent selective syntheses of 1-phenylpentane-1,4-diones and (*E*)-5-hydroxy-5-phenylpent-3-en-2-ones through the addition reactions of but-3-en-2-one with aldehydes in the presence of catalytic amounts of Ph_3P and tris(4-methoxylphenyl)phosphine, respectively (Scheme 630).[694] Using 20 mol % of tri(4-methoxylphenyl)phosphine as the catalyst, with THF as the solvent at 60 °C for 24 h, the reactions of several aryl aldehydes presenting electron-withdrawing groups gave (*E*)-5-hydroxy-5-arylpent-3-en-2-ones in moderate yields. When Ph_3P was used as the catalyst for the reactions, performed under otherwise identical conditions, 1,4-additions of aryl aldehydes to but-3-en-2-one occurred to afford 1-arylpentane-1,4-diones in moderate yields.

6.7. Phosphine-Catalyzed [2 + 1 + 1] Annulation

In 2008, Shi reported a rare annulation process for the formation of functionalized oxoimidazolidines.[695] The reaction follows a phosphine-catalyzed general base mechanism with MVK and furnishes a range of oxoimidazolidines. In the proposed mechanism (Pathway A), nucleophilic addition of methyldiphenylphosphine into the imine **384** leads to formation of the intermediate **385** (Scheme 631). Opening of the epoxide from the hydrolyzed aryl amine **386** generates the diamine **387**, which undergoes addition into another molecule of **385** to give the triamine **388**. Activation of the triamine **388** with the phosphonium anion (generated from the MVK dimerization cycle) affords the functionalized oxoimidazolidine **389**. The formation of the transient epoxide **385** is unprecedented. This uncommon intermediate hints at the likelihood of an alternative mechanism (Pathway B) involving general base catalysis.

Once optimized, the reactions involving *m*-fluorobenzaldimine and *m*-trifluoromethylbenzaldimine provided their oxoimidazolidine derivatives in good yields (Scheme 632). When a less activated imine, namely benzaldimine, was employed, a slightly lower yield of the corresponding oxoimidazolidine was isolated. Furthermore, MVK was required as a source of the phosphonium anion to ensure efficient formation of the oxoimidazolidines.

6.8. Ketoketene Dimerization

The dimerization of ketoketene can be achieved using catalytic systems that do not involve nucleophilic phosphine catalysis. An in-depth Review by Lectka[696] covers the ketoketene dimerizations performed using cinchona alkaloids[697–699] and N-heterocyclic carbines[700] as nucleophilic catalysts to give functionalized ketoketene dimers. In 2009, Kerrigan demonstrated that various derivatized β-lactones can be acquired through nucleophilic phosphine catalysis.[701,702] In the proposed mechanism, nucleophilic addition of

tributylphosphine occurs across the activated ketoketene **390** to give the vinyl phosphonium enolate **391** (Scheme 633). In the presence of another molecule of the ketoketene, efficient dimerization occurs, leading to the intermediate **392**. Addition and elimination of the phosphine affords the functionalized *β*-lactone **393**.

After optimization of the reaction, high to excellent yields of the *β*-lactone derivatives were obtained. Both aromatic and heteroaromatic ketoketenes containing *p*-tolyl and 3-thienyl groups were compatible with the conditions (Scheme 634, entries 2 and 3). Interestingly, a high yield of the corresponding *β*-lactone, formed with a high level of stereoselectivity, was isolated when the ketoketene contained a *p*-tolyl group (entry 2).

In addition to phosphine-catalyzed annulations and umpolung additions, Kerrigan demonstrated the successful dimerization of ketoketenes using chiral Josiphos catalysts.[703] Selective dimerization was achieved using two different Josiphos catalysts. The desired enantiomer could be selected using the appropriate chiral Josiphos (Scheme 635). Both alkyl and aryl ketoketenes were amenable to the reaction conditions, furnishing functionalized *β*-lactones in good yields and with high enantioselectivities. In the case of a more sterically demanding substrate, the Josiphos **P114** was employed to increase the reaction efficiency. When an *o*-chlorophenyl group was present in the ketoketene, the product yield was lower, but without erosion of the enantioselectivity (entry 3). On the other hand, the enantioselectivity was greatly reduced when a 3-thienyl substituent was installed (entry 4).

6.9. Ketoketene–Imine/Aldehyde [2 + 2] Annulation

Kerrigan and co-workers also disclosed their preparation of *β*-lactones through chiral phosphine-promoted [2 + 2] annulations of arylketoketenes and aromatic aldehydes.[704, 705] *β*-Lactones are basic motifs found in many natural products and are also versatile synthons in organic synthetic chemistry. They reported that treatment of arylketoketenes with aromatic aldehydes in the presence of a substoichiometric amount of the chiral phosphine (*R*)-BINAPHANE (**P116**) in dichloromethane at −78 °C furnished enantioenriched *β*-lactones in moderate to excellent yields, diastereoselectivities, and enantioselectivities (Scheme 636). The reaction tolerated a variety of (hetero)arylketoketenes and electron-poor aldehydes. Two aliphatic aldehydes, pentanal and 3-phenylpropionaldehyde, were also applicable to the reaction, furnishing their corresponding *β*-lactones with excellent diastereoselectivities and enantioselectivities, albeit in moderate yields. They proposed two possible pathways for the transformations: (1) nucleophilic addition of the phosphine to the ketoketenes to form zwitterions, followed by nucleophilic addition of the zwitterions to aldehydes and subsequent ring closure along with the liberation of the phosphine; (2) nucleophilic addition of the phosphine to the aldehyde to form another type of zwitterion, followed by nucleophilic addition of the zwitterion to the ketoketene and subsequent ring closure along with release of the phosphine.

In addition to aldehydes, arylaldimines have also been explored for the formation of four-membered heterocyclic ring systems. Kerrigan and co-workers developed a route toward a diverse collection of functionalized *β*-lactams through phosphine catalysis using a chiral BINAPHANE (**P116**).[706] In combination with electron-withdrawing imines, they prepared several *β*-lactams through reactions with good efficiencies (Scheme 637). With the strongly

electron-withdrawing *p*-nitrobenzaldimine as a substrate, the yield was almost quantitative, but with lower enantiocontrol (entry 2). Interestingly, excellent diastereoselectivity was achieved from an imine bearing an *o*-fluorophenyl substituent (entry 3).

In 2015, Kerrigan developed a new method to prepare β-lactones through phosphine-catalyzed [2 + 2] cycloaddition of disubstituted ketenes with α-chiral oxyaldehydes (Scheme 638).[707] Using tributylphosphine (10 mol %) as the catalyst, various symmetrical or unsymmetrical disubstituted ketenes reacted with cyclic or acyclic α-chiral oxyaldehydes to afford highly substituted β-lactones in moderate to good yields, along with moderate to good diastereoselectivities. Subsequently, the [2 + 2] cycloaddition completely retained the stereospecificity of the α-chiral oxyaldehydes, without racemization. The good diastereoinduction was rationalized in terms of the polar Felkin–Anh model. The synthetic utility of this method was demonstrated in the synthesis of a (+)-peloruside A synthon (Scheme 639).

The Kerrigan group also reported the trialkylphosphine-catalyzed [2 + 2] cycloadditions of disubstituted ketenes and chiral β-oxyaldehydes, affording β-lactones bearing up to three stereogenic centers in moderate to excellent yields and with moderate to good diastereoselectivities (Scheme 640).[708] From a test of several nucleophilic phosphines, including (*R*)-Binaphane, (*R*)-Binepine, dppb, P(*c*-hexyl)$_3$, PMe_3, and PBu_3, the latter was the optimal catalyst for the reactions performed in dichloromethane or THF at −78 °C.

6.10. Condensation of Siloxyalkynes, Aldehydes, and Imines

In 2012, Kozmin discovered a novel silyl transfer process, generating ketoketenes, that facilitates the three-component condensations of aldehydes, siloxyalkynes, and amines to give functionalized β-hydroxyamides (Scheme 641).[709] Various β-hydroxyamide derivatives were prepared in high yields and with excellent diastereoselectivities. According to the proposed mechanism, triarylphosphine undergoes nucleophilic displacement of the triisopropylsilyl (TIPS) group of the siloxyalkyne, granting the ketoketene **394**. The siloxyphosphonium species **395** transfers the TIPS group to *p*-fluorobenzyl alcohol through another displacement event, regenerating the active phosphine catalyst. The ketoketene generated in situ reacts with the secondary amine and the aryl aldehyde through a chairlike transition state, resulting in the functionalized β-hydroxyamide **396**.

Under the optimized reaction conditions, high yields of β-hydroxyamide derivatives were afforded with high levels of diastereoselectivity (Scheme 642). The reactions of *N*-methyl-*p*-methoxybenzylamine gave its condensation products with good efficiencies (entries 1–3). Once the secondary amine was switched to the less reactive *N*-allylbenzylamine or the sterically demanding diisopropylamine, the conversions to the β-hydroxyamide derivatives decreased (entries 4 and 5). Overall, the reactions performed using TIPS-protected 1-hexynol and *p*-trifluorobenzaldehyde were the most efficient.

6.11. Cycloisomerization of Cyclopropene-1,1-dicarboxylates

In 2011, Ma and co-workers reported a phosphine-catalyzed cycloisomerization of cyclopropene-1,1-dicarboxylates that generated an array of substituted furans (Scheme 643).

[710] When a cyclopropene-1,1-dicarboxylate is treated with a phosphine, ring opening occurs to give the intermediate **397**. Subsequent intramolecular cyclization leads to the intermediate **398**. After elimination of the phosphine, the substituted furan **399** is afforded.

Various alkyl-substituted cyclopropene-1,1-dicarboxylates (e.g., *n*-butyl, cyclohexyl, and benzyl derivatives) were well suited to the reaction conditions, giving excellent yields of their functionalized furans (Scheme 644). A lower yield of product was observed, however, when the cyclopropene-1,1-dicarboxylate bore a phenyl group.

6.12. Catalytic Heine Reaction

The Heine reaction, the rearrangement of acylazridines to oxazolines, was first disclosed by Heine and co-workers in 1959.[711–713] Recently, Morgan and co-workers reported a phosphine-catalyzed Heine reaction that they used to prepare a collection of functionalized oxazolines (Scheme 645).[714] In the presence of a phosphine, nucleophilic ring opening of the acylaziridine occurs to give the intermediate **400**. Subsequent cyclization through O-alkylation displaces the catalyst and provides the functionalized oxazoline **401**.

Acylaziridines bearing aryl groups (e.g., *p*-chlorophenyl, *o*-nitrophenyl, and *m*,*m*-dinitrophenyl rings) were compatible with the reaction (Scheme 646). In particular, a strongly electron-withdrawing *m*,*m*-dinitrophenyl group was required to provide the oxazolines in high yields.

6.13. Rearrangement of Dicarbonyloxiranes

Another rare phosphine-catalyzed rearrangement was documented by Lee and co-workers in 2009: the reaction of dicarbonyloxiranes to generate functionalized α-aroyl acrylates (Scheme 647).[715] Initial nucleophilic addition of the phosphine occurs to generate the intermediate **402**. After addition and elimination of the catalyst, the α-aroyl acrylate **403** is produced.

Heating various dicarbonyloxiranes provided α-aroyl acrylates bearing various substituents (e.g., phenyl, *o*-chlorophenyl, *p*-fluorophenyl, and *p*-tolyl groups) in moderate yields (Scheme 648). The reaction gave a better yield when the phenyl ring presented an electron-withdrawing *p*-fluoro group.

6.14. Cyclopropanation

In 2014, Tang and Li realized the first phosphine-catalyzed cyclopropanation of α,β-unsaturated carbonyl compounds mediated by an ether side arm-assisted phosphine catalyst (Scheme 649).[716] Under the optimized reaction conditions (using 10 mol % of the ether side arm-assisted phosphine as the catalyst and 2 equiv of Cs_2CO_3 as the base in $CHCl_3$ at 65 °C), α,β-unsaturated carbonyl compounds worked well to afford their desired [*n*.1.0] bicycloalkanes, as a single diastereoisomer, in good to excellent yields. Enals and α,β-unsaturated esters were also suitable substrates for this reaction, giving their corresponding products.

6.15. Trifluoromethylation/Annulation

In 2015, Liu, Tan, and co-workers disclosed the first organophosphine-catalyzed tandem radical process enabling the highly selective remote β-C_{sp3}–H bond functionalization of amine derivatives triggered through trifluoromethylation of alkenes using Togni's reagent (Scheme 650).[717] This reaction proceeded through a sequential phosphine-catalyzed bistrifluoromethylation followed by intramolecular cyclization in one-pot, affording a diverse array of trisubstituted 5-(trifluoromethyl)oxazoles. Using 10 mol % of 1,2-bis-(diphenylphosphino)benzene as the catalyst, treatment of various alkenyl *N*-ethyl-amides with Togni's reagent in DCE at 80–100 °C produced bistrifluoromethylated products in moderate to excellent yields and with moderate to excellent *E*/*Z* selectivities. In the presence of dppbz (10 mol %), the trifluoromethylation of alkenyl *N*-ethyl-amides, followed by oxidative cyclization, afforded the oxazole derivatives in one-pot, in yields of 46–78%.

In further studies, Liu and Dang described the phosphine-catalyzed radical reactions of alkenes and the remote α-C–H bond functionalization of alcohols occurring via intramolecular 1,5(6,7)-hydrogen atom transfer triggered by the addition of the CF_3 radical to alkenes in a highly controlled site-selective manner, providing remotely functionalized carbonyl compounds (Scheme 651).[718] When using PPh_3 (15 mol %) in DCE at 80 °C for 16 h under argon, a range of diversely functionalized linear alkenols and aryl-tethered substrates gave their trifluoromethylation products in good to excellent yields.

6.16. Hydrohalogenation of Enynes

In 2015, Zhang and co-workers described a Ph_3P-catalyzed regioselective and stereoselective hydrohalogenation of electron-deficient enynes with metal halides, performed in the presence of acetic acid, allowing the synthesis of multifunctionalized 3,4-disubstituted 2-halo-1,3-dienes (Scheme 652).[719] Under catalysis of Ph_3P (20 mol %), the hydrobrominaiton of various 2-(1-alkynyl)-2-alken-1-ones with $LiBr{\cdot}H_2O$ in HOAc (1 M)/toluene proceeded smoothly to afford the corresponding products as essentially single geometrical isomers (Z/E > 20:1) in moderate to good yields. Under the same conditions, the hydrochlorination of 2-(1-alkynyl)-2-alken-1-ones with LiCl furnished their desired products in yields of 48–71%.

6.17. Photorearrangement and Addition of Enones

In 2015, König and co-workers reported the photorearrangement and methanol addition reactions of aryl chalcones in the presence of PPh_3 under UV-A irradiation (Scheme 653).[720] When using 0.5 equiv of PPh_3, the reactions of the aryl chalcones proceeded smoothly in CH_3OH under the light from 400 nm purple LEDs at 20 °C, affording their corresponding products in yields of 32–84%. The [2 + 2] cycloaddition occurred when the enones featured a strongly electron-withdrawing or -donating substituent (e.g., OMe, NO_2, CN) on either of the aromatic rings.

7. YLIDES FORMED THROUGH NUCLEOPHILIC ADDITION OF PHOSPHINE

While the MBH reaction is facilitated by both tertiary phosphine and amine catalysts, most of the reactions described in the previous sections are uniquely facilitated only by phosphines. Perhaps the most important difference between nucleophilic phosphine and amine catalysis is the presence and absence of phosphonium and ammonium ylide intermediates, respectively. In fact, reactions of phosphonium enolates and ylides were discovered contemporaneously during the early developmental stage of nucleophilic phosphine catalysis in the 1960s. In this regard, the formation of ylides through nucleophilic addition of phosphines to activated multiple bonds and their subsequent Wittig reactions, despite being stoichiometric in nature, is intimately related to nucleophilic phosphine catalysis. Consequently, this section catalogues the chemistry of ylides that are formed through nucleophilic addition of phosphines.

7.1. Ylides from Alkenes

In 1962, Takashina and Price reported the formation of a crystalline hexameric adduct of acrylonitrile when using triphenylphosphine as a catalyst in alcoholic solvents.[721] Based on the cyanoethylation of the acrylonitrile dimer leading to a hexameric adduct, Price proposed 1,4-dicyano-2-butene **405** as the intermediate in this reaction (Scheme 654). The formation of the hexameric adduct was later investigated independently by Baizer and Anderson[722] and McClure,[723] who analyzed aliquots of the reaction mixture through gas chromatography. They found and confirmed that 1,4-dicyano-1-butene **406** was the intermediate. As the reaction proceeded, the concentration of **406** decreased and the concentration of the hexameric adduct increased, but the intermediate 1,4-dicyano-2-butene **405** proposed by Price was never detected. Although 1,4-dicyano-2-butene **405** was never formed in the reaction, this incident led Price to propose one of the most important and fundamental equilibria in phosphine catalysis: the formation of the ylide **404** from the immediate β-phosphonium enolate zwitterion as a means of interpreting the formation of the hexameric adduct.

In the subsequent year (1964), Oda and co-workers trapped the ylide **404** with aromatic aldehydes, when using triphenylphosphine in an alcoholic solvent, validating Price's proposed zwitterion–ylide equilibrium.[724] The resulting transformation was Wittig olefination, but it was not catalytic. Nevertheless, this process was the first phosphine-mediated reaction of an electron-deficient olefin with an aldehyde. Oda's finding was of a unique route for the generation of a phosphorus ylide, differing from the traditional reaction of an alkyl halide with a tertiary phosphine through substitution followed by treatment with a base.[725–759] Despite the many traditional methods for preparing phosphorus ylides, this section of the Review will feature only recent stoichiometric phosphine reactions involving nucleophilic addition.

7.1.1. Wittig Reaction.—Employing triphenylphosphine and a protic alcohol solvent, Oda demonstrated the formation of functionalized styrenes in mediocre yields (Scheme 655).[724] Although not highly efficient, that study confirmed the zwitterion–ylide equilibrium

proposed by Price[721] and marked the beginning of the study of the reactions of phosphines with aldehydes.

7.1.2. Intramolecular Wittig—Pyrrole Synthesis.—Applying the intramolecular Wittig reaction, transformations can be devised to form functionalized pyrroles. In 2009, Arndtsen and co-workers reacted enimines and acyl chlorides in the presence of a phosphine to facilitate intramolecular Wittig reactions that provided functionalized pyrroles.[760] Looking at the suggested mechanism, mixing the enimine with the acyl chloride in the presence of the phosphine leads to the phosphonium ion **407** (Scheme 656). After treatment with the base, the ylide **408** undergoes an intramolecular Wittig reaction to afford the pyrrole **409**.

With various accessible enimines and acyl chlorides, a diverse range of pyrroles could be prepared using this intramolecular Wittig strategy (Scheme 657). Good to high yields of pyrroles were generated, bearing various substitution patterns of high synthetic value. Aside from generic acyl chlorides, ethyl chloroformate and ethyl chloroglyoxylate were also both suitable for this transformation, providing further structural diversity (entries 3 and 4).

7.1.3. Intramolecular Wittig—Dihydropyrrole Synthesis.—Although their reaction is not catalytic, Arndtsen and co-workers disclosed an efficient way to generate functionalized dihydropyrroles (Scheme 658).[761] Because of the way in which our Review is organized, the proposed mechanism is covered in later sections (vide infra). Using chiral **P117** as the catalyst, they synthesized, in moderate yields and good enantiomeric excesses, dihydropyrroles bearing various substituents (e.g., *i*Pr, *p*-tolyl, and *p*-methoxyphenyl groups).

7.1.4. Intramolecular Wittig—Furan Synthesis.—A similar strategy can be applied to the synthesis of furan derivatives. In 2010, Lin reported that the reaction of highly activated arylidene-1,3-diketones and acyl chlorides in the presence of a stoichiometric amount of tributylphosphine afforded furan derivatives in high efficiency.[762] According to the proposed mechanism, facile nucleophilic addition occurs across the activated olefin to generate the corresponding *β*-phosphonium enolate **410** (Scheme 659). In the presence of the acyl chloride, O-acylation is triggered, followed by deprotonation with triethylamine to yield the active phosphonium ylide **411**. Upon formation of the ylide **411**, an intramolecular Wittig reaction proceeds to furnish the functionalized furan **412**.

This reaction tolerated acyl chlorides bearing strongly electron-withdrawing *p*-nitrophenyl and electron-donating 2-furyl systems, affording good yields of the derivatized furans (Scheme 660, entries 1 and 2). While furan-2-carbonyl chloride was a suitable substrate, a slightly lower yield was observed, accompanied by a prolonged reaction time (entry 2). Aside from phenyl ketones, other activating groups, including ethyl ester and cyano functionalities, were employed to provide discrete functionalization of the furan ring system (entries 3 and 4). Interestingly, a significant enhancement in reaction rate was discerned when a nitrile was installed as an activating group on the olefin, producing the desired furan within minutes (entry 4).

In 2011, Lin expanded the scope of the intramolecular Wittig reaction to facilitate the formation of trisubstituted furans.[763] Using 1,3-diarylprop-2-en-1-one scaffolds, furan derivatives were generated with good efficiencies within short reaction times (Scheme 661). Overall, good yields of the isolated products were obtained when the 1,3-diarylprop-2-en-1-one bore electron-withdrawing *p*-cyanophenyl or *p*-trifluoromethylphenyl groups (entries 1 and 3). Alkyl and 2-furyl substituents were also compatible, albeit providing their products with lower conversions (entries 2, 4, and 5).

He and co-workers adopted a similar strategy for generating a collection of functionalized furans (Scheme 662).[764] Interestingly, they used enoates as the starting material, instead of enones. Under the reaction conditions, enoates underwent an initial C-acylation to give β'-ketoenoate intermediates that then proceeded through the same mechanism as proposed by Lin to give furan products. Acyl chlorides bearing various aryl groups, including *p*-methylphenyl and *p*-nitrophenyl units, were compatible, yielding their functionalized furans with good efficiencies. In contrast, acyl chlorides bearing heteroaryl systems (e.g., a 2-furyl group) resulted in moderate yields.

More recently, in 2012 Lin demonstrated the formation of furocoumarin derivatives through an intramolecular Wittig strategy (Scheme 663).[765] Similar to the previous examples, substrates bearing nitro or bromo groups provided higher product yields (entries 1, 2, and 4). Cyclohexanecarbonyl chloride was also applied in the reaction, giving a moderate yield of the corresponding furocoumarin (entry 3).

Further investigating the efficient preparation of functionalized heterocycles, Lin disclosed a strategy for generating furo[3,2-*c*]coumarin derivatives through an intramolecular Wittig reaction.[766] Unlike previous reports, the transient phosphonium species in this case could be isolated and characterized. Taking the isolated phosphonium zwitterions and treating them with acyl chlorides and triethylamine, functionalized furo[3,2-*c*]coumarins were prepared in high yields (Scheme 664). While many substrates reacted smoothly, the use of terephthalaldehyde resulted in a lower yield of the desired zwitterion, possibly because of a competitive aldol reaction at the second aldehyde unit (entry 4). Aside from aromatic aldehydes, the reaction of ethyl glyoxylate also led to the formation of a furo[3,2-*c*]coumarin bearing an ester moiety (entry 5).

7.1.5. Intramolecular Wittig—Cyclopentene Synthesis.—In addition to phosphine-catalyzed annulations, the intramolecular Wittig reaction can also be used to access cyclic ring systems. He and co-workers developed an efficient method for generating functionalized cyclic imides (Scheme 665).[767] This transformation proceeds through an initial RC-type addition, followed by proton transfers, prior to the intramolecular Wittig reaction. Various β'-arylketoenoates featuring different aryl rings (e.g., *p*-tolyl and *p*-fluorophenyl units) were obtained in good yields.

7.1.6. Formal [4 + 2] Cycloaddition—Wittig Cascade.—The synthesis of carbocycles with defined quaternary centers has remained a challenge for the synthetic community. In 2006, Schaus and co-workers reported a formal [4 + 2] cycloaddition triggered by a phosphine, leading to an intramolecular Wittig olefination to generate

multifarious bicyclo[3.2.1]octane derivatives.[768] The reaction involves the addition of dimethylphenylphosphine into the 1,4-dienone **415**, with subsequent annulation producing the zwitterionic species **416** (Scheme 666). After proton transfer, the intramolecular Wittig reaction occurs, rendering the bicyclo[3.2.1]octane **417**.

The reaction proceeded smoothly to afford highly complex carbocycles in good yields. Using 5-(2-furyl)-2-methyl-1,4-dienone as a substrate, no change in reaction efficiency occurred, granting access to bicyclo[3.2.1]octanes bearing polyheteroaryl substituents (Scheme 667, entry 2). A significant loss in product yield occurred when 2-ethyl-1,4-dienone was employed as the substrate, presumably because of increased steric hindrance (entry 3). Aside from aryl groups, a long alkyl substituent was also well-suited, providing a good conversion to a bicyclo[3.2.1]octane product (entry 4).

7.1.7. 1,3-Dipolar Cyclization via Phosphorus Ylides.—In 2007, Arndtsen reported seminal results regarding the use of phosphorus ylides as efficient 1,3-dipoles.[769] Modeling after the famous münchnones, Arndtsen devised a multicomponent reaction to generate, in situ, a phosphorus ylide 1,3-dipole that undergoes cycloaddition to give functionalized pyrroles with good efficacies. Although the detailed mechanism is under investigation, a proposed reaction pathway can be reasoned involving the formation of a mesoionic intermediate (Scheme 668). Mixing the imine and the acyl chloride, the acyl iminium species **418** is generated. With nucleophilic addition and deprotonation, the mesoionic species **419** is formed. In the presence of the dipolarophile, the pyrrole **420** is formed with exclusion of the phosphine oxide.

When using 2-phenoxy-1,3,2-benzodioxaphosphole, high yields of functionalized pyrroles were prepared through this multicomponent design (Scheme 669). A diverse substrate scope was observed for this reaction, ranging from alkyl to aromatic imines, from alkyl to aromatic acyl chlorides, and from DMAD to acetylenes. Although it occurred with moderate yield, the reaction of *N*-benzyl formaldimine as the substrate was possible (entry 3). Another rare example involved the use of an unactivated acetylene to furnish a 1,2,5-trisubstituted pyrrole (entry 4). This study marked the first example of a phosphorus ylide undergoing 1,3-dipolar cyclization.

7.1.8. Indane Synthesis.—A different reaction pathway was followed when Shi and co-workers treated bis-cyclopropenones with 1,1-bis(diphenylphosphino)methane (dppm), forming several functionalized indanes (Scheme 670).[152] The reaction proceeded to give the zwitterion **421**, as discussed previously. After ring opening events, the intermediate **422** was formed. In the presence of water, addition to the phosphine occurred, leading to extrusion of the phosphine oxide and production of the indane **423**.

Alkyl esters of various chain lengths were employed as substrates under the optimal reaction conditions, (Scheme 671). Bis-cyclopropenones bearing various aromatic groups (e.g., *p*-fluorophenyl and 2-thienyl units) were tolerated, giving their target indanes in good yields.

7.2. Ylides from Allenes

7.2.1. Wittig Olefination.—In 2009, He and co-workers employed tertiary phosphines to promote internal ylide generation from γ-substituted allenoates (Scheme 672).[179] Employing the phosphonium ylide generated from nucleophilic addition of the phosphine to the allenoate, various functionalized diene systems were formed, exclusively with the *E,E*-configuration.

Under the optimal conditions and using triphenylphosphine as the catalyst, excellent yields of functionalized dienes were obtained, entirely as the *E,E*-isomers (Scheme 673). The reaction efficiency was greater when electron-withdrawing *o*-cyano or *p*-nitrobenzaldehyde units were employed. 2-Furaldehyde was also amenable to the reaction conditions, but formed its product with a slight decrease in yield. When using electron-donating *p*-methoxybenzaldehyde, a more nucleophilic phosphine catalyst, 1,3,5-triaza-7-phosphaadamantane (PTA), was necessary, albeit providing a moderate isolated yield of the target diene.

Reminiscent of He's work, Gothelf documented the olefination of 2-alkynoates with aromatic aldehydes in the presence of PTA.[770] Known through Lu's original [3 + 2] annulation, 2-alkynoates can be isomerized to generate 2,3-allenoates in situ in the presence of nucleophilic phosphines (Scheme 675). Taking advantage of this fact, strongly nucleophilic PTA was employed for isomerization, followed by Wittig olefination, to provide good yields of *E,E*-dienes selectively. According to the proposed mechanism, initial addition of the phosphine catalyst generated the vinylphosphonium enolate **424** (Scheme 674). Through a series of proton transfer events, the ylide **425** was produced in situ, followed by olefination with an aromatic aldehyde to afford the corresponding *E,E*-diene **426**.

In contrast to He's conditions, these reactions were performed at elevated temperature to give high yields of functionalized *E,E*-dienes (Scheme 675). The reactions of both weakly electron-withdrawing *o*-chlorophenyl and electron donating *p*-tolualdehyde proceeded smoothly to provide their corresponding dienes with high efficiency. Unexpectedly, no products were isolated when strongly electron-withdrawing *o*-nitrobenzaldehyde and electron donating *p*-methoxybenzaldehyde were employed. This observation was very different from He's finding when reacting *o*-cyanobenzaldehyde and *p*-methoxybenzaldehyde.

After having success in Wittig olefinations involving nucleophilic phosphine addition to γ-substituted allenes, He reported a similar Wittig olefination process using a vinylidenesuccinate.[771] This reaction proceeded through a pathway congruous with that in the case of the γ-substituted allenoates (Scheme 676).

Good yields of derivatized diene systems were obtained with high diastereoselectivity under the optimized conditions. Unlike the previously reported findings with γ-substituted allenoates, both electron-donating and -withdrawing aldehydes provided their corresponding dienes with high efficiency and good diastereoselectivity (Scheme 677). With *p*-methoxybenzaldehyde as the substrate (50% yield in the case of the γ-substituted allenoate),

the target diene was isolated in good yield and with a good level of selectivity (entry 1). Several changes were made for the olefinations of γ-substituted allenoates with *p*-nitrobenzaldehyde (Scheme 677): (1) the reaction time was shorter in the case of the vinylidenesuccinate (entry 3); (2) the product yield and selectivity were poorer; and (3) a more nucleophilic methyldiphenylphosphine was used. In addition to the vinylidenesuccinate, an α-benzyl allenoate was also well suited to the reaction conditions, giving comparable results when employing tributylphosphine, a more nucleophilic catalyst (entry 4).

Aside from the Wittig reactions, He also reported a novel type of olefination.[772] In 2008, He disclosed a short Communication describing a vinylogous Wittig reaction using 2-methyl-2,3-butadienoate and salicylaldehyde to generate diene derivatives. A more in-depth study, documented by Kwon, explored its reactivity and mechanism.[407] In the proposed mechanism, addition of triphenylphosphine occurs, generating the vinylogous ylide (Scheme 678). With coordination to boron trifluoride, nucleophilic addition to the aldehyde occurs in close proximity to furnish the phosphonium alkoxide **427**. Through a series of proton transfers, the six-membered oxaphosphorine **428** is formed; it collapses to give the functionalized diene **429** and triphenylphosphine oxide.

For this reaction, moderate yields of the vinylogous Wittig products were isolated when electron-withdrawing aldehydes (e.g., *p*-cyano-, *p*-nitro-, and *m*-fluorobenzaldehyde) were substrates (Scheme 679). In all cases, the dienes were obtained as mixtures of geometric isomers, slightly favoring the *E*-olefin geometry. Higher selectivity was observed when strongly electron-withdrawing *p*-nitrobenzaldehyde was employed as a substrate. Notably, the presence of Lewis-acidic boron trifluoride etherate—a rare additive in phosphine catalysis—was critical for improving the reaction yield.

Further expanding the repertoire of vinylogous Wittig reactions, He disclosed a practical and synthetically useful route for the preparation of functionalized 1,3-dienes when using tributylphosphine as the catalyst.[773] He proposed an alternative mechanistic route for the vinylogous Wittig reaction without the assistance of boron trifluoride etherate. According to the suggested mechanism, addition of tributylphosphine provides the vinylogous ylide (Scheme 680). In the presence of water, isomerization of the vinylogous ylide to **430** occurs, followed by an S_N2' reaction with another molecule of tributylphosphine to generate the phosphonium species **431**. After deprotonation by hydroxide, a Wittig reaction occurs to afford the functionalized 1,3-diene **432**.

Using chloroform as the solvent, various aromatic aldehydes (e.g., *p*-fluorobenzaldehyde, 1-naphthaldehyde, 2-furaldehyde) were suitable as substrates, giving their desired 1,3-dienes in excellent yields and good isomeric selectivity (Scheme 681, entries 2, 4, and 5). Interestingly, the yield was lower when employing *o*-trifluoromethylbenzaldehyde as the substrate, possibly because of steric hindrance (entry 3).

7.2.2. γ-Umpolung–Wittig.—In the umpolung addition, the transient phosphorus ylide species is generated prior to elimination of the catalyst. There have been no successful reports of the capture of such an elusive intermediate during an umpolung addition event. In

2006, Virieux reported the isolation of a functionalized pyrrolizine from the annulation of 2,3-butadienoate and pyrrole-2-carboxaldehyde through an umpolung addition followed by an intramolecular Wittig olefination, trapping the reactive phosphorus ylide species.[192] Based on the proposed pathway, the reaction proceeds through an initial γ-umpolung addition into the 2,3-butadienoate to afford the transient phosphorus ylide **433** (Scheme 682). Having a tethered aldehyde in place, intramolecular Wittig olefination proceeds and eliminates triphenylphosphine oxide, giving a low yield of the pyrrolizine. Although its yield is not ideal for synthetic applications, the transformation serves as a proof of concept that such a novel annulation route is possible.

7.2.3. Fluoranthene and Benzo[*a*]aceanthrylene Synthesis.—

In 2014, Nair and co-workers reported a method for accessing functionalized polyaromatic compounds, including fluoranthenes and benzo[*a*]aceanthrylenes, through a phosphine-mediated pathway (Scheme 683).[774] In the presence of triphenylphosphine, the zwitterion is generated from a penta-2,3-dienoate. Nucleophilic addition to the dione and subsequent elimination of the phosphine oxide provides the intermediate allenoate **434**. Another molecule of triphenylphosphine then undergoes addition to the allenoate **434**, triggering an intramolecular cyclization to give the intermediate **435**. After a series of proton transfers, elimination of the phosphine, and dehydration, the polyaromatic compound **436** is obtained.

With various 1,2-diones as substrates, efficient benzannulations occurred to give several functionalized fluoranthenes and benzo[*a*]aceanthrylenes in good yields (Scheme 684).

7.3. Ylides from Alkynes

7.3.1. Wittig Olefination with Ylides from Triphenylphosphine and DMAD.—

Wittig olefination through nucleophilic addition can also be achieved in alkyne systems. In 2000, Ramazani and co-workers provided a brief report documenting Wittig reactions performed in the presence of an alcohol, a phosphine, and DMAD.[775] In the proposed pathway, triphenylphosphine undergoes nucleophilic addition to DMAD to generate the vinyl phosphonium enolate (Scheme 685). Facile protonation of the enolate and addition of methoxide generates the ylide **437**. In the presence of ninhydrin as the carbonyl source, a Wittig reaction occurs after dehydration of ninhydrin, giving rise to the alkoxysuccinate **438**. The use of the in situ-generated phosphorus ylide **437** in the Wittig reactions is reminiscent of Oda's work.[724]

Good yields of alkoxysuccinates can be obtained when performing the reaction at low temperature in methanol (Scheme 686). Sterically bulky di-*tert*-butyl acetylenedicarboxylate (DBAD) can also be used to give a good yield of the corresponding alkoxysuccinate. Other than methanol, the reaction can tolerate the use of benzyl alcohol to provide a comparable yield of the functionalized succinate. Although the reaction can afford various alkoxysuccinates, the process is very limited to the use of DMAD and DBAD.

Cyclizations can also occur when a carbonyl unit is tethered within the pronucleophile, generating functionalized dihydropyrrolones (Scheme 687).[776–778] The reactions proceeded to give products bearing various aryl rings (e.g., *o*-tolyl, 8-quinolinyl, and *o,o*-

diisopropylphenyl systems) in good yields. In addition to dihydropyrrolones, 4-oxazolines could also be formed through this method.[779]

To further expand the scope of the reaction, Yavari and co-workers employed benzimidazolone,[780] saccharin,[781] spirohydantoin,[782] and thiazolidin-2,4-dione[783] as pronucleophiles (Scheme 688). The mechanism involves the formation of a phosphorus ylide followed by an intramolecular Wittig reaction. In contrast to the previous example, however, the four-membered intermediate formed in this case undergoes a retro [2 + 2] ring opening event to afford an azadienoate. Under the reaction conditions, various azadienoates were generated, in good to high yields, from a range of heterocycles.

7.3.2. Furan Synthesis.—Using butyn-1,4-diones, Yavari and co-workers reported an efficient route toward functionalized furans (Scheme 689).[784] In the presence of triphenylphosphine, activation of the pronucleophile and nucleophilic attack occur to give the ylide **439**. The intermediate **440** is obtained after a series of proton transfers and cyclization. Finally, the functionalized furan is formed after elimination of the phosphine oxide.

When applying imidazoles bearing various substituents (e.g., methyl and nitro groups) as substrates, the reaction led to the formation of functionalized furans in excellent yields (Scheme 690). Although the reaction was efficient, only a limited substrate scope was disclosed. The results led, however, to subsequent publications describing the use of 2-mercaptoacetate[785] and 4-methyleneoxetan-2-one[786] as alternative pronucleophiles.

Formation of furan derivatives has also been observed from the reactions of activated alkynes in the presence of a phosphine catalyst. In addition to olefin formation, annulation can also occur through a Wittig-like pathway, affording elaborated furan systems. Krische capitalized on this strategy by generating the highly reactive allenoate in situ, through a Wittig-like process, for annulation leading to functionalized furans.[787] Based on the proposed mechanism provided by Krische (Pathway A), the reaction proceeds through an allenoate intermediate (Scheme 691). Immediately after the allenoate intermediate is formed, nucleophilic addition of the phosphine occurs. After elimination of the phosphine, a highly functionalized furan is formed. Notably, the speculated pathway features (1) a highly reactive allenoate; (2) a less common ring closure of **441** onto a vinyl phosphonium species; and (3) an unfavorable proton transfer of **442** leading to the final product. For these considerations, an alternative mechanism (Pathway B) is also presented to explain the formation of the furan without proceeding through the unstable allenoate intermediate and avoiding the unfeasible proton transfer. While both mechanisms are consistent with the isotopic labeling experiment, they are difficult to verify.

Regardless of the reaction mechanism, a variety of functionalized furans have been synthesized in high yields under the optimized conditions (Scheme 692). Higher reaction yields were achieved when using electron-withdrawing γ-acyloxy groups. Aside from the alkynoate, the reaction was also efficient when a more highly activated alkynone was used, with comparable productivity observed at room temperature (entry 2). Furthermore, the reaction could tolerate perfluorophenyl and 2-furyl substituents, albeit giving slightly lower

product yields (entries 3 and 4). A nonaryl moiety could also be invoked, giving rise to an alkyl-substituted furan without affecting the yield (entry 5). When a more elaborate alkynoate was employed, a trisubstituted furan was obtained in high yield (entry 6).

Ylide generation can also be achieved through an in situ–generated nucleophile tethered to the activated alkyne. One such example was demonstrated by Kuroda and co-workers, who used conjugated enyne systems with aldehydes to facilitate the formation of furans (Scheme 693).[788] Under phosphine catalysis, addition of the phosphine led to formation of the ylide **443**. In the presence of an aldehyde, Wittig olefination occurred to generate the furan.

This strategy was, however, very limited, with minimal functionalization tolerated on the enyne and selected aldehydes (Scheme 694). Nevertheless, aldehydes bearing phenyl, *p*-methoxyphenyl, and ethyl groups reacted to afford their corresponding furans in good yields.

7.3.3. *α*–Umpolung-Wittig: Pyrrole Synthesis.—Anary-Abbasinejad and co-workers reported a three-component coupling reaction involving 2-aminothiazole, DMAD, and arylglyoxals (Scheme 695).[789] The reaction features initial ylide formation from 2-aminothiazole, DMAD, and triphenylphosphine to produce a phosphorus ylide that undergoes Wittig olefination to give the intermediate **444**. Subsequent condensation and aromatization leads to functionalized pyrroles with good efficiencies. In this system, various arylglyoxals presenting phenyl, *p*-chlorophenyl, and *p*-nitrophenyl groups were tolerated, leading to good yields of their products.

7.3.4. Cyclopentadiene Synthesis.—Adib and co-workers described a method for constructing functionalized cyclopentadienes through RC addition followed by Wittig olefination (Scheme 696).[790] Under the reaction conditions, an RC-type addition occurs, triggering an intramolecular cyclization to generate the intermediate **445**. Elimination of triphenylphosphine affords the target cyclopentadiene. The reaction is suitable for arylidenemalononitriles bearing various substituents (e.g., *p*-methyl and *p*-fluoro groups), providing their products in good yields.

7.4. Ylides from MBHADs

7.4.1. Wittig Reaction.—Based on their similar reactivity to allenes, MBHADs can also be employed in the Wittig reaction to afford functionalized trisubstituted dienes.[791] As one of the pioneers in the field of diene synthesis through nucleophilic addition, He reported an efficient transformation of MBHADs into functionalized dienes when using triphenylphosphine as the catalyst (Scheme 697). When employing a Boc-protected MBHAD, the phosphorus ylide is generated through deprotonation with *tert*-butoxide that is generated in situ; it undergoes olefination when in contact with an aldehyde.

In this reaction, electron-withdrawing *p*-nitrobenzaldehyde and 2-furaldehyde were tolerated as substrates, giving high yields of their corresponding trisubstituted dienes (Scheme 698, entries 1 and 2). Varying the substituents on the MBHAD did not affect the efficiency of the overall transformation (entries 2 and 3). In addition to aromatic aldehydes, alkyl aldehydes were also suitable as substrates, but required the use of the more nucleophilic

tributylphosphine as catalyst; although the transformation was facile, the diene product was obtained with lower diastereoselectivity (entry 4).

In addition to using trifluoromethyl ketones for the formation of 2,3-dihydrofuran derivatives, Ye has also employed MBHADs and tributylphosphine for Wittig olefination with trifluoromethyl ketones to provide functionalized dienes.[792] Diene derivatives featuring the *E,E*-isomeric geometry were prepared in good yields (Scheme 699). Moderate yields of the dienes were isolated when the trifluoromethyl ketones featured *p*-methoxyphenyl or 2-thienyl groups (entries 1 and 2). Similar efficiencies were observed when varying the aryl functionality on the Boc-protected MBHAD (entries 3 and 4). Compared with the olefination using aryl aldehydes, this transformation offers the ability to install a trifluoromethyl substituent on the diene system but with lower conversion to the product.

7.4.2. Benzannulation.—In 2012, Huang and co-workers reported an efficient method for generating various functionalized benzenes through intermolecular Wittig olefination followed by 6π-electrocyclization (Scheme 700).[793] When treating MBHADs with triphenylphosphine, the zwitterion forms and then reacts with the enone to give the intermediate **446**. After elimination of triphenylphosphine oxide, the triene **447** is obtained. The functionalized benzene is generated through pericyclic rearrangement and subsequent oxidation.

For activated arylenones bearing *p*-bromo, *p*-nitro, and *p*-methyl groups, highly substituted benzene derivatives were obtained in good yields (Scheme 701). Furthermore, both MBHADs with and without substituents were well suited for the reaction.

Two years later, Shi and co-workers employed various chromenones as reaction partners to generate a collection of functionalized benzchromenones (Scheme 702).[643] Chromenones bearing various substituents gave good yields of their desired products.

Although not catalytic, Zhou reported an example of asymmetric Michael–Wittig annulations using chiral phosphonium ylides.[794] Unlike the examples shown above, the 1,3-cyclohexadiene did not aromatize to form a benzene ring, presumably because the reaction was run without heating. Among several tested asymmetric phosphines, the chiral phosphine **P118** appeared to be the most efficient chiral source in the form of the phosphonium ylide. The reaction pathway is believed to involve initial Michael addition into the chalcone, followed by an intramolecular Wittig reaction to expel the phosphonium oxide as a byproduct (Scheme 703).

Moderate yields were achieved from various chalcones with good enantioselectivity (Scheme 704). Unfortunately, the reaction appeared to be sluggish when an alkyl substituent was present in the chalcone (entry 3). Although decent levels of enantioselectivity were achieved, the use of a stoichiometric amount of the chiral phosphine was inefficient in terms of both cost and material consumption.

7.4.3. Aza-Wittig Reaction.—In addition to Wittig olefination, annulation through an aza-Wittig process has also been reported, granting access to functionalized pyridazines. Zhu and Cheng disclosed a one-pot transformation combining amine and phosphine catalysis to

afford various pyridazines (Scheme 705).[795] In the reaction catalyzed by DABCO, the diazo-intermediate was generated in situ. Without workup, the phosphine was added to trigger the aza-Wittig annulation and provide pyridazines.

7.4.4. Butenolide Synthesis.—In addition to simple olefinations and benzannulations, Zhao and co-workers reported, in 2014, a phosphine-mediated procedure for butenolide formation from trifluoromethylketone and MBHADs (Scheme 706).[796] After forming the zwitterion, nucleophilic addition occurs to give the intermediate **448**. Lactonization then proceeds to give the ion pair **449**. Finally, deprotonation generates the phosphorus ylide in situ, with Wittig olefination affording the butenolide.

Surveying the reaction scope, trifluoromethylketones bearing various aryl groups were well tolerated, giving good yields of their products (Scheme 707). Although lower yields were obtained when the aryl ring contained an electron-donating functionality (e.g., *p*-methoxy group), the corresponding butenolides were isolated with high stereoselectivities, favoring the *Z*-isomers.

7.5. Ylides from Cyclopropene-1,1-Dicarboxylates

Rather than generating phosphorus ylides through nucleophilic addition of triphenylphosphine to DMAD, Ma and co-workers disclosed, in 2013, a method for diene formation using ylides generated from nucleophilic opening of cyclopropene-1,1-dicarboxylates (Scheme 708).[797] Based on the proposed mechanism, the zwitterion can be produced by treating an arylphosphine with cyclopropene-1,1-dicarboxylate. In the presence of an arylaldehyde, Wittig olefination occurs to give the diene.

Arylaldehydes bearing various functional groups, including *m*-methoxy and *p*-cyano units, reacted with the ylides generated from cyclopropene-1,1-dicarboxylate, producing functionalized dienes in good yields (Scheme 709).

7.6. Ylides from Gramine

Gramine can also be used to generate phosphorus ylides for Wittig olefination. In 2005, Magomedov and co-workers disclosed a method to access phosphorus ylides by treating gramine with tributylphosphine (Scheme 710).[798] Through the assistance of the phosphine, elimination of dimethylamine occurs to give the enimine **450**. After proton transfers, the ylide **451** is obtained. Eventually, the functionalized indole is afforded after Wittig olefination and the release of tributylphosphine oxide.

Functionalized indoles are important molecular scaffolds, especially in the areas of drug development and natural products synthesis. Using the ylides generated from gramine, a range of functionalized indoles could be accessed in good yields (Scheme 711). Although both aryl and alkylaldehydes were employed as substrates, the latter provided significantly lower yields.

7.7. Isolation of Stable Ylides

7.7.1. Ylides from Phosphine–DMAD–Nucleophiles.—In addition to the traditional approach of substitution of an alkyl halide with a tertiary phosphine and subsequent base treatment, the generation of phosphorus ylides can be realized through the use of pronucleophiles and an addition event. These pathways have been documented well by Yavari and Ramazani, using DMAD and triphenylphosphine in the presence of pronucleophiles. Ramazani and Odinets have written thorough Reviews providing further details.[759,799]

A general reaction mechanism can be depicted with initial nucleophilic addition of the tertiary phosphine into DMAD, facilitating the generation of a zwitterion (Scheme 712). Subsequent activation of the pronucleophile through deprotonation triggers nucleophilic addition into the resulting vinyl phosphonium species **452**, affording the phosphorus ylide **453**.

When haloacetylacetones are used as pronucleophiles, elimination of hydrogen halide can occur, with a subsequent annulation event generating the cyclic phosphoranes. According to the proposed mechanism, the vinyl phosphonium zwitterion deprotonates the haloacetylacetones (e.g., chloroacetylacetone).[800, 801] The corresponding conjugate base **454** then undergoes nucleophilic addition into the vinyl phosphonium species to form the phosphorus ylide **455**. Elimination of hydrogen chloride allows cyclization to occur, affording a moderate yield of the phosphorane (Scheme 713).

A similar process was observed by Maghsoodlou and co-workers when treating acetylenedicarboxylic acid with pronucleophiles (Scheme 714).[802] Unlike the reaction with DMAD, however, a decarboxylation event occurred during the formation of the phosphorus ylide, generating functionalized *phospho*-betaines. Various heterocyclic pronucleophiles, including carbazole, 2-oxindole, and isatin, were well suited to the reaction conditions, generating their products in good yields.

A more recent report of phosphorus ylide formation was disclosed by Anary-Abbasinejad and co-workers, who used 2-aminothiazole as the pronucleophile (Scheme 715).[803] Treating activated alkynes with 2-aminothiazole led to the efficient formation of phosphorus ylides, which were obtained in good yields. In addition to 2-aminothiazoles, the reactions of other nitrogen-based pronucleophiles, including phthalazin-1-one, 3-(phenylimino)indolin-2-one, and oxazolidin-2-one, also led to the formation of functionalized phosphorus ylides.[804]

7.7.2. Ylides from Phosphine–DMAD–Electrophiles.—Because of the huge number of literature reports of ylide formation, this Review does not cover the traditional approach toward phosphorus ylide formation under basic conditions. Several in-depth reports have been published that address this topic.[725,759,805,806] For the scope of this Review, only selected recent examples are presented in this section.

Nucleophiles can be used to generate stabilized phosphoranes; electrophiles can also be employed, forming different phosphorane derivatives. In 1997, Murata reported a rare cyclopropanation of a fullerene, using a stoichiometric amount of triphenylphosphine and

DMAD to generate a potent phosphonium cyclopropanating agent.[807] When DMAD is treated with triphenylphosphine, a vinyl phosphonium zwitterion is generated. In the presence of an olefin, cyclopropanation occurs across the π-system, leading to a stable phosphorane (Scheme 716). Chuang observed a similar transformation when using more nucleophilic phosphines.[808] Furthermore, Yang reported an example of ylide formation when using $Dy@C_{82}$.[809]

After working with DMAD and fullerenes, Chuang further explored the reactivities of fullerenes with more elaborate alkyne systems in the presence of various phosphines.[810] For ynoate–enoate systems, a formal [3 + 2] annulation occurred with fullerenes (Scheme 717). In contrast to the previously mentioned [3 + 2] annulation, the phosphine catalysts were not released from the substrates, thereby generating several functionalized phosphoranes.

From the reactions of a range of phosphines, various fullerene derivatives were prepared in modest yields (Scheme 718). Moderate conversions to the desired annulation products were observed when using tris(*p*-methoxyphenyl)phosphine and triphenylphosphine (entries 1 and 2). While their reactions proceeded to afford annulation products, low yields were obtained with other phosphines (entries 3 and 4).

In addition to Murata's reports, Nair demonstrated the efficient formation of functionalized phosphoranes when using the vinyl phosphonium zwitterion generated from DMAD and triphenylphosphine.[811] In the proposed pathway, the vinyl phosphonium zwitterion adds into benzylidenemalononitrile to afford the intermediate **456** (Scheme 719). Subsequent cyclization occurs to give the dienol **457** after tautomerization. Deprotonation of the dienol **457** with methoxide generated in situ furnishes the derivatized phosphorane. This reaction is reminiscent of Winterfeldt's DMAD–aldehyde/ketone γ-butenolide synthesis (Scheme 1).[3] Unlike the situation in Winterfeldt's example, cyclopentenone is not formed. This result can be attributed to the formation of an acidic benzylic proton, located at the α-position of the dicyano group, leading to rapid dienol–enone tautomerization that prevents conjugate addition of the methoxide anion.

Under the reaction conditions, functionalized phosphoranes have been prepared in good yields from various aryl- and alkylidenemalononitriles (Scheme 720). The reaction yield was better when an electron-withdrawing *p*-trifluorophenyl group was installed on the olefin (entry 1). When the less electron-withdrawing cinnamylidenemalononitrile was employed, the yield was significantly lower (entry 2). A strongly electron-withdrawing aryl nitroalkene also gave a comparable yield of the desired phosphorane (entry 3).

More complex substrates, including isatin-derived electrophiles, were used by Yan and co-workers to give functionalized spiro phosphorus compounds (Scheme 721)[812,813] Under the reaction conditions, both isatylidenemalononitrile and 3-aroylmethyleneoxindole generated their corresponding complex spirooxindole-derived ylides in good yields. Nevertheless, the scope of the reaction appeared limited.

In 2011, Chuang reported another phosphine-mediated annulation for the preparation of cyclic phosphoranes from highly conjugated enynes and aromatic aldehydes (Scheme 722).[814] Under the reaction conditions, highly activated aldehydes (e.g., *p*-nitro- and *p*-

cyanobenzaldehyde) were necessary to provide moderate yields of the desired phosphoranes. A variety of phosphines could also be used to generate corresponding phosphoranes with various substituents on the phosphorus center. Although aldehydes were employed in this reaction, none of the olefination product was observed. An improved procedure was reported a year later, with the use of tris(*p*-tolyl)phosphine allowing a lower reaction temperature.[815] In addition to enyne systems, a diyne substrate had also been employed, triggering the same transformation.[816] Furthermore, an example of the use of *o*-nitrocinnamaldehyde has also been reported.[817]

Further exploring the reactions producing ylide-containing butenolides, Chuang and co-workers expanded the repertoire to incorporate arylaldimines, resulting in functionalized ylides bearing dihydropyrrolones (Scheme 723).[818] Under the optimized conditions, the products were obtained in moderate yields when using electron-poor arylaldimines bearing such substituents as *p*-nitro, *p*-cyano, and *m*-nitro groups.

Chuang and co-workers also demonstrated the formation of ylide-containing furans from activated diyne systems (Scheme 724).[819] Upon nucleophilic addition, the zwitterion is generated in the presence of an arylaldehyde. Subsequent intramolecular cyclization and aromatization produce the ylide.

Various ylide-containing furans were isolated in high yields, with the reaction tolerating a range of arylaldehydes bearing such substituents as *p*-nitro and *p*-cyano groups (Scheme 725). The product yields were lower, however, when using less activated arylaldehydes.

In a more elaborate system, Huang and Chen discovered a novel method for phosphorane formation from an enone–enoate and an enoylester in the presence of a stoichiometric amount of tributylphosphine.[153] In the proposed mechanism, the intermediate generated from the enone–enoate and enoylester undergoes elimination of the phosphine, with a proton transfer event providing the intermediate **458** (Scheme 726). Subsequent nucleophilic addition of tributylphosphine leads to an annulation event that furnishes the phosphonium intermediate **459**. Upon dehydration, the functionalized phosphorane **460** is generated.

Under the ideal reaction conditions, the phosphorane derivatives were prepared in high yields. Both *m*-methoxyphenyl and *p*-fluorophenyl functionalities on the enone–enoate were compatible with the conditions, giving high yields of their desired phosphoranes (Scheme 727, entries 2 and 3). When a more sterically demanding 2-naphthyl substituent was present on the enoylester, a significantly lower yield of the phosphorane was observed, accompanied by a prolonged reaction time (entry 4).

8. MISCELLANEOUS TOPICS

8.1. Hüisgen Zwitterions

8.1.1. Annulation of Hüisgen Zwitterion and DMAD.—

In 1963, Cookson and Locke studied the reactivity of phosphonium zwitterion species and discovered an annulation reaction between diethyl azodicarboxylate (DEAD) and DMAD that generated pyrazoles.[820] Although the product pyrazole was successfully isolated and characterized

well, the identity of the active zwitterion was not determined. It was not until 1969 that Hüisgen revealed the structure of the active phosphonium zwitterion (Hüisgen zwitterion), which was later recognized as the reactive intermediate in the famous Mitsunobu reaction.[821] The mechanism of the annulation between DEAD and DMAD in the presence of a phosphine begins with nucleophilic addition of the phosphine into DEAD to generate the Hüisgen zwitterion (Scheme 728). This zwitterion undergoes annulation with DMAD, followed by formation of the oxaphosphetane **461**. After an aza-Wittig reaction, the functionalized pyrazole is formed with high efficiency. The reaction with the Hüisgen zwitterion occurs with DMAD predominantly; reactions with regular acetylenes are not known. In this Review, we cover only selected examples of stoichiometric phosphine reactions. There is a wonderful Review, written by Nair, covering studies up to 2006, with an in-depth discussion of annulations involving nucleophilic phosphines and DEAD.[10] In addition, Swamy has provided a detailed Review of the Mitsunobu reaction.[822]

8.1.2. Reactions of Hüisgen Zwitterion and Ketones/Aldehydes.—In addition to DMAD, activated ketones and aldehydes are also well suited to annulation with the Hüisgen zwitterion. In 2005, Lee demonstrated the synthesis of derivatized 1,3,4-oxadiazolines from the Hüisgen zwitterion and glyoxylates.[823] In the proposed mechanism, the reaction begins with addition of the Hüisgen zwitterion across the glyoxylate, leading to the intermediate **462** (Scheme 729). After an aza-Wittig process, the functionalized 1,3,4-oxadiazoline is afforded.

Using various glyoxylate derivatives, substituted 1,3,4-oxadiazolines have been prepared in high yields under mild reaction conditions (Scheme 730). Both phenyl and methyl substituents were suitable side chains on the glyoxylates, giving their products with high efficiency (entries 1 and 2). Interestingly, a notable drop in product yield occurred when the more activated 2,3-butanedione was applied (entry 4). Although ketones could be used in annulations with the Hüisgen zwitterion, highly activated ketones (e.g., glyoxylate) were required for good efficacy.

A similar transformation was documented by Nair, in the same year, when using isatins as substrates.[824] Here, functionalized spiro-1,3,4-oxadiazolineoxindoles were prepared in moderate to high yields (Scheme 731). In this reaction, both DEAD and DIAD were suitable sources of the Hüisgen zwitterion, giving fair yields of their spirocyclic products.

The first report on catalytic reactions of Hüisgen zwitterions with ketones appeared in 2015. Inspired by the work of O'Brien[825] and Beller,[826] Voituriez and Fourmy disclosed the first phosphine-catalyzed reaction between diazoesters and α-ketoesters (Scheme 732).[827] The key step is the in situ reduction of the formed triphenylphosphine oxide to give the corresponding tertiary phosphine suitable for the next catalytic cycle. Through a catalytic system combining 9-phenylphosphine-fluorene (15 mol %) as the catalyst, $PhSiH_3$ (2.5 equiv) as the reducing agent, $(4\text{-}NO_2C_6H_4O)_2PO_2H$ (5 mol %) as the acidic additive, and diisopropylethylamine (DIPEA, 5 mol %) as the base, various dialkyl azodicarboxylates cyclized with alkyl α-ketoesters to afford 1,3,4-oxadiazolines in yields of 33–80%. Similar to Nair's results, the reactions of aryl α-ketoesters, under slightly modified conditions, led to the generation of *N,N*-dicarboethoxy monohydrazones in yields of 36–66%. They postulated

a plausible mechanism for the transformations, involving the phenylsilane-mediated reduction of triphenylphosphine oxide to the corresponding tertiary phosphine in the presence of bis(*p*nitrophenyl)phosphate/diisopropylethylamine (Scheme 733).

In addition to the formation of 1,3,4-oxadiazolines from glyoxylate derivatives, Nair reported the formation of functionalized dihydro-1,2,3-benzoxadiazoles from the Hüisgen zwitterion and 1,2-benzoquinones.[824] According to the proposed reaction pathway (Pathway A), the Hüisgen zwitterion attacks the 1,2-benzoquinone to form the intermediate **463** (Scheme 734). A subsequent aza-Wittig reaction produces the intermediate **464**, which undergoes rearrangement to give the functionalized dihydro-1,2,3-benzoxadiazole **465**. An alternative mechanism (Pathway B) can be proposed for both reactions. The formation of the immediate oxaphospholane **466** leads to the elimination of triphenylphosphine oxide, with subsequent ring closure granting the dihydro-1,2,3-benzoxadiazole **465**.

After optimization, the reaction produced dihydro-1,2,3-benzoxadiazole derivatives in high yields (Scheme 735). Both bulky *tert*-butyl and diphenylmethyl substituents were compatible on the 1,2-benzoquinone ring system, giving high yields of the annulation products. Although good yields of the dihydro-1,2,3-benzoxadiazoles were obtained, the reaction appears very limited in terms of its substrate scope.

Further expanding the repertoire of Hüisgen zwitterion annulations, Nair and co-workers demonstrated, in 2007, an elegant process using 1,3-diarylprop-2-en-1-one and diarylidene acetone systems to access functionalized pyrazolines and pyrazolopyridazines.[828] According to the mechanism (Pathway A), the Hüisgen zwitterion undergoes nucleophilic addition at the carbonyl carbon of the chalcone (Scheme 736). Formation of the oxaphosphetane **467** and elimination of the phosphine oxide generates the intermediate oxadiazole **468**. The corresponding oxadiazole **468** undergoes rearrangement, forming the functionalized pyrazole. As previously mentioned, an alternative mechanism (Pathway B) can be proposed, passing through a common oxaphospholane intermediate.

Under the reaction conditions, the activated chalcone bearing a *p*-nitrophenyl substituent gave a high yield of its pyrazoline within a short period of time (Scheme 737). When an electron-donating chalcone presenting a *p*-methoxyphenyl group was used, a lower yield was obtained. Switching from the 1,3-diarylprop-2-en-1-one system to a more extended diarylidene acetone system, functionalized pyrazolines were formed and immediately underwent hetero-Diels–Alder reactions with diisopropyl azodicarboxylate (DIAD) to afford pyrazolopyridazines with good efficiency. Similar to the formation of the pyrazolines, a higher yield of product was isolated when using a diarylidene acetone bearing an electron-withdrawing *o*-fluorophenyl group. A 2-thienyl substituent was also applicable under the reaction conditions, albeit with the product formed in lower yield.

When attempting to generate oxadiazoles, hydrazone derivatives were isolated. In 2005, Nair reported the formation of hydrazones from reactions of benzil derivatives with the Hüisgen zwitterion.[829] In the proposed mechanism, the Hüisgen zwitterion undergoes nucleophilic addition into benzil to give the intermediate oxaphospholane **469** (Scheme 738). Upon elimination of triphenylphosphine oxide and transesterification, the desired hydrazone is

obtained. In this mechanism, the formation of the oxaphospholane **469** is most consistent with the alternative mechanisms in Schemes 734 and 736 and is also consistent with the mechanism proposed by Shi in Scheme 741.

Benzil derivatives bearing electron-withdrawing trifluoromethyl and electron-donating methyl substituents were tolerated under the reaction conditions (Scheme 739, entries 1 and 2). Because of the electronic nature of the substituent, a significantly lower yield was observed when a methyl substituent was located on the benzil system (entry 1). Di-2-thienylethanedione could also be reacted, albeit with a low yield of product (entry 3). Although symmetrical benzil derivatives have been used to avoid regioselectivity issues, they make the transformation less practical.

α-Ketoester derivatives were also compatible substrates for this reaction.[830] In the presence of 1.5 equiv of $P(NMe_2)_3$, the reactions of various aryl *α*-ketoester derivatives with DIAD and DEAD afforded *N*-acyl hydrazones in moderate to excellent yields (Scheme 740).

Another method for the formation of functionalized hydrazones from the Hüisgen zwitterion was reported by Shi in 2009—in this case, using cyano ketones.[831] Notably, in addition to the formation of hydrazones, the intermediate azadienes were also isolated, supporting the proposed mechanism. Accordingly, the active Hüisgen zwitterion undergoes addition into the cyano ketone to form the five-membered oxaphospholane **470** (Scheme 741). Upon elimination of triphenylphosphine oxide, following ester group transfer, the functionalized azadiene **471** is generated. Further heating of the azadiene **471** leads to the generation of the hydrazone through a second ester migration.

While both electron-donating and -withdrawing substituents were suitable for the reaction (Scheme 742), an electron-donating *p*-methoxyphenyl group facilitated a higher yield for the generation of its corresponding azadiene. The formation of the azadiene or the hydrazone could be selected merely by varying the reaction temperature.

When an electrophile–nucleophile system was employed, in the case of salicylaldehyde, the generation of the hydrazone was accompanied by Boc-protection of the phenolic alcohol (Scheme 743). Based on the mechanism proposed by Girard (Pathway A),[832] the reaction proceeds through an initial transcarbonation, followed by an aza-Wittig reaction, affording the hydrazone. Alternatively, the reaction can also progress through the familiar oxaphospholane **472**, promoting the generation of the Boc-protected hydrazone, in concordance with Shi's proposal (Pathway B).

Good yields of Boc-protected hydrazones were obtained from the reactions of functionalized salicylaldehydes bearing methoxy and hydroxy functionalities (Scheme 744). When 2,4-dihydroxybenzaldehyde was employed, superstoichiometric amounts of di-*tert*-butyl azodicarboxylate (DBAD) and triphenylphosphine were required to provide a good yield of the desired hydrazone, without protecting the hydroxyl group at the para-position, suggesting that the transfer of the Boc group occurs intramolecularly, supporting the alternative mechanism.

Without isolating the hydrazones, Lee reported the formation of vinyl hydrazine derivatives when using ketones bearing an acidic hydrogen atom at the α-carbon.[823] Similarly, the reaction proceeds through the favorable oxaphospholane structure. In the proposed pathway, the initially generated Hüisgen zwitterion adds into the ketone, producing the intermediate **473** (Scheme 745). After expelling triphenylphosphine oxide, the corresponding vinyl hydrazine **474** is constructed. This mechanism is slightly different from the mechanisms proposed by Shi (Scheme 731) and the alternative mechanisms for Nair (Schemes 724 and 726)—those involve deprotonation at the α-carbon.

Good to high yields of vinyl hydrazines were obtained under the optimized conditions (Scheme 746). In general, both acyclic and cyclic ketones were applicable, affording their corresponding hydrazines. A low efficiency was observed, however, when cycloheptanone was used as the substrate (entry 2).

In general, functionalized hydrazones were obtained when treating the Hüisgen zwitterion with simple ketones. On the other hand, when an aldehyde was used, complex bis-hydrazines were generated with the incorporation of two Hüisgen zwitterions.[823] In the reaction reported by Lee, the Hüisgen zwitterion is predicted to undergo nucleophilic addition into the alkyl aldehyde, producing the intermediate **475** (Scheme 747). With the loss of triphenylphosphine oxide and subsequent addition of another Hüisgen zwitterion, the intermediate **476** is formed, providing the bis-hydrazine **477** upon workup.

When employing a range of alkyl aldehydes, complex bis-hydrazines were constructed, but with mediocre efficiencies (Scheme 748). The scope of the reaction was, therefore, limited —it was suitable only for alkyl aldehydes and occured with low yields.

8.1.3. Annulation of Hüisgen Zwitterion and Allenes.—Informed by the studies of the reactivity of the Hüisgen zwitterion with DMAD and carbonyls, Nair reported annulation reactions using the Hüisgen zwitterion and allenoates as electrophiles to generate functionalized pyrazolines and pyrazoles.[833] No examples of the reactions of the Hüisgen zwitterion and regular alkenes were reported; more activated systems, like allenes, were needed. Looking into the proposed mechanism, the active Hüisgen zwitterion undergoes immediate addition into the α-substituted allenoate to give the zwitterionic species **478** (Scheme 749). After an intramolecular aza-Wittig reaction, the derivatized pyrazoline is formed.

When using a stoichiometric amount of triphenylphosphine, moderate yields of the pyrazolines were constructed (Scheme 750). Depending on the electronic properties of the aryl groups on the allenoate, various yields were obtained. Higher yields of the pyrazolines were obtained when more electron-withdrawing *p*-nitro and *m*,*p*-dichlorophenyl substituents were present. The mechanism has been studied using DFT.[834]

When employing γ-substituted allenoates as substrates, the reactivity of the Hüisgen zwitterion shifted to generate functionalized pyrazoles.[833] According to the reaction mechanism proposed by Nair (Pathway A), the addition of the Hüisgen zwitterion occurs across the γ-substituted allenoate to give the intermediate **479** (Scheme 751). A subsequent

ester transfer and intramolecular aza-Wittig reaction provide the pyrazoline. Upon isomerization of the olefin, the pyrazole is generated. Although this mechanism appears to be reasonable, an inconsistency is noted when comparing it with the mechanism for the formation of the pyrazolines. To avoid any discrepancy, an alternative pathway (Pathway B) can be invoked that does not require the additional ester transfer step for the intermediate **479**.

Under the optimal conditions, substituted pyrazoles were isolated in fair yields (Scheme 752). While both alkyl and aryl γ-substituted allenoates were applicable as substrates, a lower yield was obtained for the reaction of *p*-methoxyphenyl-substituted allenoates.

Two years after Nair's report, Swamy and co-workers used DEAD and allenes as electrophiles to achieve annulations in the presence of a phosphine (Scheme 753).[835,836] Instead of employing common allenoates, they used allenyl phosphonates. The reaction proceeds through a mechanism similar to that proposed by Nair for pyrazoline formation (Scheme 728). Under the ideal conditions, functionalized pyrazoles were synthesized in good yields when using allenyl phosphonates and DEAD. In contrast to the formation of pyrazolines reported by Nair, the resulting phosphonate group could be removed in an acidic medium, furnishing the corresponding pyrazole when an α-substituted allenyl phosphonate was used.

8.1.4. Annulation of Hüisgen Zwitterion and Imines.—

Analogous to the annulation between DEAD and carbonyls, imines can also serve as potent electrophiles of choice, promoting the formation of nitrogen-rich heterocycles. In 2011, Shi reported an annulation process using imines and the Mitsunobu reagent to prepare several triazole derivatives.[837] Notably, instead of administering the imine directly into the reaction mixture, a precursor carbamate was used to generate the active imine species in situ. In this reaction, nucleophilic attack of the phosphine into DEAD affords the classic Hüisgen zwitterion, which promotes the in situ formation of the imine (Scheme 754). Further nucleophilic addition by a second Hüisgen zwitterion gives the intermediate **480**, followed by an aza-Wittig reaction that provides the triazole.

When using a superstoichiometric amount (3 equivalents) of the Mitsunobu reagent, excellent yields of triazole derivatives were obtained from various imines (Scheme 755). For this reaction, highly activated aryl ring systems, including *p*-nitro- and *p*-trifluoromethylphenyl, were preferred, giving excellent yields of their triazole compounds. In addition to aromatic imines, a cyclohexyl imine was generated in situ to provide its target triazole, albeit in slightly lower yield.

8.2. Phosphine-Mediated Reduction

8.2.1. Deoxygenation of Propargyl Alcohol.—

In addition to their use in well-established phosphine-catalyzed annulations and nucleophilic additions, tertiary phosphines can also be employed as reductants for such substrates as propargyl alcohols, glyoxylates, and isatin derivatives. A short Communication by Lu in 1993 reported a mild deoxygenation–isomerization process involving the assistance of triphenylphosphine.[838] The proposed reaction pathway begins with nucleophilic addition of triphenylphosphine into the

activated alkynoate (Scheme 756). Upon proton transfer, the vinyl phosphonium alkoxide **481** is generated, leading to formation of the oxaphosphetane **482**. After elimination of triphenylphosphine oxide, the corresponding allenoate isomerizes to the dienoate under phosphine catalysis.

Under the optimal reaction conditions, high yields of dienoates were obtained after treatment with triphenylphosphine at ambient temperature (Scheme 757). Alkynoates bearing an *n*-propyl group at the γ-position also reacted to afford their target dienoates with comparable efficiencies. After switching the activating ester group to a more electrophilic ketone functionality, the transformation preserved its reactivity and maintained the yield of the product.

8.2.2. Reduction of α,β-Unsaturated Carbonyls.—In 2003, Giri and co-workers demonstrated a reduction of maleimides, mediated by phosphines in methanol (Scheme 758).[839] The reduction begins with nucleophilic addition of triphenylphosphine to the maleimide, followed by formation of the intermediate **483** through protonation and oxidation. After elimination of triphenylphosphine oxide, the succinimide is obtained.

Treating maleimides bearing various protecting groups (e.g., benzyl, cyclohexyl, and aryl units) with triphenylphosphine in methanol under reflux produced functionalized succinimides in good yields (Scheme 759). Nevertheless, the reaction appears to be limited in its substrate scope.

Further expanding the scope of phosphine-mediated reductions, Shi demonstrated that a stoichiometric amount of trimethylphosphine can efficiently reduce functionalized isatin derivatives.[840] In the proposed reaction mechanism, nucleophilic addition of the phosphine generates the phosphonium enolate **484**, which is protonated by water (Scheme 760). Ketone–enol tautomerization then gives the phosphonium intermediate **485**. Oxidation of the phosphine catalyst, followed by elimination, affords the 2-oxindole derivative.

For this reaction, both methyl and trifluoromethyl groups on the isatin ring system are suitable substituents, providing excellent yields of the corresponding 2-oxindoles (Scheme 761, entries 3 and 5). Comparable efficiencies were observed when using both ketones and esters as activating groups (entries 1 and 2). Removing the protecting group on the isatin nitrogen, the reaction proceeded smoothly to give an excellent conversion to the 2-oxindole, without an erosion in yield (entry 4). Interestingly, the yield was significantly lower when a trifluoromethyl group was installed at the 7-position (entry 5). A lower yield was also observed when an electron-withdrawing Boc protecting group was used instead of the electron-donating benzyl protecting group (entry 6).

In 2011, Trofimov and co-workers applied triphenylphosphine to reduce a variety of arylalkynones to arylalkenones with good efficiencies (Scheme 762).[841] Initial addition of the phosphine and deprotonation of water led to the ion pair. After further proton transfers, the zwitterion **486** undergoes Wittig olefination, resulting in formation of the alkenone.

Arylalkynones with various substituents (e.g., phenyl, 2-furyl, and 3-pyridinyl groups) were well suited for the reaction, giving their product alkenones in great yields (Scheme 763).

8.2.3. Reduction of Ketones to Alcohols.—A novel reduction of aromatic glyoxylates, mediated by trimethylphosphine, was documented by Shi in 2006.[842] When using the highly nucleophilic trimethylphosphine, glyoxylates were reduced to give functionalized α-hydroxy esters with high efficiency. In the proposed mechanism, nucleophilic addition of trimethylphosphine occurs at the ketone center of the glyoxylate, forming the intermediate **487** (Scheme 764). Rearrangement of the intermediate **487** provides the reduced intermediate **488**. Upon workup, the reduced α-hydroxy ester is afforded.

Both aromatic and alkyl glyoxylates reacted under the optimized conditions, producing high yields of their α-hydroxy esters (Scheme 765). The reaction tolerated mildly electron-withdrawing substituents (e.g., *p*-chlorophenyl) and strongly electron-donating functionality (e.g., *p*-methoxylphenyl) (entries 1 and 2). When a cyclohexyl ring was present as a substituent, an excellent yield of the reduced product was isolated (entry 3). As an alternative to using an ester as the activating group, a phosphonate was also well suited to the conditions, giving its corresponding reduction product (entry 4).

In the following year, Shi and co-workers reported a phosphine-mediated reduction of trifluoromethylketones (Scheme 766).[843] In the presence of tributylphosphine, addition to a trifluoromethylketone occurs to give the intermediate **489**. Through intramolecular delivery of hydride, the alcohol is afforded after elimination of tributylphosphine oxide.

Under the reaction conditions, various trifluoromethylketones bearing aryl groups (e.g., *p*-chlorophenyl, *p*-bromophenyl, and *o*-tolyl rings) provided high yields of their corresponding alcohols (Scheme 767). Notably, more activated trifluoromethylketones provided higher product yields.

In 2006, Moiseev, James, and Hu documented the phosphine-mediated reductions of aromatic aldehydes to benzyl alcohols in water.[844] In the presence of a stoichiometric amount of tris(3-hydroxypropyl)phosphine $[HO(CH_2)_3]_3P$, (THPP), a wide spectrum of aromatic aldehydes underwent reduction to substituted benzyl alcohols in water under an Ar atmosphere for 72 h. Good yields were obtained for most cases, except from the reaction of bulky 2,4,6-trimethylbenzaldehyde (10% yield; Scheme 768). Based on deuterium-labeling experiments, they proposed a plausible mechanism for the reduction (Scheme 769).

In addition to reporting simple reductions of carbonyl compounds, Shi and co-workers also disclosed a reductive coupling reaction (Scheme 770).[845] Nucleophilic addition of a phosphine activates a cyanoketone to undergo addition and elimination processes, generating the intermediate **490**. With water assisting the oxidation of the phosphine, the cyanohydrin is afforded. All three proposed mechanisms for the reduction of ketones to alcohols have been supported through recent computational analyses, with distinct intermediates.[846]

Arylcyanoketones bearing a range of substituents, including *p*-chloro and *p*-methyl groups, were compatible with the reaction conditions, providing their products in high yields (Scheme 771). 2-Furylcyanoketone was also applicable to the reaction, leading to a good yield of its cyanohydrin.

8.2.4. Reduction of Nitrones.—Toy reported another phosphine-mediated reduction: using tributylphosphine to reduce nitrones and generate endocyclic imines (Scheme 772).[847] Upon addition of tributylphosphine, Wittig reactions occurred to give the reduced cyclic imines in moderate yields. Although the efficiencies were good, the scope of the reaction was limited.

8.2.5. Reductive Aziridination.—In contrast to the reactions between alkenes/allenes/alkynes and electrophiles, the phosphine-catalyzed reactions of aldehydes and imines yield functionalized aziridines. Shi demonstrated that the addition of a phosphine into an imine generates an amino phosphonium species that undergoes aziridination in the presence of an aldehyde.[848] In the proposed mechanistic pathway, addition of triethylphosphite into the imine generates the amino phosphonium species (Scheme 773), which, in contact with *p*-nitrobenzaldehyde, forms the oxazaphospholane **491** intermediate. Upon elimination of the phosphine oxide, the functionalized aziridine is afforded.

Shi reported that triethylphosphite mediates the efficient aziridination of aromatic aldehydes, providing diaryl-substituted aziridines in good yields. Under the ideal conditions, the reaction produced a high yield when applying an imine bearing a *p*-bromophenyl ring system, with the product obtained as a nearly equal mixture of cis and trans isomers (Scheme 774, entry 1). A dramatic drop in reaction efficiency and a prolonged reaction time were observed when using *p*-tolualdimine (entry 3). Thus, although aziridination of aldehydes is possible, the reaction scope is limited to highly activated *p*-nitrobenzaldehyde and only a selected number of imines.

8.2.6. Reductive Cyclopropanation.—Along with the examples of aldehyde aziridination, Shi also reported examples of cyclopropanation of cyano ketones proceeding through a *β*-phosphonium anion intermediate (Scheme 775).[849] In the proposed mechanism, nucleophilic addition of tributylphosphine occurs across the activated benzylidenemalononitrile with subsequent addition into the highly activated cyano ketone. The generated oxaphospholane **492** undergoes collapse of the ring system to afford the functionalized cyclopropane and tributylphosphine oxide.

Under the optimized conditions, various functionalized cyclopropanes were synthesized in good yields (Scheme 776). A highly activated cyano ketone was required to ensure an efficient transformation. The functionalized cyclopropane was obtained in good yield when reacting an arylidenemalononitrile presenting a *p*-bromo group (91%), but a significant decrease in yield occurred when a more sterically demanding orthosubstituted system was present (47%). Although the amount of product formed was lower in the reaction of 2,3-dichlorobenzylidenemalononitrile, the level of diastereoselectivity was higher (85:15 vs. 57:43 for *p*-bromobenzylidenemalononitrile).

He and co-workers also reported a phosphine-mediated reductive cyclopropanation of arylpyruvates and activated oxindoles (Scheme 777).[850] The Kukhtin–Ramirez adduct **493** is generated when treating the pyruvate with the phosphine; it undergoes addition to the activated oxindole. After elimination of the phosphine oxide, the functionalized cyclopropane **494** is produced.

Excellent efficiencies were observed for arylpyruvates bearing various aryl groups, including *p*-tolyl and 2-thienyl units (Scheme 778). Furthermore, various oxindoles were compatible with the reaction conditions, giving excellent yields of their spirocyclopropaneoxindoles along with good diastereoselectivities.

Phosphine-mediated cyclopropanation can also be applied to allenoate systems. In 2010, He published an efficient route toward functionalized cyclopropanes starting from activated allenoates (Scheme 779).[851] As in the case of cyclopropanations using a cyano ketone and arylidenemalononitriles, the reaction proceeds through a familiar oxaphospholane intermediate (Scheme 775). From the vinylidenesuccinate, the initially generated vinyl phosphonium anion undergoes γ-addition to the aldehyde, leading to the vinylogous ylide **495**. Subsequent isomerization of **495** gives the ylide **496**, which forms the five-membered oxaphospholane **497**. After elimination of triphenylphosphine oxide, the functionalized cyclopropane is isolated.

The highly activated aldehydes *o*-trifluoromethylbenzaldehyde and 4-pyridinecarboxaldehyde provided higher yields of their desired vinyl cyclopropanes, each favoring the *trans*,*Z*-isomer (Scheme 780, entries 1 and 2). When using the strongly electron-withdrawing *p*-nitrobenzaldehyde, the yield of the reaction was maintained, but with significantly lower selectivity (entry 3). Interestingly, the yield from the reaction with 4-tolualdehyde plummeted, and the reaction time was longer (entry 4).

8.2.7. Reduction of Azobenzene.—In 2012, Radosevich and co-workers disclosed a novel phosphine that catalyzes the transfer hydrogenation of azobenzene (Scheme 781).[852] In the presence of ammonia–borane complex, the planar phosphine acquired a molecule of hydrogen through hydrogen transfer, forming the dihydridophosphorane **498**, which, in turn, transferred the hydrogen to azobenzene with excellent efficiency. This transformation is a rare example of a main group element undergoing two-electron redox catalysis.

8.2.8. Reductive Coupling of α-Ketoesters.—In addition to phosphine-catalyzed transfer hydrogenation, Radosevich and co-workers also demonstrated a novel phosphine-mediated reductive coupling of an α-ketoester and pronucleophiles (Scheme 782).[853] In the proposed mechanism, the intermediate **499** is formed in the presence of the phosphine. Protonation then results in the formation of **500**. After elimination of the phosphine oxide, the functionalized ester is obtained.

Various pronucleophiles, including phenols, carboxylic acids, alcohols, and imidazoles, tolerated the optimal reaction conditions, giving high yields of their product esters (Scheme 783). Furthermore, other nitrogen-based pronucleophiles, including tosylamides, phthalimide, and pyrazole, were also compatible.

Having found successful examples of oxygen- and nitrogen-based pronucleophiles for the reductive coupling reactions, Radosevich's group expanded the scope of the reaction to include carbon-based pronucleophiles, including dimethyl malonate, acetoacetone, and α-cyanoesters (Scheme 784).[854] Under the reaction conditions, α-ketoesters bearing various

substituents (e.g., *p*-tolyl, *p*-trifluoromethylphenyl, 2-thienyl, and phenylethyl units) provided functionalized 1,4-dicarbonyl compounds in high yields.

8.2.9. Homocondensation of Benzylidenepyruvates.—Trailblazing the area of phosphine-mediated reductive couplings, Radosevich and co-workers also disclosed an efficient homocondensation of benzylidenepyruvates (Scheme 785).[855] In this reaction, homocondensation occurs in the presence of a phosphine to generate the zwitterion **501**. Further incorporation of another molecule of the arylidenepyruvate produces the intermediate **502**. After cyclization and elimination of the phosphine oxide, nucleophilic ring opening mediated by HMPT affords the intermediate **503**. A series of proton transfers then leads to the functionalized dihydropyran.

Under the optimized conditions, arylidenepyruvates bearing various aryl groups (e.g., *p*-fluorophenyl, *p*-methoxylphenyl, and 2-furyl rings) provided their corresponding dihydropyrans in good yields (Scheme 786). Although a heteroaryl 2-furylidenepyruvate could also be employed, a lower product yield was observed.

8.3. Phosphonium Salt Catalysis

Phosphonium salt organocatalysis, especially its chiral variants, has attracted much attention and has made great progress in the past decade. Generally, phosphonium salts are applied as phase-transfer catalysts or Lewis acid organocatalysts in organic synthesis. They have been used extensively in a wide range of C–C, C–O and C–N bond-forming reactions under homogeneous conditions. For asymmetric catalysis, various phosphonium salt organocatalysts (e.g., P-spiro chiral tetraaminophosphonium salts with halides as well as carboxylates as counterions; binaphthyl-based *P*-spirocyclic arylaminophosphonium barfates; binaphthyl-based phosphonium salts functionalized at the 2- and 2′-positions with phosphonium and hydroxyl, amide, urea, and sulfonamide groups; amino acid-based bifunctional or multifunctional phosphonium salts with amide, urea, and thiourea moieties) have been applied in an array of asymmetric reactions. Several Reviews, including one in 2017, have summarized the applications of phosphonium salts as Lewis acidic catalysts as well as phase-transfer catalysts in organic synthesis.[856–860] Therefore, our Review does not further discuss phosphonium salt catalysis.

8.4. Iminophosphorane Catalysis

In the area of asymmetric organocatalysis, chiral Brønsted base-catalyzed asymmetric reactions rank among the most studied in organocatalysis, enabling rapid access to simple as well as architecturally complex chiral compounds. Typically, the catalytic cycles of these reactions involve formation of ion pairs, with the chiral cation providing the stereochemical control. Among these reactions, cinchona alkaloids and their variants are commonly used as chiral catalysts. Some reactions, however, require the use of stronger bases. Therefore, chiral bases bearing guanidine,[861–864] cyclopropenimine,[865] and iminophosphorane[866] structural motifs have been developed and used as powerful Brønsted bases for organocatalysis. Among them, the iminophosphoranes have attracted much attention since Schwesinger first reported the phosphazenes[867]—derivatives of iminophosphoric acid bearing three aminoalkyl groups connected to the phosphorus atom. In the past decade, various

iminophosphoranes have been prepared and applied as organosuperbase catalysts in organic synthesis. In this Review, we briefly discuss those asymmetric reactions using iminophosphorane organosuperbases as chiral catalysts.

8.4.1. Aldol and Nitroaldol Reactions.—In 2007, the Ooi group synthesized a series of chiral tetraaminophosphonium salts, each possessing a phosphorus-centered [5.5]-spirocyclic core, in a single step from an L-valine-derived diamine (Scheme 787).[868] In the presence of a strong base (e.g., *t*BuOK), a chiral P-spiro tetraaminophosphonium salt generated a triaminoiminophosphorane, which could deprotonate nitroalkanes, thereby successfully catalyzing the Henry reaction between aldehydes and various nitroalkanes. The adducts were obtained in good yields and with high enantioselectivities (Scheme 788).

According to a proposed mechanism (Scheme 789), the iminophosphorane, generated from the tetraaminophosphonium salt in the presence of a strong base, deprotonates the nitroalkane to give a nitronate anion, which interacts with the phosphonium cation through double hydrogen-bonding. In such a manner, a chiral environment is provided, and the addition of the nitroalkane to the aldehyde gives the corresponding products in a highly enantio- and diastereoselective manner.

The further potential of this type of tetraaminophosphonium salt as a catalytic stereocontroller was demonstrated through diastereo- and enantioselective Henry reactions of pyruvates. In the presence of a (*P*,*S*)-tetraaminophosphonium salt and the strong base *t*BuOK, the reaction provided *syn*-β-nitro alcohols as major isomers in 50–98% yield and 72–92% ee (Scheme 790).[869]

In 2010, the Ooi group further applied a tetraaminophosphonium salt in the addition of nitroalkanes to ynals. The first efficient, highly antiselective, and enantioselective direct Henry reaction of ynals was achieved to give synthetically valuable and optically active propargylic alcohols (Scheme 791).[870] In this reaction, DMF was used as a crucial cosolvent for facilitating the catalysis of chiral tetraaminophosphonium chlorides. In the presence of DMF, the catalyst decomposition pathway could be suppressed because the overall polarity of the solvent system had a beneficial effect on the stabilization of the aminophosphonium alkoxide intermediate. In particular, optically active *anti*-β-nitropropargylic alcohols were employed as precursors to accomplish rapid syntheses of (+)-xestoaminol C, (−)-2-epicodonopsinine, and (−)-codonopsinine.

In 2012, Johnson and Ooi investigated the application of iminophosphorane catalysis in aldol addition of aldehydes (Scheme 792).[871] With the use of 20 mol % of KO*t*Bu in THF at −78 °C, the reactions of a variety of alkyl, alkenyl, aryl, and heteroaryl aldehydes with α-substituted α-hydroxy trialkyl phosphonoacetates gave their α-hydroxy β-phosphonyloxy esters in yields of 78–98% and with up to 6.7:1 dr. Highly enantio- and diastereoselective variants were achieved using a chiral iminophosphorane catalyst. Using 10 mol % of the iminophosphorane **P119d** in 2-MeTHF at −50 °C, various aldehydes provided the corresponding products in 56–91% yield, with >30:1 dr, and with up to 94% ee.

8.4.2. Mannich Reaction.—In 2013, Dixon designed and synthesized a series of bifunctional Brønsted iminophosphorane (BIMP) organocatalysts,[872] and applied them in the enantioselective organocatalytic nitro-Mannich reactions of nitromethane with unactivated ketone-derived imines to construct β-nitroamines bearing a fully substituted carbon atom. Using the bifunctional iminophosphorane **P120a** as the catalyst, aromatic ketone-derived imines bearing either electron-withdrawing or -donating substituents reacted with nitromethane at 0 or −15 °C under solvent-free conditions to provide their corresponding products in moderate to excellent yields and with good to excellent enantioselectivities (Scheme 793). Notably, aliphatic ketimine was also tolerated well as a substrate. The immobilized chiral BIMP superbase organocatalyst **P120b**, conveniently obtained through formation of the iminophosphorane superbase at the point of immobilization, was also workable in the nitro-Mannich reactions of diphenylphosphinoyl protected ketimines.[873] The yields and enantioselectivities of the nitro-Mannich products were comparable with those obtained previously when applying the homogeneous bifunctional iminophosphorane under similar conditions (Scheme 794).

Using a bis(guanidino)iminophosphorane as the chiral catalyst, the Terada group realized the asymmetric addition of benzyloxycarbonyl-1,3-dithiane to *N*-Boc-protected aromatic imines (Scheme 795).[874] The reaction proceeded in excellent yield, with high to excellent enantioselectivity, to produce optically active α-amino-1,3-dithiane derivatives, which could be further transformed into chiral 3-amino-1,2-diols.

Using a similar bis(guanidino)iminophosphorane catalyst, Terada also disclosed an asymmetric direct Mannich-type reaction of α-iminophenylacetate esters with thionolactones.[875] The reaction afforded densely functionalized amino acid derivatives having vicinal quaternary stereogenic centers, one of which was an all-carbon quaternary stereogenic center, in moderate to excellent yield with good to excellent diastereo- and enantioselectivities (Scheme 796).

8.4.3. Pudovik Reaction.—In 2009, the Ooi group explored the application of iminophosphorane catalysis in the asymmetric hydrophosphonylation of aldehydes.[876] In the presence of 1 mol % of the phosphonium salt **P119c** and 1 mol % of *t*BuOK, the reaction of dimethyl phosphonate with various aromatic and aliphatic aldehydes proceeded well in THF at −98 °C, providing the corresponding α-hydroxyphosphonates in excellent yields and with excellent enantioselectivities (Scheme 797). An investigation of the reaction's progress using ^{31}P NMR spectroscopy disclosed that the dimethyl H-phosphonate reacted in its tautomeric form, the dimethyl phosphite, with the iminophosphorane catalyst, generated in situ upon treatment of the tetraaminophosphonium chloride with *t*BuOK. The chiral tetraaminophosphonium phosphite served as a reactive P-nucleophilic species, thereby realizing asymmetric catalysis (see Scheme 222).

A similar strategy was applied in the asymmetric Pudovik reactions of ynones for the synthesis of optically active α-tetrasubstituted α-hydroxy phosphonates (Scheme 798).[877] The iminophosphorane catalyst formed in situ from the salt in the presence of *t*BuOK efficiently catalyzed the Pudovik reactions between the dimethyl H-phosphonate and the ynones in THF at low temperature (−78 °C), providing α-hydroxy phosphonates in high

yields and enantioselectivities. A limitation was that the methodology had only been investigated in the Pudovik reactions of methyl ketone substrates. As displayed in Scheme 799, under catalysis of the triaminoiminophosphorane produced in situ from the aminophosphonium chloride in the presence of tBuOK, the catalytically generated tetraaminophosphonium phosphite nucleophile, which was stabilized through double hydrogen-bonding, underwent addition to a ketone to give an intermediary organic ion pair. Subsequent rapid proton transfer from the weakly acidic N–H proton of the aminophosphonium cation to the intermediary alkoxide anion occurred in a pseudointramolecular manner, which could prevent both retro-hydrophosphonylation and phospha-Brook rearrangement, thereby yielding the desired α-tetrasubstituted α-hydroxy phosphonates as sole products. The mechanism for this type of triaminoiminophosphorane-catalyzed Pudovik reaction was also investigated computationally.[878]

In 2016, chiral bifunctional Brønsted iminophosphoranes were further applied in the enantioselective phospha-Mannich reactions of unactivated N-DPP ketimines (Scheme 800).[879] All of these reactions proceeded well in the presence of 10 mol % of the BIMP superbase organocatalyst **P120c**, and tolerated a range of electron-rich and -poor aromatic ketimines: yields were typically up to 99% and enantiomeric excesses ranged from 41 to 71%.

8.4.4. Michael Addition.—In 2013, Ooi and co-workers described an asymmetric Michael addition of azlactones to methyl propiolate under proton transfer conditions, with the catalysis of a P-spiro chiral triaminoiminophosphorane (Scheme 801).[880] The *E*/*Z*-selectivity depended on the structure of the proton donor, the conjugate acid of the catalyst, and the properties of the electrophile. Under the influence of the iminophosphorane generated in situ through treatment of an aminophosphonium salt with KO*t*Bu in toluene at −60 °C, high *Z*-selectivity was observed in the reaction of azlactones with methyl propiolate. In the presence of 5 mol % of an L-isoleucine-derived iminophosphorane, (*E*)-isomers were obtained as major products. Under the same reaction conditions, (*Z*)-isomers were the major products of the Michael additions of azlactones to cyanoacetylene.

Ooi also applied chiral iminophosphorane in asymmetric conjugate addition of nitroalkanes with vinylic 2-phenyl-1*H*-tetrazol-5-ylsulfones (Scheme 802).[881] The conjugate addition proceeded smoothly in tetrahydrofuran at −78 °C in the presence of 4Å molecular sieves to afford the products with high stereocontrol. A wide range of 2-alkyl-substituted vinylic sulfones were tolerated, regardless of whether they featured elongation of simple carbon chains or the incorporation of various functional groups. Julia-Kocienski olefination was also explored under appropriate conditions, and a further one-pot operation of a Michael reaction–olefination sequence was realized in moderate yield and with excellent enantiomeric excesses.

Furthermore, Dixon used the immobilized chiral BIMP superbase organocatalysts in the conjugate additions of substituted malonates and *N,N*-dimethyl β-keto amides to nitrostyrene (Scheme 803).[873] All the conjugate additions of a variety of substituted malonates or β-keto amides to nitrostyrene occurred in moderate to excellent yields and with

good to excellent enantioselectivities. Notably, catalyst system recycling was possible over 10 cycles with no significant loss of activity or stereoselectivity.

Using bifunctional Brønsted iminophosphoranes as chiral catalysts, Dixon further developed highly enantioselective sulfa-Michael additions (SMAs) of alkyl thiols to unactivated α-substituted acrylate esters (Scheme 804).[882] A wide range of thiols and α,β-unsaturated esters reacted well to afford their sulfa-Michael adducts in moderate to excellent yields and with excellent enantioselectivities. In particular, a reaction performed on a decagram scale, using catalyst loadings as low as 0.05 mol % and at elevated temperature, gave its product without loss of yield or ee.

With **P120f** as the catalyst, highly enantioselective SMAs of alkyl thiols to unactivated β-substituted-α,β-unsaturated esters was also achieved (Scheme 805).[883] The low acidity of the alkyl thiol pronucleophiles was overcome by the high Brønsted basicity of the BIMP, and the chiral scaffold/thiourea hydrogen bond donor moiety provided the required enantiofacial discrimination in the addition step. The reactions were applicable to a range of linear, branched, cyclic alkyl, and benzylic thiols and various β-substituted-α,β-unsaturated esters, affording their sulfa-Michael adducts in moderate to excellent yields and enantioselectivities.

Scheme 806 provides a proposed mechanism. The strong Brønsted basicity of the BIMP overcomes the low inherent electrophilicity of the Michael acceptor by increasing the concentration of the thiol conjugate base after deprotonation. Following C–S bond formation, selective enantiofacial protonation of the transient enolate intermediate would deliver the enantioenriched Michael adduct and release the catalyst back into the cycle (Scheme 806).

Using a different type of iminophosphorane, a P-spiro chiral iminophosphorane, Ooi overcame the challenge of stereochemical control of Michael additions to internal alkynes (Scheme 807).[884] The transformations went well in toluene at 0 °C when reacting a wide array of the Michael acceptors of alkynyl *N*-acyl pyrazoles presenting various aromatic and aliphatic β-substituents, as well as with various α-amino acid-derived thiazolone nucleophiles. After further steps, this process provided access to structurally diverse, optically active α-amino acids bearing a geometrically defined trisubstituted olefinic component at the α-position. The mechanisms of this transformation and of the related additions were very recently investigated through computational studies.[885]

8.4.5. 1,6- and 1,8-Addition.—The same year, Ooi developed the 1,6-addition of azlactones to δ-monosubstituted dienyl *N*-acylpyrroles and 1,8-addition of azlactones to ζ-substituted trienyl *N*-acylpyrroles, using a chiral P-spiro triaminoimino-phosphorane as a strong organic base catalyst (Scheme 808).[886] In the presence of 5 mol % of the catalyst, the 1,6-additions of azlactones to δ-substituted dienyl *N*-acylpyrroles gave their corresponding products in near-quantitative yields and with excellent enantioselectivities. Under the same reaction conditions, the catalytic regio- and stereoselective 1,8-additions of azlactones to trienyl *N*-acylpyrroles led to their desired products in excellent yields, diastereoselectivities, and enantioselectivities. A computational study of the origin of the high regio-, diastereo-,

and enantioselectivities of the 1,6-additions of azlactones to dienyl N-acylpyrroles has also been performed.[887]

Most recently, Ooi reported a catalyst-directed pinpoint inversion of diastereochemical preference in the 1,6-additions of azlactones to δ-aryl dienyl carbonyl compounds (Scheme 809).[888] The 1,6-adducts were obtained with high regio-, diastereo-, and enantioselectivity and in excellent yields. This rigorous diastereodivergence was achieved with only minimal modification of a chiral iminophosphorane catalyst. This methodological study led to the preparation of various α-tetrasubstituted α-amino acids, including densely functionalized proline derivatives after further treatment. The efficient diastereodivergent catalysis of iminophosphoranes was extended to the reactions with other δ-aryl dienyl carbonyl compounds.

Ooi then explored the potential of using chiral iminophosphoranes as a means to address the complex issues of distance- and direction-selectivity associated with asymmetric Michael additions to alkenyl dienyl ketones (Scheme 810).[889] A highly regio-, diastereo-, and enantioselective 1,6-addition of azlactones to various alkenyl dienyl ketones was achieved using a P-spiro chiral triaminoiminophosphorane, despite the presence of three electrophilic reaction sites in an alkenyl dienyl ketone.

8.4.6. Amination.—In 2013, the Terada group investigated the application of a chiral bis(guanidino)iminophosphorane as an uncharged organosuperbase catalyst in the reaction of azodicarboxylates with 2-alkyltetralones and their analogues as the less acidic pro-nucleophiles (Scheme 811).[890,891] The desired products incorporating a quaternary chiral center at the α-position of carbonyl group were obtained in 7–99% yield with up to 98% ee.

8.4.7. Sulfenylation.—Under catalysis of a chiral iminophosphorane, the asymmetric sulfenylation of *N*-Boc-protected oxindoles is also possible (Scheme 812).[892] Using *N*-(phenylthio)phthalimide as the sulfur agent, a series of optically active 3-phenylthiooxindoles were obtained in excellent yields (90–99%) and with good enantioselectivities (up to 90% ee). Interestingly, the absolute configuration relied on the substrate. 3-Aryl- and 3-methyl-substituted oxindoles provided their sulfenylated products in the *S*-configuration, while 3-arylidene- or 3-isobutyl-substituted substrates afforded corresponding *R*-sulfenylated oxindoles.

8.4.8. Chlorination and Hydroxymethylation.—In 2015, the Wang group designed and developed a new family of [7,7]-P-spirocyclic iminophosphoranes as organocatalysts from L-(+)-tartaric acid (Scheme 813).[893] These catalysts were successfully applied in the NCS-mediated asymmetric chlorinations of 3-substituted oxindoles. The process went well at ambient temperature with a low catalytic loading, with the desired chlorinated products obtained in excellent yields and with high enantioselectivities (90–99% ee). The reaction could be scaled up to multigram quantities with >99% ee. Importantly, recovery of the catalyst, after simple chromatographic separation, for reuse in the model reaction was realized, with the catalyst capable of being recycled more than six times with no loss in enantioselectivity.

Subsequently, the new catalytic asymmetric system was employed for the hydroxymethylation of 3-substituted oxindoles, with paraformaldehyde as a useful C1 unit (Scheme 814).[894] Various substituted oxindoles bearing quaternary stereocenters were synthesized with high efficiencies (81–98% yield) and good to excellent enantioselectivities (up to 94% ee).

8.4.9. Multicomponent Coupling Reaction.—Using the [5,5]-P-spirocyclic iminophosphorane **P119d** as a superbase organocatalyst, Ooi developed a highly stereoselective, fully organic multicomponent coupling reaction between isatins and aldehydes, employing dialkyl phosphites as economical reductants (Scheme 815).[895] Several substituted aromatic aldehydes were tolerated in reactions performed at −78 °C, providing their coupling products in moderate to high yields and stereocontrol.

Following Ooi's report, in 2016, Johnson's group used a catalytic amount of a BIMP to realize similar three-component asymmetric reductive coupling reactions between dimethyl phosphite, benzylidene pyruvates, and aldehydes (Scheme 816).[896] The transformations proceeded smoothly when aryl aldehydes presenting electron-withdrawing groups at the para- or meta-position were reacted in THF at −60 °C, except that lower stereoselectivity resulted from the reaction of *p*-nitrobenzaldehyde. When benzaldehyde was applied, however, only the byproduct was observed. The other variable partner, the benzylidene pyruvate, had an influence on the reaction time, due to the electronic properties of its aromatic group; the process ran faster with electron-deficient substituted substrates than with electron-rich pyruvates. This methodology could also be applied on a larger weight scale, with >20:1 dr and 97.5:2.5 er after a single recrystallization.

8.4.10. Payne-Type Oxidation.—Through the combined use of H_2O_2 and trichloroacetonitrile under catalysis of a chiral P-spiro triaminoiminophosphorane, Ooi, Tsutsumi, and Uraguchi developed an efficient and highly enantioselective Payne-type oxidation of *N*-sulfonyl imines (Scheme 817).[897] Using 5 mol % of the catalyst in toluene at 0 °C, with Cl_3CCN as an additive, the *N*-sulfonyl imines gave their oxidation products in good yields and with excellent enantioselectivities. A further investigation of the details of the reaction resulted in extension of the substrate scope to a diverse array of *N*-sulfonyl oxaziridines.[898] Mechanistic investigations revealed that the reaction proceeded via a Payne-type oxidation pathway.

Using an L-isoleucine-derived triaminoiminophosphorane as the catalyst, the Ooi group accomplished the asymmetric oxidation of *N*-sulfonyl *α*-imino esters with H_2O_2, giving a novel class of chiral *N*-sulfonyl oxaziridines as uniquely reactive and modular chiral organic oxidants (Scheme 818).[899] One of the oxaziridine products exhibited high reactivity and enantiospecificity in the asymmetric oxidation of a silyl enol ether and *N*-sulfonyl allylic and homoallylic amines.

8.4.11. Prototropic Shift/Furan Diels–Alder (IMDAF) Cascade Reaction.—A BIMP has also been employed in the first enantioselective total synthesis of (−)-himalensine A, in 22 steps (Scheme 819).[900] The first enantio- and diastereoselective prototropic shift/furan Diels–Alder (IMDAF) cascade reaction of an N-Boc-protected furan under catalysis of

a BIMP enabled construction of the ACD tricyclic core in a single step, five stereogenic centers (including two that were vicinal and quaternary) within the carboskeleton. Compared with the reactions of DABCO and cinchona catalysts, the BIMP catalyst allowed a good conversion to the product within 24 h when using as low as 5 mol % of the catalyst. Using the BIMP **P120h** as the catalyst, the IMDAF cascade product was delivered in 86% yield, 92:8 dr, and 90% ee on a multigram scale.

8.4.12. Ring-Opening Polymerization (ROP) of Cyclic Esters.—BIMP catalysts have also been employed in the ROP of cyclic esters, including L-lactide (LA), *δ*-valerolactone (VL), and *ε*-caprolactone (CL) (Scheme 820).[901] The BIMPs (*rac*-**P120f** and *rac*-**P120g**) were suitable for the preparation of poly-LA and poly-VL within short reaction times, with excellent monomer conversions, low polydispersity, and high end-group fidelity. The catalyst system was also excellent for the formation of short-length poly-CL with good control over the molecular weight distribution.

8.5. Catalytic Variants of Phosphine Oxide–Generating Reactions

Traditionally, tertiary phosphines have been used as reagents that facilitate reactions that are driven by the formation of a phosphine oxide with a strong P=O bond [bond dissociation energy (BDE) = 130 kcal/mol]. However, phosphine oxide is not water-soluble, coelutes with the product during chromatography, and (for a solid product) readily precipitates with the product, impeding its purification, particularly in large-scale (industrial) processes.[902,903] In 2009, to address the problem of phosphine oxide waste, O'Brien reported the first phosphine oxide-catalyzed Wittig reaction, in which the phosphine oxide byproduct was reduced by a silane in situ back to the phosphine.[825] This strategy has since been employed to promote Wittig, Appel, Staudinger, and Mitsunobu reactions, as well as other reactions thermodynamically driven through formation of a phosphine oxide.[44, 904–906] In 2010, O'Brien filed a patent involving the reducing strategy, "Catalytic Wittig Reaction and Mitsunobu reactions,"[907] implying the potential value of these catalytic reactions.

8.5.1. Catalytic Wittig Reaction.—In 2009, O'Brien, Chass, and co-workers innovatively developed a Wittig reaction occurring with in situ reduction of the phosphine oxide byproduct (Scheme 821).[825,907] Their strategy involved using a silane as a reducing agent to reduce the precatalyst phosphine oxide to the active phosphine, which then underwent the Wittig reaction to provide the product olefins and the precatalyst for the next catalytic cycle. A wide range of aromatic or aliphatic aldehydes and various alkyl halides were treated with 10 mol % of 3-methyl-1-phenylphopholane-1-oxide (**P121**), 1.1–1.5 equiv of the silane Ph_2SiH_2, and 1.5 equiv of Na_2CO_3 in refluxing toluene to generate their corresponding olefins. Moderate to good yields, and *E*/*Z* ratios from 64:40 to >95:5, were obtained. Various aldehydes (heteroaryl, aryl, alkyl) and a diverse array of alkyl halides (bearing cyano, arylcarbonyl, alkoxycarbonyl substituents) were compatible with the reactions. This protocol highlighted the approach of avoiding the production of stoichiometric phosphine oxides, and opened a new path for green olefination chemistry.[908–910]

The aforementioned method was a greener approach for the formation of olefins from carbonyl building blocks, when compared with the classic Wittig reaction. Nevertheless, the transformation was conducted at 100 °C, which is not sufficiently benign to the environment with respect to energy. To address this problem, O'Brien and co-workers improved their approach to perform the catalytic Wittig reactions at room temperature (Scheme 822).[911] They found that using an acid as an additive could sufficiently tune the required temperature from 100 °C to room temperature, presumably by accelerating the rate of silane-mediated reduction of the phosphine oxide. In the presence of the 1-butylphospholane-1-oxide **P122** and $PhSiH_3$, various aldehydes (aromatic or aliphatic bearing bulky substituents) and primary or secondary alkyl bromides reacted to afford di- or trisubstituted alkenes in moderate to good yields, along with good to excellent *E*/*Z* stereoselectivities. One example of this reaction was performed on a multigram scale, giving a 72% yield and an 88:12 *E*/*Z* ratio. In addition, O'Brien and co-workers disclosed that acyclic phosphine oxides [e.g., $(n\text{Oct})_3P{=}O$, $Ph_3P{=}O$] were also viable catalysts for the catalytic Wittig reactions in the presence of appropriate silanes at 100 °C.

In 2013, O'Brien and co-workers described in detail the development and optimization of their catalytic Wittig reactions.[912] They carefully examined the reaction parameters, including the structure of the phosphine oxide precatalyst, the loading amount, the organosilane, the temperature, the solvent, and the base, for their catalytic Wittig reactions. The optimal conditions involved using the 3-methyl-1-phenylphospholane-1-oxide **P121** (10 mol %) as the precatalyst, the silane Ph_2SiH_2 (1.1–1.5 equiv) as the reductant, and Na_2CO_3 (1.5 equiv) or $i\text{Pr}_2\text{NEt}$ (1.1–1.5 equiv) as the base, in the refluxing toluene (Scheme 823). Under the optimal conditions, various aldehydes reacted with alkyl bromides to give a vast range of olefins (46 examples) in moderate to excellent yields and with varying *E*/*Z* stereoselectivities (up to 95:5). Notably, compared with Na_2CO_3, using DIPEA as a soluble base led to improved efficiency, with a broader substrate scope and a lower precatalyst loading. Furthermore, O'Brien and co-workers demonstrated the synthetic utility of this methodology in the preparation, on a multigram scale, of a known precursor of the anti-Alzheimer drug donepezil hydrochloride (Scheme 824).

In 2014, O'Brien and co-workers further expanded the scope of their catalytic Wittig reactions to include semi- and non-stabilized ylides prepared using a controllable base, sodium *tert*-butyl carbonate, and ylide tuning (Scheme 825).[913] A wide spectrum of alkyl halides (bromides, chlorides) underwent the Wittig reactions with various aldehydes via semi-stabilized ylides, in moderate to good yields and *E*/*Z* stereoselectivities, when treated with several phosphine oxides, Ph_2SiH_2, and sodium *tert*-butyl carbonate or DIPEA. Similarly, under slightly modified conditions, an array of primary alkyl halides underwent these Wittig reactions with various aldehydes via nonstabilized ylides, in moderate to excellent yields along with moderate *E*/*Z* stereoselectivities. Notably, the stereoselectivities could be finely-tuned to excellent levels by varying the structure of the appropriate precatalyst.

In 2014, Werner and co-workers documented the first enantioselective catalytic Wittig reaction (Scheme 826).[914] They examined the applicability of a series of chiral mono- and diphosphines for the desymmetrization of a prochiral ketone, under microwave irradiation or

conventional heating. In the presence of a tertiary phosphine as the catalyst, a silane as the reducing agent, and a base at 125 or 150 °C, a prochiral ketone underwent catalytic Wittig reaction to give a bicyclic product in varying yields and enantioselectivities. The enantiomeric excess when using **P93** as the catalyst reached up to 90%, but with considerably compromising the yield, and vice versa. The results are promising, but much work remains to be done to ensure the practical utility of this catalytic Wittig reaction.

Werner and co-workers also reported the first microwave-assisted catalytic Wittig reactions with considerably enhanced efficiency and reaction rates.[915] Assessing various phosphine oxides and conditions led to identification of the optimal conditions: using Bu_3PO (10 mol %) as the precatalyst, $PhSiH_3$ as the reductant, 1,2-butylene oxide as the capped base, in dioxane, under microwave irradiation of 150 W, at 150 °C for 3 h (Scheme 827). Under these conditions, various aromatic and aliphatic aldehydes were condensed with electron-deficient alkyl halides to form corresponding olefins in moderate to good yields, along with excellent stereoselectivities in most cases. Interestingly, after replacing the procatalyst Bu_3PO with the chiral phosphine **P93**, a prochiral carbonyl compound underwent an intramolecular catalytic Wittig reaction, under otherwise identical conditions, to form its product in 39% yield and with an 81:19 enantiomeric ratio.

Later in 2015, Werner and co-workers studied in detail the scope and limitation of their microwave-assisted catalytic Wittig reactions (Scheme 828).[916] Among an intensive examination of a series of phosphine oxide procatalysts, Bu_3PO was found to provide superior catalytic activity. In addition, both Ph_2SiH_2 and $PhSiH_3$ were identified as competent reducing agents, and various epoxides were suitable as masked bases. Under the optimal conditions, as described in the previous report, a wide range of olefins (more than 40 examples) were obtained from corresponding their aldehydes in moderate to good yields and with excellent *E*/*Z* selectivities.

In 2015, the Werner group prepared a novel cyclic phosphine oxide, 2-phenylisophosphindoline 2-oxide **P123**, and employed it successfully as a precatalyst for catalytic Wittig reactions (Scheme 829).[917] In the presence of **P123**, $HSi(OMe)_3$, and Na_2CO_3, a wide range of aldehydes underwent Wittig reactions with organohalides to provide their olefins in good yields and *E*/*Z* stereoselectivities. Various aromatic, heteroaromatic, and aliphatic aldehydes were compatible with the transformation. Notably, because of poor solubility in organic solvents, the particle size of the base Na_2CO_3 affected the reproducibility; as such, the particle size was restricted to the range 125–250 μm.

In 2015, Plietker and co-workers combined accessible Fe complex-catalyzed hydrosilylation of carbonyl groups and phosphine oxides with phosphine-catalyzed Wittig olefination to realize dual catalysis in one pot (Scheme 830).[918] The $[Fe(CO)_3(NO)]$ anion-derived Fe–H complex (dppp)Fe(CO)(NO)H displayed excellent activity for the hydrosilylation and the phosphine oxides were converted into their corresponding phosphines. In the presence of a base, the yield of the hydrosilylation was increased significantly. A catalytic amount of triphenylphosphine was employed in the Wittig reaction. Various aromatic and aliphatic aldehydes underwent olefination with ethyl α-bromoacetate or α-chloroacetonitrile in moderate to good yields and *E*/*Z* selectivities. Importantly, NMR spectroscopic analysis of

the crude product disclosed that under standard conditions, the corresponding alcohol (i.e., the product of a competing carbonyl reduction of aldehydes) was not formed.

In 2017, Ding and co-workers applied the phosphine/phosphine oxide catalytic cycle along with TMDS/Ti(O*i*Pr)$_4$ to realize intramolecular Wittig reactions of carbonyl-containing bromides (Scheme 831).[919] A variety of carbonyl-containing bromides were suitable substrates, affording isoquinolin-1(2*H*)-one derivatives (including *N*-acylindoles, 2,3-dihydro-1*H*-2-benzazepin-1-ones, 1,2-dihydro-quinolines, and benzofurans) in moderate to good yields when reacted in the presence of NEt_3 in refluxing toluene.

8.5.2. Base-Free Catalytic Wittig Reaction.—In 2015, Werner and co-workers reported the first base-free catalytic Wittig reaction of aldehydes with acceptor-substituted alkenes, with Bu_3P (5 mol %) as the catalyst (Scheme 832).[920] They obtained 22 succinate derivatives from the reactions of various aldehydes with maleates and fumarates, in good to excellent yields (up to 95%). For aromatic and heteroaromatic compounds, very good *E*/*Z* selectivities were acquired, with the selectivity for aliphatic products being slightly lower. Scheme 833 presents the mechanism. Initially, a Michael addition of the phosphine occurs to the alkene, followed by a [1,2]-H shift leading to an ylide under base-free conditions. Conversion with an aldehyde affords a succinate, with $Bu_3P{=}O$ produced subsequently. Finally, the phosphine is regenerated in situ by reducing the phosphine oxide.

In 2015, Lin and Tsai developed an efficient method for the synthesis of multifunctional alkenes through phosphine-catalyzed Wittig reactions of aldehydes and substituted acrylates under mild conditions (30–60 °C) (Schemes 834 and 835).[921] Several aldehydes and substituted 3-aroyl acrylates were tolerated in this reaction, affording their corresponding products in moderate to excellent yields (up to 95%) and with high stereoselectivity (E/Z > 95/5) within a short reaction time. When using phenyl silane ($PhSiH_3$) as the reducing agent, the phosphine/phosphine oxide catalytic cycles were closed.

To obtain milder conditions for the base-free catalytic Wittig reaction, Werner and co-workers studied the effect of Brønsted acidic additives in 2016.[922] With the catalysis of tri-*n*-butylphosphine (5 mol %), in combination with benzoic acid as an additive (5 mol %) and $(MeO)_3SiH$ as the reducing agent, the scope of aldehydes was examined for reactions with activated alkenes in toluene at 100 °C for 14 h (Scheme 836). Highly functionalized alkenes were obtained in good to excellent yields (up to 99%) and with good to excellent *E*/*Z* selectivities after the reactions of aromatic aldehydes with symmetric and asymmetric maleates and maleimides. Aliphatic aldehydes were also suitable for the transformation, furnishing their corresponding products in up to 93% yield, but with weak stereocontrol. The conversions of heteroaromatic aldehydes with dimethyl maleate were also possible, giving their heteroaryl substituted alkenes in low to high yields and with corresponding stereoselectivities.

In 2016, the Lin group developed a novel protocol for the synthesis of highly functionalized furans, using 10 mol % of a phosphine and 20 mol % of Et_3N as catalysts (Scheme 837), through intramolecular Wittig reactions in dry THF under an Ar atmosphere.[923] Furans presenting various functionalized groups (FG = COPh, CO_2Et, CN) were obtained in yields

of 33–99%. The concept of using recyclable Et_3N was employed for the first time in a catalytic Wittig reaction. Notably, silyl chloride and the in situ-generated byproduct, triethylammonium chloride, accelerated the reduction of the phosphine oxide. This process could prove to be significant on an industrial scale, because it avoids the need for stoichiometric amounts of a phosphine and a base.

In 2016, Voituriez developed a method for the synthesis of 9*H*-pyrrolo[1,2-*a*]indoles and pyrrolizines through phosphine-catalyzed reactions.[924] In the presence of the phosphine oxide **P125** (5 mol %), and combining a silane with a Brønsted acid, a wide range of substituted 1*H*-indole-2-carbaldehydes reacted with various acetylenedicarboxylates to provide a diverse array of functionalized 9*H*-pyrrolo[1,2-*a*]indoles and pyrrolizines in generally high yields (Scheme 838). The transformation, which was triggered by the phosphine after silane-mediated in situ reduction of the phosphine oxide, proceeded well through a sequential umpolung addition/Wittig reaction. Voituriez extended the reaction to other bifunctional substrates for the synthesis of heterocycles and cyclopentenone derivatives.[925] Various cyclic amino-carbaldehyde and amino ester derivatives, as well as acyclic amino-aldehyde and amino ester derivatives, were compatible substrates (Scheme 839). The asymmetric umpolung addition/intramolecular Wittig reaction has also been investigated using several commercially available chiral phosphines, giving the corresponding products with up to 81% ee.

Most recently, Kwon reported a new bridged [2.2.1] bicyclic phosphine oxide **P126** and its application in the base-free phosphine oxide-catalyzed Wittig reaction of *o*-sulfonamidobenzaldehydes with allenoates.[926] Initial attempts to employ either PBu_3 or the phosphine oxide **P121** as the catalyst for the reaction were unsuccessful, due to the high reaction temperature (>100 °C) necessary for the in situ reduction of the phosphine oxide. After careful analysis of the silane-mediated reduction of the phosphine oxide, Kwon designed the new strained [2.2.1] bicyclic phosphine oxide **P126**, which demonstrated superior capability in the silane-mediated reduction (Scheme 840). Using 15 mol % of the phosphine oxide **P126**, tandem γ-umpolung addition/Wittig olefination between allenoates and *o*-sulfonamidobenzaldehydes (**504**) proceeded smoothly at 80 °C within 4–6 h, giving 1,2-dihydroquinolines (**505**) in moderate to good yields. One of these products was elaborated to afford the antitubercular furanoquinolines **506**. A reasonable mechanism is presented in Scheme 841. Viable reduction of the [2.2.1] bicyclic phosphine oxide by the silane makes this catalytic cycle possible.

8.5.3. Catalytic Mitsunobu Reaction.—The Mitsunobu reaction (Scheme 842) is the conversion of a primary or secondary alcohol, featuring an acidic prenucleophilie (NuH), to a functionalized moiety, mediated by a nucleophilic phosphine (commonly triphenylphosphine) and an azo-containing electrophile (commonly diallyl azodicarboxylate), during which the alcohol undergoes an inversion of stereochemistry. Because of its mild reaction conditions, wide substrate scope and tolerance, and particularly high stereocontrol, the Mitsunobu reaction is used widely by the chemical community to synthesize optically active esters, amines, azides, and thioesters. A plausible mechanism is provided below. The tertiary phosphine plays two crucial roles during a Mitsunobu reaction: (i) nucleophilic addition to the azodicarboxylate to form a zwitterion that can deprotonate

the prenucleophile and (ii) polarization of the O–C bond for substitution of an alcohol. There is, however, an intrinsic drawback of Mitsunobu reactions: production of stoichiometric amounts of phosphine oxides and substituted hydrazines as byproducts. An emerging subfield is the development of Mitsunobu reactions that are catalytic with respect to the phosphines or the azodicarboxylates. Classic Mitsunobu reactions have been investigated intensively and reviewed in a vast volume of literature.[822,927–929] In this section, we briefly discuss the basic principles of catalytic Mitsunobu reactions,[45,930–934] which have been achieved through two strategies: using a catalytic amount of the phosphine and using a catalytic amount of the azo reagent. Nevertheless, whether a fully catalytic reaction has been realized remains debatable.

In 2006, Toy and co-workers developed a first Mitsunobu reaction system that was catalytic in the oxidizing azo reagent and that used a hypervalent iodine species as the stoichiometric oxidant (Scheme 843a).[935, 936] The benefit of using $PhI(OAc)_2$ is that its byproducts (iodobenzene and acetic acid) are relatively simple to remove, while at the same time the amount of formed hydrazine byproduct is decreased dramatically. Using this strategy, a range of alcohols, as well as 4-nitrobenzoic acid and aliphatic carboxylic acids (e.g., phenyl acetic acid and Boc-protected glycine), were reacted in THF at room temperature, giving their esters in yields of 54–90%. In these cases, the catalytic reactions afforded similar or lower yields than did their corresponding stoichiometric reactions. In 2013, using a combination of an arylhydrazinecarboxylate and iron phthalocyanine-catalyzed aerobic oxidation, Taniguchi and co-workers accomplished a similar Mitsunobu reaction, catalytic in the azo reagent (Scheme 843b).[937, 938] Ethyl 2-(3,4-dichlorophenyl)hydrazinecarboxylate was identified as the best azo reagent catalyst.

In 2010, O'Brien reported the first Mitsunobu reaction that was "catalytic" in a phosphine (Scheme 844).[907] Using 20 mol % of the phosphine **P121** as the catalyst and $PhSiH_3$ (1.1 equiv) as the reducing agent, benzyl alcohol reacted with *p*-nitrobenzoic acid in the presence of diisopropyl azodicarboxylate (DIAD, 1.5 equiv) at 80 °C for 24 h to give the ester product in 63% yield.

In 2015, Aldrich and Buonomo reported the first Mitsunobu reaction "catalytic" in both a phosphine and an azo reagent (Scheme 845).[939] Inspired by O'Brien's phosphine oxide-catalyzed Mitsunobu reactions, they used the silane $PhSiH_3$ for in situ reductions of the phospholane oxides to phosphines and, thereby, regenerate the catalysts. Using **P127** (10 mol %) as the precatalyst and $PhSiH_3$ (1.1 equiv) as the reducing agent, in the presence of DIAD (1.1 equiv) at 80 °C, a wide range of primary and secondary alcohols and various prenucleophiles, including aryl carboxylic acids, amines, and a sulfamide, underwent the Mitsunobu reactions to give their products in yields of 50–87% (Scheme 845a). These catalysis conditions provided yields comparable to those from the stoichiometric conditions. Aldrich and Buonomo also conceptualized fully catalytic Mitsunobu reactions by combining these phosphine catalyst conditions with Taniguchi's azocarboxylate catalytic system. Using **P127** (10 mol %), $PhSiH_3$ (1.1 equiv), 3,4-dichlorophenylhydrazine (10 mol %), iron(II) phthalocyanine [Fe(pc), 10 mol %], and 5-Å molecular sieves in THF at 70 °C under an O_2-enriched atmosphere, benzyl alcohol underwent Mitsunobu reactions with 4-nitrobenzoic acid to form its ester in up to 68% yield (Scheme 845b). Recent studies have, however,

questioned this fully catalytic reaction. Taniguchi noted that there were only a few examples with a limited scope of substrates: namely, the condensations of two benzyl alcohols (4-methoxylbenzyl alcohol, benzyl alcohol) with 4-nitrobenzoic acid.[940] They tentatively decided to adapt a model reaction using (−)-ethyl lactate (>99:1 er) and 4-nitrobenzoic acid to evaluate the "fully catalytic" Mitsunobu reaction. The ester product was obtained with a yield and inversion ratio inferior to the reported values, implying that these reaction conditions were not sufficiently optimized for a fully catalytic Mitsunobu reaction. The same results were obtained if the hydrazine catalyst was omitted, indicating that this was not a Mitsunobu reaction. Without any doubt, future work remains to be done to develop and optimize the catalytic Mitsunobu reaction.

8.5.4. Reduction of Peroxides.—The reductions of the O–O bonds of peroxides by stoichiometric amounts of phosphines have been investigated for over 80 years. In contrast, phosphinecatalyzed reductions of the O–O bonds of peroxides using catalytic amounts of a phosphine did not emerge until 2010, when Woerpel and co-workers reported the reductions of protected hydroperoxides mediated by substoichiometric amounts of phosphines in the presence of appropriate reducing agents.[941] Inspired by O'Brien's catalytic Wittig reactions, they achieved the phosphine-catalyzed reductions of silylated hydroperoxides using two reducing agents [Ti(O-*i*Pr)$_4$ and HSiMe$_2$OSiMe$_2$H] and involving three reduction processes. Various protected alkyl hydroperoxides were reduced to their corresponding ethers in good yields under the optimized conditions, using a substoichiometric amount of PPh$_3$ (5 mol %) as the catalyst, and Ti(O-*i*Pr)$_4$ (50 mol %) and HSiMe$_2$OSiMe$_2$H (2.0 equiv) as the reducing agents, in toluene at 100 °C (Scheme 846). Regeneration of the phosphine catalyst for the reduction of the alkyl hydroperoxides arose from in situ reduction of the formed phosphine oxide by a titanium(IV) hydride. The titanium(IV) hydride was itself produced in situ from reduction of the titanium(IV) alkoxide Ti(O-*i*Pr)$_4$ by the siloxane HSiMe$_2$OSiMe$_2$H (Scheme 847). They also presented a plausible pathway for silyl group transfer involving a concerted step (Scheme 848).

8.5.5. Catalytic Appel Reaction.—Phosphines are widely used in Appel reactions: the transformations of alcohols to alkyl chlorides (or other halides) mediated by tertiary phosphines; commonly used reagents include triphenylphosphine and carbon tetrachloride (Scheme 849).[942] Appel reactions have several salient features, including mild reaction conditions, ease of operation, and high yields. Nevertheless, they possess two intrinsic shortcomings: the use of toxic and eco-unfriendly carbon tetrachloride (or other halides) as the halogen source, and generation of stoichiometric amounts of phosphine oxides as byproducts. Classic Appel reactions have been summarized in several Reviews.[942,943]

Here, we briefly discuss catalytic Appel reactions mediated by phosphines.[934] To minimize the production of byproducts and increase atom economy, van Delft and Rutjes developed Appel reactions catalytic in the phosphine (Scheme 850).[944,945] Inspired by O'Brien's catalytic Wittig reactions, van Delft realized catalytic Appel reactions involving silane-mediated in situ reduction of the phosphine oxide. Various primary and secondary alkyl alcohols underwent these catalytic Appel reactions under the optimized conditions, using the dibenzophosphole **P128a** (10 mol %) as the catalyst, diphenylsilane (1.1 equiv) as the

reducing agent, and diethyl bromomalonate (DEBM, 1.5 equiv) as the bromine source, furnishing corresponding alkyl bromides in yields of 20–72%. Notably, the tertiary alcohol 1-adamantanol and the bulky secondary alcohol β-cholesterol gave their products in good yields (71 and 72%, respectively). Nevertheless, **P128a** was not an effective catalyst for chlorination, where the more electron rich 2,8-dimethoxydibenzophosphole **P128b** displayed superior activity. A catalytic amount of **P128b** under similar conditions converted 2-phenylethanol to (2-chloroethyl)benzene in 40% yield.

8.5.6. Catalytic Staudinger Reaction.—The Staudinger reaction refers to the preparation of iminophosphoranes (also known as aza-ylides or phosphinimines) and their derivatives from tertiary phosphines and organic azides (Scheme 851).[946] Because of the mild conditions, high yields, wide substrate scope, and versatile reactivities of iminophosphoranes, Staudinger reactions are fundamental reactions in the fields of chemistry and chemical biology. One common application is the reduction of azides with tertiary phosphines to form amines via iminophosphorane intermediates (i.e., Staudinger reduction). The Staudinger reaction was modified to Staudinger ligation by Bertozzi and Saxon in 2000 for the highly selective labeling or modifying of biomolecules of living systems.[947,948] Shortly thereafter, Staudinger ligation was further developed to become traceless Staudinger ligation.[949,950] Significant applications include the cross-linking of two different biomolecules, through stable amide bonds, for the construction of novel functionalized biomolecules, and the incorporation of probes into biomolecules. Classical Staudinger reactions and their applications in synthetic chemistry have been reviewed by Gololobov, Eguchi, and others.[951–953] Bertozzi, van Hest, Breinbauer, and others have reviewed the significant applications of Staudinger ligation in biochemistry.[954–956] The applications of Staudinger reactions in the selective functionalization of polysaccharides have been reviewed recently by Edgar and Liu.[957]

Here, we focus on exploring the roles of phosphines in organocatalysis and in organic synthesis, so we do not thoroughly discuss the Staudinger ligation. For readers who are interested in the applications of Staudinger ligation, please refer to several elegant Accounts and Reviews.[948,954–957] Generally, the Staudinger reaction begins with nucleophilic addition of a tertiary phosphine to an organic azide, forming a phosphazide. This phosphazide loses dinitrogen, via a four-membered transition state, to generate an iminophosphorane. Because of the good nucleophilicity of the nitrogen atom in an iminophosphorane, it reacts with various electrophiles (e.g., water, carbonyl compounds, carboxylate esters). These reactions are classic Staudinger reactions in organic synthesis, requiring a stoichiometric amount of a phosphine; they have been studied extensively and intensively[951–953,958,959] and employed[960,961] for almost a century by the chemistry community. In this Review, we discuss catalytic examples of Staudinger reactions. As revealed in Scheme 827, the key step for a catalytic Staudinger reaction is the use of an appropriate reducing agent to convert a phosphine oxide to a phosphine catalyst.

In 2012, the first catalytic Staudinger reduction was reported by van Delft and co-workers. Interestingly, the catalytic Staudinger reaction was achieved via P=N double bond reduction, instead of P=O double bond reduction. The reducing agent (the silane $PhSiH_3$ or Ph_2SiH_2) reduced the iminophosphorane intermediate in situ to an amine, and the catalyst phosphine

was regenerated concomitantly, as displayed in Scheme 852.[962] The optimal conditions were identified as the substrates being heated under reflux in dioxane for 16 h, with the dibenzophosphole **P128a** (5 mol %) as the catalyst and the silane $PhSiH_3$ (1.5 equiv) as the reducing agent. Under these conditions, various azides were reduced to their corresponding amines in moderate to quantitative yields (Scheme 853). A wide range of organic azides, including aromatic azides (bearing electron-donating or -withdrawing substituents) and primary or cyclic secondary azides, were competent substrates. In addition, van Delft and co-workers found that the dibenzophosphole **P128a** exhibited catalytic activities superior to those of PPh_3 under otherwise identical conditions.

Shortly after in 2012, Ashfeld and co-workers designed an alternative strategy for catalytic Staudinger ligations.[963] Using the silane $PhSiH_3$ to reduce the phosphine oxide in situ to the catalyst phosphine, they achieved a catalytic Staudinger ligation. A survey of a series of phosphines and silanes resulted in improved conditions: treating substrates with PPh_3 (10 mol %) as the catalyst and $PhSiH_3$ (1.0 equiv) as the reducing agent in toluene, from room temperature to 110 °C, allowed various carboxylic acids to react with a diverse array of aromatic or aliphatic organoazides to afford corresponding amides in moderate to excellent yields (Scheme 854). A vast range of aromatic or aliphatic carboxylic acids was amenable to the transformations. Even an example of an intramolecular amidation was accomplished in 77% yield. Interestingly, complete chirality transfer occurred during these transformations. Ashfeld and co-workers proposed a plausible mechanism involving equilibrium between a tight phosphonium carboxylate ion pair and an ester (Scheme 855).

8.5.7. Aza-Wittig Reaction.—In 2013, van Delft and co-workers developed a novel method to prepare *N*-heterocycles from azidoketones or azido esters, involving a phosphine-catalyzed Staudinger/intramolecular aza-Wittig sequence (Scheme 856).[964] The key to achieve the catalytic Staudinger reactions was the rapid rate of the subsequent aza-Wittig reaction and the diphenylsilane-mediated in situ reduction of the 5-phenyldibenzophosphole oxide (Scheme 857). In the presence of the 5-phenyldibenzophosphole **P128a** (10 mol %) and diphenylsilane (1.1 equiv), a wide range of azidoketones or azido esters was converted in dioxane at 101 °C to corresponding *N*-heterocycles, including benzoxazoles, benzodiazepine imidates, and a 2-methoxypyrrole, in satisfactory to good yields. In some cases, Staudinger reduction products were obtained as minor byproducts.

In 2014, Ding and co-workers developed a catalytic aza-Wittig reaction based on a phosphine(III)/phosphine(V) oxide catalytic cycle (Scheme 858).[965] The method was demonstrated in an efficient synthesis of 4(3*H*)-quinazolinones, in high yields, when using a catalytic amount of Ph_3P and the tetramethyldisiloxane/titanium tetraisopropoxide [TMDS/$Ti(O\text{-}i\text{Pr})_4$] reductant system in refluxing toluene. All reactions proceeded smoothly to give the corresponding products in yields of 81–95%, regardless of the electronic properties or steric bulk of the substituents on the azides. In the absence of either Ph_3P or $Ti(O\text{-}i\text{Pr})_4$, however, no 4(3*H*)-quinazolinone was produced. Ding and co-workers also adopted this method for the synthesis of some medicinal and natural products, including methaqualone, deoxyvasicinone, and (*S*)-vasicinone, each with >99% ee.

In 2014, the Herdewijn group reported the first example of an organophosphorus-catalyzed diaza-Wittig reaction and its application to construct pyridazine and phthalazine derivatives (Scheme 859).[966] Various substrates containing a diazo functionality were examined as starting materials. Most of the pyridazines bearing electron-withdrawing groups were obtained as precipitates in good to excellent yields. In the proposed mechanism (Scheme 860), the trivalent phosphine reacted with the diazo derivative (e.g., the 2-diazo-3,5-dioxo-5-phenylpentanoate) to form a phosphazine intermediate. The latter species was converted to a cyclic oxaphosphetane-like intermediate, which could deliver the corresponding pyridazine derivative and the phosphine oxide as a byproduct. After diphenylsilane-mediated in situ reduction, the phosphine catalyst was regenerated to re-enter the catalytic cycle. This method represents a novel catalytic approach to relevant heterocycles, known as “privileged structures,” in the pharmaceutical industry.

In 2016, Ding, Huang, and co-workers developed both aza-Wittig and catalytic aza-Wittig reactions of anhydrides, based on a phosphine/phosphine oxide catalytic cycle involving reduction by copper (Scheme 861).[967] The number of examples of 4*H*-benzo[*d*][1,3]-oxazin-4-ones and 4-benzylidene-2-aryloxazol-5(4*H*)-ones products were greater than 100 and the yields were up to 98%. In addition, the direct one-pot catalytic aza-Wittig reactions of carboxylic acids and chlorides occurred in the presence of triphenylphosphine under the optimal conditions.

8.5.8. Catalytic Amidation.—In 2014, Mecinović and co-workers achieved the formation of amides under the conditions of a catalytic Appel reaction (Scheme 862).[968] Inspired by O’Brien’s and van Delft’s results for catalytic Wittig and Appel reactions, they investigated the applicability of the conditions for catalytic Appel reactions to amidation reactions. Large arrays of aromatic carboxylic acids and aromatic or aliphatic amines were treated with PPh_3 (25 mol %), $(EtO)_2MeSiH$ (1.5 equiv), CCl_4 (2.0 equiv), and bis(4-nitrophenyl)phosphate in refluxing toluene for 20 h to generate their amides in moderate to good yields (up to 77%). Nevertheless, the reaction performed in the absence of the silane and the phosphate, under otherwise identical condition, led to only a low yield (<20%).

8.5.9. Deoxygenative Condensation of α-Ketoesters.—In 2015, Radosevich used a highly strained four-membered phosphacycle to catalyze the deoxygenative condensation of α-keto esters and carboxylic acids (Scheme 863).[969] The reaction, performed in DCE at 80 °C, provided a chemoselective catalytic synthesis of α-acyloxy ester products with good functional group compatibility (25 examples, 65–94% yields). The aminophosphetane P-oxide **P130** was readily reduced by $PhSiH_3$ under mild conditions to the tricoordinate aminophosphetane **P129**, which promoted the deoxygenative condensation of acid and keto esters, yielding the corresponding α-acyloxy esters and regenerating the aminophosphetane P-oxide **P130**.

8.5.10. Catalytic Cadogan Cyclization.—More recently, the Radosevich group reported that a readily prepared small-ring phosphacycle, 1,2,2,3,4,4-hexamethylphosphetane, was a suitable catalyst for the Cadogan indazole synthesis (Scheme 864).[970] The scope of the substrate was broad, including *o*-nitrobenzaldimines, *o*-nitroazobenzenes, and related substrates, in the presence of a hydrosilane terminal reductant.

2*H*-Indazoles, 2*H*-benzotriazoles, and related fused heterocyclic systems were synthesized in toluene at 100 °C with good functional group compatibility (37 examples, 34–95% yield). From both stoichiometric and catalytic mechanistic experiments, the reaction was proposed to proceed via catalytic P^{III}/P^{V}=O cycling, with DFT modeling suggesting a turnover-limiting (3 + 1) cheletropic addition between the phosphetane catalyst and the nitroarene substrate. In addition, strain/distortion analysis of the (3 + 1) transition structure highlighted the controlling role of frontier orbital effects underpinning the catalytic performance of the phosphetane.

8.5.11. Redox-Neutral Phosphine Oxide Catalysis.—In the aforementioned processes, the phosphine oxide byproduct is converted to a phosphine in situ, then re-enters the catalytic cycle. In related phosphine oxide-generating reactions, the phosphine oxide can be converted directly into an other reactive phosphorus(V) species by virtue of the generation of CO_2 gas.[934] In the presence of a phospholene oxide catalyst, isocyanates can be converted to carbodiimides in high yields under mild conditions (Scheme 865).[971] The structure of the isocyanate had a strong influence on the formation of the carbodiimide. For aromatic isocyanates, electron-withdrawing groups increased the rate of the reaction markedly. For example, molten *p*-nitrophenyl isocyanate reacted almost explosively at 60 °C (95% yield, 15 min). Conversely, electron-donating groups decreased the reaction rate, with the most pronounced effect being found for *o*-substituted derivatives. For example, for *o*-methyl- and *o*-methoxy-substituted isocyanates, the time required for the conversions to carbodiimides were 5 and 16 h, respectively.

In 2008, the Marsden group accomplished organophosphorus-catalyzed heterocycle synthesis through iminophosphorane formation/intramolecular aza-Wittig cyclizations (Scheme 866).[972] The reaction was used in the synthesis of both azine (e.g., phenanthridine; 5 examples, 52–82% yield) and azole (e.g., benzoxazole; 15 examples, 38–87% yield) heterocycles. Specifically, the catalyst loading could be decreased to 1 mol % in these cyclizations with little or no loss in efficiency, but simply necessitating extended reaction times.

Denton and co-workers reported the phosphine oxide-catalyzed Appel-type chlorination of alcohols (Scheme 867).[973] Their new method was effective for acyclic primary and secondary alcohols with yields of 7–87%, merely with the generation of CO and CO_2 as byproducts. The reaction was tolerant of aryl, vinyl, and alkynyl substituents.

The Denton group further investigated the catalytic phosphorus(V)-mediated chlorination and bromination of alcohols in detail (Scheme 868).[974] Here, oxalyl chloride was used as a consumable stoichiometric reagent, generating the halophosphonium salts used for the halogenations. The phosphine oxides were transformed from stoichiometric waste products into catalysts, and the catalytic phosphorus-based activation and nucleophilic substitution of alcohols was realized. Both chlorinations (21 examples, 7–98% yield) and analogous brominations (11 examples, 44–75% yield) of unhindered primary and secondary alcohols worked well with corresponding loads of the catalyst. All the reactions proceeded at room temperature as highly efficient and atom-economical alternatives to the PPh_3/CX_4 systems used traditionally for the chlorination and bromination. DFT calculations of the proposed

intermediates suggested that the catalytic cycle involved halo- and alkoxyphosphonium salts as intermediates (Scheme 869).

The Przeslak group developed a stereospecific triphenylphosphine oxide-catalyzed 1,2-dichlorination of epoxides (Scheme 870).[975] Various terminal and internal epoxides were applied in this dichlorination process. In the presence of 15 mol % of triphenylphosphine oxide, these reactions proceeded well, with yields of 56–91% (10 examples), generating CO and CO_2, instead of the usual stoichiometric triphenylphosphine oxide, as waste. In particular, this method further validated the concept of redox-neutral catalysis for phosphorus(V)-mediated conversions, as well as the use of oxalyl chloride to induce phosphine oxide turnover in such processes.

In 2013, Denton and co-workers reported the phosphorus(V)-catalyzed conversion of aldehydes into geminal dichlorides. In this deoxydichlorination process, phosphine oxide turnover was achieved using oxalyl chloride as a consumable reagent (Scheme 871).[976] The new method was applicable to a range of aldehydes, including aryl and aliphatic aldehydes, and the desired germinal dichloride products were obtained in isolated yields of 32–91%.

In addition to the Appel-type processes mentioned above, the Denton group also performed phosphine oxide-catalyzed conversion of aldoximes to nitriles in the absence of a metal catalyst (Scheme 872).[977] The desired nitrile derivatives were formed at room temperature when using oxalyl chloride (1.2 equiv) in combination with 5 mol % of triphenylphosphine oxide. The dehydration process was effective for a wide of aliphatic, aromatic, and heteroaromatic aldoximes, with good to excellent yields (73–99%) obtained in all cases. A plausible mechanism was proposed (Scheme 873).

9. CONCLUSION

Starting from Horner's discovery of phosphonium zwitterion species, nucleophilic phosphine catalysis has emerged as a prominent and powerful strategy for constructing functionalized carbo- and heterocyclic structures that have important applications in the fields of pharmaceutical design and natural products synthesis. The use of phosphine catalysts facilitates reaction manipulation and eliminates the need for complex postreaction workup, thereby minimizing waste and carbon emissions. The recent rise in catalytic versions of traditionally phosphine oxide-generating reactions—particularly Wittig, Mitsunobu, and Staudinger reactions—alleviates the classical distinction between catalytic and stoichiometric processes that employ phosphine. These developments are encouraging, considering that environmental- and energy-related issues are becoming more urgent than ever in the 21st century.[978] With the inevitable discoveries of novel reaction pathways, phosphine catalysis will continue to evolve and provide further insights into the roles of phosphines in facilitating molecular transformations while broadening the horizons of organocatalysis.

ACKNOWLEDGMENTS

We thank the NIH (GM071779 to O.K.), the Natural Science Foundation of China (Nos. 21172253, 21372256, and 21572264 to H.G.), the Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education,

Guizhou University (No. 2014GDGP0103 to H.G.), and the Program for Changjiang Scholars and the Innovative Research Team Project (No. IRT1042 to H.G.) for financial support. We also thank Andrew J. Smaligo for preparing the TOC graphic.

Biographies

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Yi Chiao (Joseph) Fan was born in 1986 in Taiwan. He received his BA in chemistry from the University of California, Davis in 2008. In 2014, he completed his PhD in chemistry at the University of California, Los Angeles, under the instruction of Professor Ohyun Kwon. His research focused on tandem phosphine–palladium catalysis and natural products syntheses. He is currently employed as a Research Scientist at AIM Biosciences.

Zhanhu Sun obtained his MS (2010) from Nankai University under the guidance of Professor Yu Liu and his PhD (2013) from RWTH Aachen University, Germany, supervised by Professor Markus Albrecht. He then co-worked, from 2014 to 2017, with Professor Mihail Barbiou at the University of Montpellier 2 (France), Professor Hongchao Guo at China Agricultural University (China), and Professor Zheng-Rong Lu at Case Western Reserve University (USA). In 2018, he will join Professor David Leigh’s group at East China Normal University in Shanghai to work on molecular machines and molecular motors. He is one of the 2013 SciFinder Future Leaders in Chemistry. His research ranges from supramolecular chemistry, organic synthesis, and organocatalysis to the applications of synthetic products in BME and artificial water/ion channels.

Yang Wu was born in 1991 in Jiangsu, China. She studied chemistry at China Agricultural University, where she obtained her BSc in 2013. She then joined the group of Professor Hongchao Guo at China Agricultural University to pursue her PhD. Her research is focused on phosphine-catalyzed annulations to develop novel synthetic methodology.

Ohyun Kwon, Professor of Chemistry and Biochemistry at UCLA, received her BS and MS degrees from Seoul National University in 1991 and 1993, respectively. After obtaining her PhD from Columbia University in 1998 and a postdoctoral stint at Harvard University, she began her independent career at UCLA in 2001. She has played key roles in establishing phosphinocatalysis as one of the main areas of organocatalysis research. She is recognized as one of the key leaders in the field.

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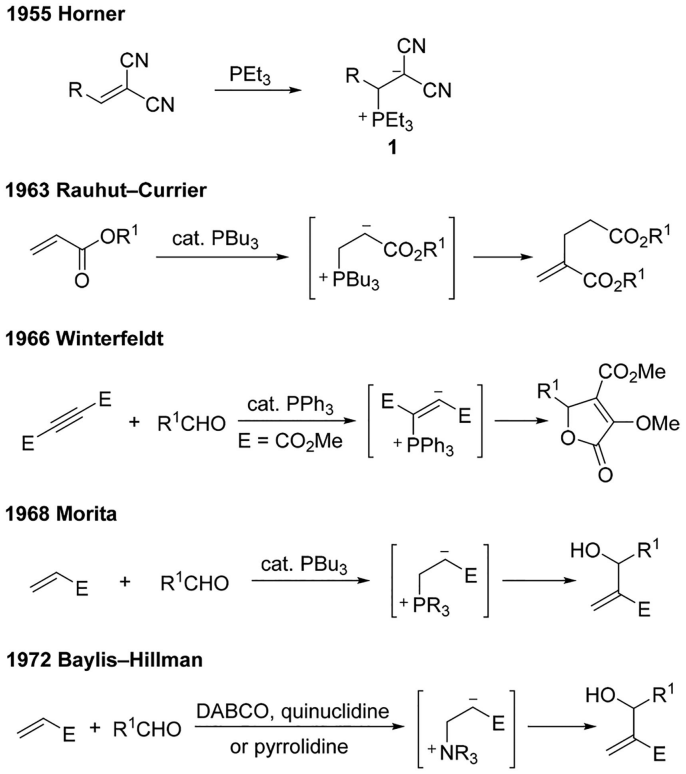
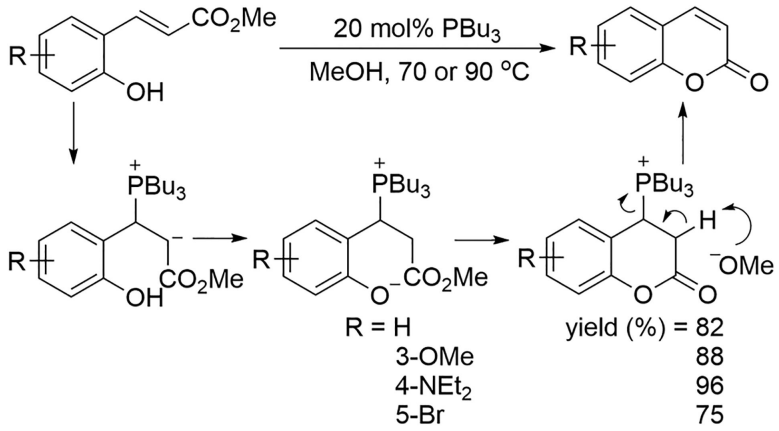
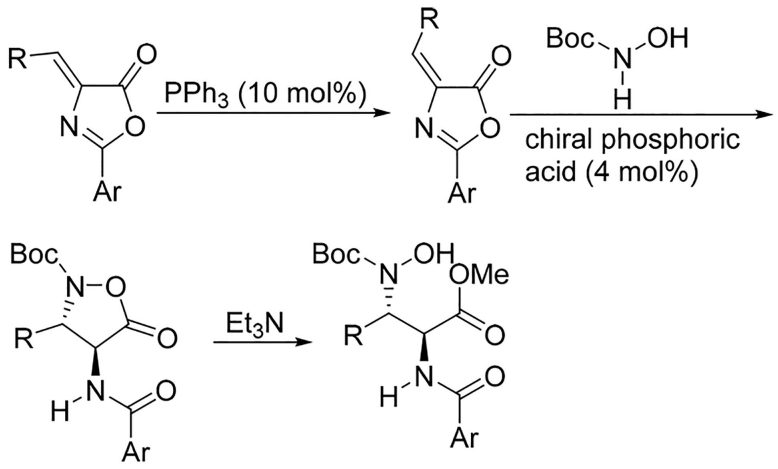


Scheme 1.
History of Early Phosphine Catalysis

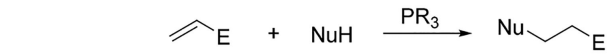


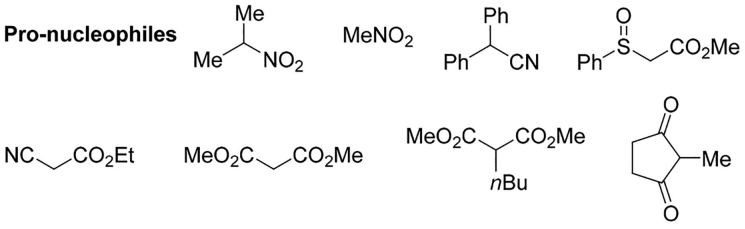
Scheme 2.
Phosphine-Catalyzed Alkene Isomerization–Lactonization



Scheme 3.

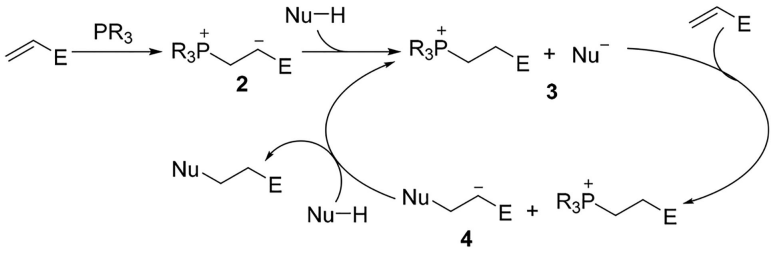
Tandem Orthogonal Organocatalysis Involving Phosphine-Catalyzed Isomerization of *Z*-Alkylideneoxazolones



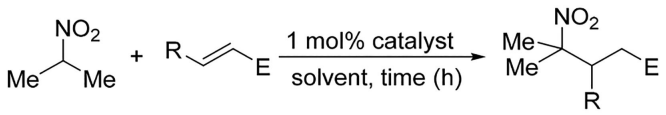
Phosphines	PCy_3, PBu_3, PMe_2Ph, $PMePh_2$, PPh_3
Activating groups	CO_2Me, CO_2Et, COMe, $CO(CH_2)_nCH_3$, CN, SO_2Ph
Pro-nucleophiles	

Scheme 4.

Scope of Pronucleophiles, Activating Groups, and Phosphines

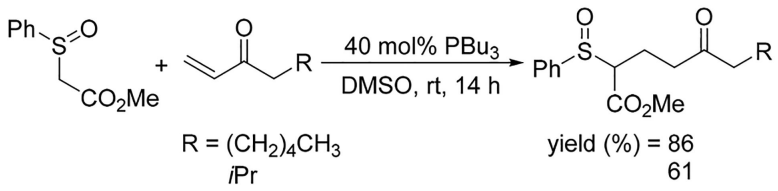


Scheme 5.
Phosphine-Promoted General Base Catalysis

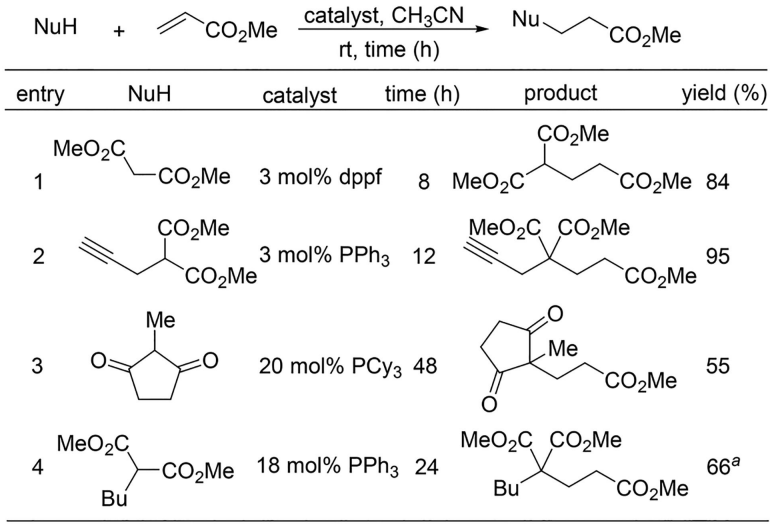


entry	R	E	catalyst	solvent	time (h)	yield (%)
1	H	CO_2Et	NMe_2Ph	THF	1.5	No reaction
2	H	CO_2Et	PMe_2Ph	THF	1.5	79
3	Me	CN	PBu_3	neat	16	75

Scheme 6.
Michael Additions of 2-Nitropropane



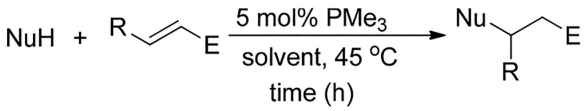
Scheme 7.
Michael Addition of Methyl Phenylsulfinylacetate



Scheme 8.

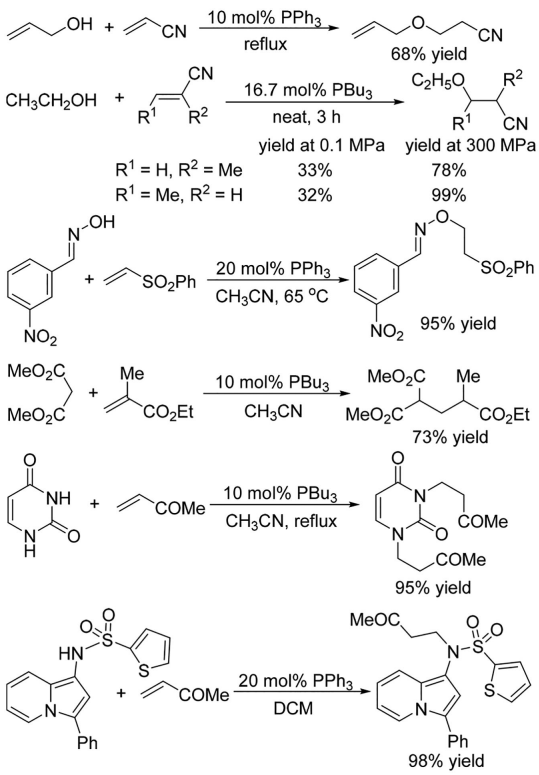
Michael Additions of Hindered Carbon-Centered Nucleophiles

[a]Reaction was performed under reflux.

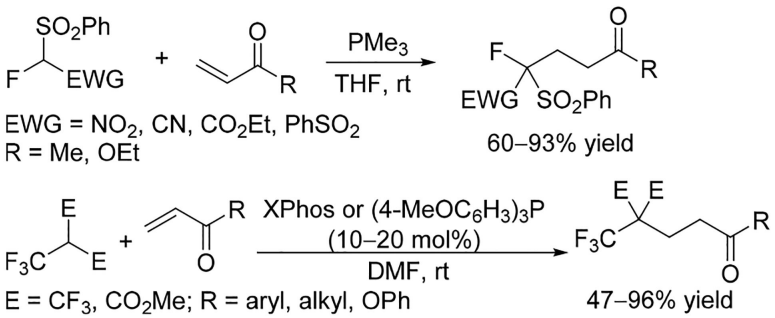


entry	NuH	R	E	solvent	time (h)	yield (%)
1	MeOH	H	CN	MeOH	4	79
2	PhOH	H	COMe	CH_3CN	16	59
3	H_2O	Me	CO_2Et	H_2O	20	77
4	MeOH	Ph	COMe	MeOH	72	72

Scheme 9.
Michael Additions of Oxygen Pronucleophiles

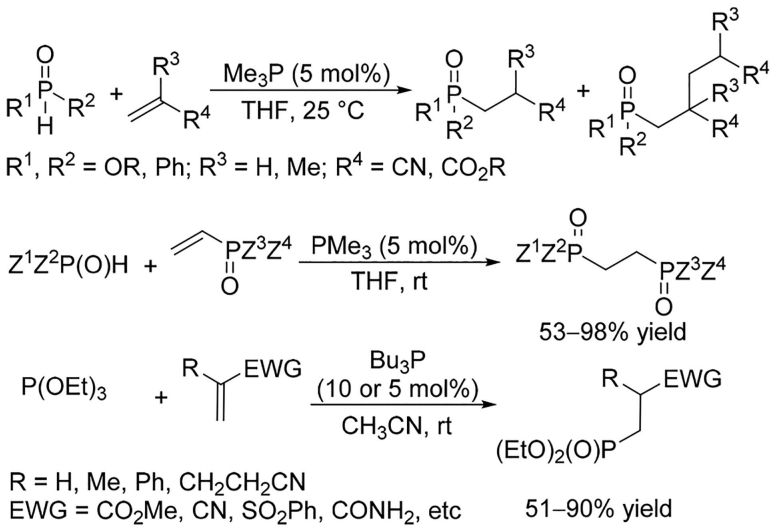


Scheme 10.
Michael Additions of Various Pronucleophiles



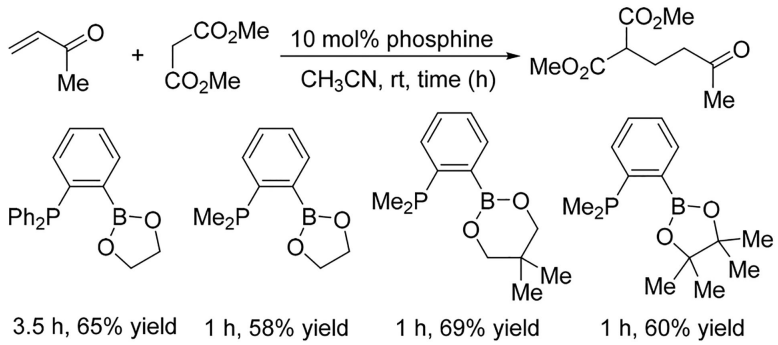
Scheme 11.

Phosphine-Catalyzed Michael Reactions of F-and CF_3-Containing Compounds with Alkenes

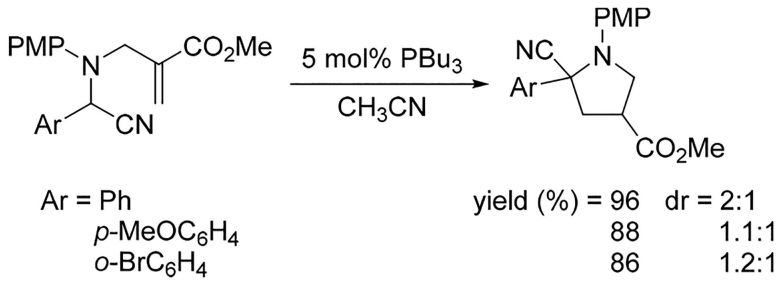


Scheme 12.

Phosphine-Catalyzed Michael Additions of Phosphorus-Centered nucleophiles



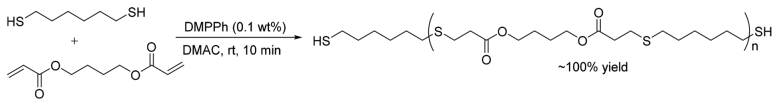
Scheme 13.
Michael Additions Catalyzed by Phosphine–Borane Catalysts



Ar = Ph	yield (%) = 96	dr = 2:1
p-$MeOC_6H_4$	88	1.1:1
o-BrC_6H_4	86	1.2:1

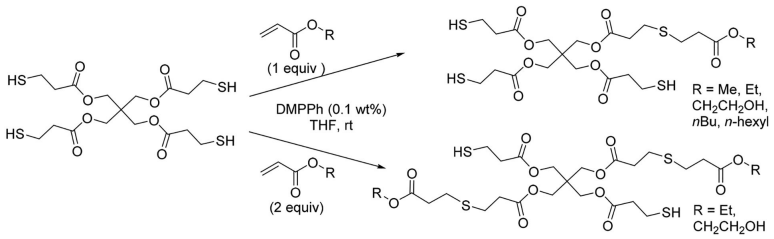
Scheme 14.

Syntheses of Functionalized Pyrrolidines through Intramolecular Michael Additions



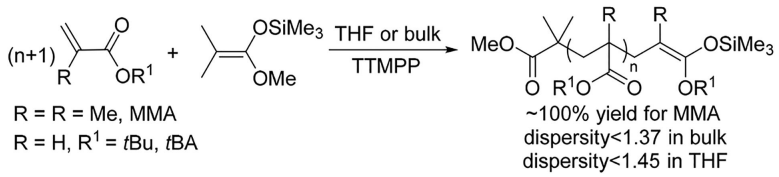
Scheme 15.

Preparation of Thiol-Terminated Oligomers via Phosphine-Catalyzed Michael Additions between 1,6-Hexanedithiol and 1,4-Butanediol Diacrylate

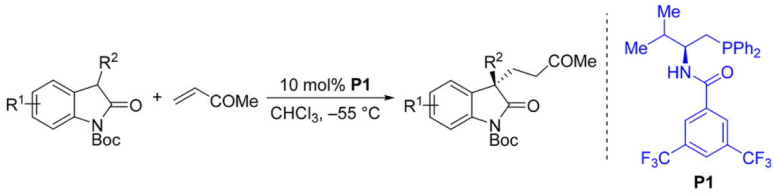


Scheme 16.

Phosphine-Catalyzed Michael Reactions between Pentaerythritol Tetrakis(3-mercaptopropionate) and Alkyl or Hydroxyl Alkyl Acrylates

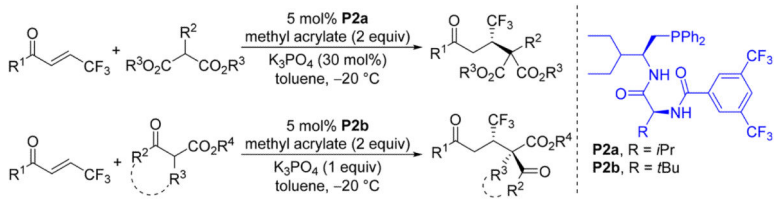


Scheme 17.
Phosphine-Catalyzed Group Transfer Polymerizations of Acrylates



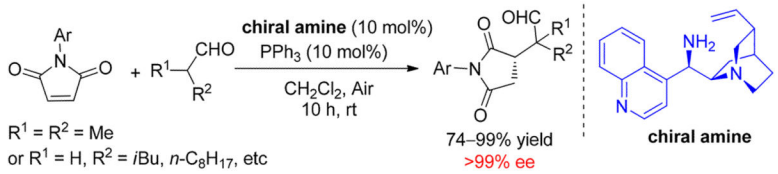
entry	R^1	R^2	yield (%)	ee (%)
1	H	Ph	96	94
2	H	*p*-$MeOC_6H_4$	97	94
3	7-F	Ph	94	96
4	H	*i*Bu	78	79

Scheme 18.
Phosphine-Catalyzed Asymmetric Michael Addition.



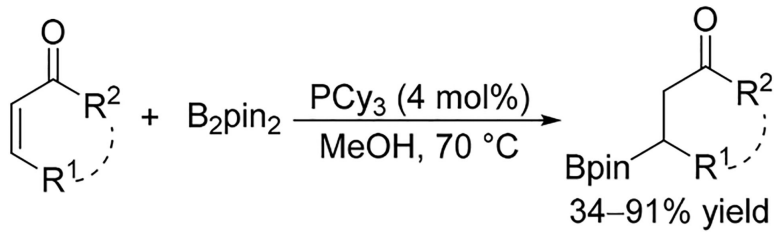
Scheme 19.

Phosphine-Catalyzed Enantioselective Michael Addition of β-Carbonyl Esters to β-Trifluoromethyl Enones

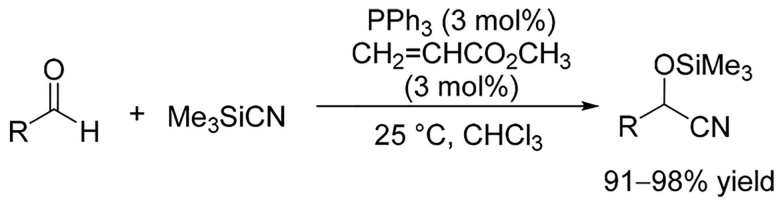


Scheme 20.

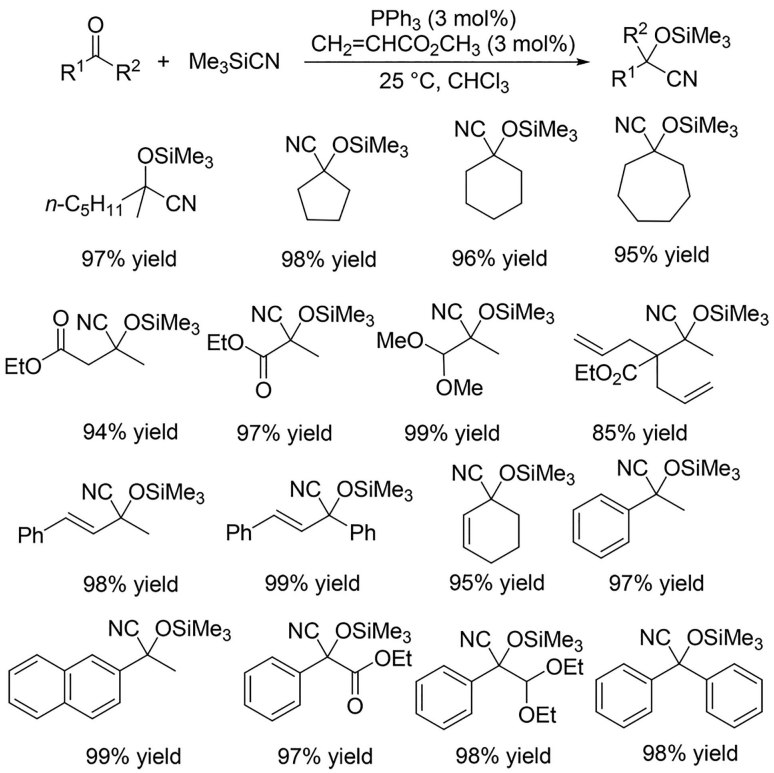
Dual-Component Catalyst System for Michael Additions between Aldehydes and Maleimides



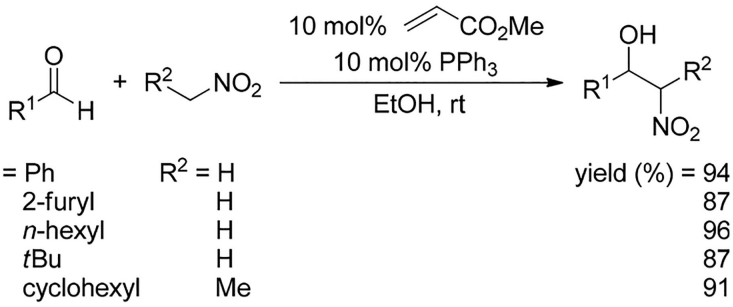
Scheme 21.
Organocatalytic β-Boration of α,β-Unsaturated Carbonyl Compounds



Scheme 22.
Phosphine-Catalyzed Cyanosilylation of Aldehydes



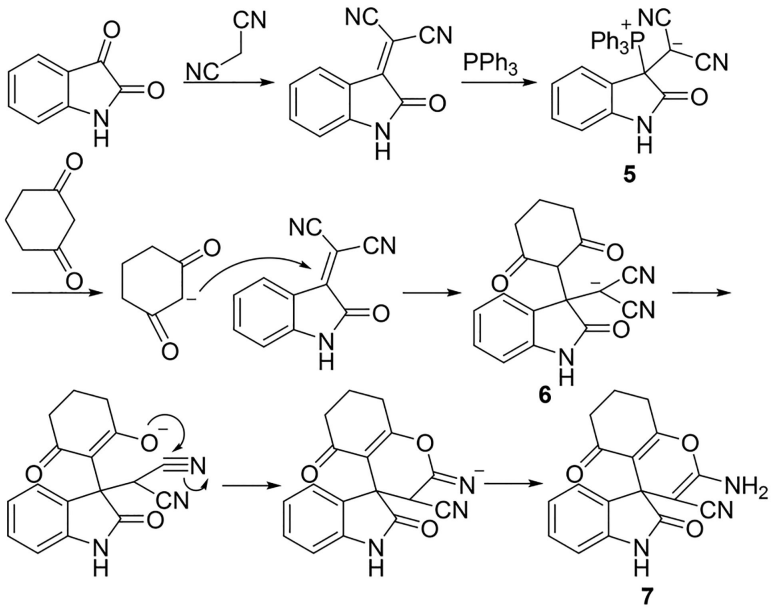
Scheme 23.
Phosphine-Catalyzed Cyanosilylation of Ketones



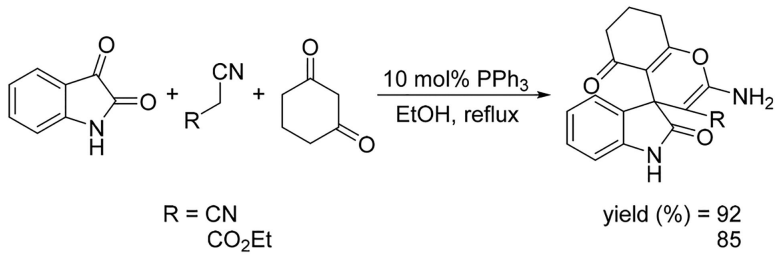
R^1 =	R^2 =	yield (%) =
Ph	H	94
2-furyl	H	87
n-hexyl	H	96
*t*Bu	H	87
cyclohexyl	Me	91

Scheme 24.

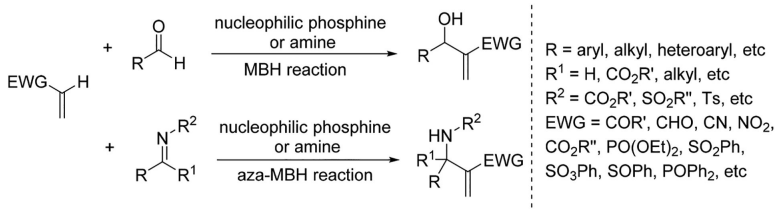
Phosphine-Catalyzed Henry Reactions Generating Functionalized *β*-Nitroalkanols



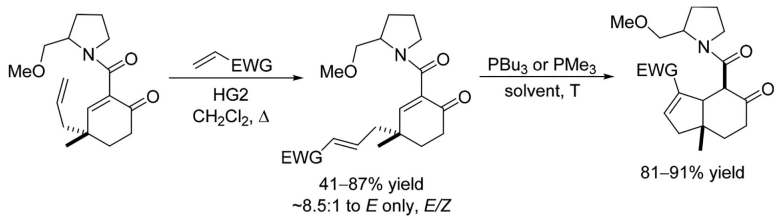
Scheme 25.
Proposed Mechanism of Spirooxindole Formation



Scheme 26.
Synthesis of Spirooxindoles

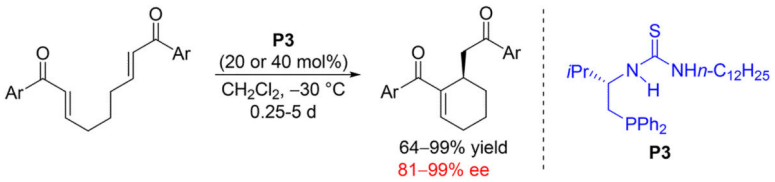


Scheme 27.
Organocatalyzed MBH and Aza-MBH Reactions



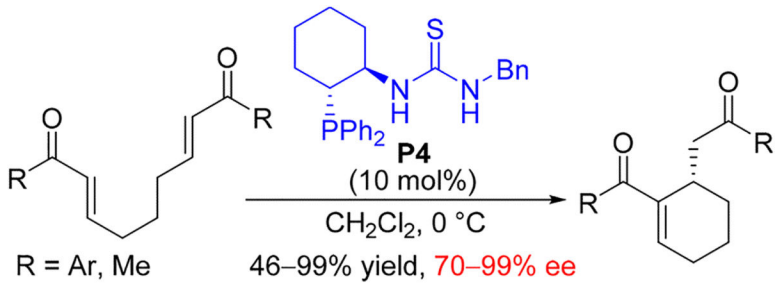
Scheme 28.

An Olefin Metathesis and Phosphine-Catalyzed RC Reaction Sequence



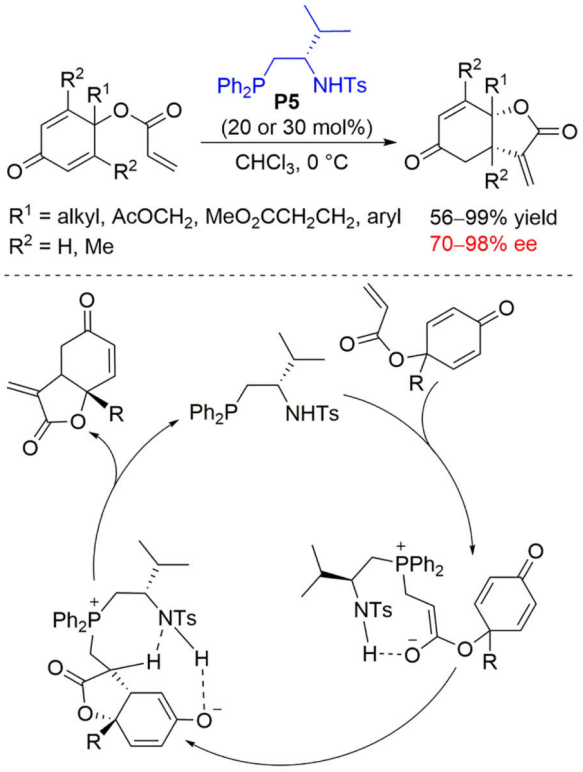
Scheme 29.

Phosphine-Catalyzed Enantioselective Intramolecular RC Reaction

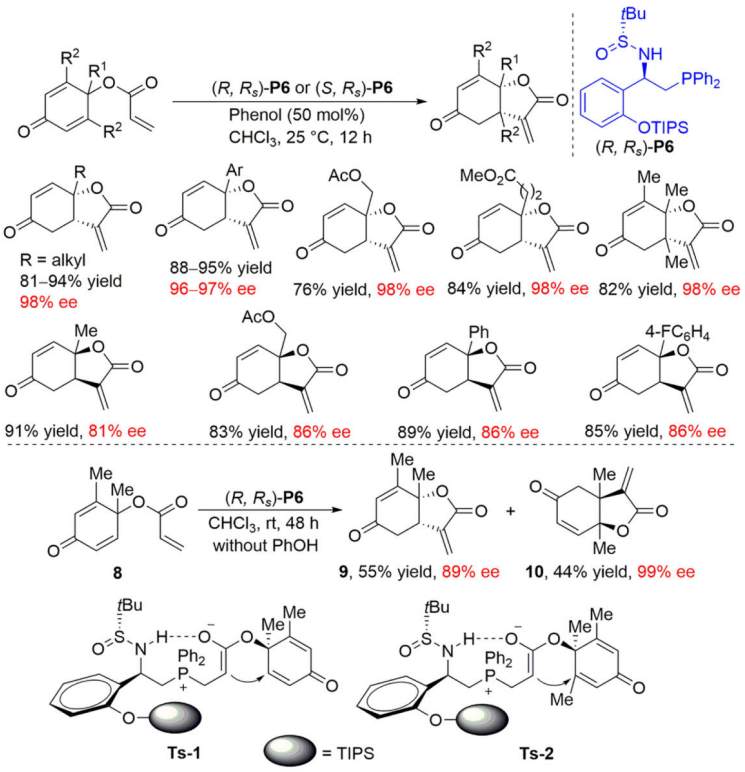


Scheme 30.

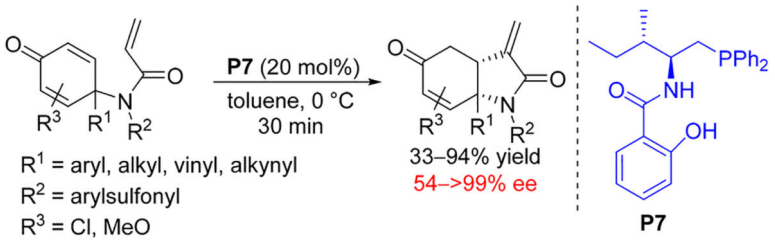
Chiral Cyclohexane-Based Thiourea–Phosphine-Catalyzed Intramolecular RC Reaction



Scheme 31.
Chiral Phosphine-Catalyzed Intramolecular RC Reaction

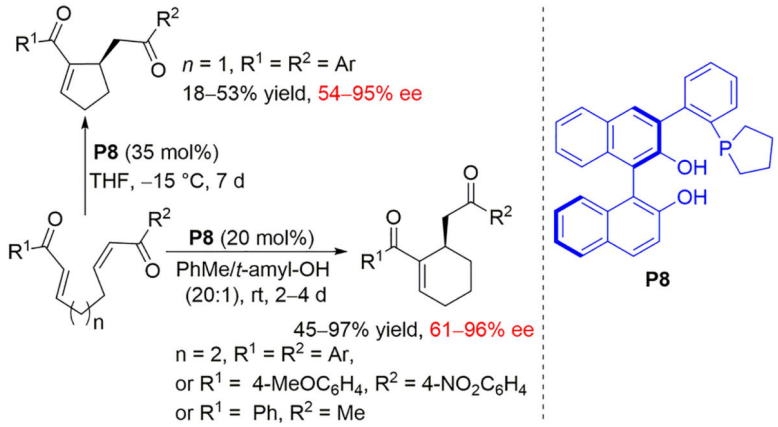


Scheme 32.
Intramolecular RC Reactions Catalyzed by the Chiral Phosphine P6



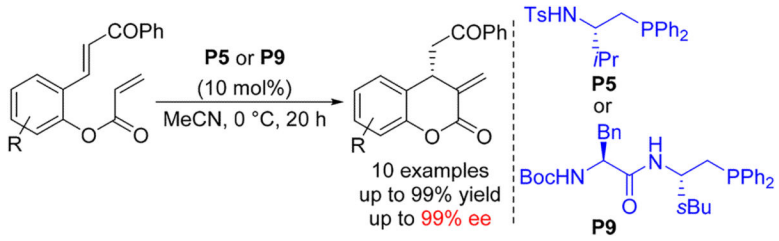
Scheme 33.

Phosphine-Catalyzed Asymmetric Intramolecular RC Reaction of Cyclohexadienone

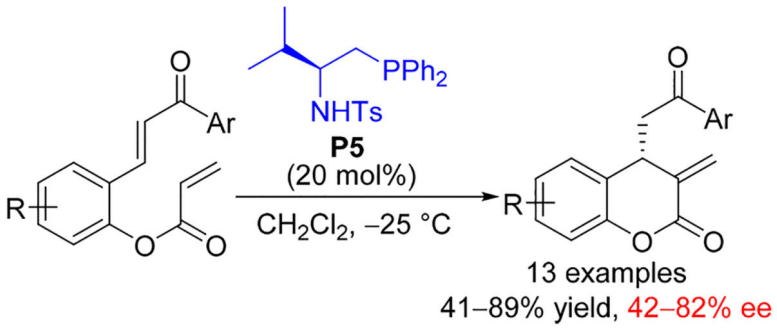


Scheme 34.

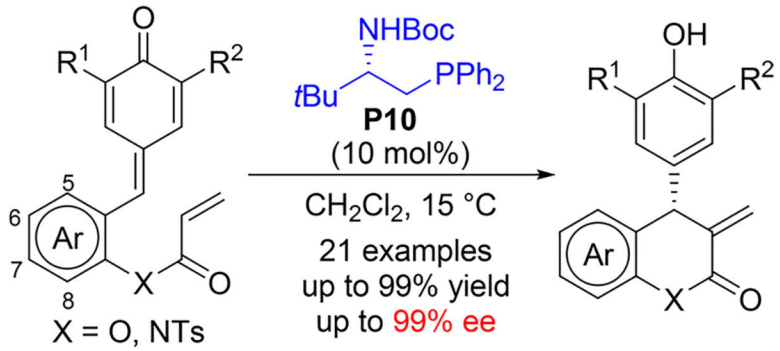
Phosphine-Catalyzed Intramolecular RC Reactions to Prepare Chiral Cyclopentenes and Cyclohexene Derivatives



Scheme 35.
Enantioselective Intramolecular RC Reaction

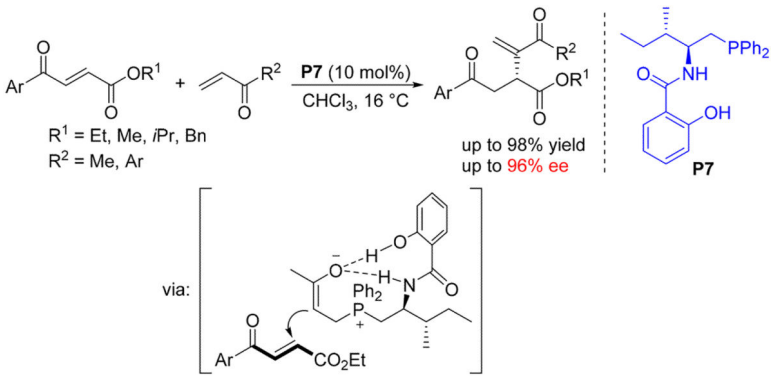


Scheme 36.
Enantioselective Intramolecular RC Reaction



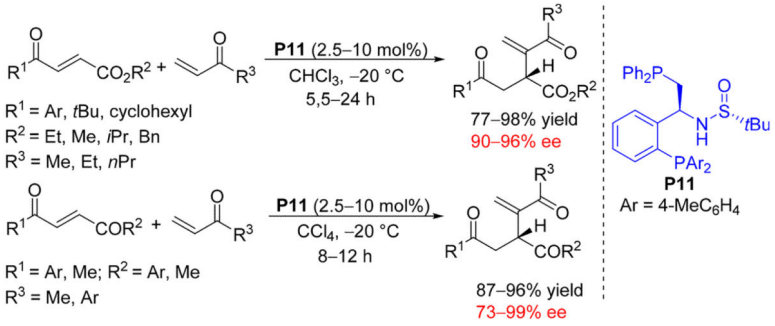
Scheme 37.

Chiral Phosphine-Catalyzed Intramolecular Vinylogous RC Reaction of *para*-Quinone Methides (*p*-QMs)

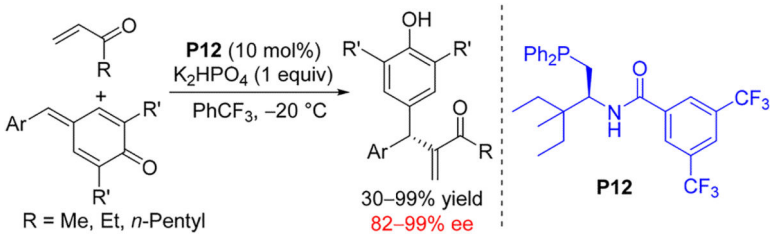


Scheme 38.

Phosphine-Catalyzed Asymmetric Intermolecular Cross RC Reaction of Electron-Deficient Olefins

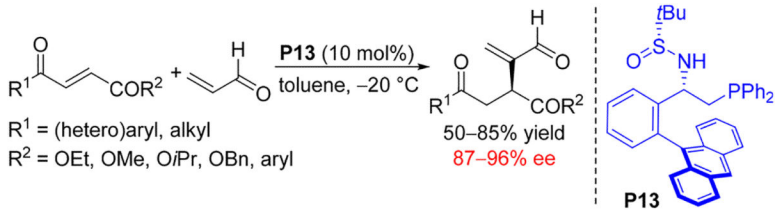


Scheme 39.
Asymmetric Intermolecular RC Reactions



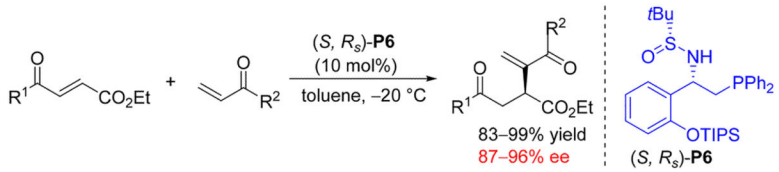
Scheme 40.

Phosphine-Catalyzed Enantioselective Intermolecular RC Reactions of Alkyl Vinyl Ketones with *para*-Quinone Methides



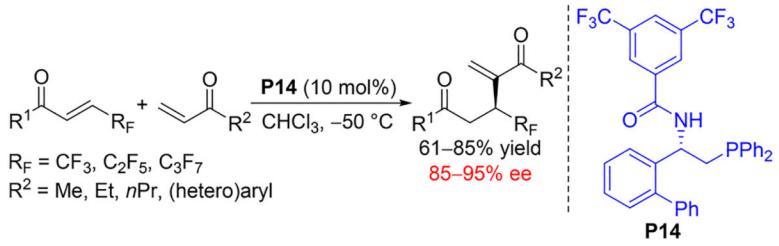
Scheme 41.

Enantioselective Intermolecular Cross RC Reaction of Active Alkenes and Acrolein



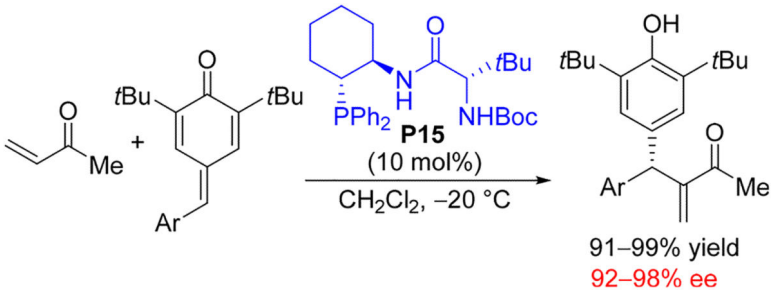
Scheme 42.

Xiao-Phos–Catalyzed Highly Enantioselective Cross Intermolecular RC Reaction of Activated Alkenes with Vinyl Ketones



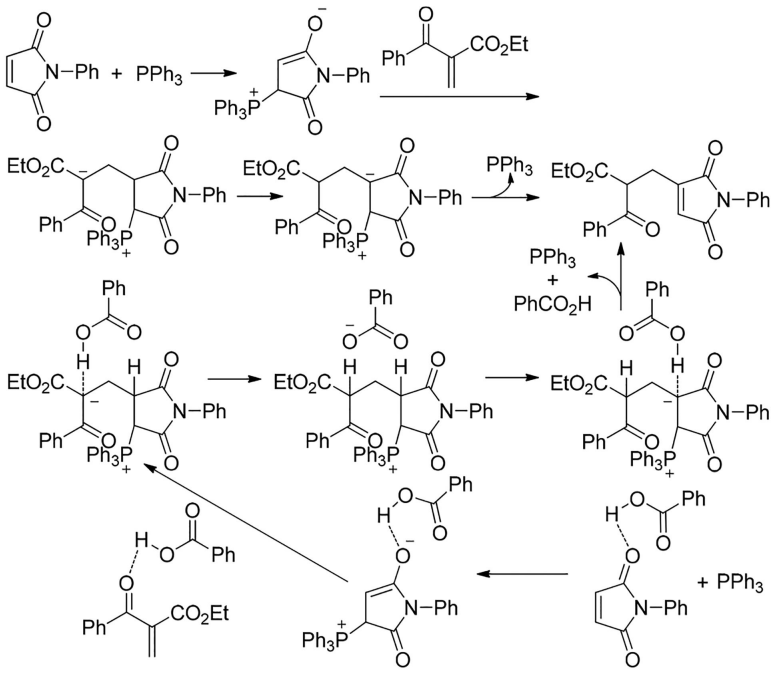
Scheme 43.

Phosphine-Catalyzed Asymmetric Intermolecular Cross-RC Reaction of β-Perfluoroalkyl-Substituted Enones and Vinyl Ketones



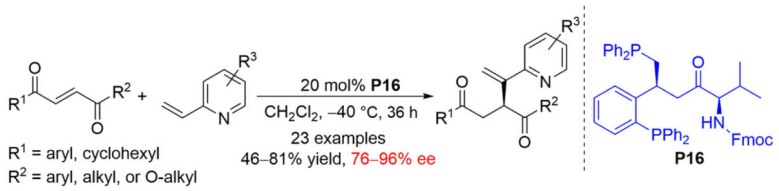
Scheme 44.

Phosphine-Catalyzed Enantioselective RC-Type 1,6-Conjugate Addition of Methyl Vinyl Ketone to *para*-Quinone Methides



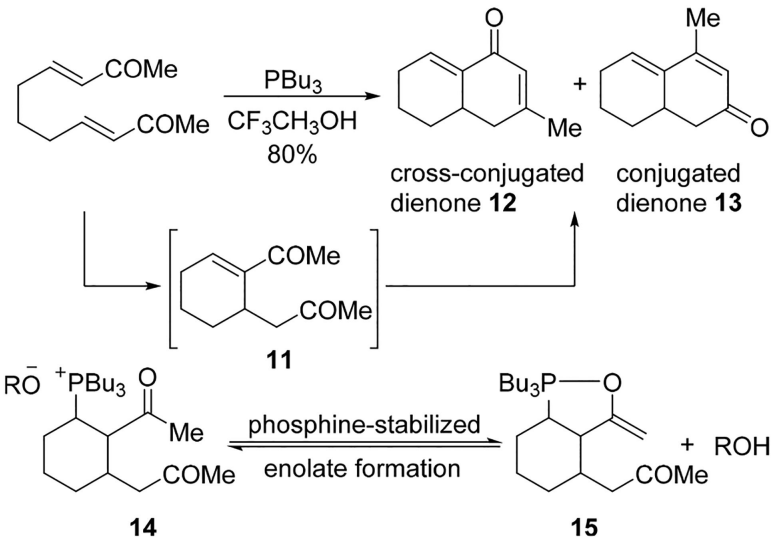
Scheme 45.

Mechanism of Phosphine-Catalyzed RC Reaction of *N*-Phenylmaleimide and 2-Benzoyl Acrylate



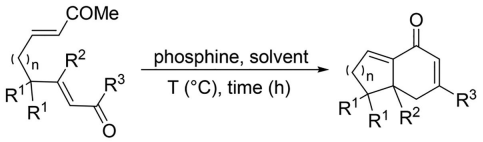
Scheme 46.

Chiral Phosphine-Catalyzed RC Reaction of 2-Vinylpyridines with 3-Aroyl Acrylates or 2-Ene-1,4-diones



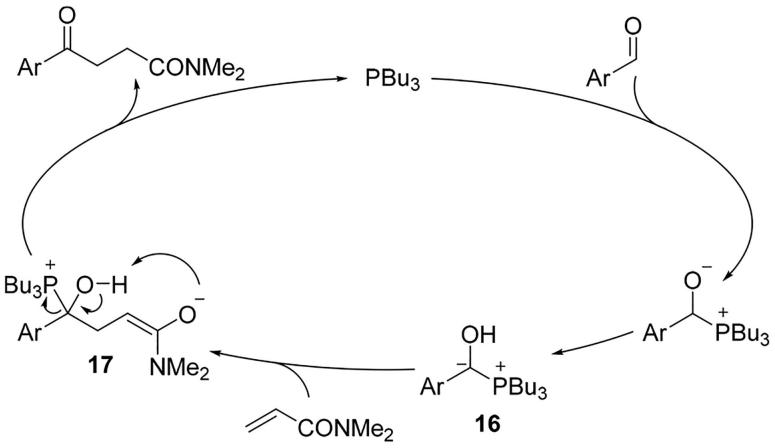
Scheme 47.

A Phosphonium-Stabilized Enolate

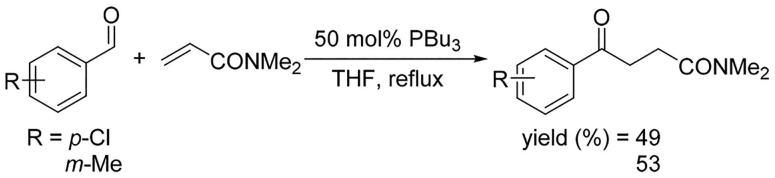


entry	R^1	R^2	R^3	*n*	phosphine	solvent	T (°C)	time (h)	yield (%)
1	H	H	Me	1	1 eq. PBu_3	CF_3CH_2OH	60	3	76
2	Me	H	Me	2	1 eq. PBu_3	CF_3CH_2OH	60	48	71
3	H	Me	Me	2	5 eq. PMe_3	*t*-AmylOH	80	24	60
4	H	Me	*i*Pr	2	5 eq. PMe_3	*t*-AmylOH	80	14	64

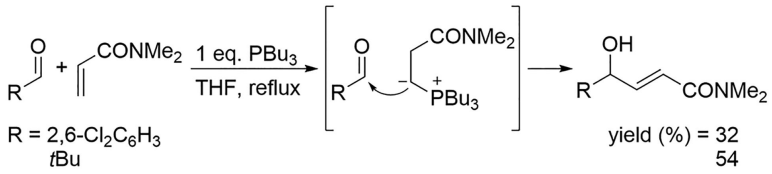
Scheme 48.
Formation of Functionalized Cross-Conjugated Dienones



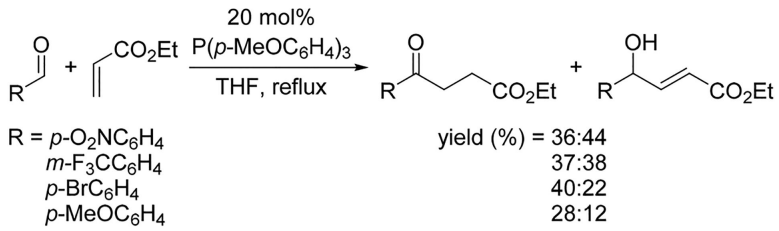
Scheme 49.
Proposed Mechanism for Phosphine-Catalyzed Stetter Reaction



Scheme 50.
Phosphine-Catalyzed Stetter Reaction

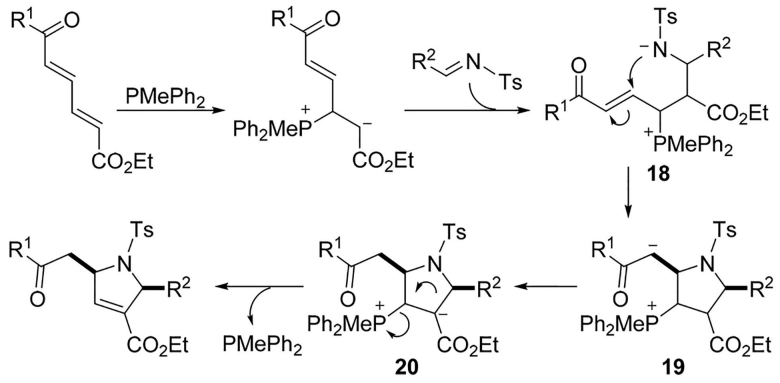


Scheme 51.
Phosphine-Catalyzed β-Umpolung Reaction

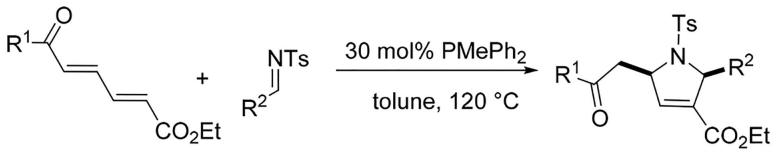


Scheme 52.

Synthesis of γ-Ketoesters and γ-Hydroxyacrylates

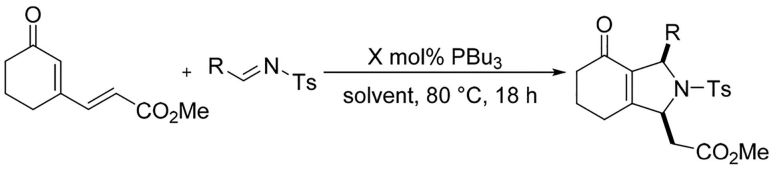


Scheme 53.
Proposed Mechanism of Aza-MBH–Michael Annulation



entry	R^1	R^2	yield (%)	dr
1	Ph	Ph	64	90:10
2	*t*Bu	Ph	92	>99:1
3	cyclohexyl	Ph	70	>99:1
4	*t*Bu	*i*Pr	69	>99:1
5	*t*Bu	*p*-$CF_3C_6H_4$	85	>99:1

Scheme 54.
Formation of Functionalized Pyrrolines

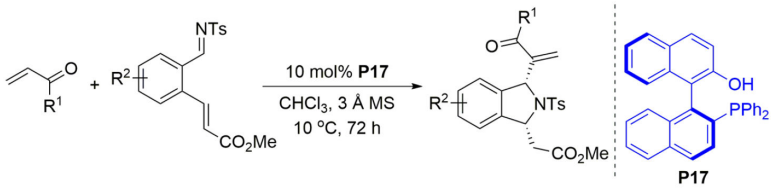


entry	R	X (mol%)	solvent	yield (%)
1	*p*-ClC_6H_4	10	MEK[a]	93
2	*p*-$F_3CC_6H_4$	30	MEK[a]	78
3	*p*-$O_2NC_6H_4$	30	*t*BuOH	47
4	*i*Pr	30	*t*BuOH	71

Scheme 55.

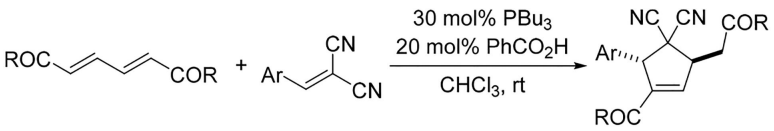
Formation of Hexahydroisoindol-4-ones

[a]MEK = methyl ethyl ketone



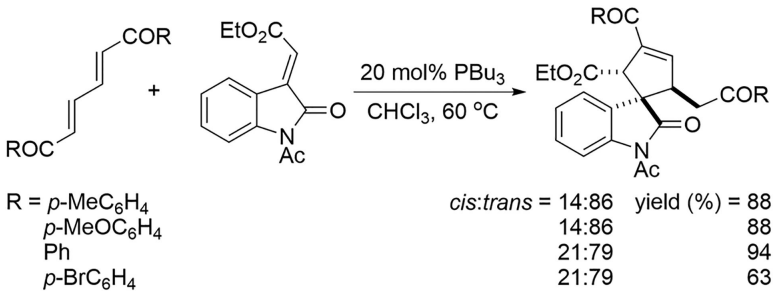
entry	R^1	R^2	yield (%)	ee (%)
1	Me	H	98	92
2	H	H	49	87
3	OPh	H	66	68
4	Me	5-Me	75	89
5	Me	6-Cl	88	82

Scheme 56.
Enantioselective Preparation of Functionalized Isoindolines



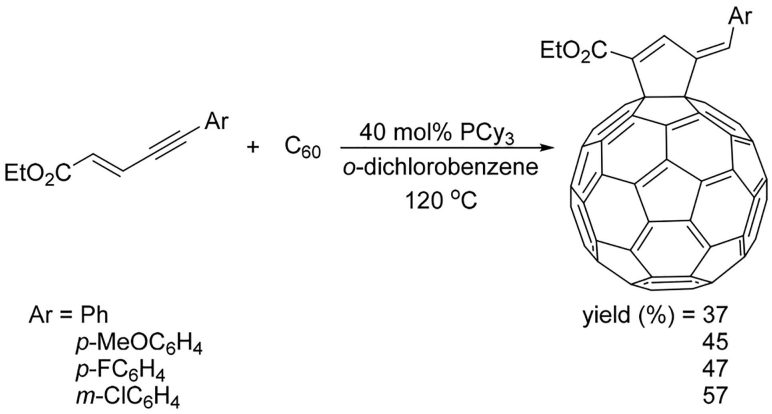
entry	R	Ar	yield (%)	trans:cis
1	*p*-MeC_6H_4	2,4-ClC_6H_4	94	91:9
2	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	59	>95:5
3	*p*-MeC_6H_4	Ph	81	84:16
4	2-thienyl	*p*-FC_6H_4	75	80:20
5	OEt	*p*-FC_6H_4	0	—

Scheme 57.
Synthesis of Functionalized Cyclopentenes

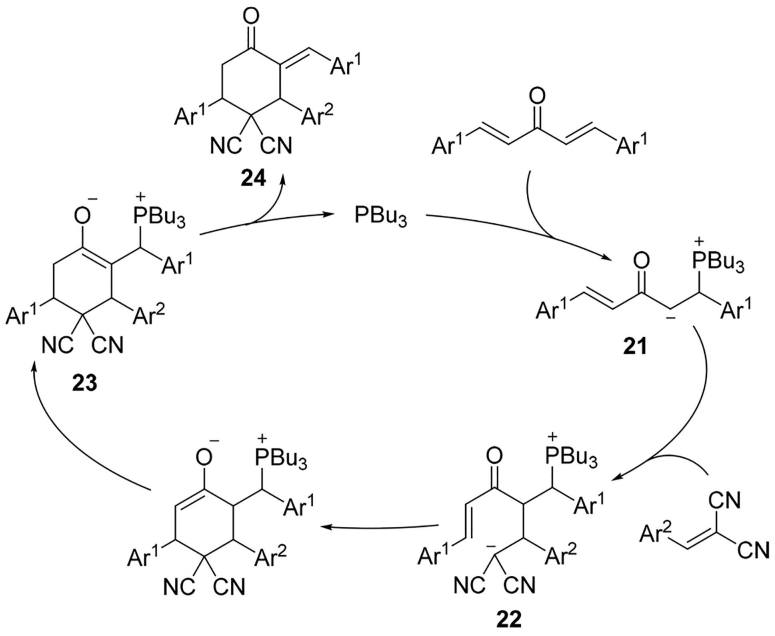


R =	*cis*:*trans* =	yield (%) =
p-MeC_6H_4	14:86	88
p-$MeOC_6H_4$	14:86	88
Ph	21:79	94
p-BrC_6H_4	21:79	63

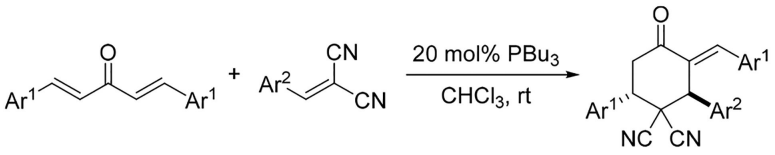
Scheme 58.
Synthesis of Functionalized Spirooxindoles



Scheme 59.
Functionalization of Fullerenes

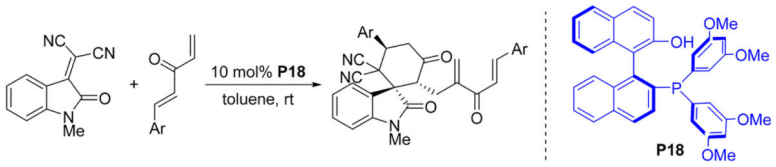


Scheme 60.
Suggested Reaction Pathway for the Michael-Intervened RC Reaction



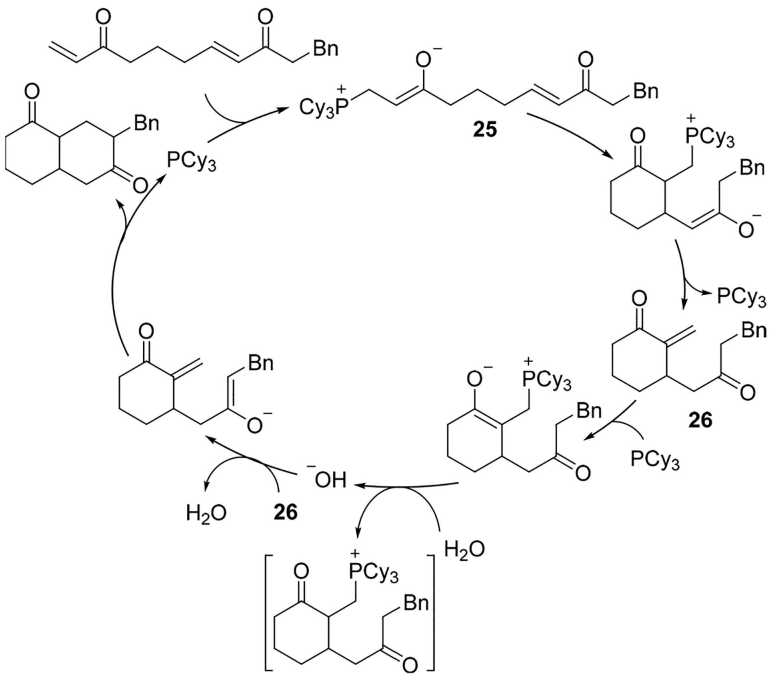
entry	Ar^1	Ar^2	yield (%)	dr
1	Ph	*p*-MeC_6H_4	86	7:1
2	Ph	2-thienyl	62	20:1
3	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	74	5:1
4	*p*-$F_3CC_6H_4$	Ph	46	8:1

Scheme 61.
Preparation of Cyclohexanone Derivatives

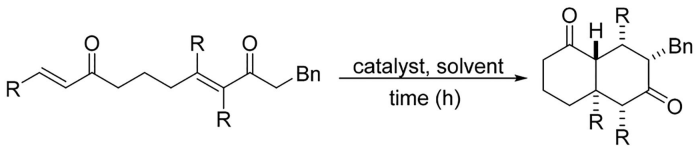


entry	Ar	yield (%)	ee (%)	dr
1	*p*-MeC$_6$H$_4$	89	92	15:1
2	*p*-FC$_6$H$_4$	86	95	15:1
3	2-furyl	80	94	>20:1
4	Cy	75	94	>20:1

Scheme 62.
Asymmetric Synthesis of Functionalized Spirocyclohexanoneoxindoles

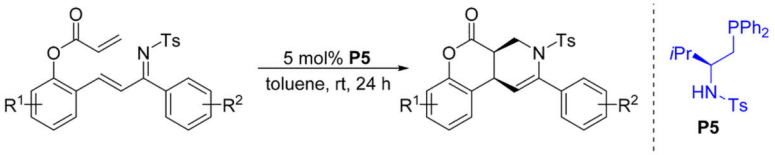


Scheme 63.
Proposed Reaction Pathway for RC–Michael Annulation



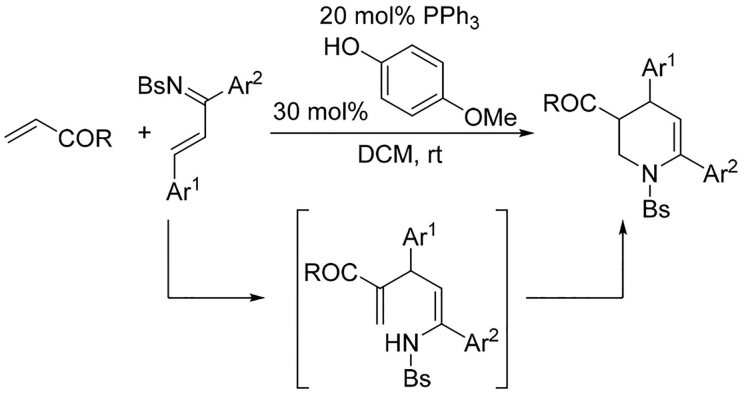
entry	R	catalyst	solvent	time (h)	yield (%)	dr
1	H	1 eq. PCy_3/H_2O	CH_3CN	24	50	12:1:1
2	H	20 mol% PBu_3	*i*PrOH	2	46	12:1:1
3	Me	1 eq. PMe_3/Cs_2CO_3	CH_3CN	16	75	4:3:2:1

Scheme 64.
Tandem Intramolecular RC–Michael Annulation



entry	R^1	R^2	yield (%)	ee (%)
1	6-*t*Bu	H	99	96
2	5-MeO	H	52	98
3	H	*p*-Me	70	99
4	H	*m*-Cl	55	97

Scheme 65.
Enantioselective Synthesis of Multicyclic Ring Systems

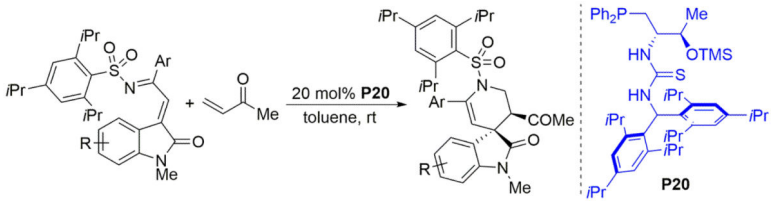


entry	R	Ar^1	Ar^2	yield (%)	dr
1	Me	*m*-BrC_6H_4	Ph	95	19:1
2	Me	Ph	*p*-IC_6H_4	92	>20:1
3	Ph	Ph	Ph	92	>20:1
4	2-furyl	Ph	Ph	90	>20:1

Scheme 66.
Synthesis of Functionalized Tetrahydropyridines

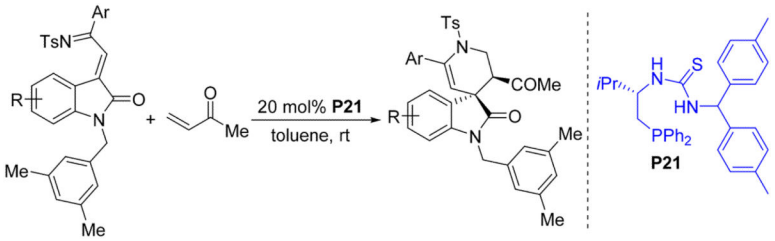
entry	R	yield (%)	ee (%)	dr
1	Ph	68	89	>95:5
2	*m*-$MeOC_6H_4$	60	92	>95:5
3	*p*-FC_6H_4	60	90	>95:5
4	2-thienyl	85	92	>95:5

Scheme 67.
Asymmetric Synthesis of Functionalized Tetrahydropyridines



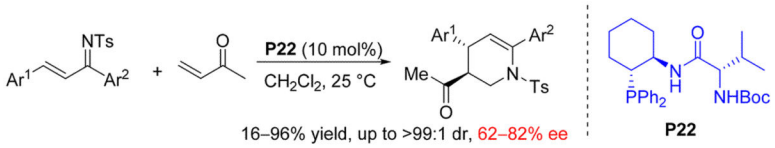
entry	R	Ar	yield (%)	ee (%)
1	H	*m*-MeOC$_6$H$_4$	85	94
2	H	*p*-O$_2$NC$_6$H$_4$	70	90
3	5-F	Ph	84	98
4	6-Cl	Ph	82	95

Scheme 68.
Asymmetric Synthesis of Functionalized Spirotetrahydropyridineoxindoles



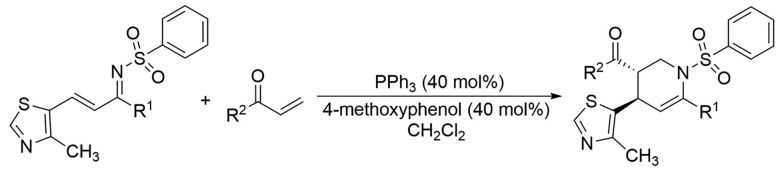
entry	R	Ar	yield (%)	ee (%)
1	H	*p*-ClC_6H_4	80	98
2	H	*p*-$O_2NC_6H_4$	47	97
3	5-F	Ph	75	99
4	6-Me	Ph	83	99

Scheme 69.
Asymmetric Formation of Functionalized Spirotetrahydropyridineoxindoles

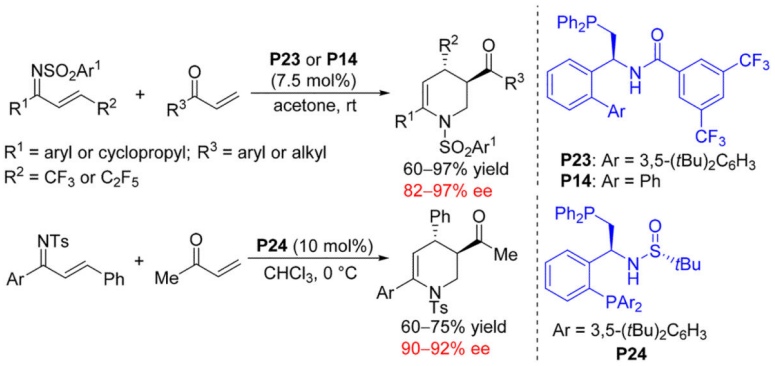


Scheme 70.

Enantioselective Phosphine-Catalyzed [4 + 2] Cycloaddition of α,β-Unsaturated Imines with Methyl Vinyl Ketone

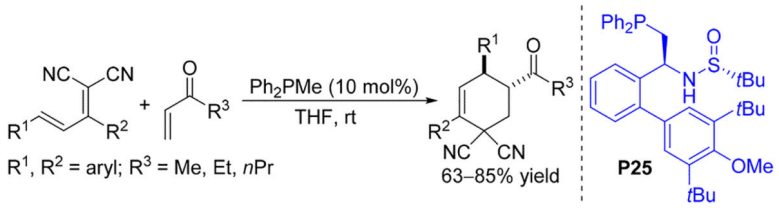


Scheme 71.
Phosphine-Catalyzed Aza-RC Reaction



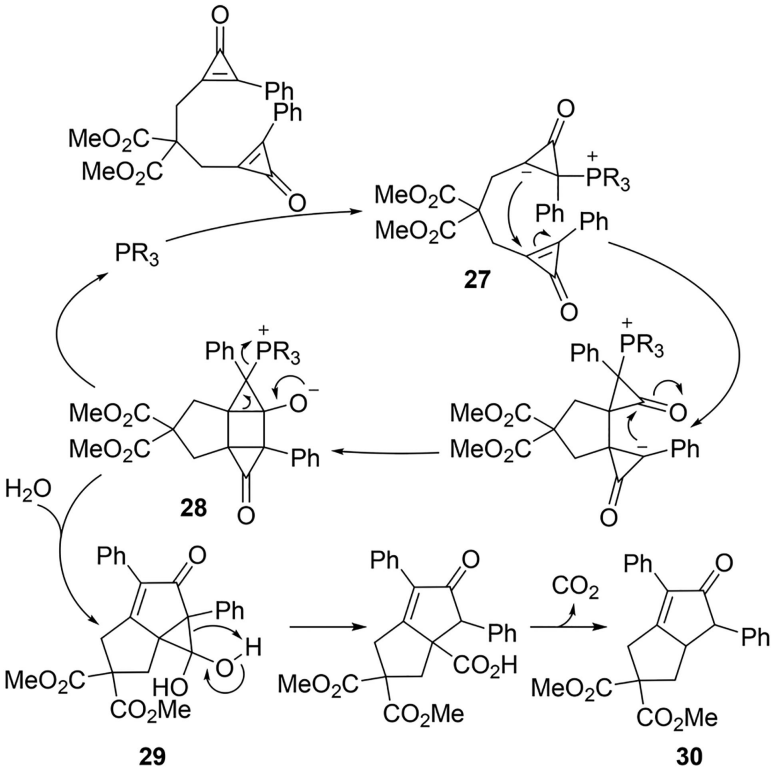
Scheme 72.

Enantioselective Phosphine-Catalyzed [4 + 2] Cycloaddition of *N*-Sulfonyl-1-aza-1,3-Dienes and Vinyl Ketones

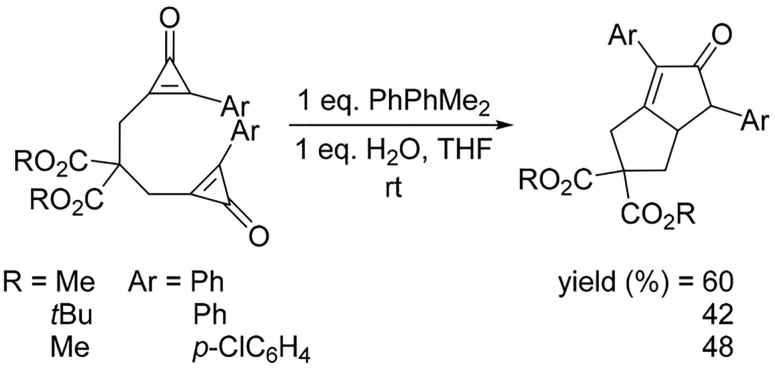


Scheme 73.

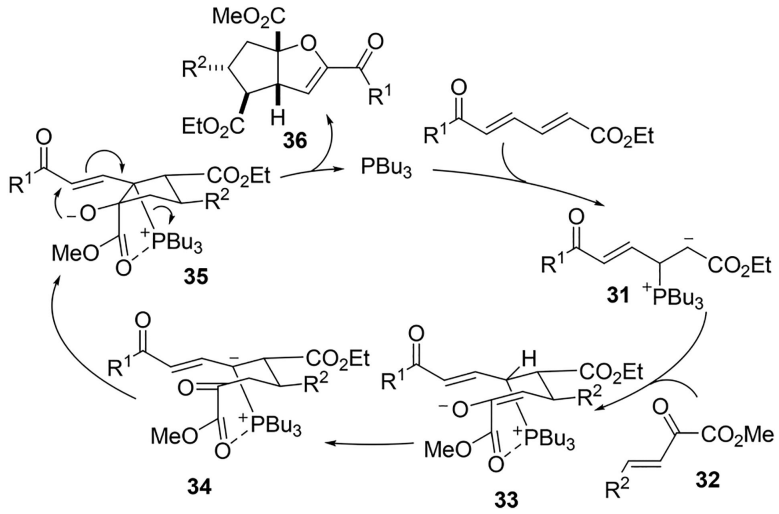
Phosphine-Catalyzed [4 + 2] Annulation of Electron-Deficient Dienes and Alkyl Vinyl Ketones



Scheme 74.
Proposed Mechanism of Hexahydropentalen-2-one Synthesis

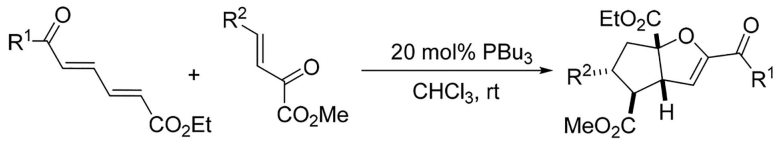


Scheme 75.
Synthesis of Functionalized Hexahydropentalen-2-ones



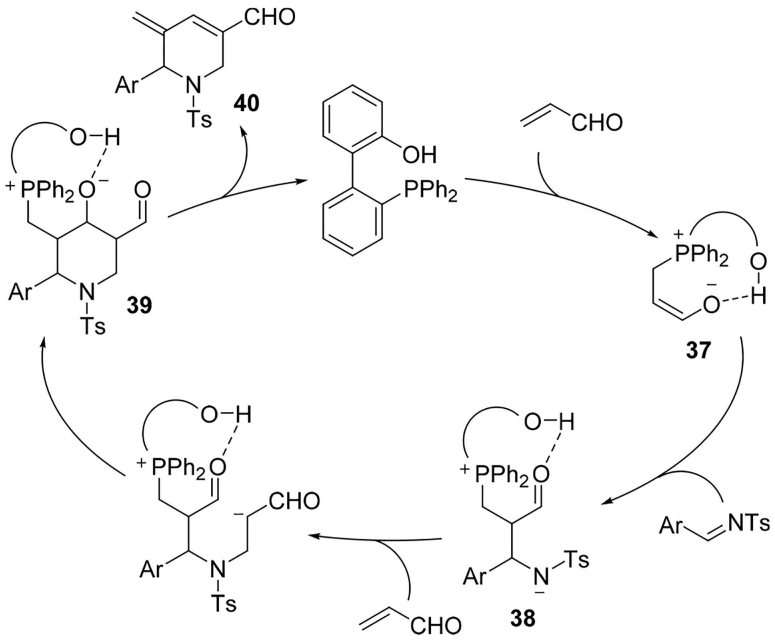
Scheme 76.

Proposed Mechanism for Phosphine-Catalyzed RC-Aldol-S_N2' Annulation

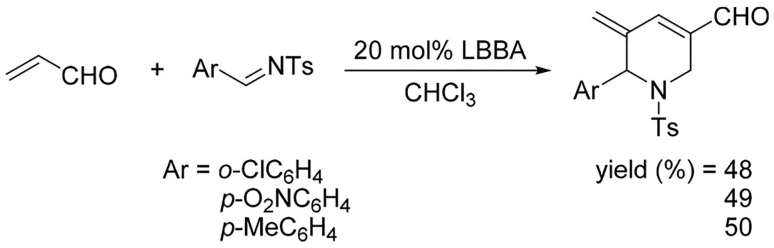


entry	R^1	R^2	time (h)	yield (%)
1	*p*-MeC_6H_4	*m*-MeC_6H_4	8	68
2	*p*-FC_6H_4	*p*-$MeOC_6H_4$	5	79
3	OEt	*p*-MeC_6H_4	24	0

Scheme 77.
Formation of Tetrahydrocyclopentafurans

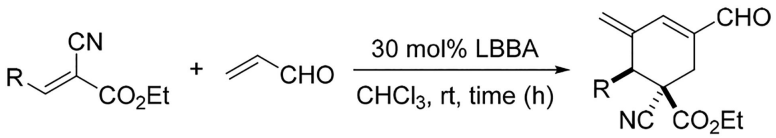


Scheme 78.
Proposed Mechanism for [2 + 2 + 2] Annulation



Ar =	yield (%) =
o-ClC_6H_4	48
p-$O_2NC_6H_4$	49
p-MeC_6H_4	50

Scheme 79.
Synthesis of Functionalized Tetrahydropyridines

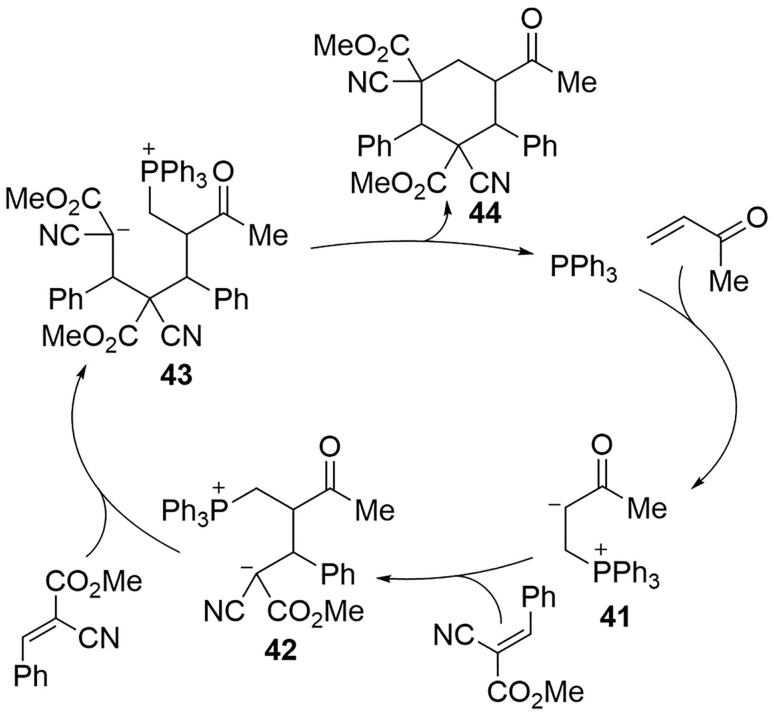


entry	R	time (h)	yield (%)	cis:trans
1	*p*-FC_6H_4	25	52	7:1
2	*p*-$MeOC_6H_4$	72	35	5:1
3	2-naphthyl	72	66[a]	2.5:1
4	2-furyl	72	30	>20:1

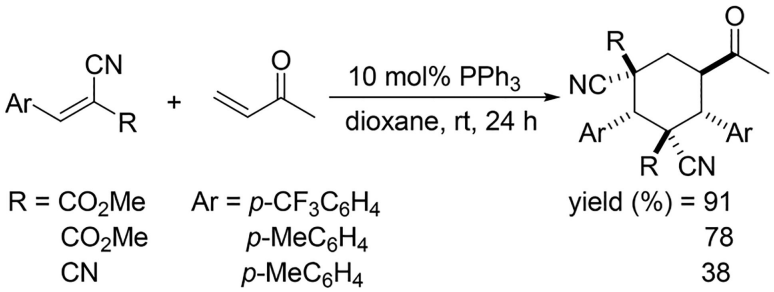
Scheme 80.

Formation of Functionalized Cyclohexenes

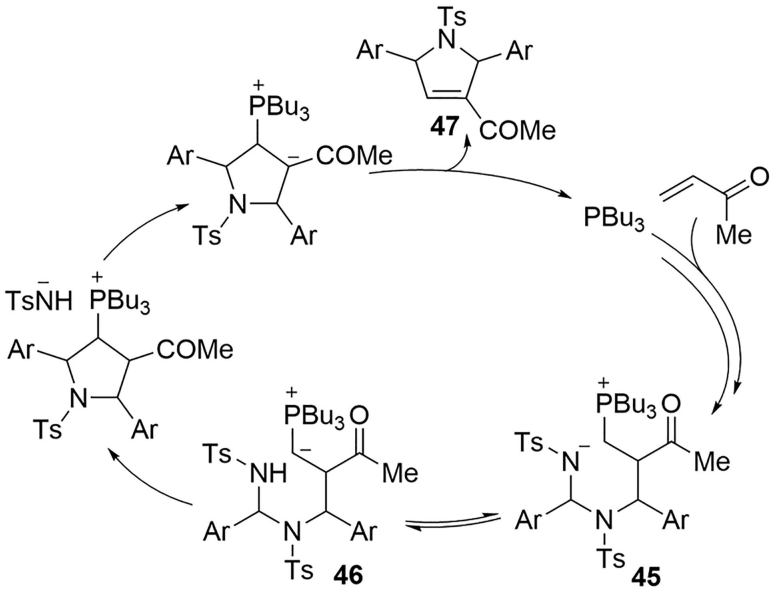
[a]45 mol % catalyst was used.



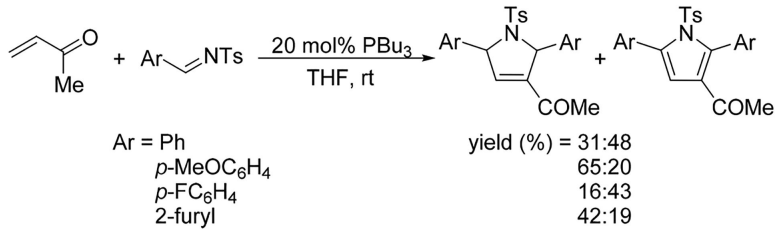
Scheme 81.
Proposed Reaction Mechanism



Scheme 82.
Formation of Functionalized Cyclohexanes

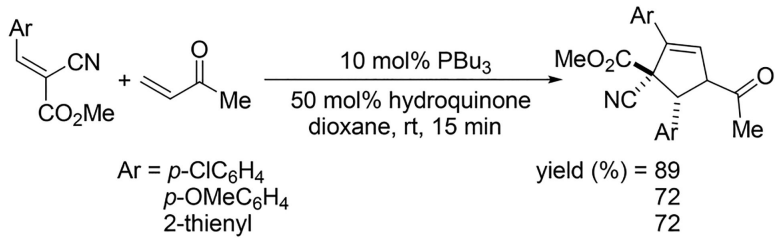


Scheme 83.
Proposed Mechanism of [2 + 2 + 1] Annulation

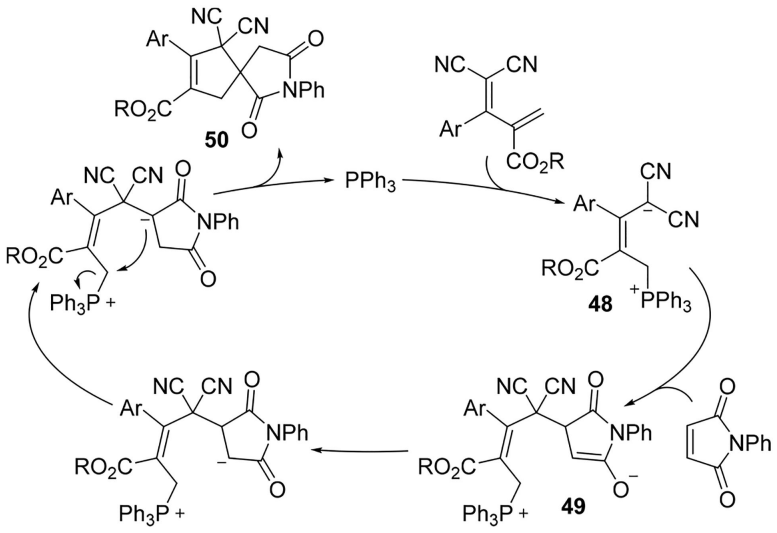


Scheme 84.

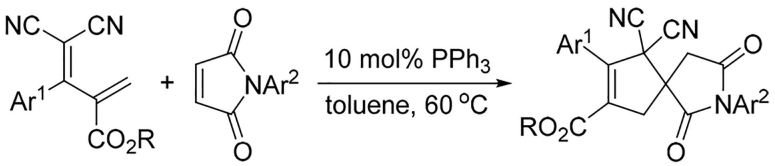
Synthesis of Functionalized Dihydropyrroles and Pyrroles



Scheme 85.
Formation of Derivatized Cyclopentenes

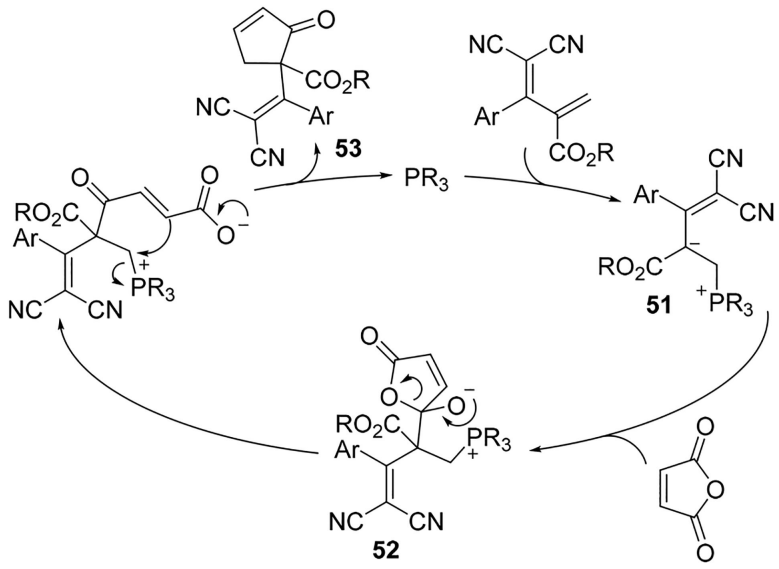


Scheme 86.
Proposed Mechanism of [4 + 1] Annulation

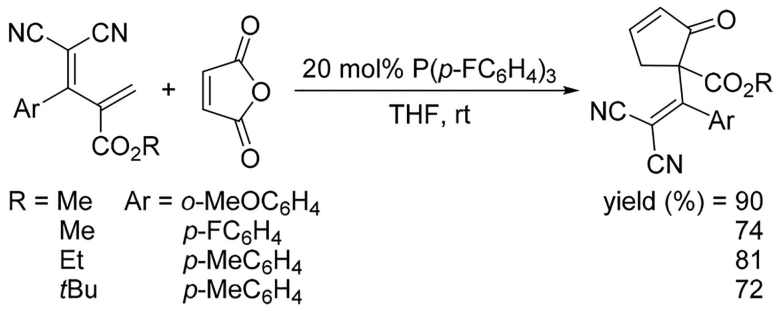


entry	R	Ar^1	Ar^2	yield (%)
1	Me	Ph	Ph	92
2	Me	*p*-$MeOC_6H_4$	Ph	93
3	Me	2-furyl	Ph	95
4	*t*Bu	*p*-MeC_6H_4	Ph	86
5	Me	*p*-MeC_6H_4	Bn	73

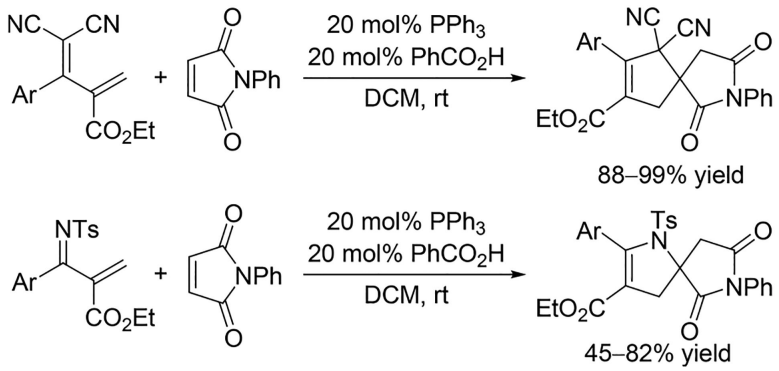
Scheme 87.
Synthesis of Functionalized Spirocyclopentenes



Scheme 88.
Proposed Mechanism of [3 + 2] Annulation

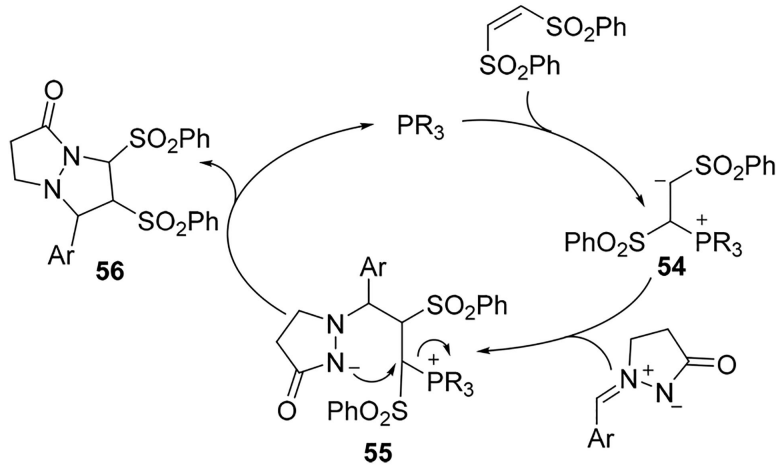


Scheme 89.
Synthesis of Functionalized Cyclopentenones

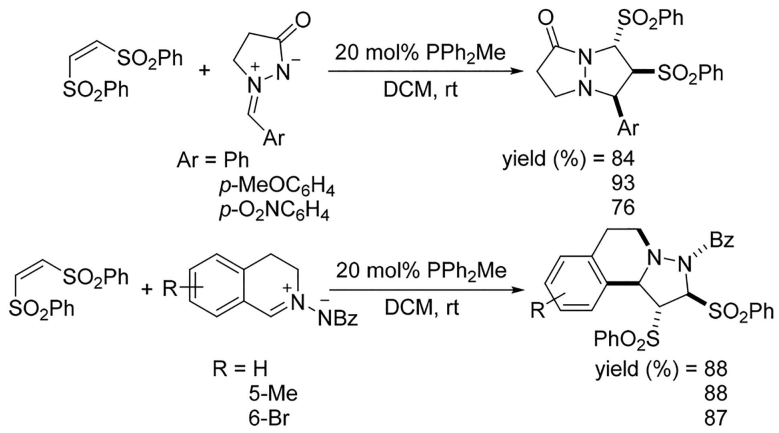


Scheme 90.

Synthesis of Spirocyclopentenes and Spirodihydropyrroles

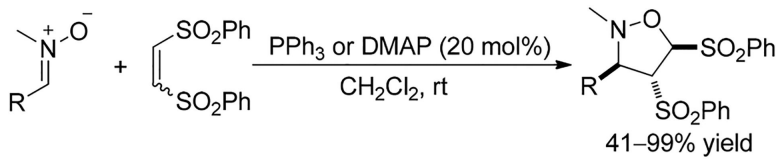


Scheme 91.
Proposed Mechanism of [3 + 2] Annulation with Diphenylsulfone Alkene



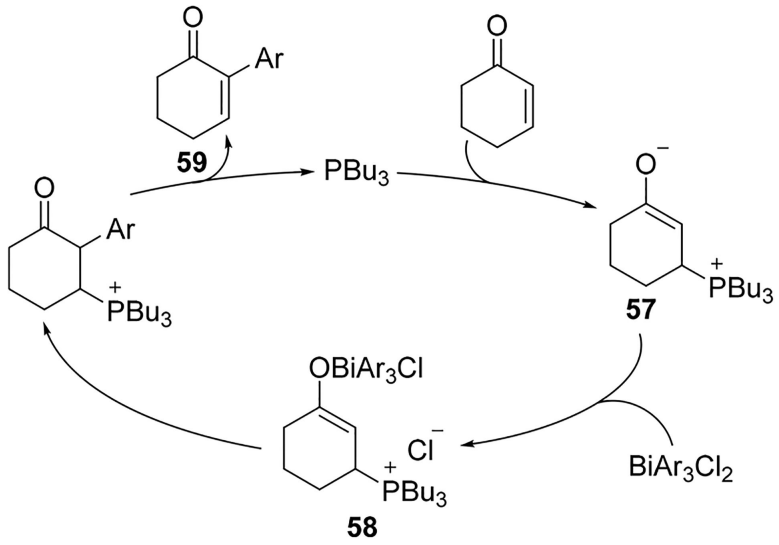
Scheme 92.

Phosphine-Catalyzed [3 + 2] Annulation with Diphenylsulfone Alkene with Azomethine Imines

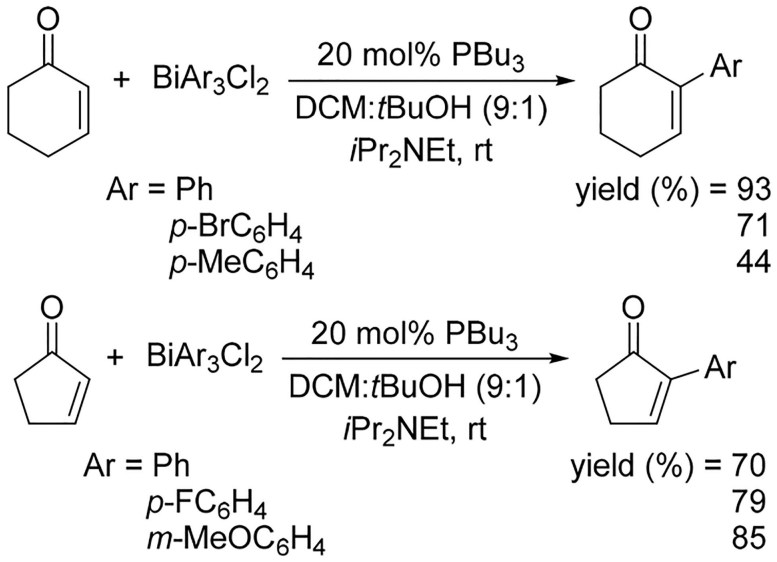


Scheme 93.

Lewis Base-Catalyzed Diastereoselective [3 + 2] Cycloaddition of Nitrones with Electron-Deficient Alkenes

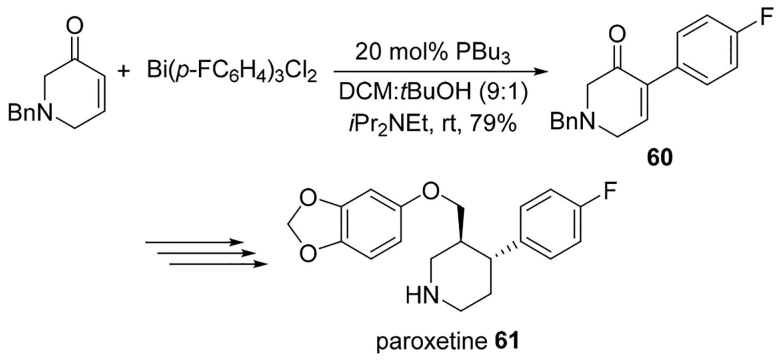


Scheme 94.
Proposed Mechanism for α-Arylation of Enones

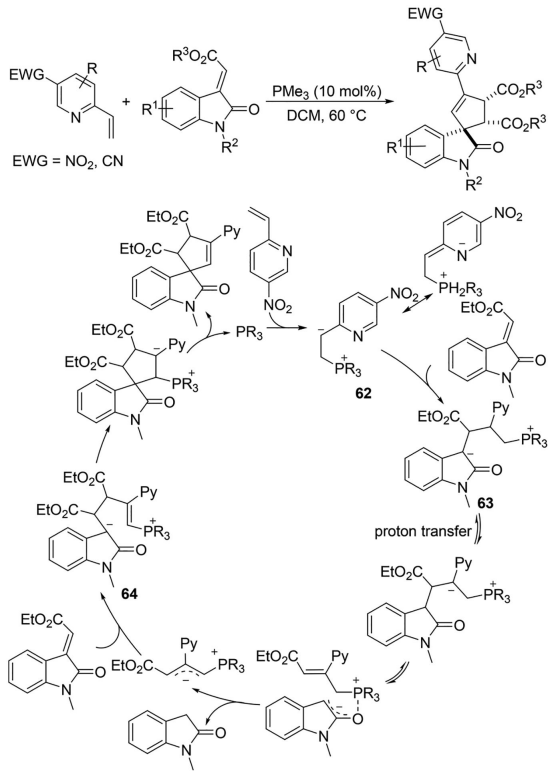


Scheme 95.

α-Arylations of Cyclohexenone and Cyclopentenone

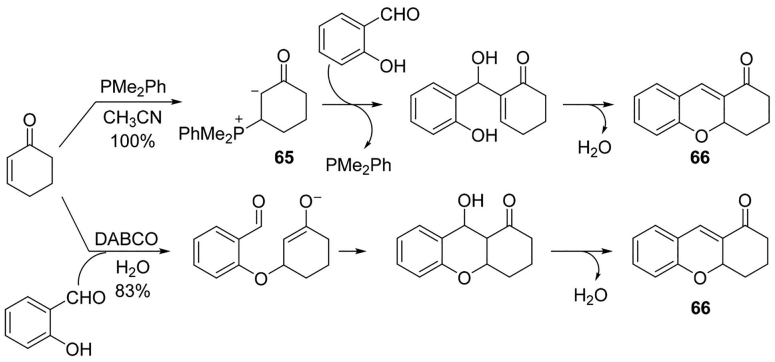


Scheme 96.
Synthesis of Paroxetine

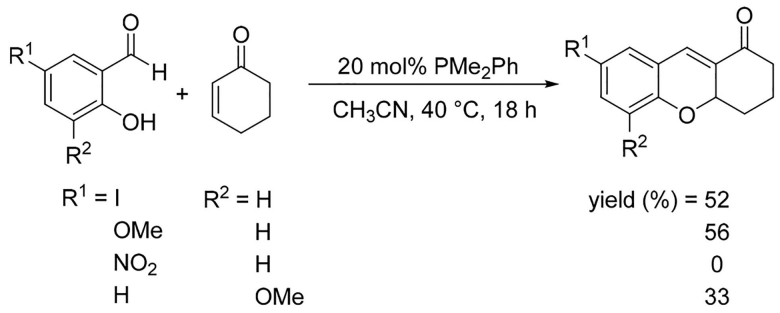


Scheme 97.

Phosphine-Catalyzed [2 + 1 + 2] Cycloaddition of Isatin-Derived Electron-Deficient Alkenes and Vinylpyridines

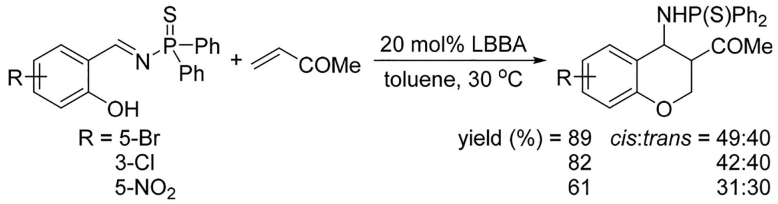


Scheme 98.
Phosphine Catalysis Versus Amine Catalysis

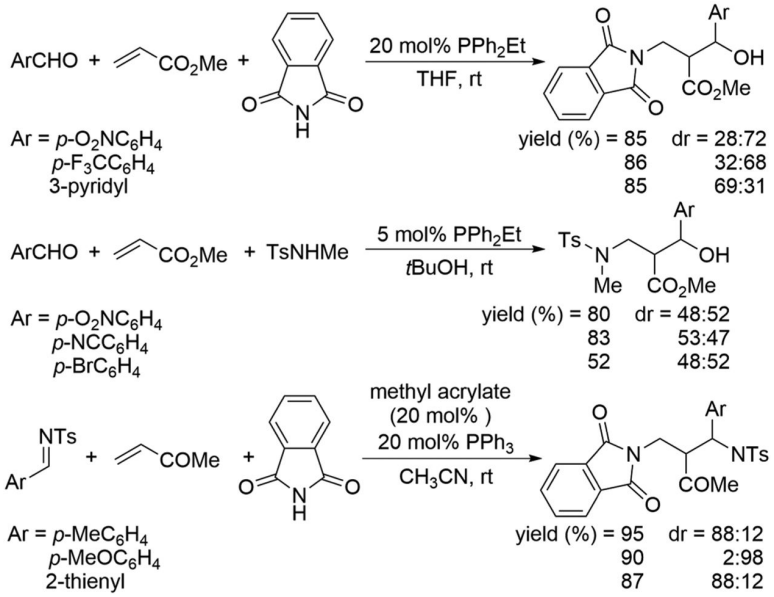


R^1 =	R^2 = H	yield (%) = 52
OMe	H	56
NO_2	H	0
H	OMe	33

Scheme 99.
Phosphine-Catalyzed DOMA Reactions

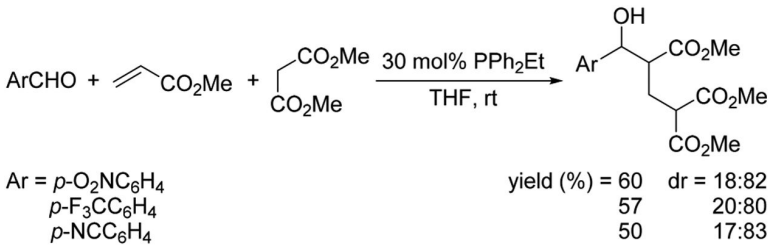


Scheme 100.
Synthesis of 4-Aminochromans



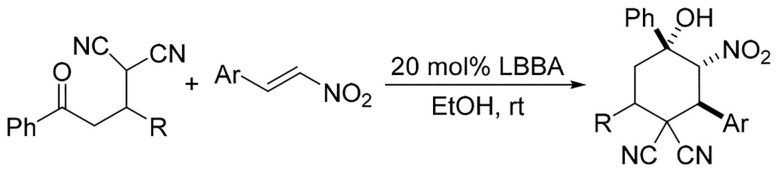
Scheme 101.

Synthesis of Functionalized Amino Alcohols and Diamines



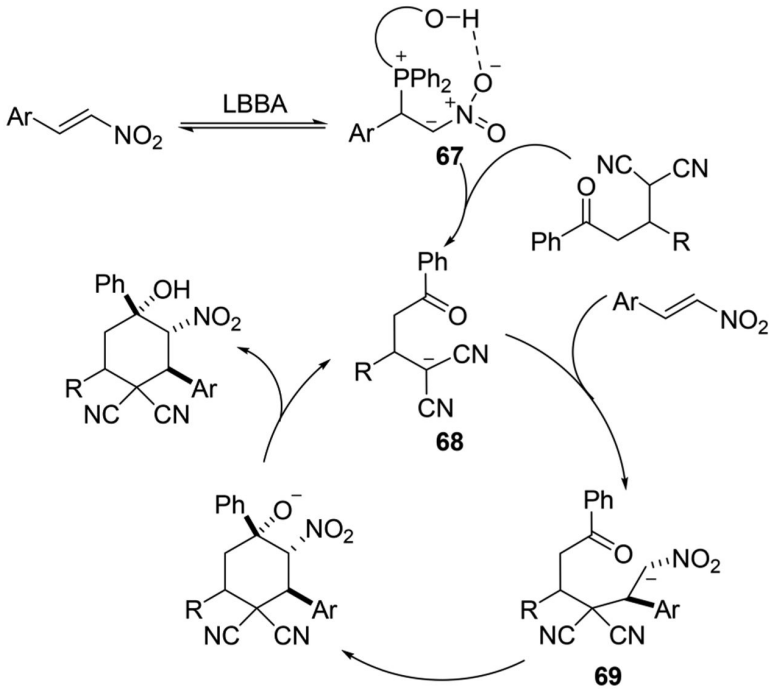
Scheme 102.

Synthesis of Functionalized α-Hydroxymethylated Alkanols

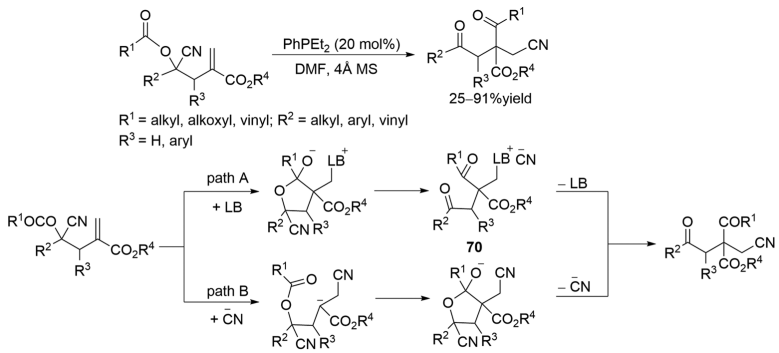


entry	R	Ar	yield (%)	dr
1	Ph	*p*-MeOC$_6$H$_4$	90	98:2
2	2-thienyl	Ph	82	99:1
3	H	Ph	91	98:2
4	*n*Pr	Ph	68	95:5

Scheme 103.
Synthesis of Functionalized Cyclohexanes

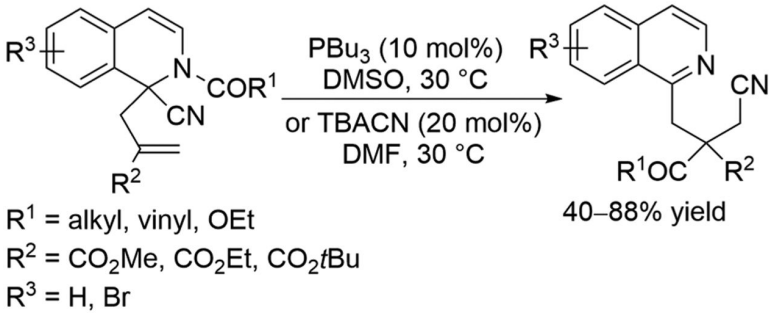


Scheme 104.
Plausible Mechanism for Phosphine-Catalyzed Michael–Henry Reaction

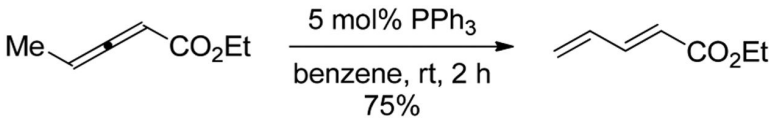


Scheme 105.

Phosphine-Promoted Intramolecular Acylcyanation of γ-Substituted Alkenes

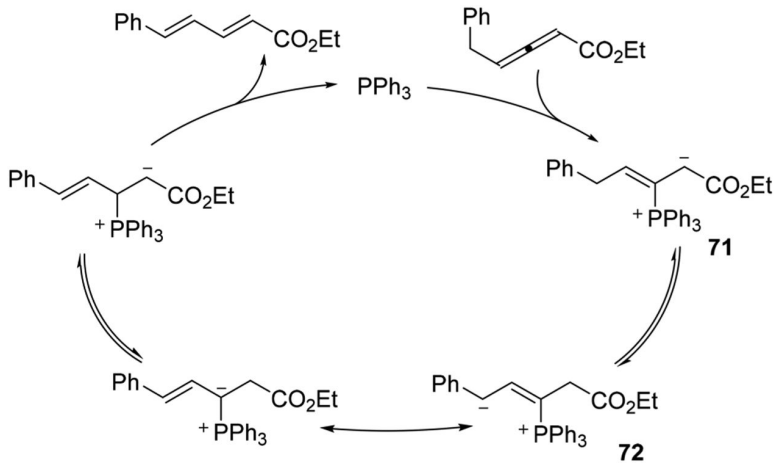


Scheme 106.
Intramolecular Acylcyanation of Activated Alkenes

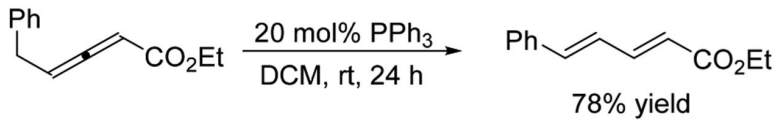


Scheme 107.

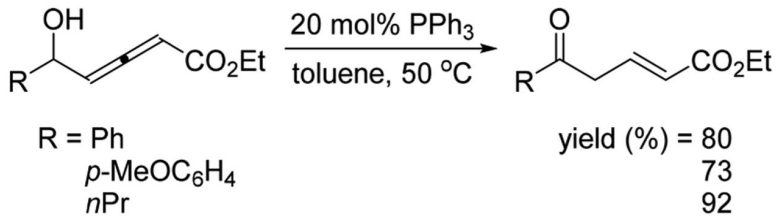
Isomerization of Ethyl 2,3-Pentadienoate to Ethyl 2,4-Pentadienoate



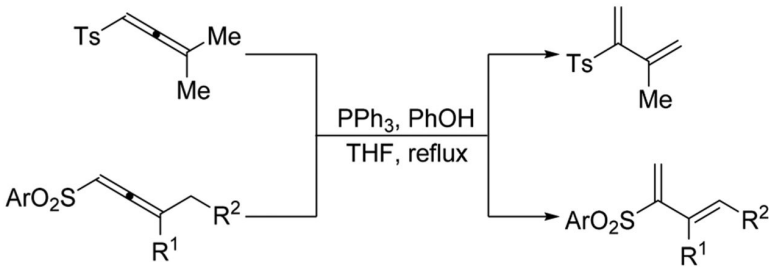
Scheme 108.
Proposed Mechanism for Isomerization



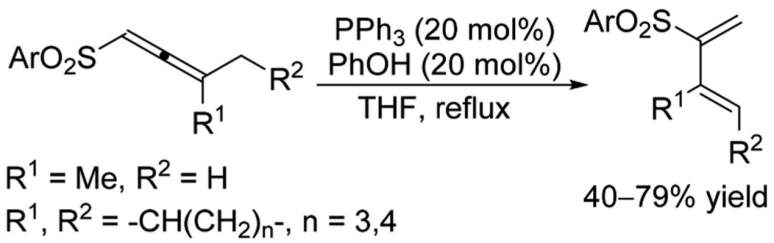
Scheme 109.
Formation of a Conjugated Dienoate



Scheme 110.
Isomerization of *δ*-Hydroxy-2,3-dienoates

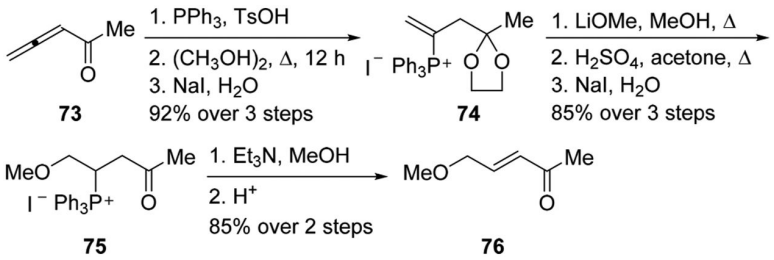


Scheme 111.
Phosphine-Catalyzed Isomerization of Allenic Sulfones

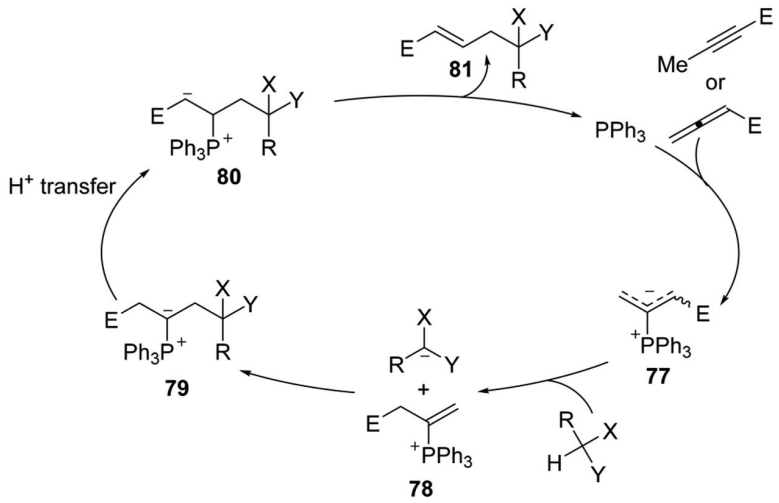


Scheme 112.

Isomerization of Allenic Sulfones to 2-Arylsulfonyl 1,3-Dienes when Treated with a Phosphine and a Proton Shuttle

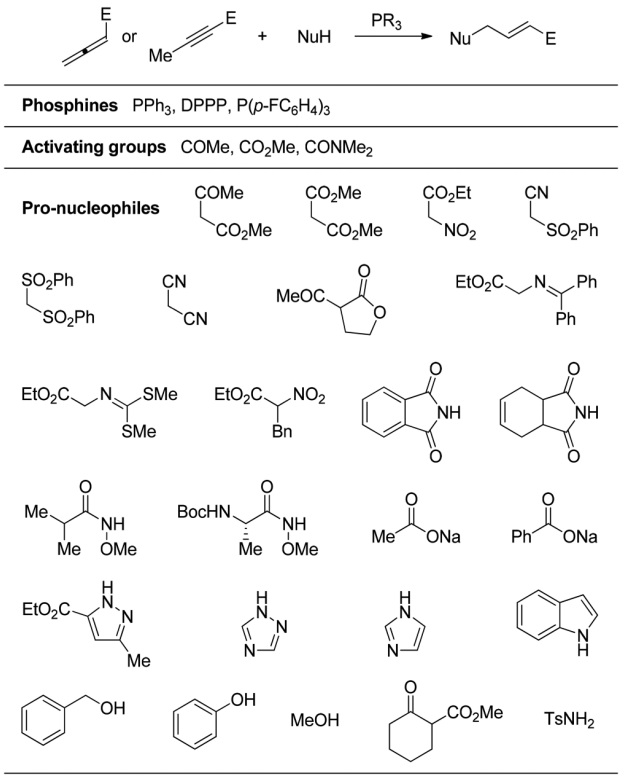


Scheme 113.
Stepwise γ-Umpolung Addition



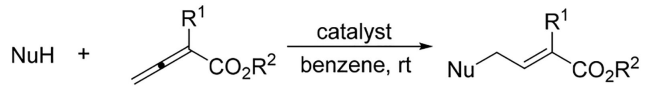
Scheme 114.

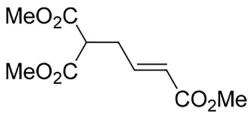
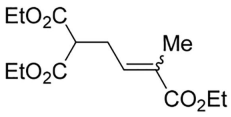
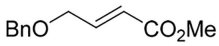
Mechanism of γ-Umpolung Reactions of Allenoates and Alkynoates



Scheme 115.

Scope of Pronucleophiles, Activating Groups, and Phosphines for γ-Umpolung Reactions of Allenoates and Alkynoates

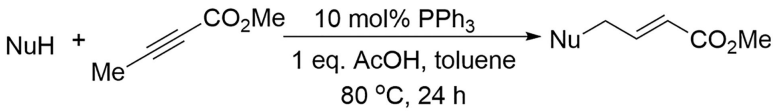


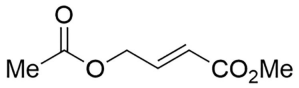
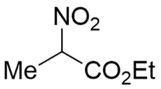
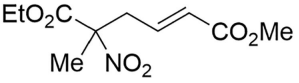
entry	NuH	R^1	R^2	catalyst	product	yield (%)
1		H	Me	5 mol% PPh_3		65
2		Me	Et	10 mol% PBu_3		89
3	BnOH	H	Me	5 mol% PPh_3		90[a]

Scheme 116.

γ-Umpolung Reactions of 2,3-Butadienoates

[a]Reaction performed with 20 mol % of AcOH as additive.

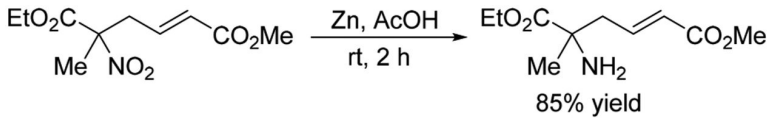


entry	NuH	product	yield (%)
1	AcOH		90[a]
2			60[b]

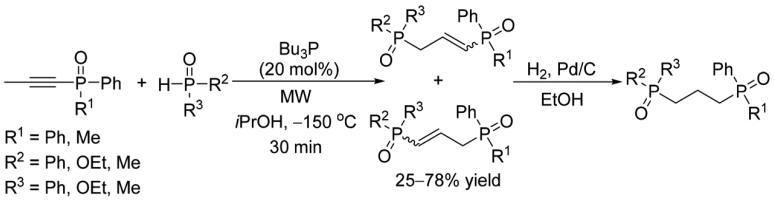
Scheme 117.

γ-Umpolung Additions of Methyl 2-Butynoate

[a]Plus 1 equiv of NaOAc. [b]Reaction performed with 50 mol % of AcOH and 50 mol % of NaOAc.

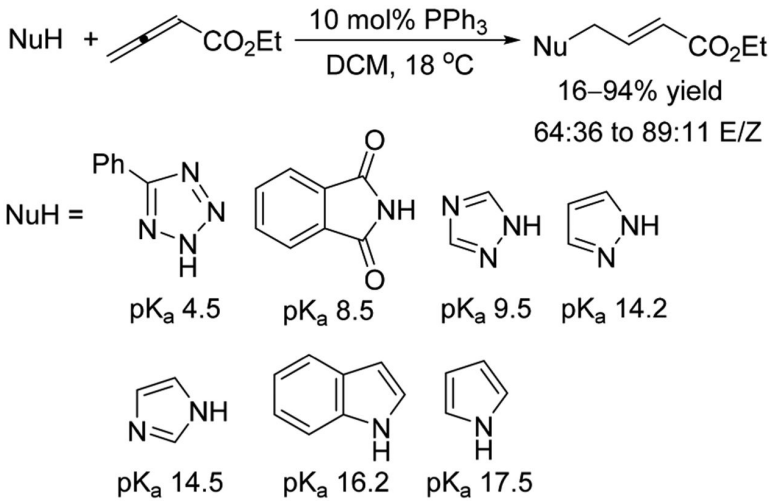


Scheme 118.
Synthesis of a γ,δ-Didehydrohomoglutamate



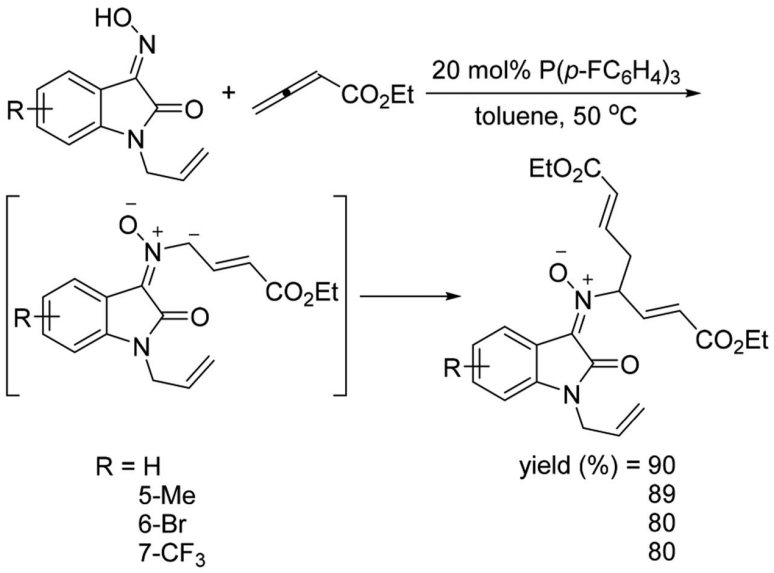
Scheme 119.

Phosphine-Catalyzed γ-Additions of Phosphorus Pronucleophiles to Electron-Deficient Alkynes

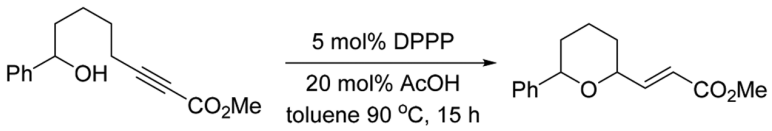


Scheme 120.

Effect of pK_a of the Pronucleophile on the Yield

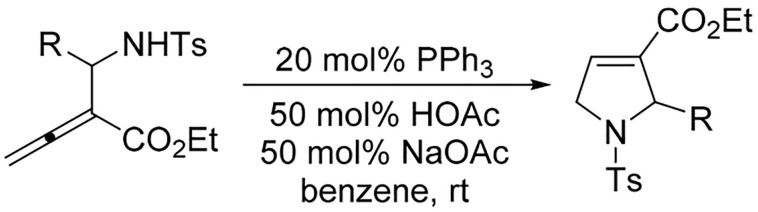


Scheme 121.
Synthesis of Functionalized Nitrones



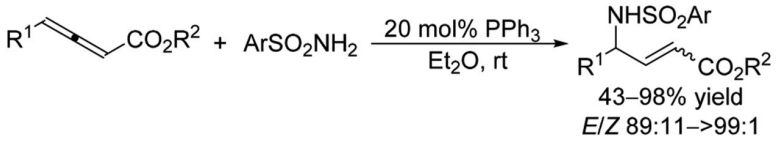
Scheme 122.

Intramolecular γ-Umpolung Addition of a Tethered Hydroxyl Alkynoate



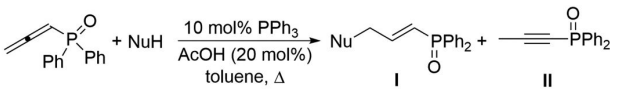
entry	R	time (h)	yield (%)
1	Me	19	99
2	*i*Pr	77	97
3	cyclopentyl	96	85
4	*p*-$MeOC_6H_4$	22	99
5	*p*-ClC_6H_4	4.5	88[a]

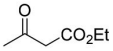
Scheme 123.
Preparation of 2-Alkylpyrroline Derivatives
[a]Reaction performed without additives.



Scheme 124.

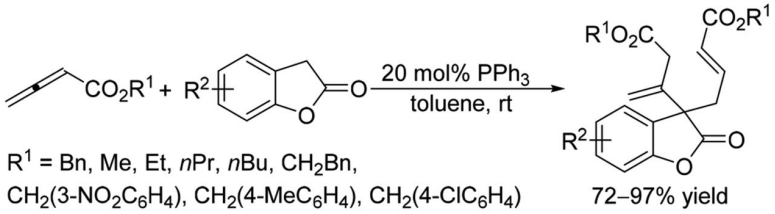
Phosphine-Catalyzed γ-Umpolung Addition of Sulfonamides to γ-Substituted Allenoates



entry	NuH	I/II	yield (%) (*cis*/*trans*)
1		2.6/1	50 (1.2/1)
2		1.2/1	47 (0/100)
3		2.7/1	42 (2.7/1)
4		1/1	51 (1.6/1)

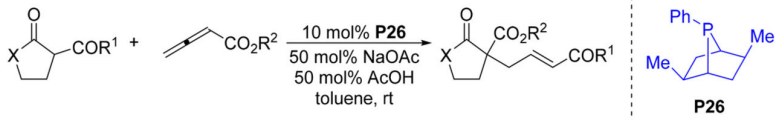
Scheme 125.

Phosphine-Catalyzed γ-Additions of Carbon Pronucleophiles to Allenyl Phosphine Oxide



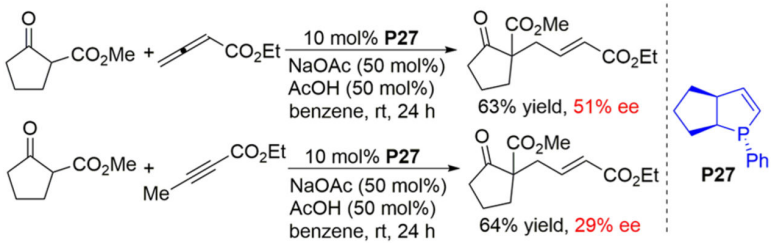
Scheme 126.

Phosphine-Catalyzed Domino β/γ-Additions of Benzofuranones with Allenoates



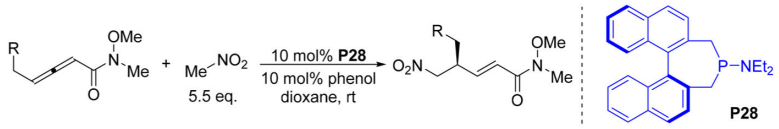
entry	R^1	R^2	X	yield (%)	ee (%)
1	OMe	Me	C	80	73
2	OMe	*t*Bu	C	74	75
3	Me	Et	C	67	56
4	Me	Et	O	83	48

Scheme 127.
First Asymmetric γ-Umpolung Reactions



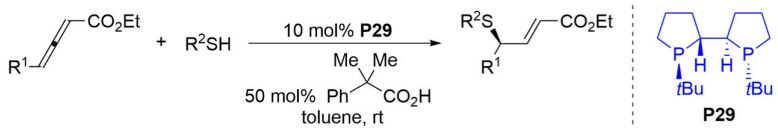
Scheme 128.

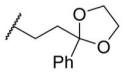
Asymmetric Formation of Functionalized Acrylates



entry	R	yield (%)	ee (%)
1	H	94	97
2	cyclohexyl	73	87
3	$(CH_2)_3OTBS$	57	92
4	Et	81	93

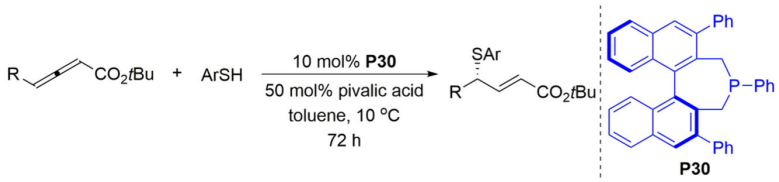
Scheme 129.
Asymmetric γ-Umpolung Reactions of Nitromethane



entry	R^1	R^2	yield (%)	ee (%)
1	$(CH_2)_2CO_2Me$	Bn	77	92
2	$(CH_2)_2CO_2Me$	cyclopentyl	80	93
3	$(CH_2)_7CH{=}CH_2$	PMB	81	91
4		PMB	89	90

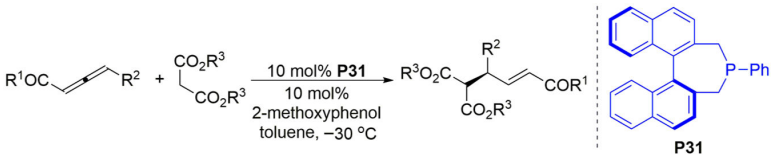
PMB: *p*-methoxybenzyl

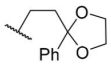
Scheme 130.
Asymmetric γ-Umpolung Reactions with Thiols



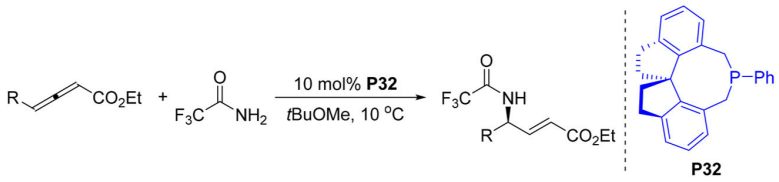
entry	R	Ar	yield (%)	ee (%)
1	Me	*p*-*t*BuC$_6$H$_4$	58	81
2	*i*Pr	*p*-*t*BuC$_6$H$_4$	61	94
3	*n*Pr	*p*-FC$_6$H$_4$	64	91
4	*n*Pr	*p*-MeOC$_6$H$_4$	76	91
5	*n*Pr	*p*-H$_2$NC$_6$H$_4$	64	86

Scheme 131.
Asymmetric γ-Umpolung Reactions of Aryl Thiols



entry	R^1	R^2	R^3	yield (%)	ee (%)
1	OEt		allyl	71	94
2	OBn	*n*Pr	Et	84	93
3	OEt	$(CH_2)_3Cl$	allyl	91	93
4	N(OMe)Me	Me	Et	71	95

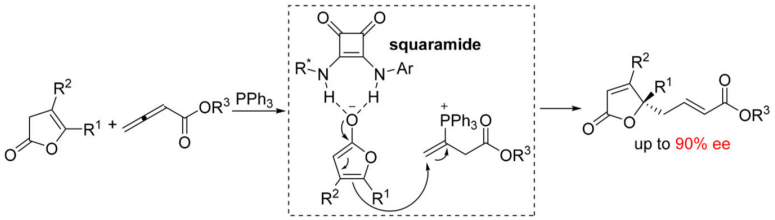
Scheme 132.
Asymmetric γ-Umpolung Reactions of Malonates



entry	R	yield (%)	ee (%)
1	Me	89	86
2	*i*Bu	92	88
3	$(CH_2)_2CO_2Me$	68	82
4	$(CH_2)_4OBn$	87	89

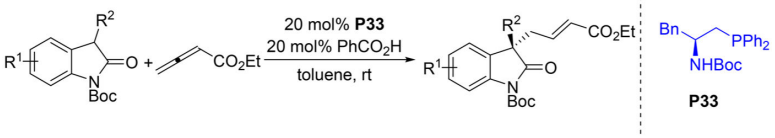
Scheme 133.

Asymmetric Synthesis of Functionalized γ-Aminoacrylates



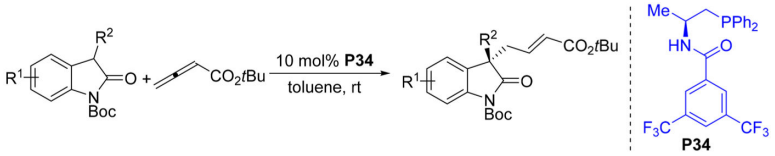
Scheme 134.

γ-Additions of α-Angelica Lactones to Allenoates Co-Facilitated by a Phosphine and a Squaramide



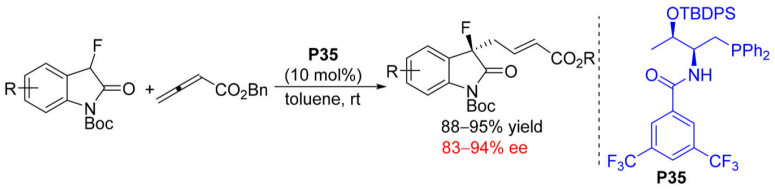
entry	R^1	R^2	yield (%)	ee (%)
1	H	Ph	95	72
2	H	Me	97	88
3	H	CH_2COPh	95	88
4	6-Cl	CH_2CO_2Et	90	85

Scheme 135.
Asymmetric Synthesis of Functionalized 3,3-Disubstituted Oxindoles



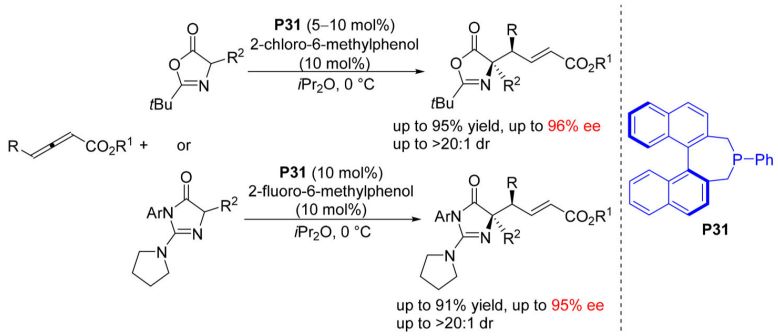
entry	R^1	R^2	yield (%)	ee (%)
1	H	*n*-pentyl	95	94
2	H	*i*Pr	98	94
3	5-Br	*i*Pr	98	85
4	5-MeO	Me	98	89

Scheme 136.
Asymmetric Synthesis of Functionalized 3-Substituted Oxindoles



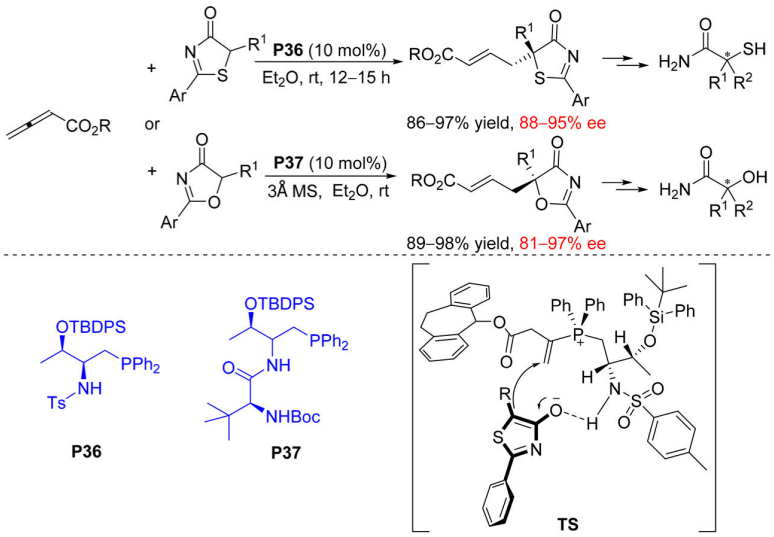
Scheme 137.

Phosphine-Catalyzed Asymmetric γ-Addition of 3-Fluoro-Oxindoles to 2,3-Butadienoates



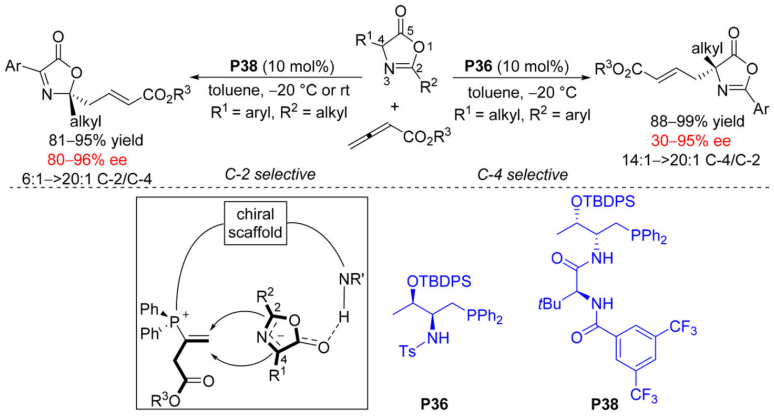
Scheme 138.

Enantioselective Phosphine-Catalyzed γ-Additions of Racemic Heterocycles to Allenoates



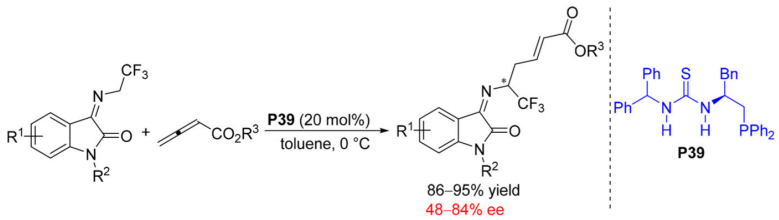
Scheme 139.

Phosphine-Catalyzed Enantioselective γ-Addition of 5*H*-Thiazol-4-ones or 5*H*Oxazol-4-ones to Allenoates



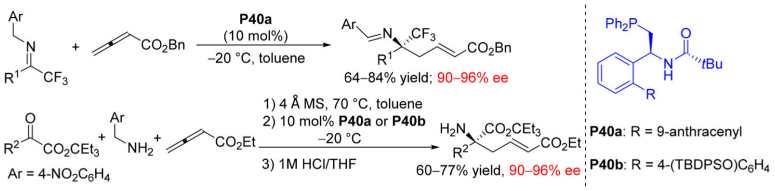
Scheme 140.

Phosphine-Catalyzed Asymmetric C-2- and C-4-Selective γ-Additions of Oxazolones to 2,3-Butadienoates



Scheme 141.

Enantioselective Phosphine Catalyzed Umpolung γ-Addition of Isatin-Derived α-(Trifluoromethyl)imines to Allenoates



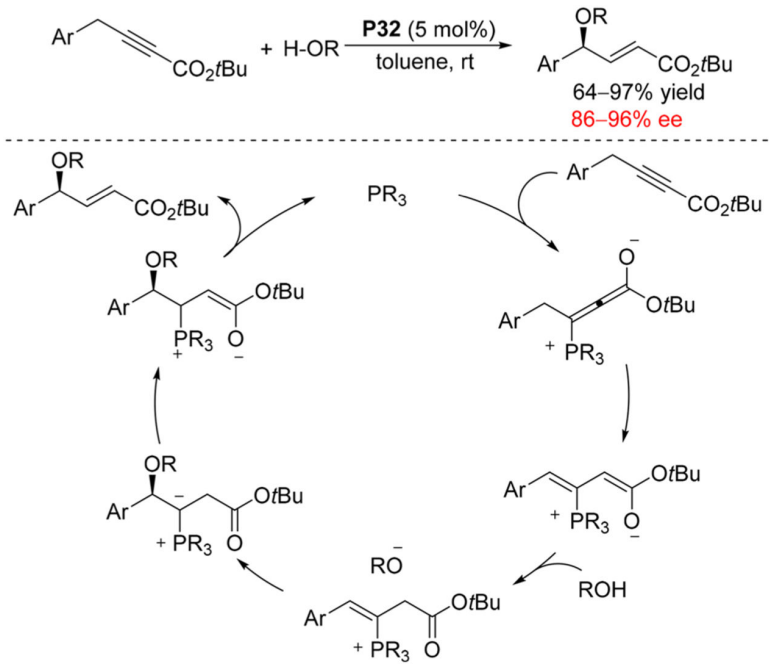
Scheme 142.

Phosphine-Catalyzed Asymmetric γ-Addition of Ketimines to Allenoates

entry	R	X (mol%)	yield (%)	ee (%)
1	Me	3	92	92
2	$(CH_2)_3CH_2Cl$	3	95	96
3	*i*Bu	10	87	98
4	$(CH_2)_2CH_2CN$	5	90	99

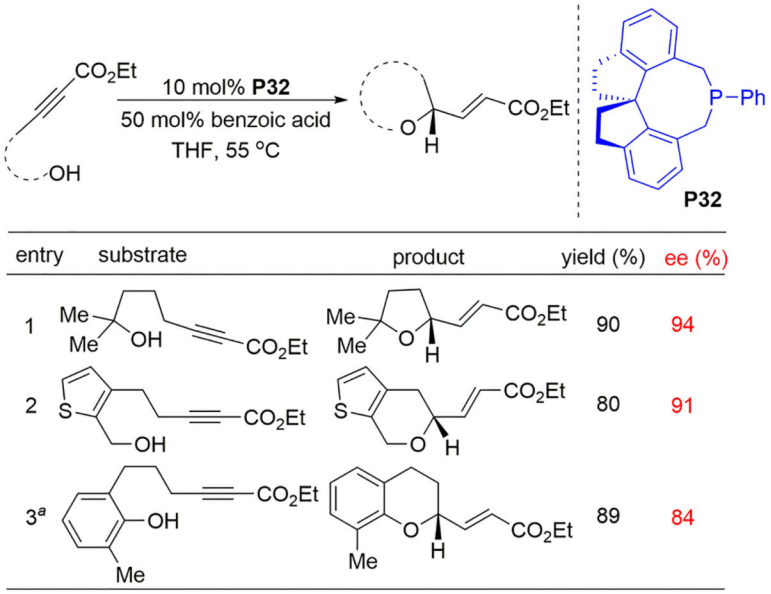
Scheme 143.

Asymmetric Synthesis of Functionalized γ-Aminoacrylates



Scheme 144.

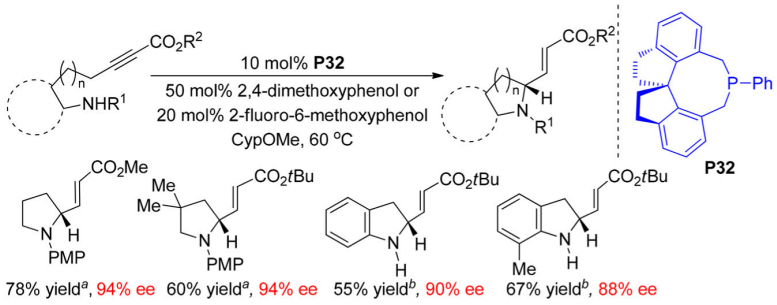
Enantioselective Phosphine-Catalyzed γ-Addition of Alcohol to γ-Aryl Alkynoates and a Proposed Mechanism



Scheme 145.

Intramolecular Asymmetric γ-Umpolung Reactions

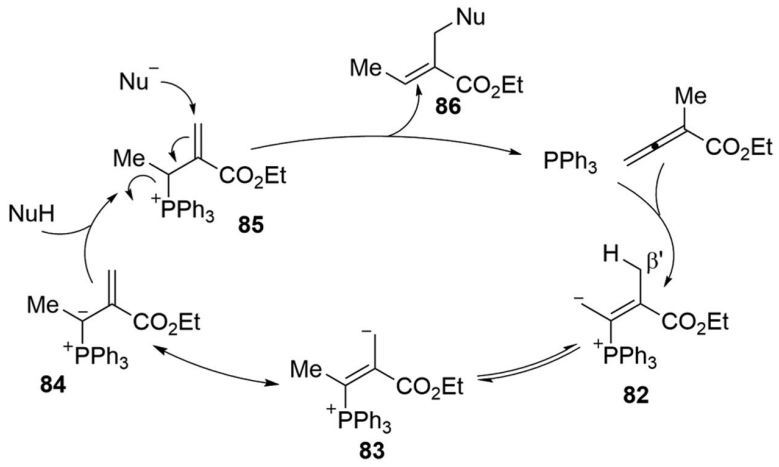
[a]Reaction was performed with 50 mol % 2-bromobenzoic acid in cyclopentyl methyl ether at 50 °C.



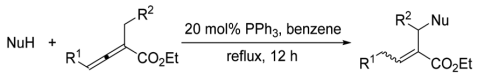
Scheme 146.

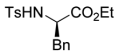
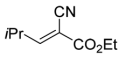
Asymmetric Synthesis of Functionalized Pyrrolidines and Dihydroindoles

[a]50 mol % of 2,4-dimethoxyphenol was used. [b]20 mol % of 2-fluoro-6-methoxyphenol was used.

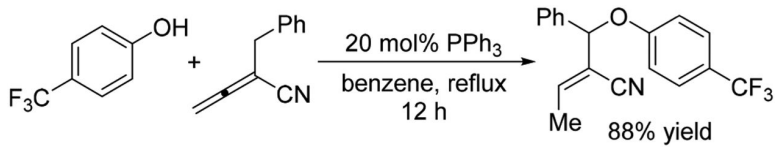


Scheme 147.
Proposed β'-Umpolung Addition



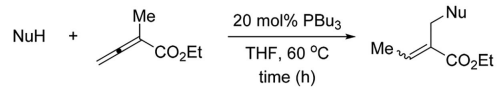
entry	NuH	R^1	R^2	yield (%)	*E*:*Z*
1	PhOH	H	H	>99	100:0
2	*p*-MeC_6H_4OH	H	H	97	100:0
3	*p*-$F_3CC_6H_4OH$	H	H	73	100:0
4		H	H	92	1:1.2
5	AcOH	H	H	97	100:0
6	BzOH	Me	H	90	100:0
7	BzOH	H	4-pentenyl	85	100:0
8	BzOH	H	Ph	95	0:100
9	BzOH	H	CO_2Et	96	1:1.5
10		H	H	86	0:100
11		H	H	79	1:2
12		H	H	77	4:1
13	PhSH	H	H	65	5:1

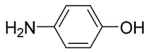
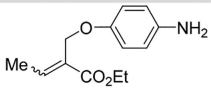
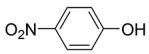
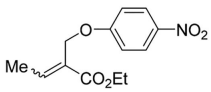
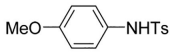
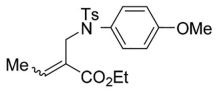
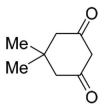
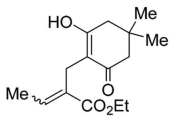
Scheme 148.
Formation of Functionalized Vinyl Acrylates



Scheme 149.

β'-Umpolung Addition to an Allenyl Nitrile

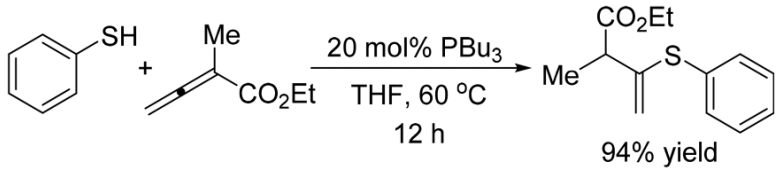


entry	NuH	time (h)	product	yield (%)	*E*/*Z*
1		12		98	16.3:1
2		12		82[a]	11.1:1
3		24		81[b]	10.5:1
4		24		81[b]	12.7:1

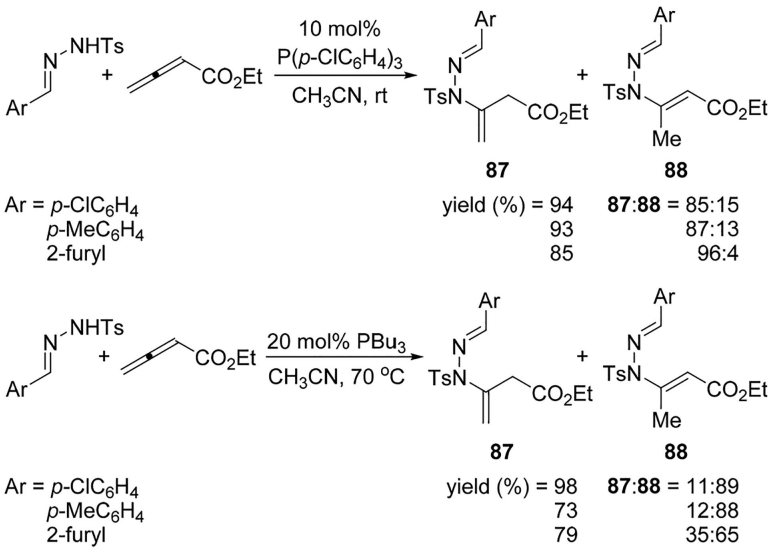
Scheme 150.

β'-Umpolung Additions Reported by Shi

[a]Reaction performed with 20 mol % of PPh_3. [b]Reaction performed at room temperature.

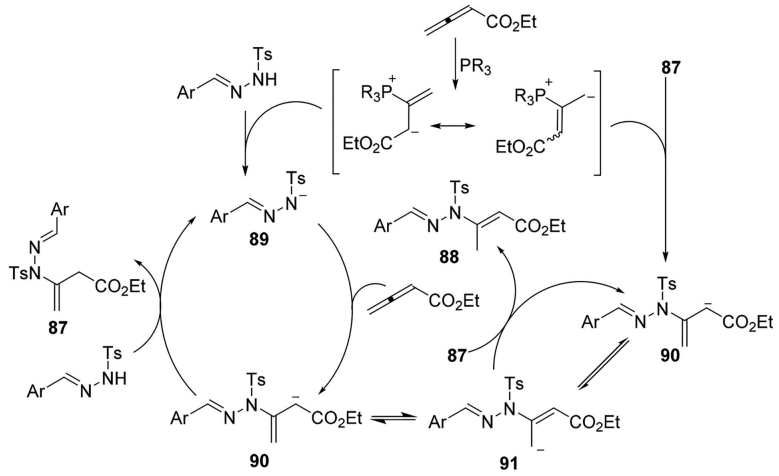


Scheme 151.
Michael Addition of Benzenethiol to an Allenoate



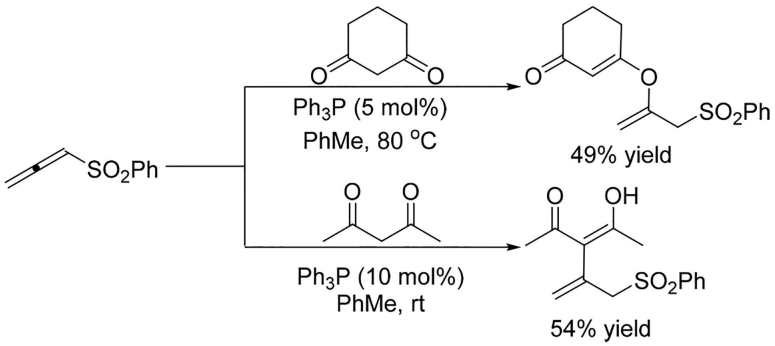
Scheme 152.

Synthesis of Functionalized β-Amino Acrylates

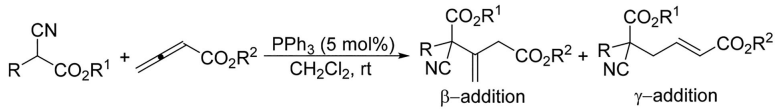


Scheme 153.

Plausible Mechanism for the Formation of Compounds 87 and 88

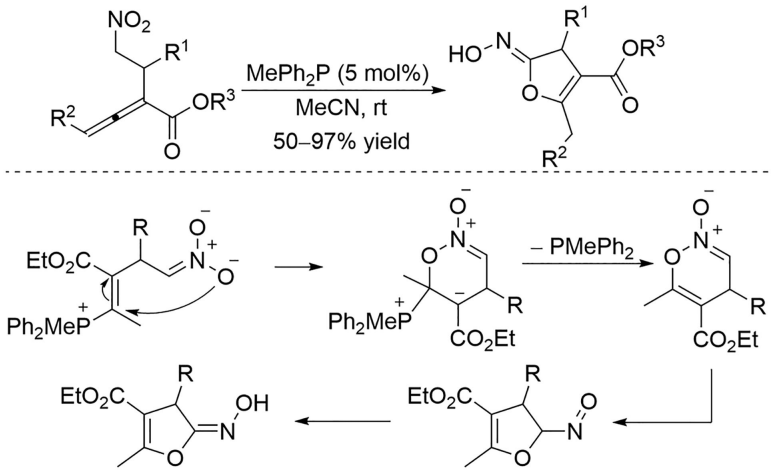


Scheme 154.
Phosphine-Catalyzed β-Addition of an Allenoate



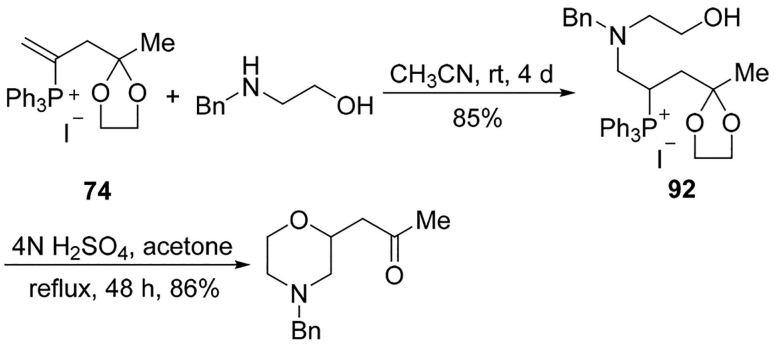
Scheme 155.

Phosphine-Catalyzed Regioselective Michael Addition of Arylcyanoacetates to Allenoates

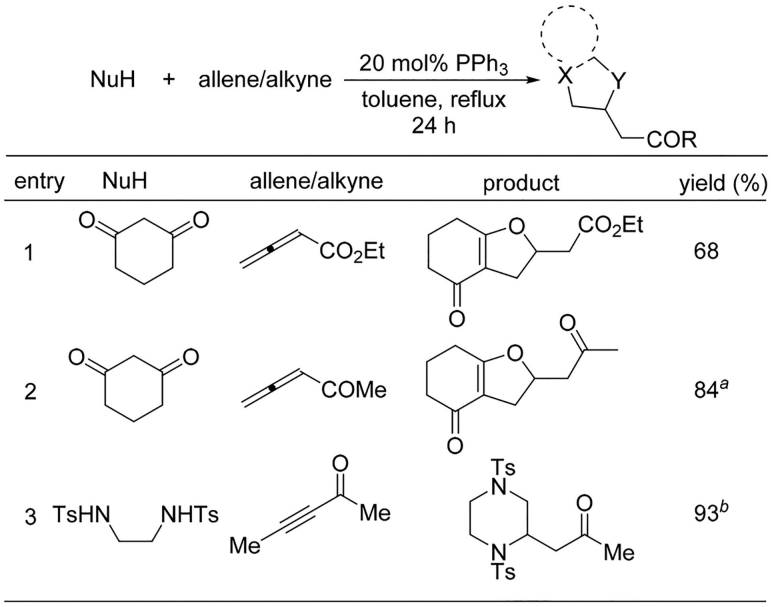


Scheme 156.

Phosphine-Catalyzed Intramolecular Cyclization of α-Nitroethylallenic Esters and Proposed Mechanism



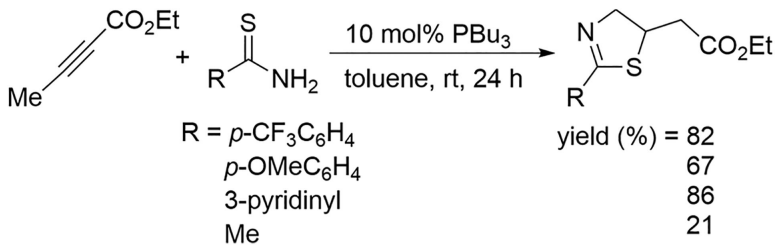
Scheme 157.
Stepwise γ-Umpolung-Michael Reaction.



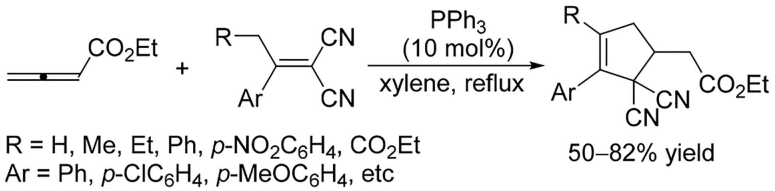
Scheme 158.

Phosphine-Catalyzed γ-Umpolung-Michael Reactions

[a]Reaction performed with 5 mol % PPh_3 at 70 °C for 2 h. [b]Reaction performed in MeCN as solvent.

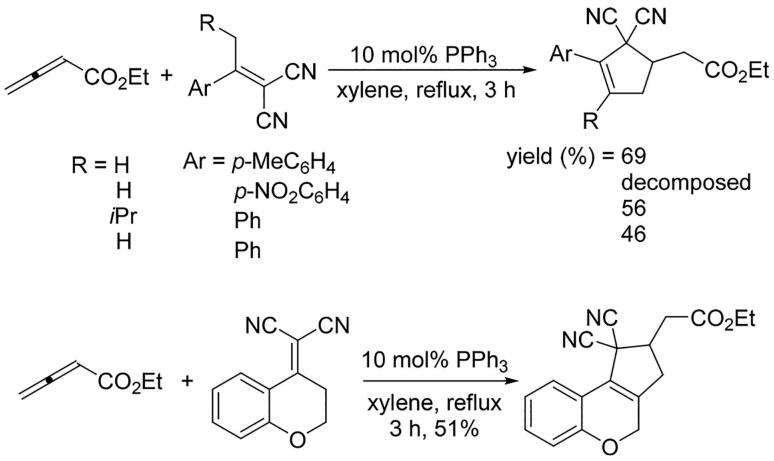


Scheme 159.
Formation of Thiazolines



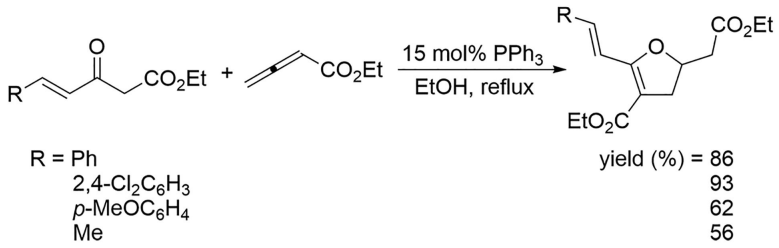
Scheme 160.

Proposed Reaction Pathway for Lu's Unusual [3 + 2] Annulation.

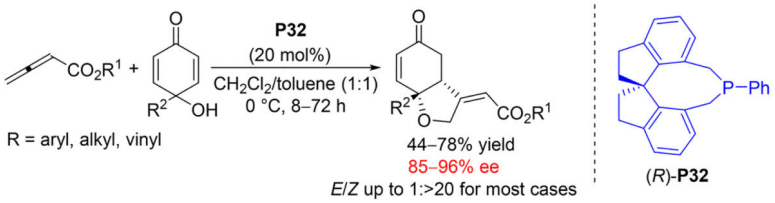


Scheme 161.

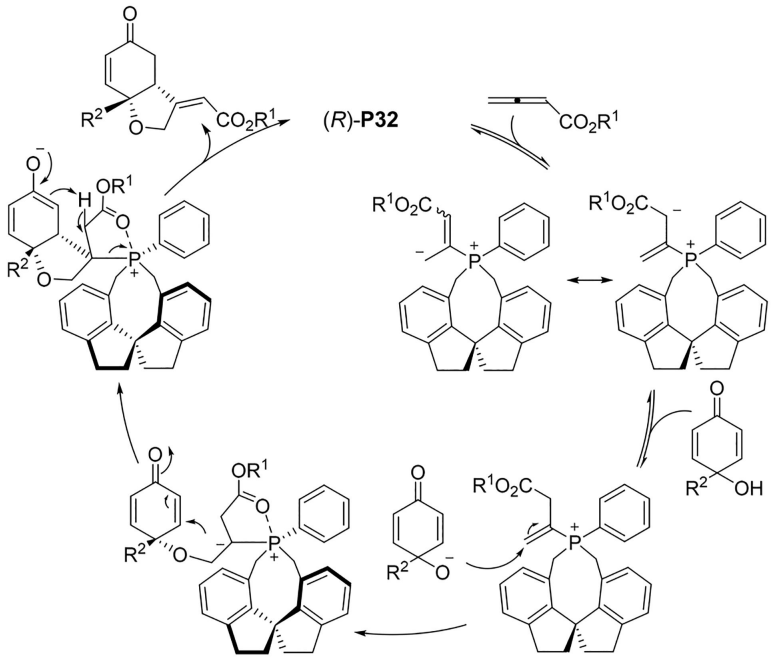
Unusual [3 + 2] Annulations of Arylidenemalononitriles



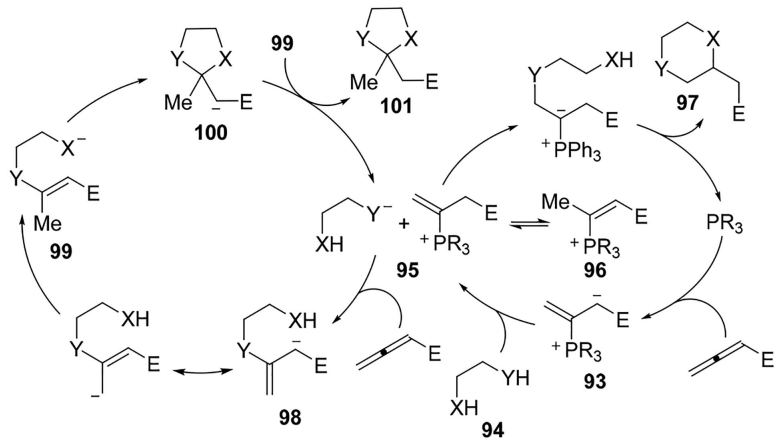
Scheme 162.
Synthesis of Functionalized Dihydrofurans



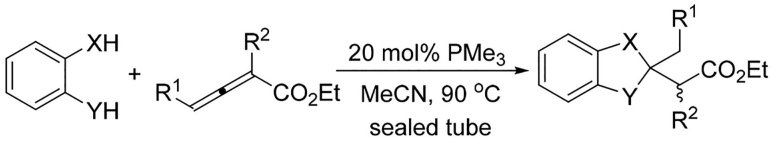
Scheme 163.
Phosphine-Catalyzed γ-Addition/Oxy-Michael Reaction



Scheme 164.
Proposed Mechanism



Scheme 165.
Proposed Mechanism for Double-Michael [4 + 1] Annulation

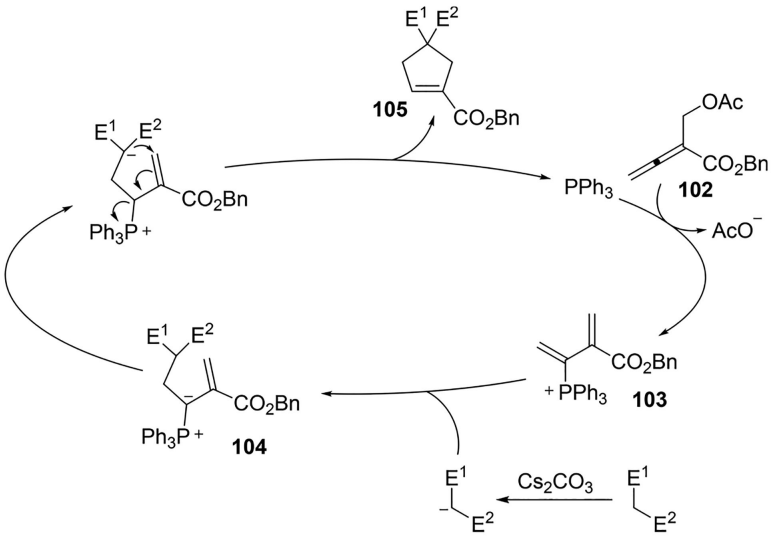


entry	X	Y	R^1	R^2	yield (%)
1	S	S	H	H	74[a]
2	S	NTs	H	H	68[a]
3	NTs	NTs	H	H	79[a]
4	O	S	Ph	H	86
5	O	O	*t*Bu	H	82
6	O	NTs	H	Me	81[b]
7	O	S	H	H	93

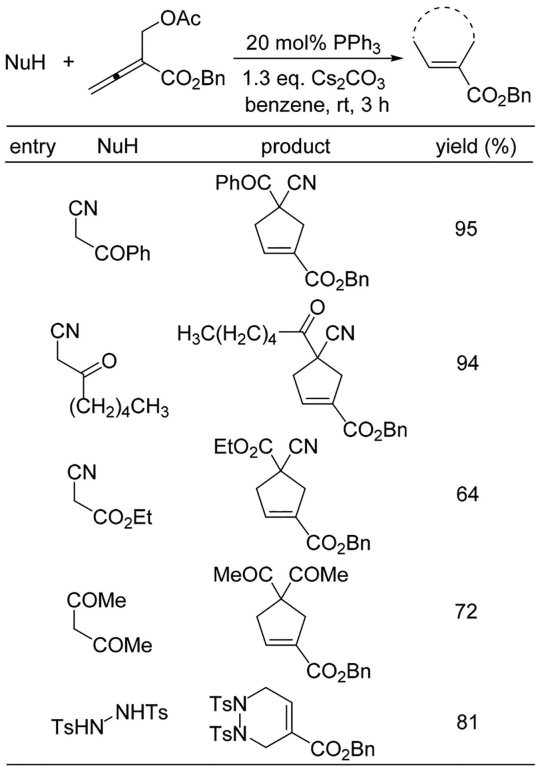
Scheme 166.

Phosphine-Initiated Allenoate Double-Michael Reactions

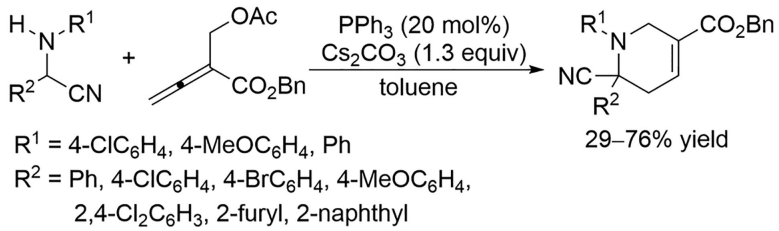
[a]10 mol % of catalyst was used. [b]dr = 1:1



Scheme 167.
Proposed Mechanism for [4 + *n*] Annulation

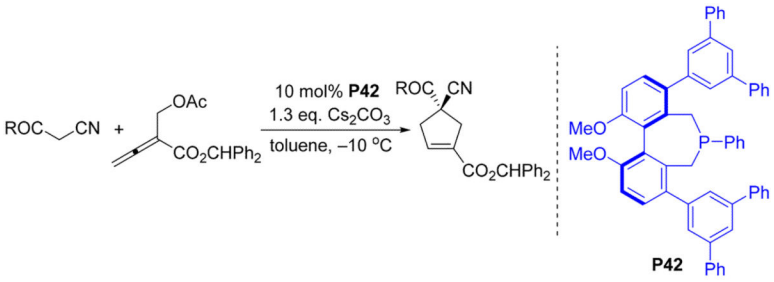


Scheme 168.
Phosphine-Catalyzed [4 + *n*] Annulations



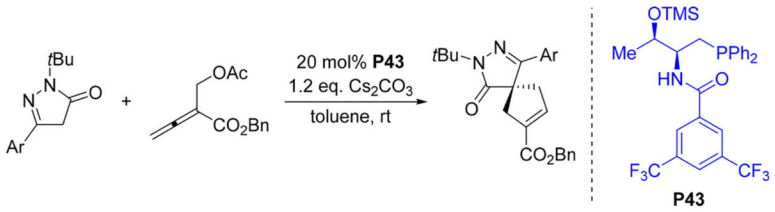
Scheme 169.

Phosphine-Catalyzed [4 + 2] Annulations of α-Aminonitriles with Allenoates



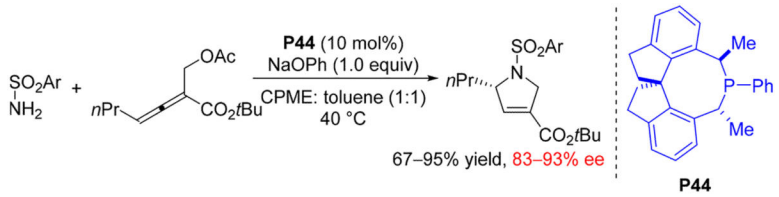
entry	R	yield (%)	ee (%)
1	Ph	85	94
2	*p*-$MeOC_6H_4$	97	94
3	*n*-hexyl	90	93
4	Me_2N	73	83
5	MeO(Me)N	73	86

Scheme 170.
Asymmetric Synthesis of Functionalized Cyclopentenes



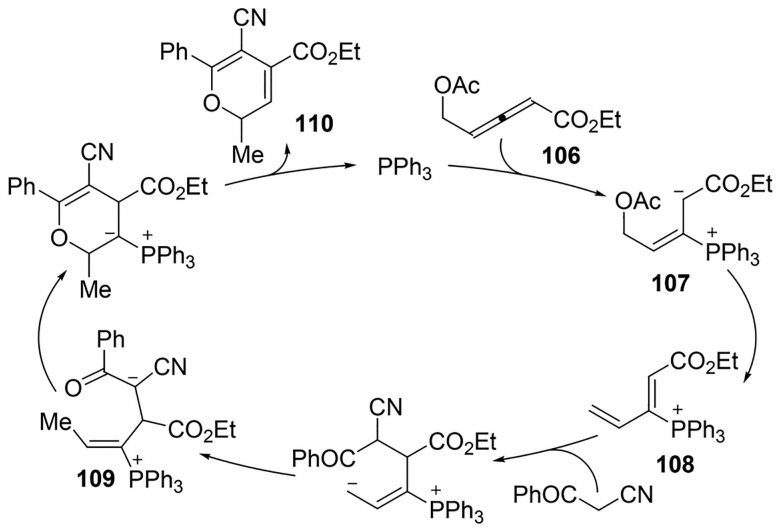
entry	Ar	yield (%)	ee (%)
1	Ph	82	91
2	*p*-$O_2NC_6H_4$	88	92
3	2-furyl	84	87
4	2-thienyl	81	90

Scheme 171.
Asymmetric Synthesis of Functionalized Spiropyrazolones

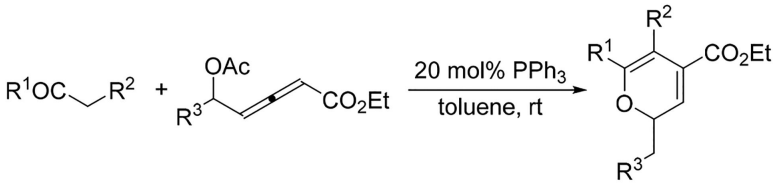


Scheme 172.

Enantioselective Phosphine-Catalyzed [4 + 1] Cycloadditions of Amines to Allenes

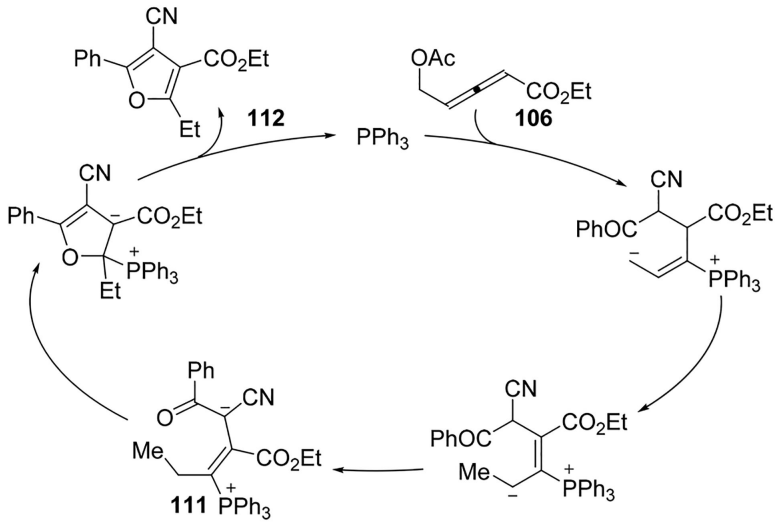


Scheme 173.
Proposed Mechanism of [3 + 3] Annulation

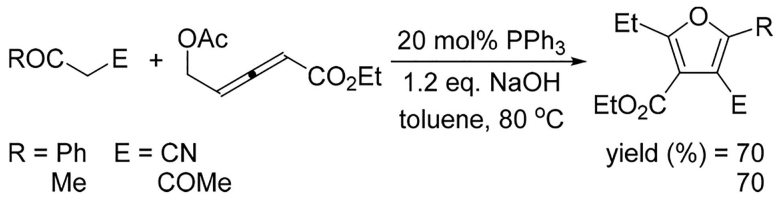


entry	R^1	R^2	R^3	yield (%)
1	Ph	CN	H	92
2	Me	CO_2Me	H	93
3	Me	Me	*n*Pr	92
4	Me	CO_2Me	Ph	trace

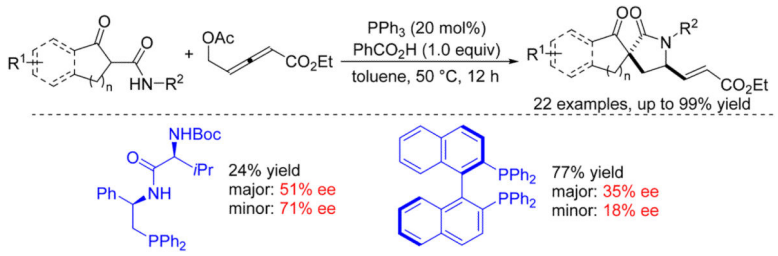
Scheme 174.
Synthesis of Functionalized Dihydrofurans



Scheme 175.
Proposed Mechanism for α-Umpolung–Michael Annulation

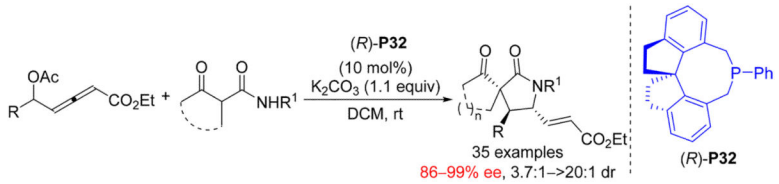


Scheme 176.
Synthesis of Functionalized Furans



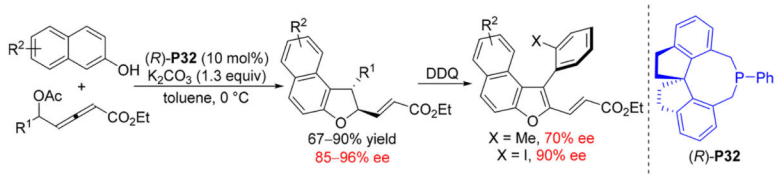
Scheme 177.

PPh_3-Catalyzed [3 + 2] Spiroannulation of 1*C*,3*N*-Bisnucleophiles Derived from Secondary *β*-Ketoamides with *δ*-Acetoxy Allenoate



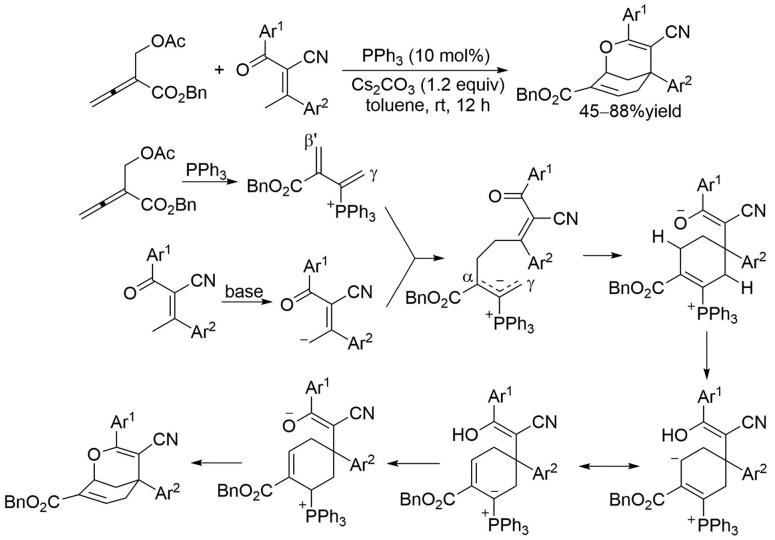
Scheme 178.

Phosphine-Catalyzed Asymmetric [3 + 2] Annulations of δ-Acetoxy Allenoates with β-Carbonyl Amides



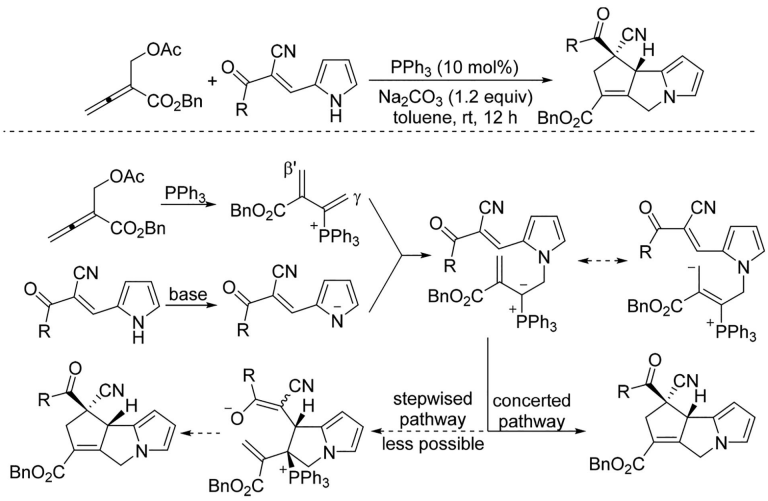
Scheme 179.

Phosphine-Catalyzed Asymmetric [3 + 2] Annulations of *δ*-Acetoxy Allenoates and 2-Naphthols



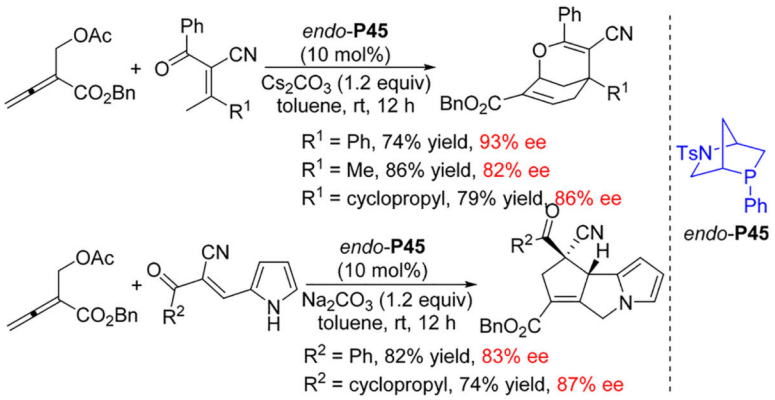
Scheme 180.

Phosphine-Promoted Domino Reactions of 2-Acetoxymethyl-2,3-Butadienoate with 2-Carbonyl-3-Methylacrylonitriles and the Proposed Mechanism



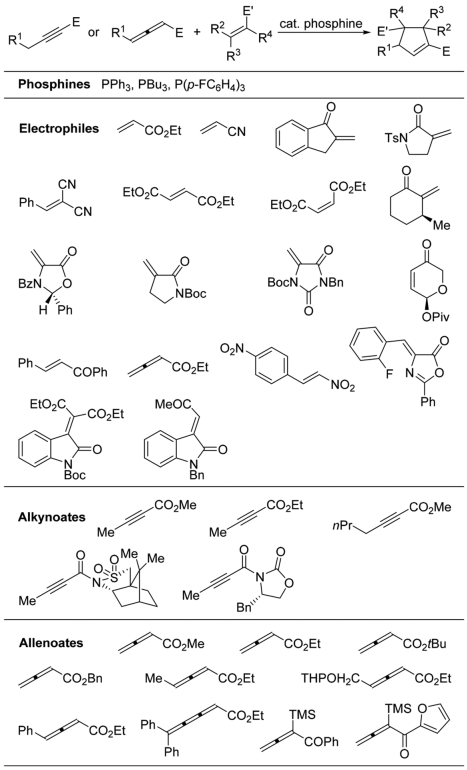
Scheme 181.

Phosphine-Promoted Domino Reactions of 2-Acetoxymethyl-2,3-Butadienoate with 2-Carbonyl-3-(2-Pyrrole)acrylonitriles and the Proposed Mechanism



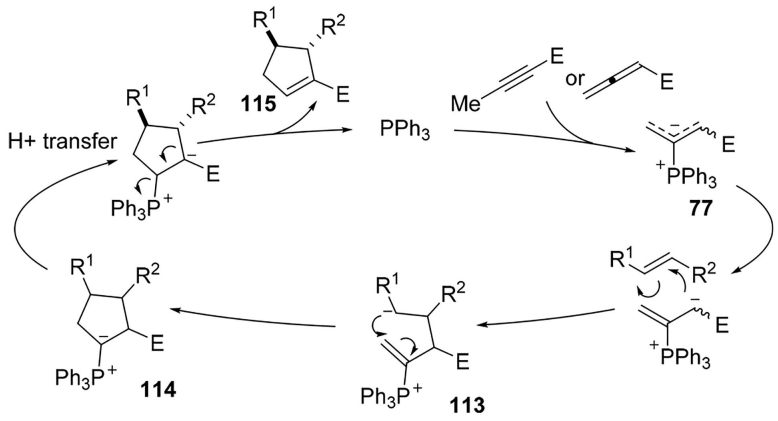
Scheme 182.

Asymmetric Version of the Phosphine-Promoted Domino Reactions

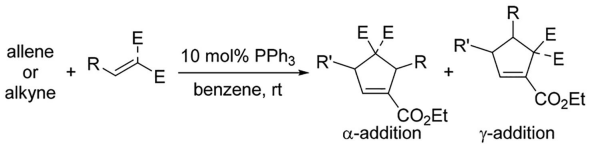


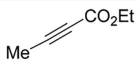
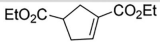
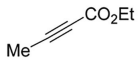
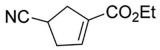
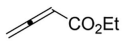
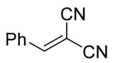
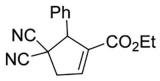
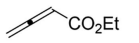
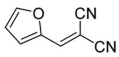
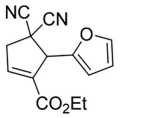
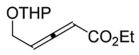
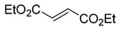
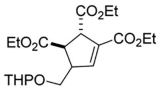
Scheme 183.

Scope of Alkynoate, Allenoate, Electrophiles, and Phosphines for Lu's Allene-Alkene [3 + 2] Annulations



Scheme 184.
Proposed Mechanism for Lu's [3 + 2] Annulation

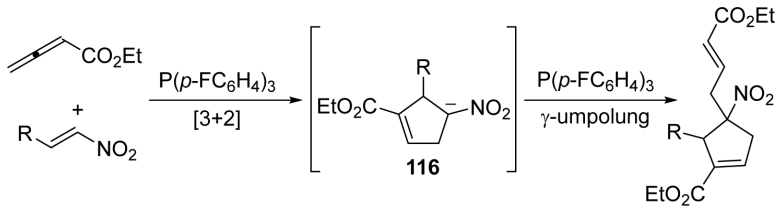


entry	allene/alkyne	olefin	product	yield (%)	α:γ
1				85[a]	89:11
2				80[a]	93:7
3				89[b]	—
4[a]				74[c,d]	—
5				47[e]	—

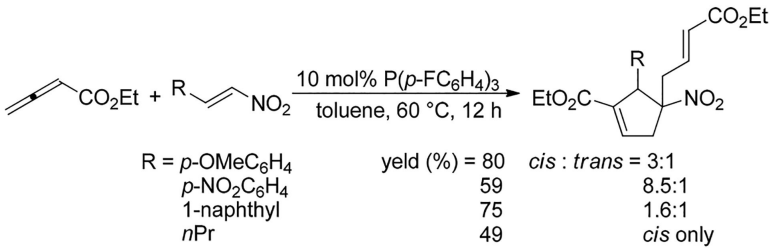
Scheme 185.

Lu's Allene–Alkene [3 + 2] Annulations

[a]PBu_3 is used as catalyst. [b]Toluene is used as solvent. [c]Olefin is formed in situ. [d]Reaction performed in toluene under reflux with 3 Å molecular sieves. [e]*cis/trans* = 1:5.

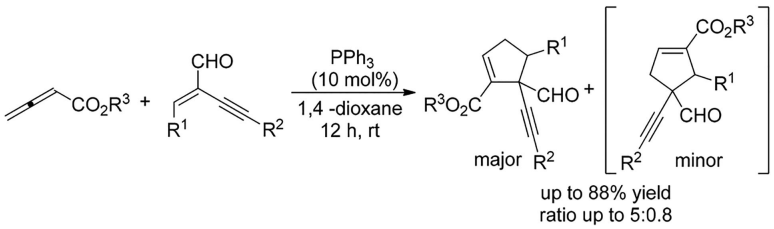


Scheme 186.
Tandem [3 + 2]/γ-Umpolung Addition Reaction Pathway



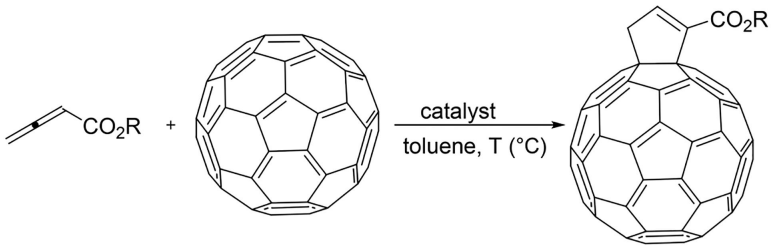
Scheme 187.

Phosphine-Catalyzed [3 + 2] Cycloaddition of Nitroalkenes with Allenoates



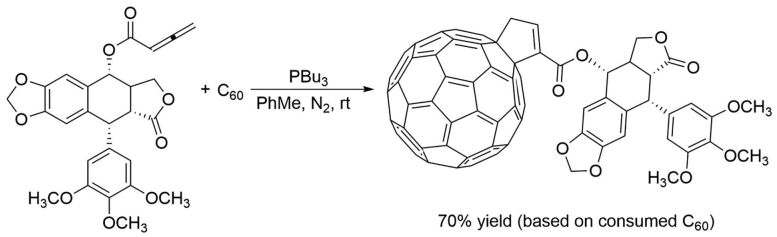
Scheme 188.

PPh_3-Catalyzed [3 + 2] Cycloadditions of Various Alkyl Allenoates with 2-(1-Alkynyl)-2-alken-1-als



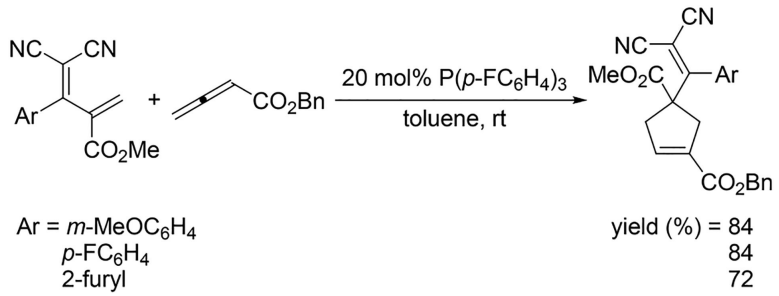
entry	R	catalyst	T (°C)	yield (%)
1	Et	PBu_3	rt	42
2	Bn	PPh_3	80	89

Scheme 189.
[3 + 2] Annulations of [60]Fullerene



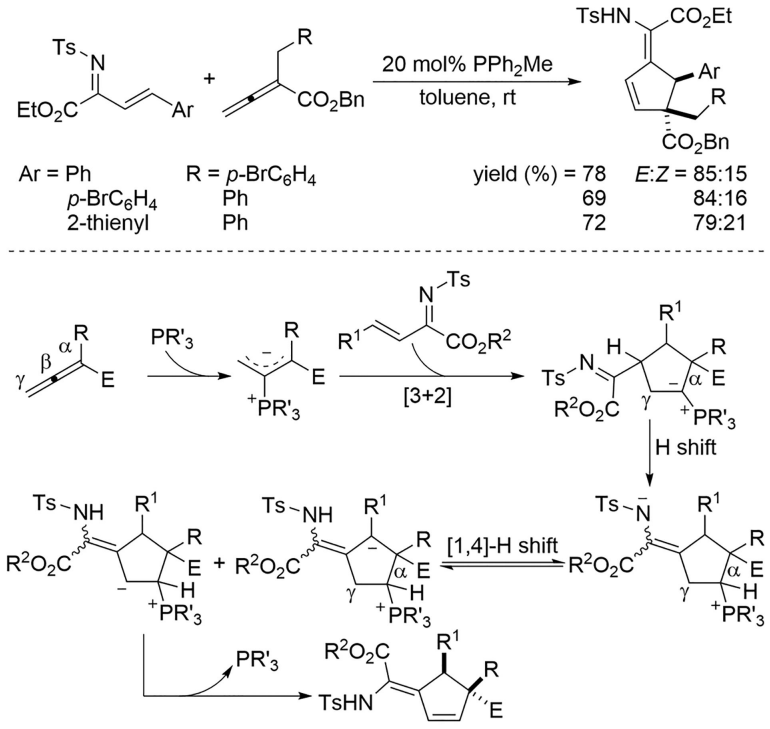
Scheme 190.

Phosphine-Catalyzed Preparation of a [60] Fullerene-Podophyllotoxin Derivative

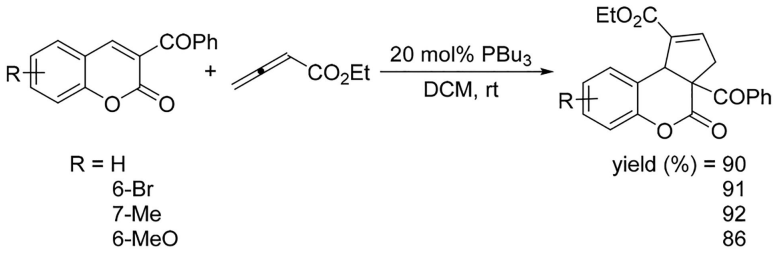


Scheme 191.

Synthesis of Cyclopentenes from 2,3-Dienoates

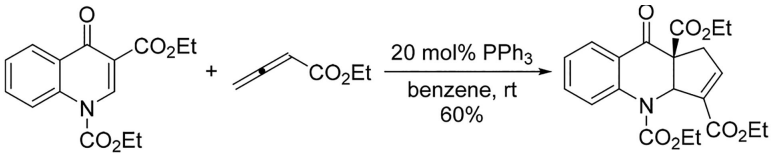


Scheme 192.
Synthesis of Cyclopentenes from Aza-Dienes



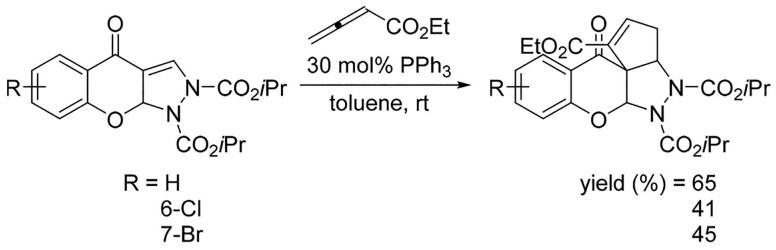
R = H — yield (%) = 90
6-Br — 91
7-Me — 92
6-MeO — 86

Scheme 193.
Synthesis of Functionalized Dihydrocoumarins

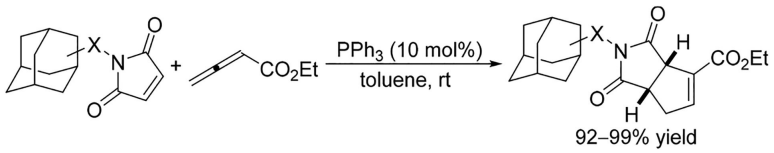


Scheme 194.

Synthesis of a Functionalized Dihydroquinolone

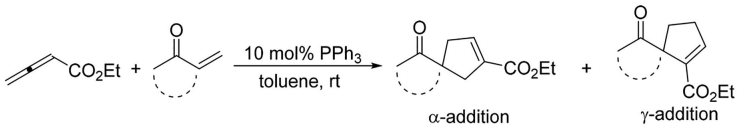


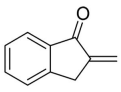
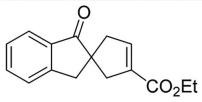
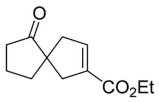
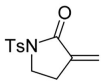
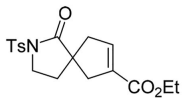
Scheme 195.
Synthesis of Functionalized Tetracycles



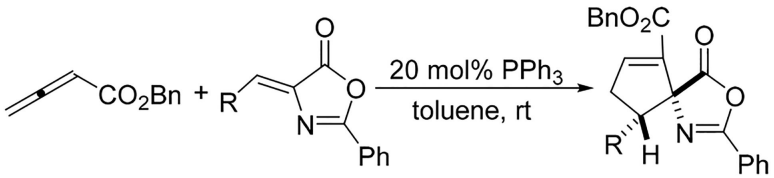
Scheme 196.

Phosphine-Catalyzed [3 + 2] Cycloaddition of Ethyl Buta-2,3-Dienoate to Adamantane-Containing N-Substituted Maleimides



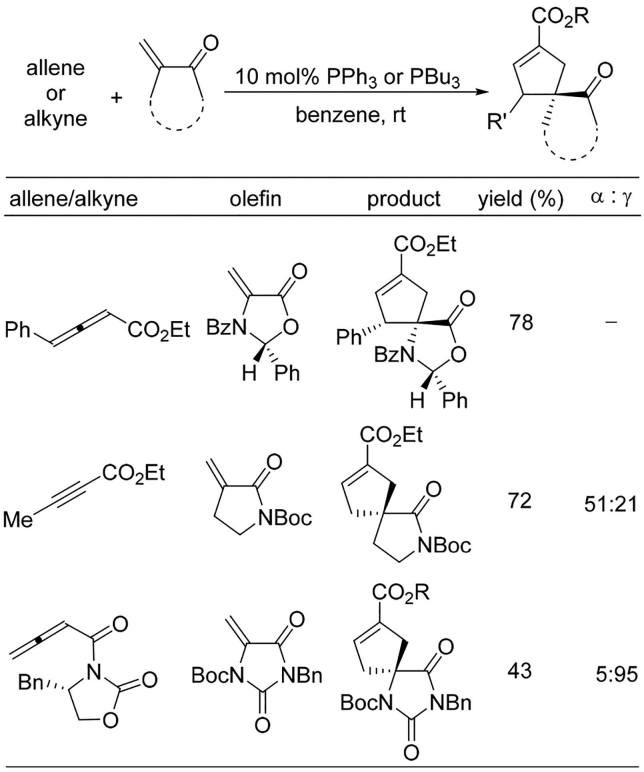
entry	olefin	time (h)	product	yield (%)	α:γ
1		6		98	84:16
2		13		73	58:42
3		13		94	82:18

Scheme 197.
Formation of Spirocyclopentenes



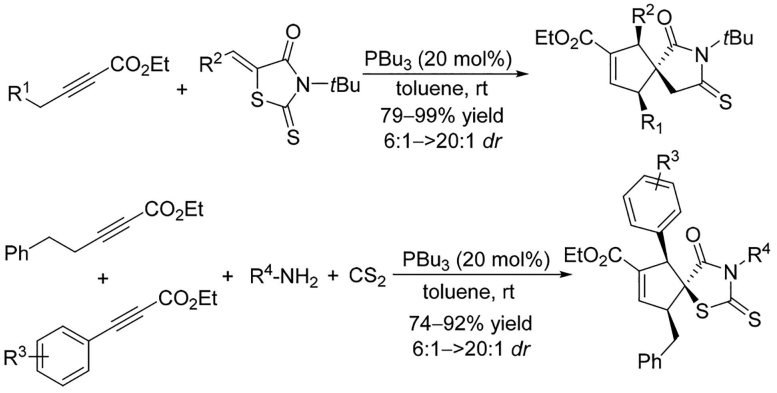
entry	R	time (h)	yield (%)	α:γ
1	*o*-FC_6H_4	2	75	25:55
2	*p*-FC_6H_4	4	87	25:75
3	3,4-$(MeO)_2C_6H_3$	48	50	15:85
4	2-furyl	48	35	54:46

Scheme 198.
Formation of Spirooxazolones



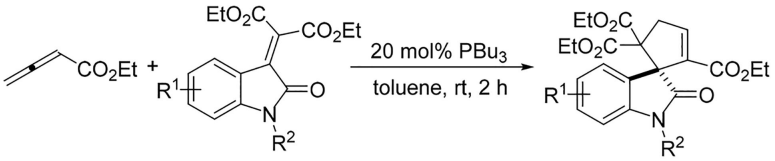
Scheme 199.

Syntheses of Biologically Active Spirocyclic L-Glutamate Analogues



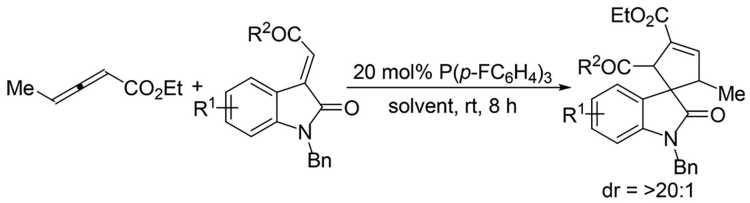
Scheme 200.

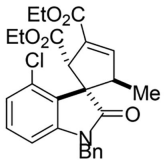
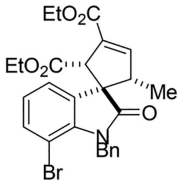
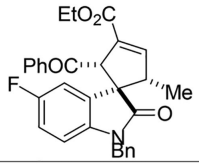
Phosphine-Catalyzed [3 + 2] Cycloadditions of Alkynoates with 5-Arylidene-3-(*tert*-butyl)-2-thioxothiazolidin-4-ones and Multi-Component Coupling Reactions



entry	R^1	R^2	yield (%)	dr
1	5-MeO	Boc	79	12:1
2	5-Br	Boc	77	>20:1
3	H	Allyl	80	3:1

Scheme 201.
Formation of Spirooxindole Derivatives

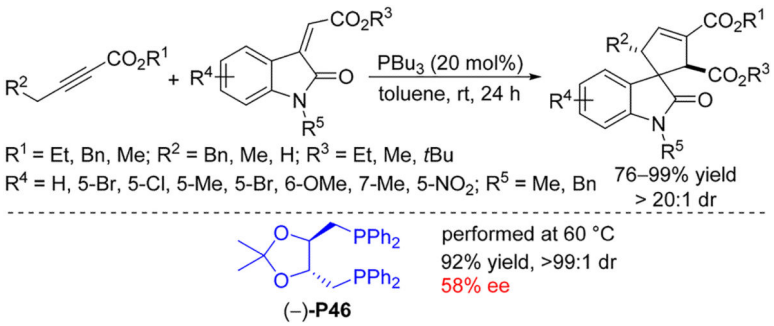


R^1	R^2	solvent	product	yield (%)
4-Cl	Me	toluene		90[a]
7-Br	Me	dioxane		92
5-F	Ph	dioxane		92

Scheme 202.

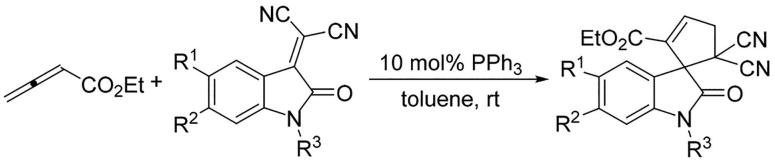
Formation of Spirooxindoles

[a]Reaction performed using PBu_3 as catalyst.



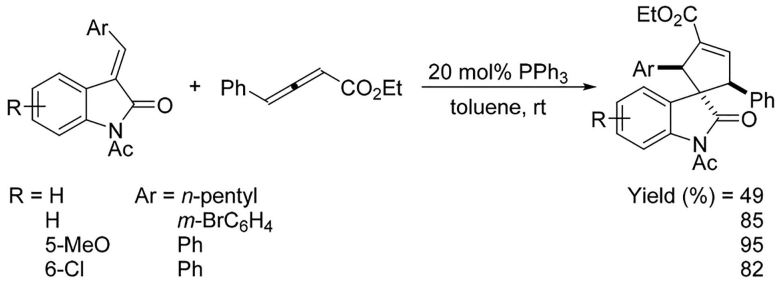
Scheme 203.

Phosphine-Catalyzed [3 + 2] Annulation of Methyleneindolinone with Alkynoate Derivatives



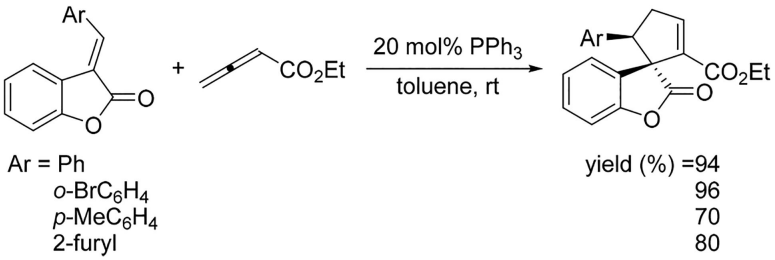
entry	R^1	R^2	R^3	time (h)	yield (%)
1	F	H	Me	4	72
2	OMe	H	Me	5	68
3	H	Br	Bn	6	73
4	NO_2	H	Bn	11	84

Scheme 204.
Preparation of Functionalized Spirooxindoles



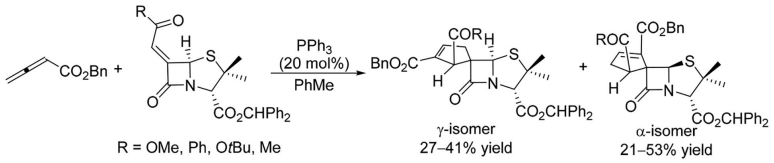
R = H	Ar = *n*-pentyl	Yield (%) = 49
H	*m*-BrC_6H_4	85
5-MeO	Ph	95
6-Cl	Ph	82

Scheme 205.
Synthesis of Functionalized Spirooxindoles



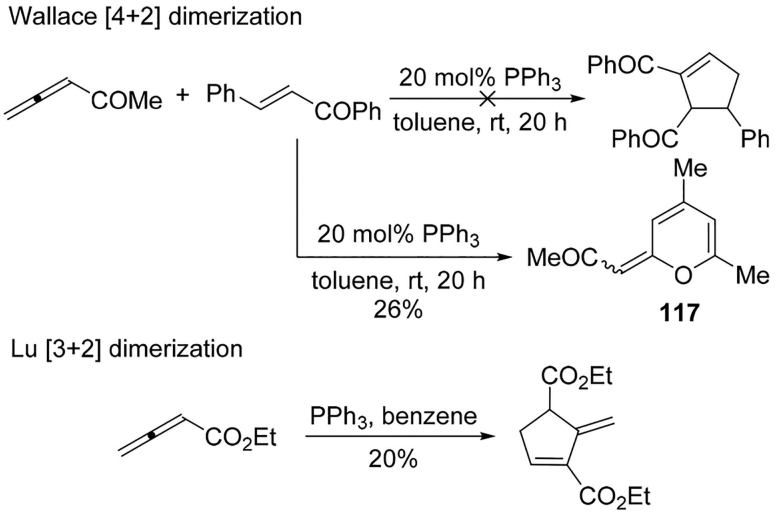
Ar = Ph — yield (%) = 94
o-BrC_6H_4 — 96
p-MeC_6H_4 — 70
2-furyl — 80

Scheme 206.
Synthesis of Functionalized Spirobenzofuranones



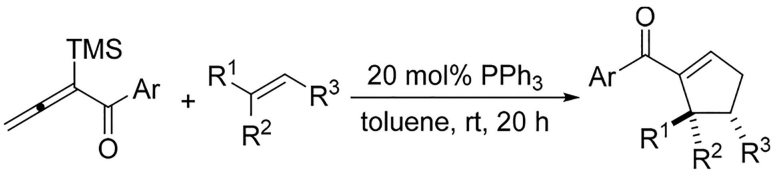
Scheme 207.

Phosphine-Catalyzed [3 + 2] Annulation of an Allenoate with 6-Alkylidenepenicillanates



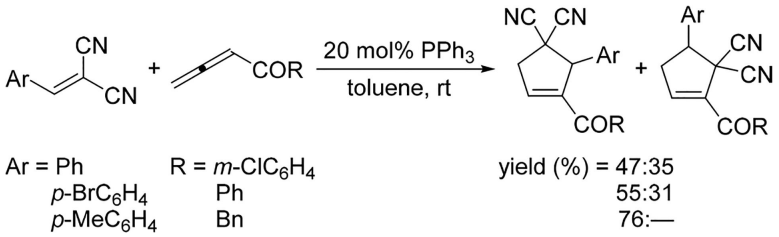
Scheme 208.

Self-Dimerization of Aromatic Allenones and Allenoates

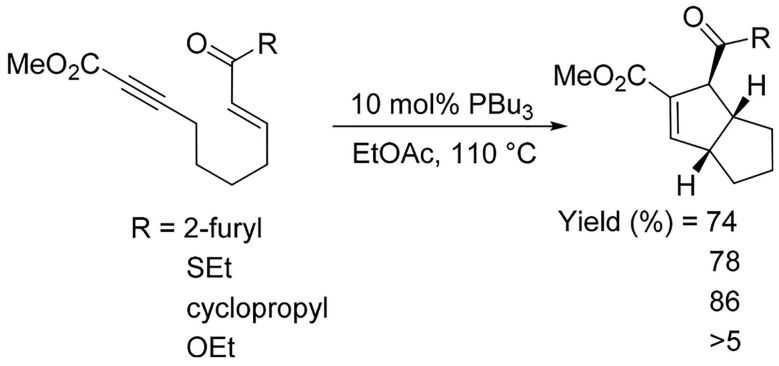


entry	Ar	R^1	R^2	R^3	yield (%)
1	Ph	H	CO_2Et	CO_2Et	72
2	Ph	CO_2Et	H	CO_2Et	82
3	2-furyl	Ph	H	COPh	75
4	2-furyl	CO_2Et	H	CF_3	72

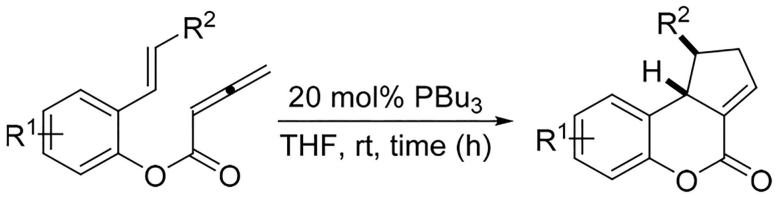
Scheme 209.
α-Trimethylsilyl Allenone [3 + 2] Annulations



Scheme 210.
Synthesis of Functionalized Cyclopentenes



Scheme 211.
Intramolecular [3 + 2] Annulations

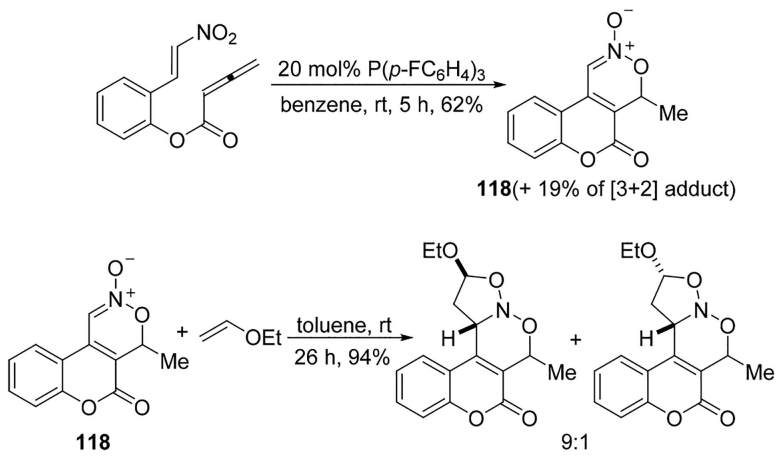


entry	R^1	R^2	time (h)	yield (%)
1	3-Me	CO_2Et	6	98
2	4-MeO	CO_2Et	6	94
3	5-F	CO_2Et	6	91
4	H	NO_2	5	48[a]

Scheme 212.

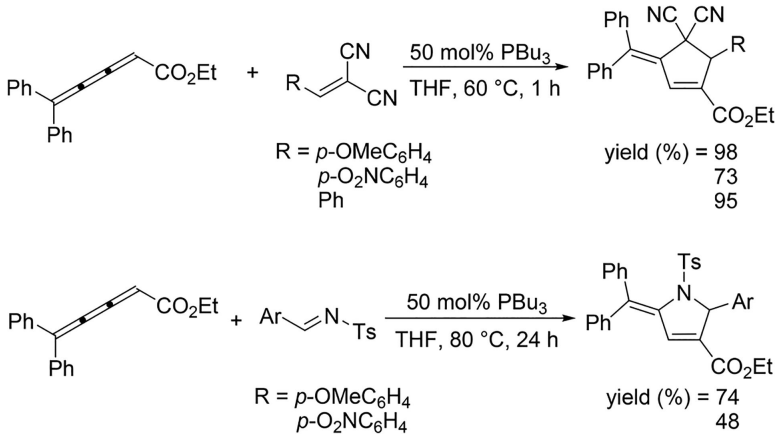
Intramolecular Allenoate–Cinnamate [3 + 2] Annulations

[a]PPh_3 was used instead of tributylphosphine. In addition to the [3 + 2] adduct, 12% of the nitronate 118 was isolated.



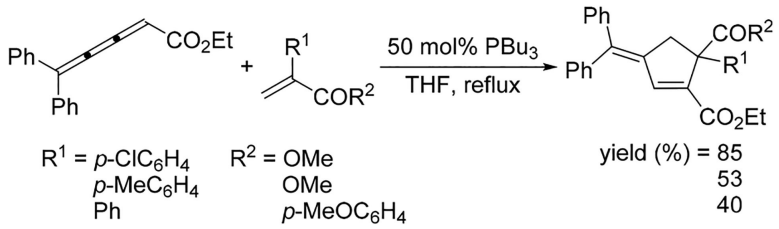
Scheme 213.

Phosphine-Catalyzed Nitronate Formation and Subsequent 1,3-Dipolar Cycloaddition

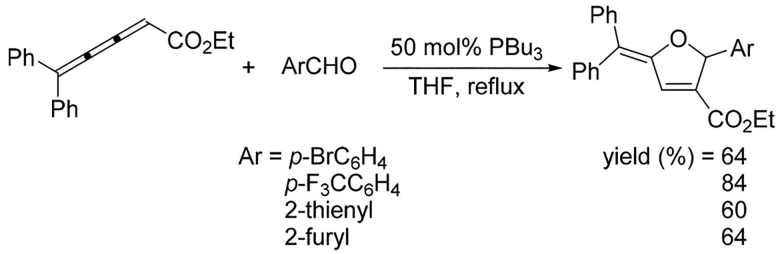


Scheme 214.

Synthesis of 5-Diarylidene-Cyclopentenes and Pyrrolidines

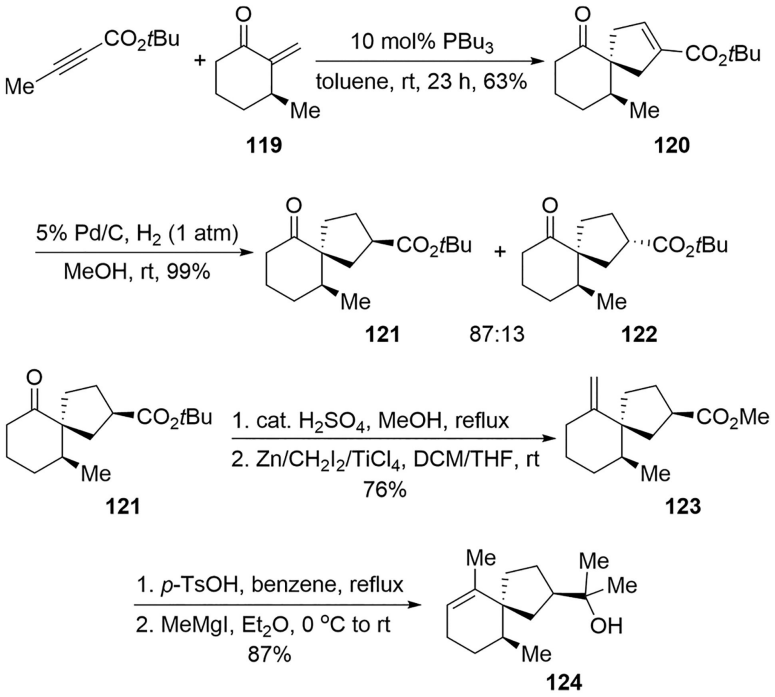


Scheme 215.
Synthesis of Functionalized Cyclopentenes

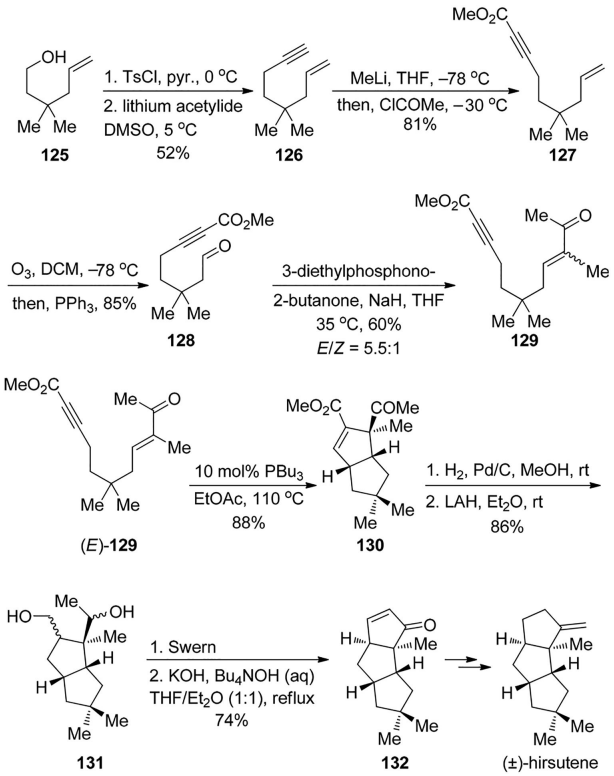


Ar	yield (%)
p-BrC_6H_4	64
p-$F_3CC_6H_4$	84
2-thienyl	60
2-furyl	64

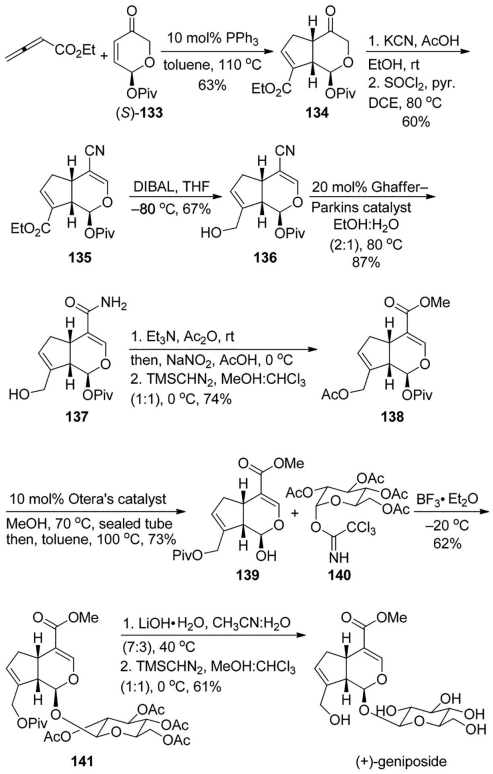
Scheme 216.
Synthesis of Functionalized Dihydrofurans



Scheme 217.
Total Synthesis of (−)-Hinesol

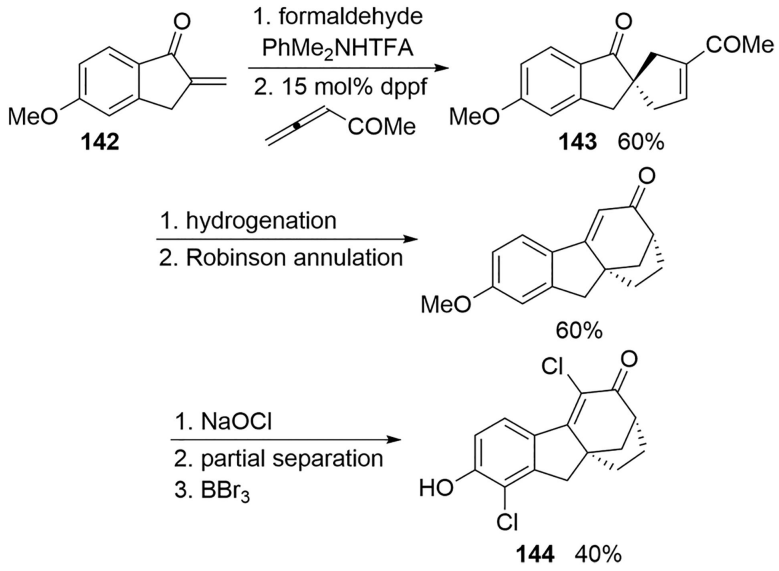


Scheme 218.
Total Synthesis of (±)-Hirsutene



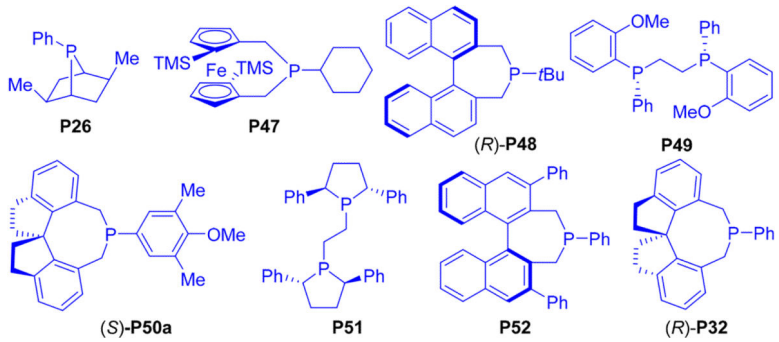
Scheme 219.

Total Synthesis of (+)-Geniposide



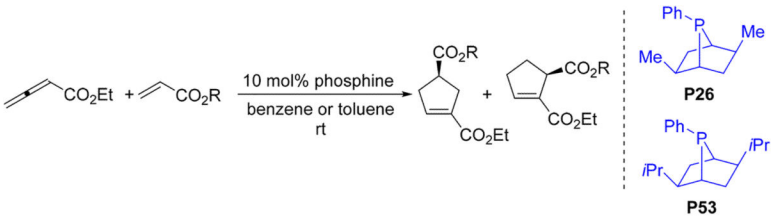
Scheme 220.

Synthesis of the Estrogen Receptor Modulator 144



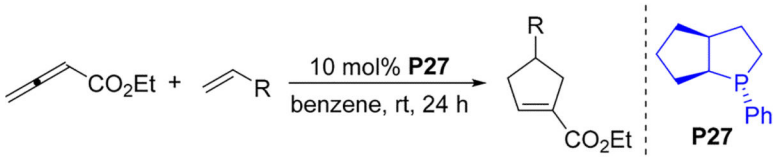
Scheme 221.

Chiral Phosphines without Hydrogen Bonding Motifs Used in [3 + 2] Annulations



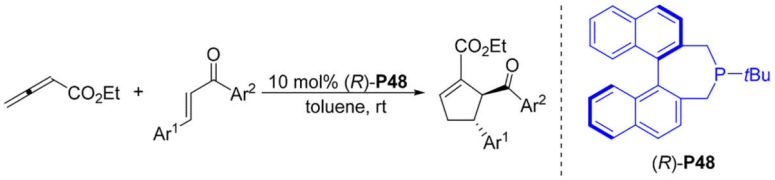
entry	R	phosphine	yield (%)	ee (%)	α:γ
1	*i*Bu	**P26**	46	86	100:0
2	*t*Bu	**P26**	69	89	95:5
3	Me	**P53**	87	79	96:4
4	*i*Bu	**P53**	92	88	100:0
5	*i*Bu	**P53**	88	93	100:0

Scheme 222.
Asymmetric [3 + 2] Annulations with Acrylates



entry	R	yield (%)	ee (%)
1	CO_2Me	62	26
2	CO_2iBu	63	14
3	SO_2Ph	71	33

Scheme 223.
Asymmetric [3 + 2] Annulations with Activated Olefins

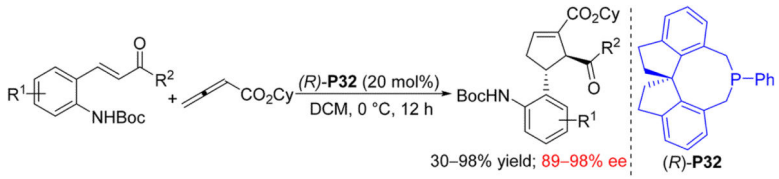


entry	Ar^1	Ar^2	yield (%)	ee (%)	α:γ
1	Ph	*p*-ClC_6H_4	76	82	1:7
2	*p*-$MeOC_6H_4$	Ph	67[a]	87	1:10
3	Ph	*p*-MeC_6H_4	61	87	1:20
4	Ph	2-thienyl	74	90	1:6

Scheme 224.

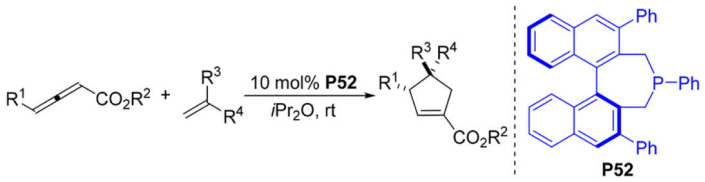
Asymmetric [3 + 2] Annulations with Chalcones

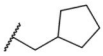
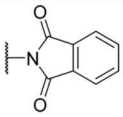
[a]Two equivalents of the butadienoate were used.



Scheme 225.

Phosphine-Catalyzed Asymmetric [3 + 2] Annulation of Chalcones with Allenoates

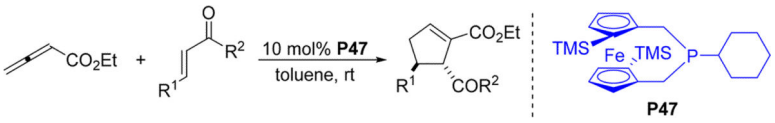


Entry	R^1	R^2	R^3	R^4	yield (%)	ee (%)
1		*i*Pr		CO_2tBu	86	98
2	CH_2CH_2Ph	*t*Bu	$P(O)(OEt)_2$	*p*-ClC_6H_4	79	97
3	Me	*t*Bu	OBz	CO_2Et	79[a]	96
4	Me	*i*Pr	S*t*Bu	CO_2Me	68[b]	98

Scheme 226.

Asymmetric [3 + 2] Annulations Giving Products with Heteroatom Quaternary Stereocenters

[a]Hexanes used as solvent. [b]$CHCl_3$ used as solvent.



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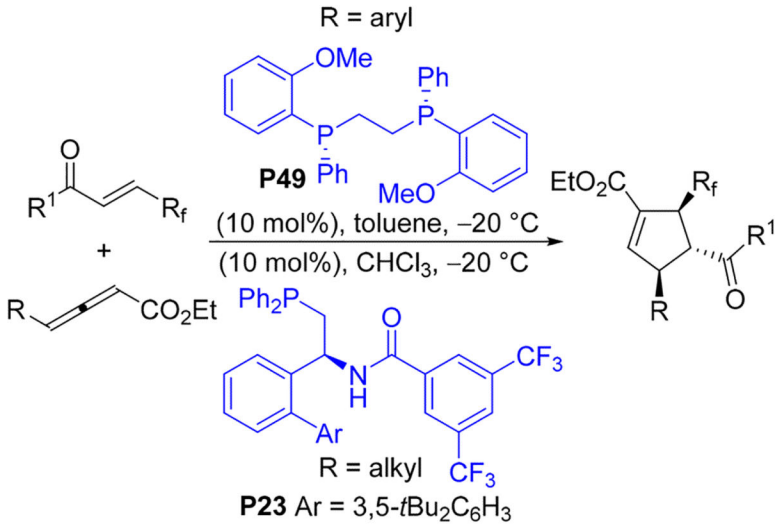
entry	R^1	R^2	yield (%)	ee (%)	α:γ
1	H	OEt	53	88	1.5:1
2	*p*-$O_2NC_6H_4$	Ph	63	92	1:10
3	Ph	*p*-$MeOC_6H_4$	85	95	1:>20
4	1-naphthyl	Ph	87	96	1:>20

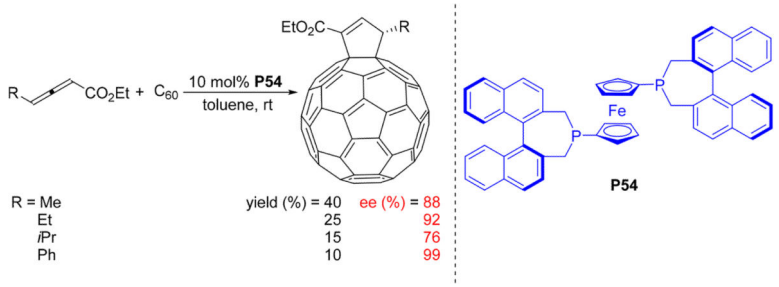
Scheme 227.

Asymmetric [3 + 2] Annulations Performed Using a Catalyst with Planar Chirality

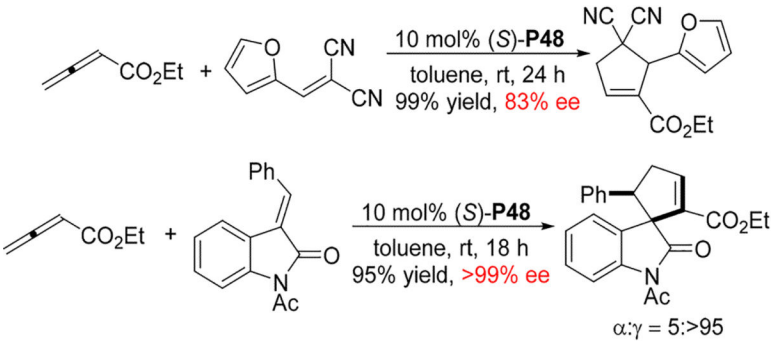


Scheme 228.

Phosphine-Catalyzed Enantioselective [3 + 2] Cycloadditions of γ-Substituted Allenoates with β-Perfluoroalkyl Enones

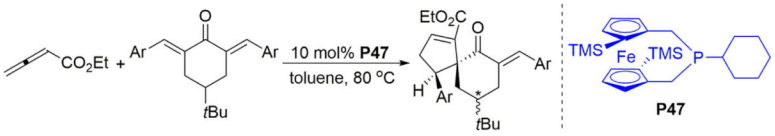


Scheme 229.
Asymmetric Synthesis of Functionalized Fullerenes



Scheme 230.

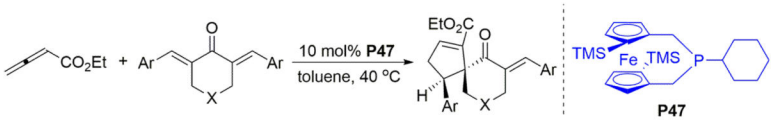
Two More Asymmetric Allene–Alkene [3 + 2] Annulations



entry	Ar	time (h)	yield (%)	ee (%)	dr
1	*p*-$MeOC_6H_4$	60	91	94	>95:5
2	*p*-ClC_6H_4	18	86	86	95:5
3	2-furyl	18	57	92	75:25

Scheme 231.

Asymmetric [3 + 2] Annulations of 2,6-Diaryidene-4-*tert*-butylCyclohexanones



entry	X	Ar	yield (%)	ee (%)
1	S	9-phenanthryl	90	95
2	S	*p*-MeC_6H_4	75	95
3	S	*p*-$O_2NC_6H_4$	65	>99
4	S	2-thienyl	80[a]	97
5	NMe	Ph	70	86

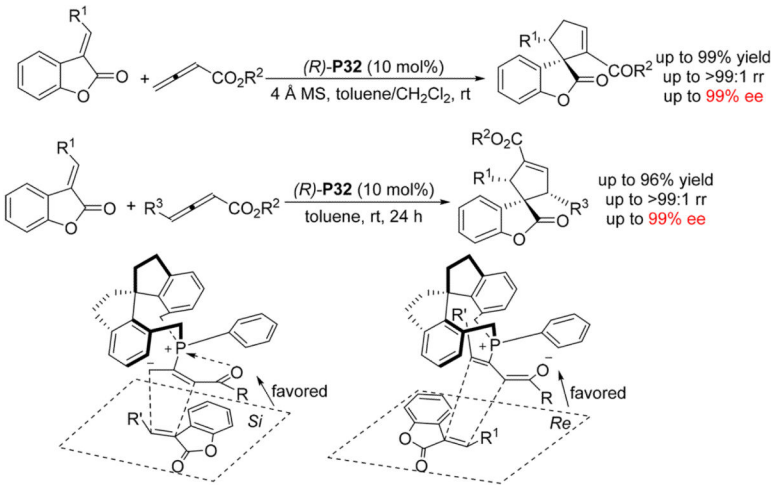
Scheme 232.

Synthesis of Spirothianones and Spiropiperidones

[a]Reaction performed at room temperature.

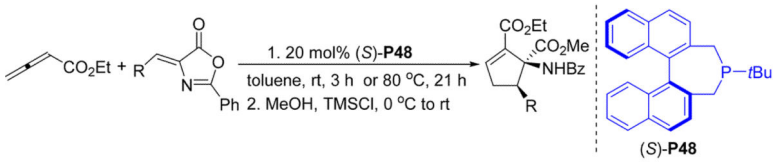
entry	R^1	R^2	yield (%)	ee (%)	dr
1	Bn	*m*-BrC_6H_4	96	95	>19:1
2	Bn	*p*-$O_2NC_6H_4$	69	93	>19:1
3	Bn	*p*-$MeOC_6H_4$	66	96	13:1
4	Bn	2-thienyl	66	94	>19:1
5	Bn	*i*Pr	68	79	>19:1
6	*i*Pr	Ph	91	94	>19:1

Scheme 233.
Preparation of Optically Pure Spirooxazolones



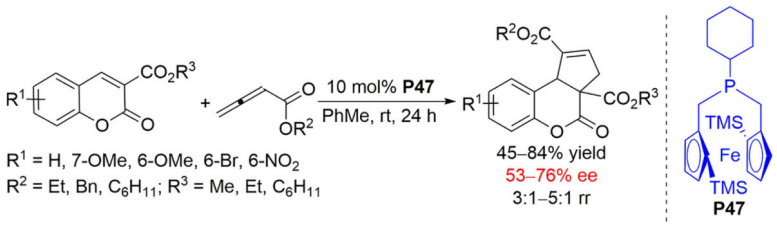
Scheme 234.

Asymmetric γ-[3 + 2] Cycloadditions of Allenoates with Olefins and Transition States



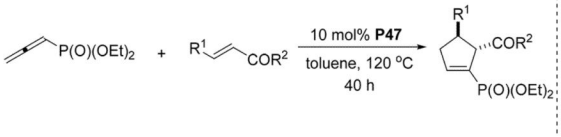
entry	R	yield (%)	ee (%)	dr
1	Ph	58	93	5:1
2	*p*-$O_2NC_6H_4$	58	94	6:1
3	*o*-BrC_6H_4	53	79	9:1
4	*p*-ClC_6H_4	51	92	7:2

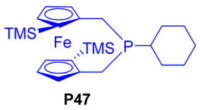
Scheme 235.
Synthesis of Optically Pure α-Amino Esters



Scheme 236.

Asymmetric Formation of Derivatized Coumarins





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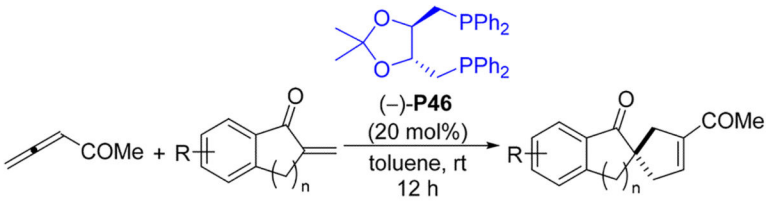
entry	R^1	R^2	yield (%)	ee (%)
1	Ph	Ph	78	90
2	2-furyl	Ph	77	91
3	Ph	2-furyl	80	83
4	Ph	Me	85	45

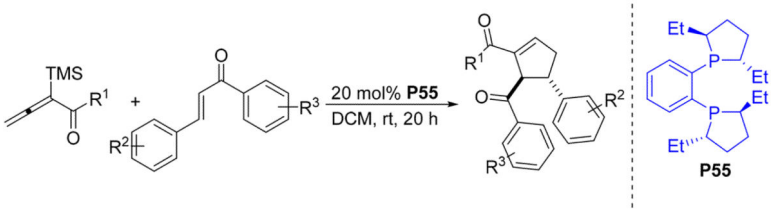
Scheme 237.

Asymmetric [3 + 2] Annulations with an Allenylphosphonate



entry	R	*n*	yield (%)	ee (%)	α:γ
1	H	2	73	61	95:5
2	4-MeO	2	75	77	91:9
3	4-MeO	1	63	53	80:20

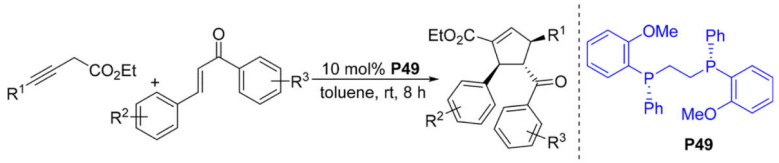
Scheme 238.
Asymmetric Formation of Derivatized Bicyclic Compounds



entry	R^1	R^2	R^3	yield (%)	ee (%)
1	Ph	H	H	52	71
2	2-furyl	H	H	54	92
3	2-furyl	4-Et	4-Me	56	70

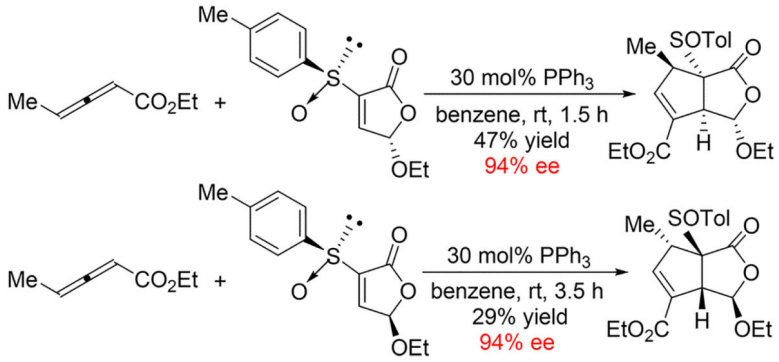
Scheme 239.

Asymmetric Formation of Cyclopentenes from Allenones



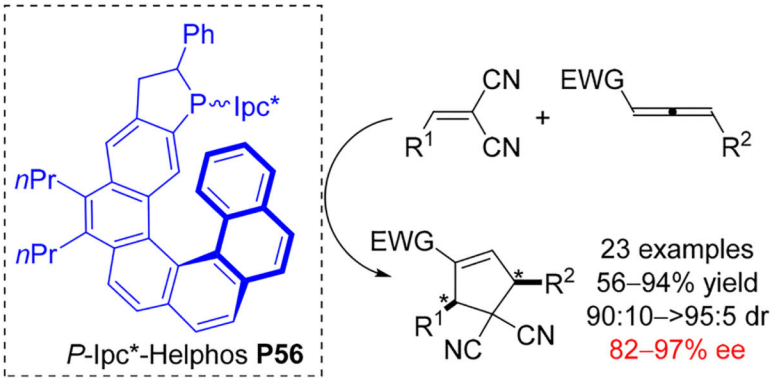
entry	R^1	R^2	R^3	yield (%)	ee (%)
1	Ph	H	H	87	95
2	Ph	4-F	4-MeO	82	98
3	3-thienyl	H	H	90	96
4	Me	H	H	87	99

Scheme 240.
Asymmetric [3 + 2] Annulations of 3-Butynoates



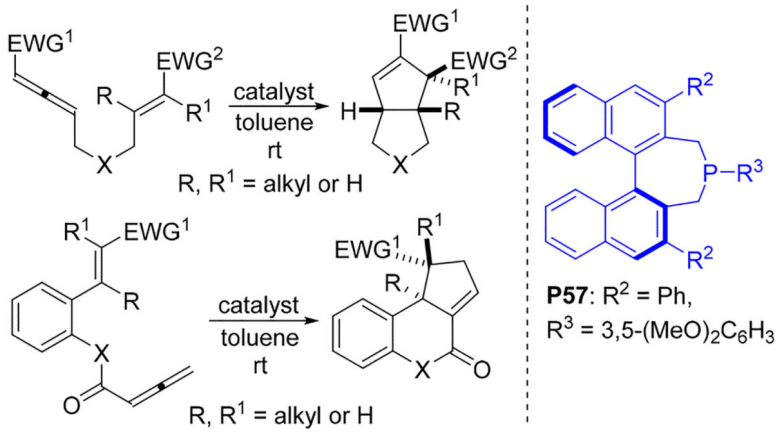
Scheme 241.

Chiral Sulfinyl Group as a Chiral Auxiliary in [3 + 2] Annulations



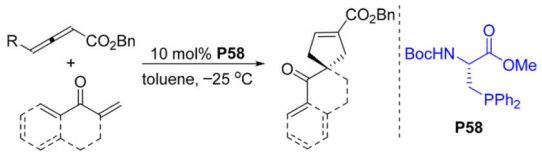
Scheme 242.

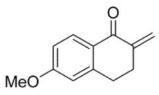
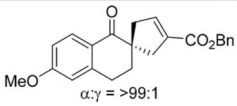
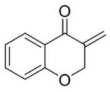
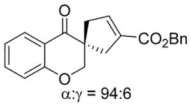
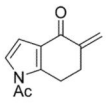
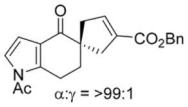
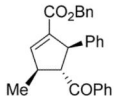
P-Ipc*-Helphos-Catalyzed [3 + 2] Cycloadditions of γ-Substituted Allenes with Activated Olefins



Scheme 243.

Enantioselective Phosphine-Catalyzed Intramolecular [3 + 2] Cycloadditions of Allenic Olefins

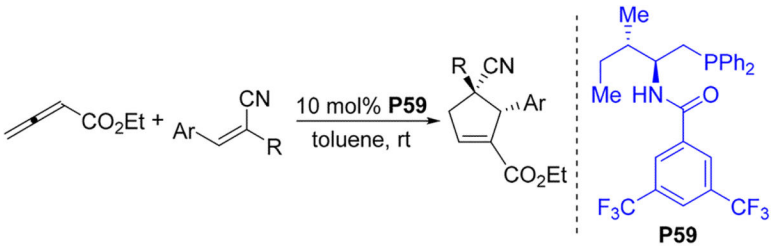


entry	R	olefin	product	yield (%)	ee (%)
1	H		 α:γ = >99:1	95	84
2	H		 α:γ = 94:6	68	65
3	H		 α:γ = >99:1	53	71
4	Me		 single regioisomer	94[a]	91

Scheme 244.

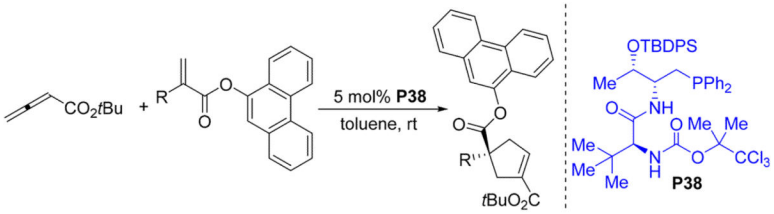
Asymmetric Formation of Cyclopentenes

[a]Reaction is performed with 100 mol % of catalyst.



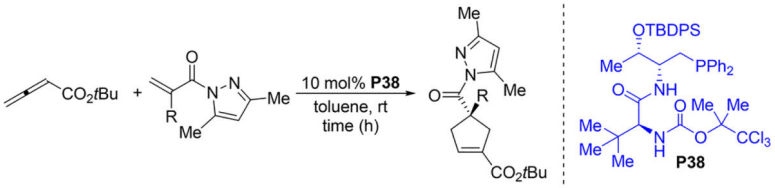
entry	Ar	R	time (h)	yield (%)	ee (%)
1	Ph	Ph	1	87	85
2	*o*-BrC_6H_4	CN	1	99	97
3	*o*-$MeOC_6H_4$	CN	1	99	91
4	*o*-FC_6H_4	CO_2Et	6	88	97
5	2-thienyl	CO_2Et	6	80	80

Scheme 245.
Asymmetric [3 + 2] Annulations with Arylidenemalononitriles



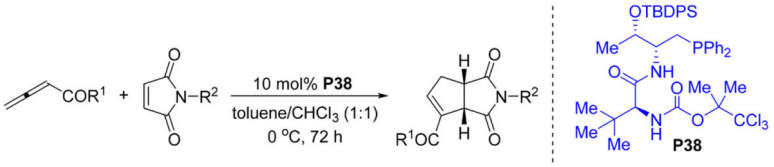
entry	R	time	yield (%)	ee (%)
1	Ph	30 min	95	91
2	*p*-ClC_6H_4	10 min	96	94
3	*p*-NCC_6H_4	10 min	97	94
4	*p*-$MeOC_6H_4$	24 h	61	87
5	Bn	5 h	91	68

Scheme 246.
Asymmetric [3 + 2] Annulations Involving Acrylates



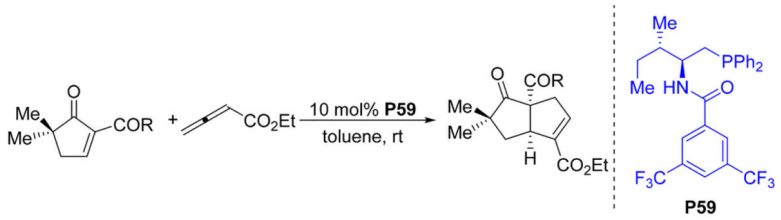
entry	R	time (h)	yield (%)	ee (%)
1	Ph	24	86	66
2	*p*-PhC$_6$H$_4$	20	93	62
3	*o*-FC$_6$H$_4$	20	91	36
4	Me	48	71	47

Scheme 247.
Enantioselective Allene–Acrylamide [3 + 2] Annulations



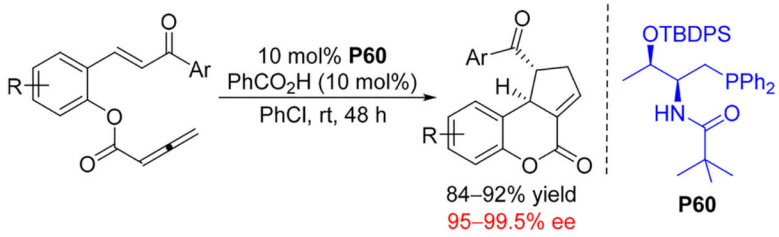
entry	R^1	R^2	yield (%)	ee (%)
1	OEt	Bn	92	92
2	OEt	*m*-$MeOC_6H_4CH_2$	79	92
3	OEt	cyclohexylmethyl	89	95
4	O*t*Bu	cyclohexylmethyl	82	77
5	OEt	*p*-$MeOC_6H_4$	87	64
6	OEt	H	trace	-

Scheme 248.
Preparation of Functionalized Bicyclic Cyclopentenes



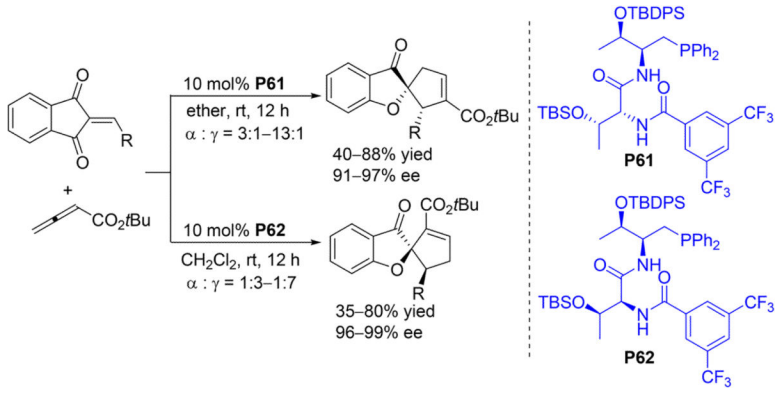
entry	R	yield (%)	ee (%)
1	Ph	72	95
2	*p*-PhC_6H_4	71	93
3	*m*,*p*-$BrFC_6H_3$	70	97
4	*i*Pr	90	96

Scheme 249.
Asymmetric Synthesis of Functionalized Bicyclic Cyclopentenes



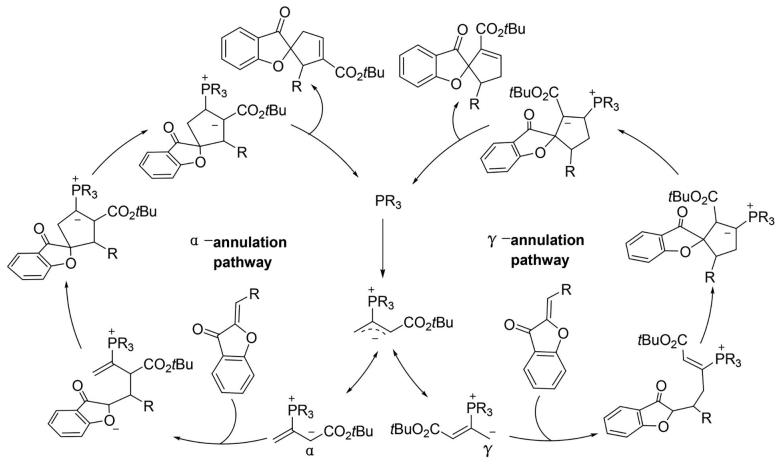
Scheme 250.

Phosphine-Catalyzed Intramolecular [3 + 2] Annulations of Chalcones Bearing an Allene Moiety



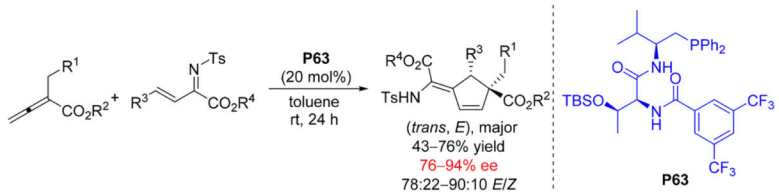
Scheme 251.

Catalyst-Controlled Regiodivergent [3 + 2] Annulations of Aurones and Allenoates



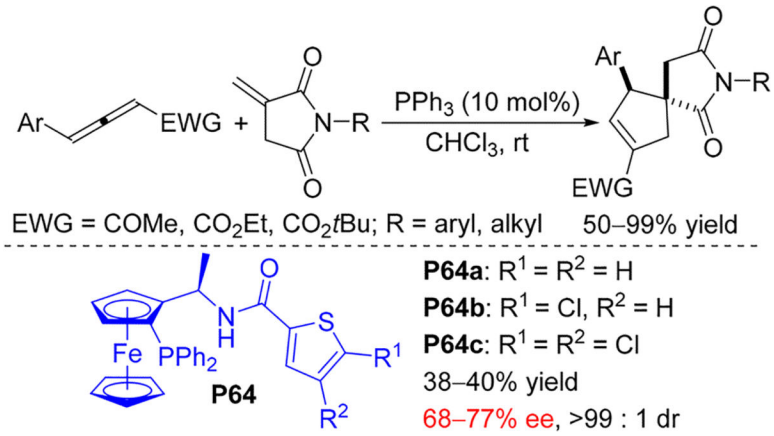
Scheme 252.

Proposed Mechanism for Phosphine-Catalyzed [3 + 2] Annulation of Aurones with an Allenoate



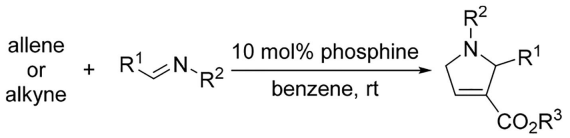
Scheme 253.

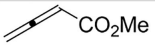
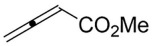
Asymmetric Phosphine-Catalyzed [3 + 2] Cycloaddition of α-Substituted Allenoates with α,β-Unsaturated Imines



Scheme 254.

Phosphine-Catalyzed [3 + 2] Annulations of γ-Substituted Allenoates with Succinimides

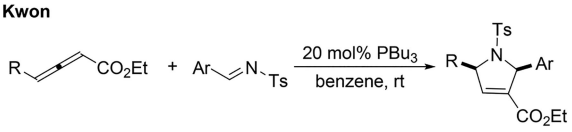


entry	allene/alkyne	R^1	R^2	phosphine	yield (%)
1		Ph	Ts	PPh_3	98
2		Ph	SES	PPh_3	96
3			Ts	PPh_3	Trace
4		*p*-$MeOC_6H_4$	Ts	PBu_3	86
5		Ph	Ts	PBu_3	96

Scheme 255.

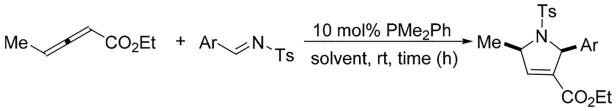
[3 + 2] Annulations of Allenes and Alkynes with Imines

Kwon



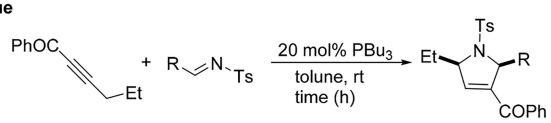
entry	R	Ar	yield (%)	*cis*:*trans*
1	Me	Ph	89	91:9
2	Ph	*o*-ClC_6H_4	99	*cis* only
3	*t*Bu	*p*-$MeOC_6H_4$	>99	*cis* only

Shi



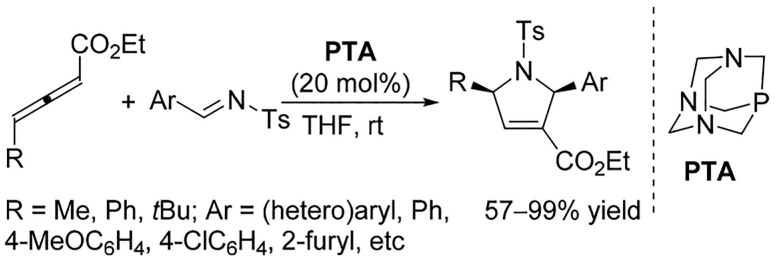
entry	Ar	solvent	time (h)	yield (%)	*cis*:*trans*
1	*p*-MeC_6H_4	DCM	24	28	18:1
2	*p*-$O_2NC_6H_4$	DCM	3	84	16:1
3	*p*-MeC_6H_4	THF	48	69	18:1

Xue

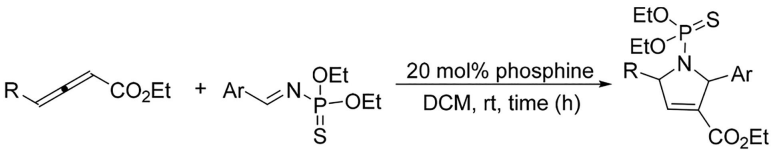


entry	R	time (h)	yield (%)
1	*p*-$O_2NC_6H_4$	3	92
2	*p*-$MeOC_6H_4$	24	64
3	$(CH_2)_2Ph$	3	No reaction

Scheme 256.
Syntheses of Tetrasubstituted Pyrrolines



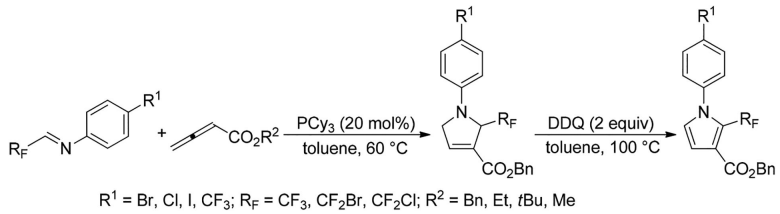
Scheme 257.
PTA-Catalyzed Allene-Imine [3 + 2] Cycloaddition



entry	R	Ar	phosphine	time (h)	yield (%)	*cis*:*trans*
1	H	Ph	PPh_3	20	49	—
2	H	*p*-$O_2NC_6H_4$	PPh_3	6	76	—
3	Me	Ph	PTA	48	77	25:1
4	Me	*p*-$O_2NC_6H_4$	PTA	48	99	6:1

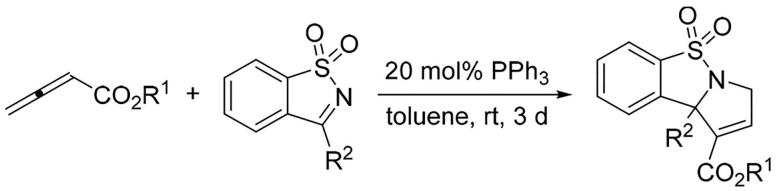
Scheme 258.

[3 + 2] Annulations of Allenes with *N*-Thiophosphorylimines



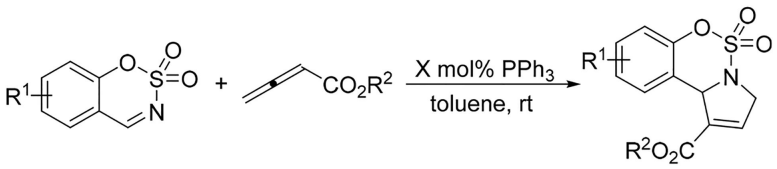
Scheme 259.

Phosphine-Catalyzed [3 + 2] Annulation of *N*-Aryl Fluorinated Imines with Allenoates



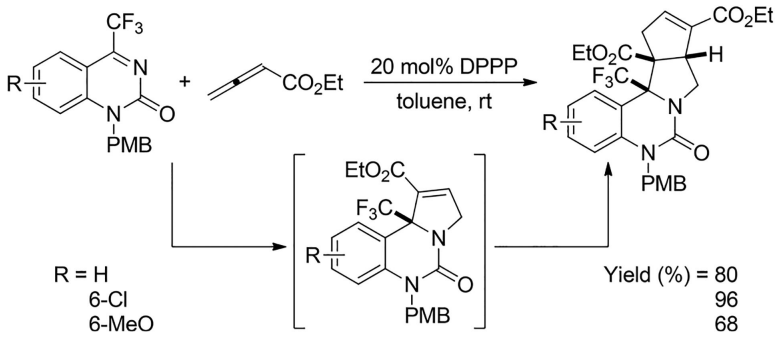
entry	R^1	R^2	yield (%)
1	Et	*m*-NCC_6H_4	77
2	Et	*p*-MeC_6H_4	54
3	cyclohexyl	Ph	72
4	*t*Bu	Ph	73

Scheme 260.
Preparation of Functionalized Pyrrolines



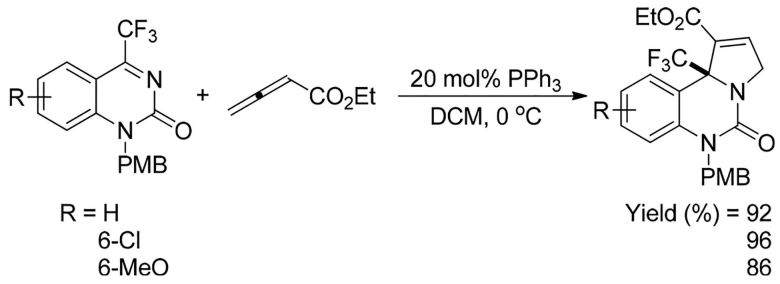
entry	R^1	R^2	X (mol%)	yield (%)
1	6-F	Bn	5	92
2	7-Et_2N	Bn	5	94
3	6-Me	Et	20	98
4	8-*t*Bu	Et	20	85

Scheme 261.
Synthesis of Functionalized Cyclic Sulfamidates

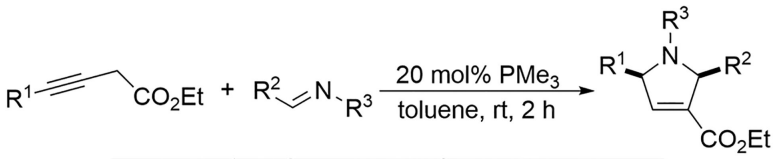


Scheme 262.

Synthesis of Functionalized Polycyclic Heterocycles

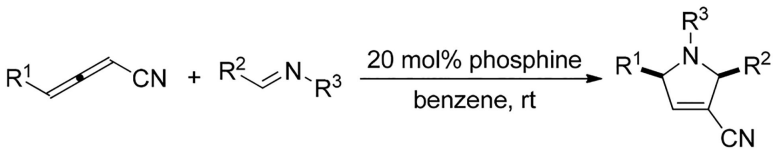


Scheme 263.
Synthesis of Functionalized Dihydropyrroloquinazolin-5-ones



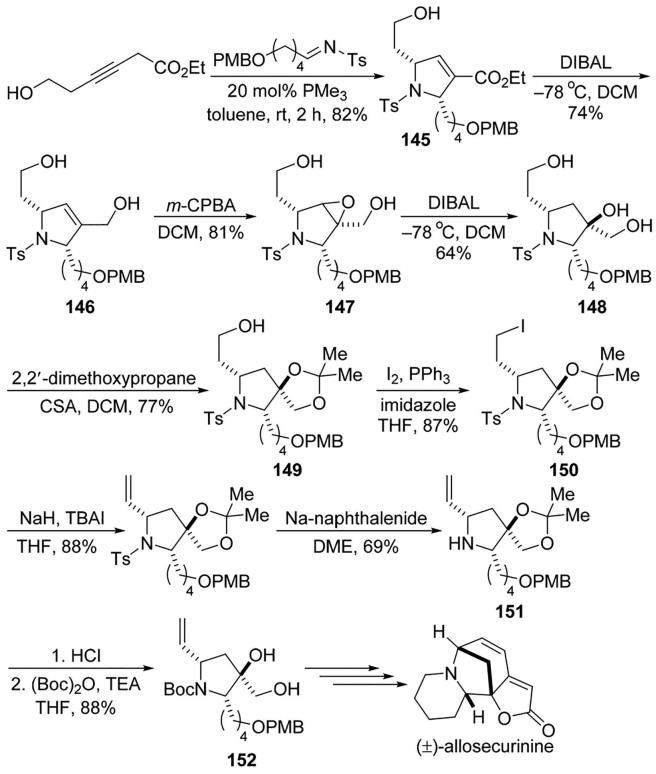
entry	R^1	R^2	R^3	yield (%)
1	H	2-furyl	Ts	70
2	Ph	2-furyl	SO_2CH_3	89
3	Ph	Bn	Ts	89
4	Ph	cyclohexyl	Ts	90
5	Ph	*n*-heptyl	Ts	81

Scheme 264.
Synthesis of Functionalized 2-Alkylpyrrolines



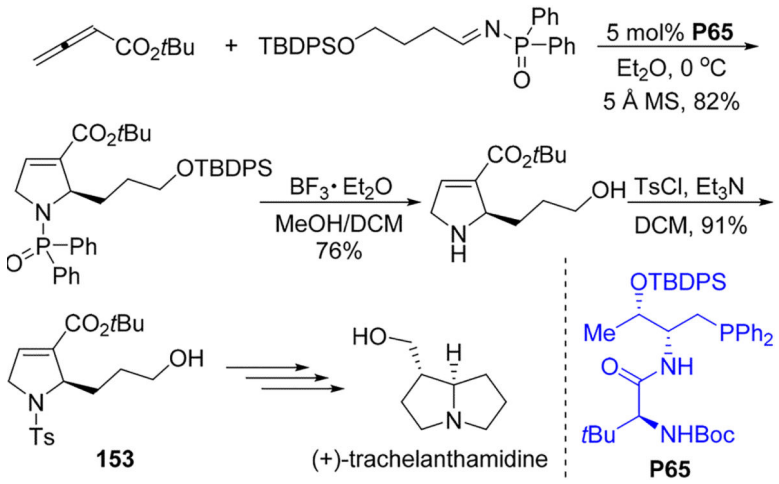
entry	R^1	R^2	R^3	PR_3	yield (%)
1	H	*p*-BrC_6H_4	Ts	PPh_3	95
2	H	*p*-$F_3CC_6H_4$	Ts	PPh_3	63
3	Me	cinnamyl	Ts	PBu_3	72
4	Me	*p*-MeC_6H_4	SES	PBu_3	81

Scheme 265.
Preparation of Cyanopyrroline Derivatives

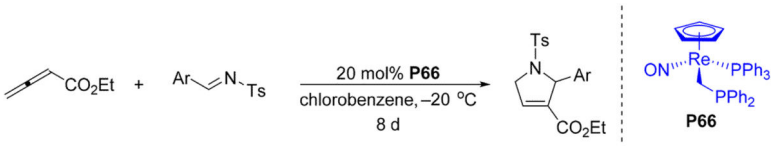


Scheme 266.

Formal Synthesis of (±)-Allosecurinine Using Lu's Allene–Imine [3 + 2] Annulation



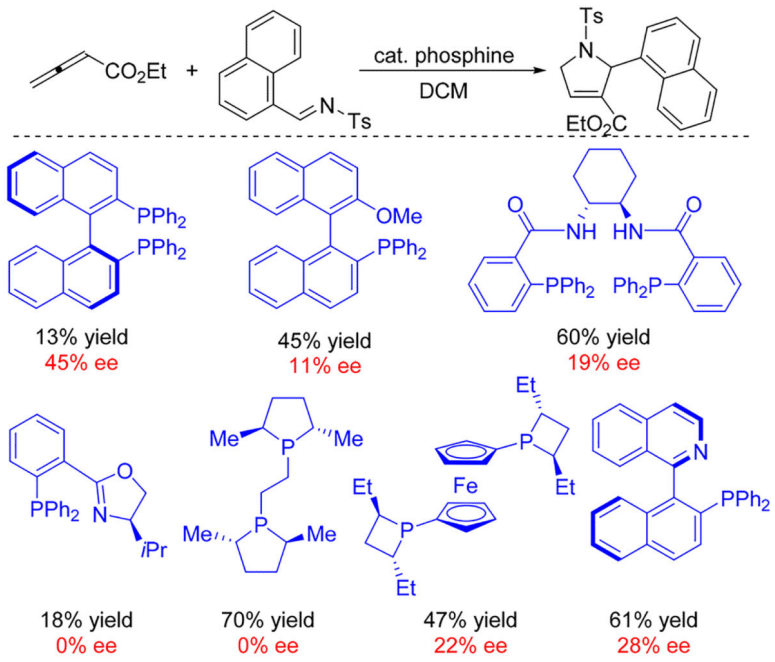
Scheme 267.
Formal Synthesis of (+)-Trachelanthamidine



entry	Ar	yield (%)	ee (%)
1	Ph	92	60
2	*p*-$MeOC_6H_4$	90	51
3	*p*-$O_2NC_6H_4$	93	54

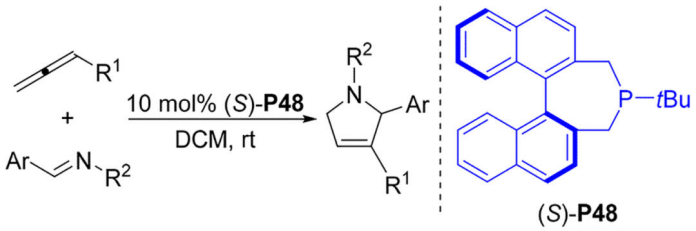
Scheme 268.

Asymmetric [3 + 2] Annulations Using a Rhenium-Containing Phosphine Catalyst



Scheme 269.

Screening of Chiral Phosphines for [3 + 2] Annulations Giving Pyrrolines

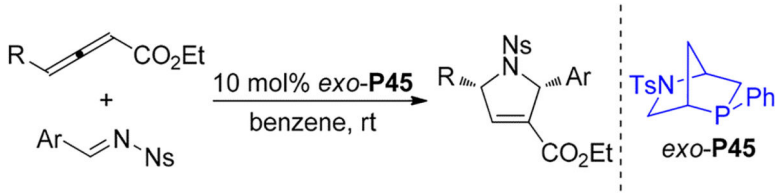


entry	R^1	R^2	Ar	yield (%)	ee (%)
1	CO_2Et	Ts	*o*-$MeOC_6H_4$	72	66
2	CO_2Cy	Ts	Ph	86	62
3	$P(O)(OEt)_2$	Ts	Ph	45[a]	57
4	CO_2Et	$P(O)Ph_2$	1-naphthyl	74	85

Scheme 270.

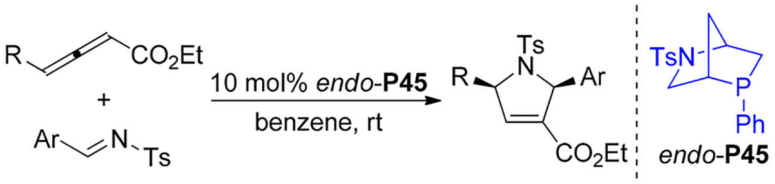
Asymmetric [3 + 2] Annulations Forming Functionalized Pyrrolines

[a]Reaction performed in dioxane at 120 °C.



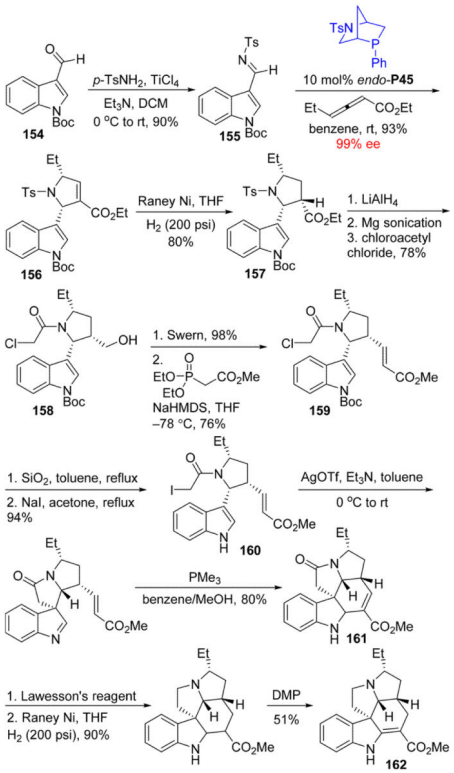
entry	R	Ar	yield (%)	ee (%)
1	*i*Pr	Ph	88	–67
2	*t*Bu	Ph	97	–97
3	*t*Bu	*m*-ClC_6H_4	93	–93
4	*t*Bu	*p*-$F_3CC_6H_4$	93	–97
5	*t*Bu	*p*-$O_2NC_6H_4$	89	–93

Scheme 271.
Asymmetric Synthesis of Functionalized (−)-Dihydropyrroles



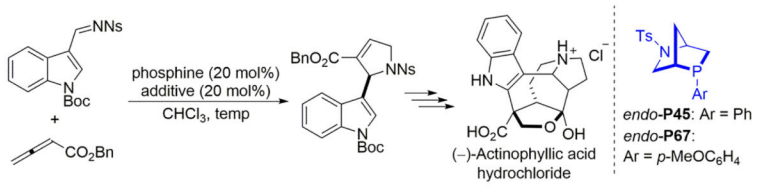
entry	R	Ar	yield (%)	ee (%)
1	H	Ph	82	72
2	Et	Ph	99	98
3	*t*Bu	*p*-NCC_6H_4	99	98
4	*t*Bu	*p*-MeC_6H_4	94	>99
5	*t*Bu	*m*-ClC_6H_4	89	99

Scheme 272.
Asymmetric Synthesis of Functionalized (+)-Dihydropyrroles



Scheme 273.

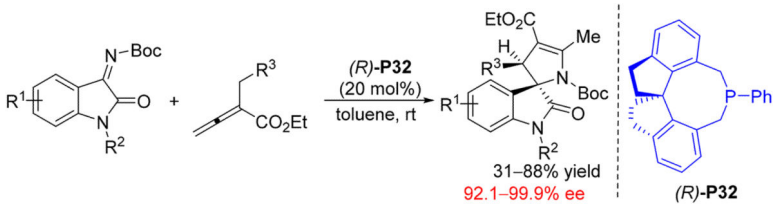
First Enantioselective Total Synthesis of (+)-Ibophyllidine



entry	phosphine	temp (°C)	additive	time (h)	yield (%)	ee (%)
1	PPh_3	rt	–	6	99	–
2	*endo*-**P45**	rt	–	5	97	75
3	*endo*-**P67**	rt	–	5	99	83
4	*endo*-**P67**	0	–	5	99	91
5	*endo*-**P67**	0	phenol	2	99	91
6	*endo*-**P67**	0	bisphenol	2	99	91
7	*endo*-**P67**	0	(*S*)-BINOL	2	99	94
8	*endo*-**P67**	0	(*R*)-BINOL	2	99	94

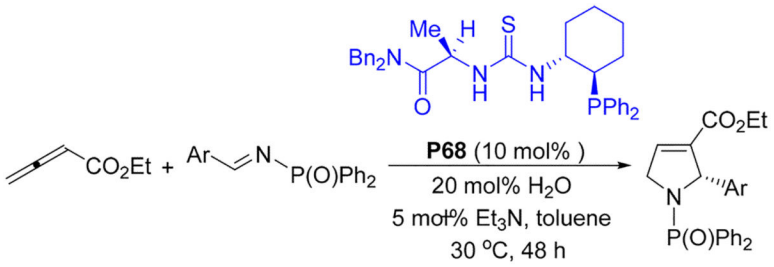
Scheme 274.

Enantioselective Phosphine-Catalyzed [3 + 2] Cycloadditions of Allenoates with *N*-(*o*-Nitrobenzenesulfonyl) (*o*-Nosyl) Imines



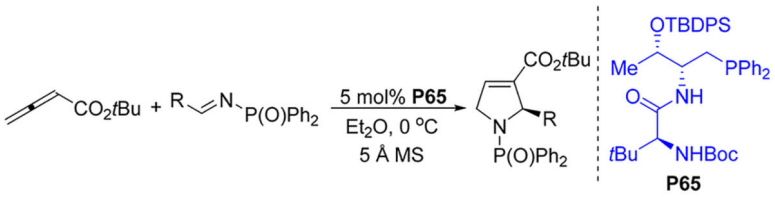
Scheme 275.

Enantioselective [3 + 2] Cycloadditions of Isatin-Derived Ketimines with α-Substituted Allenoates Catalyzed by Spiral Chiral Phosphines



entry	Ar	mol%	yield (%)	ee (%)
1	*p*-$MeOC_6H_4$	20	80	97
2	2-furyl	20	79	94
3	*o*-BrC_6H_4	2.5	77	95
4	*p*-FC_6H_4	10	72	95
5	Ph	10	84	98

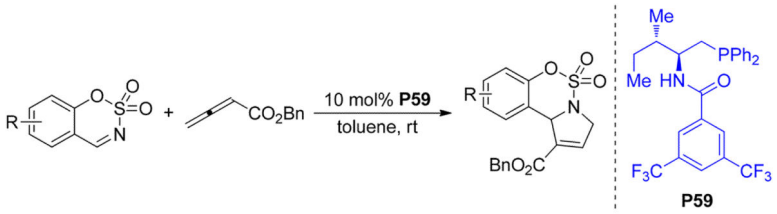
Scheme 276.
Asymmetric Formation of Pyrrolines



entry	R	yield (%)	ee (%)
1	CH_2iPr	90	95
2	CH=CHPh	81	96
3	cyclohexyl	83	99
4	Me	75	95
5	*p*-$MeOC_6H_4$	94	98
6	2-furyl	83	94

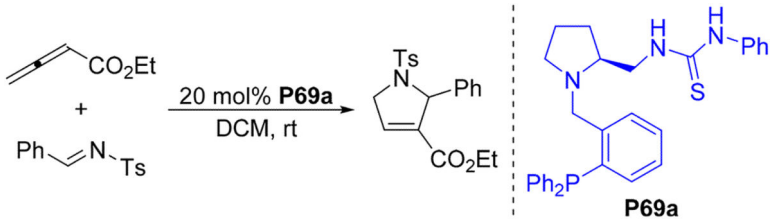
Scheme 277.

Enantioselective Synthesis of Alkyl- and Aryl- Substituted Pyrrolines



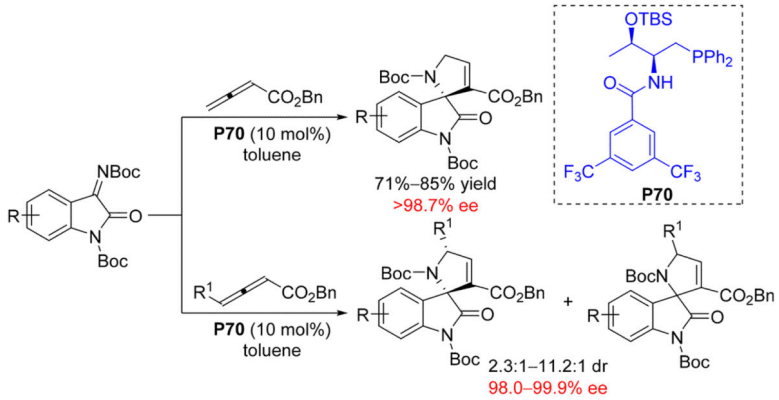
entry	R	yield (%)	ee (%)
1	H	91	90
2	8-MeO	71	98
3	8-Me	82	93
4	6-Br	77	56

Scheme 278.
Asymmetric Synthesis of Functionalized Polycyclic Sulfamidates



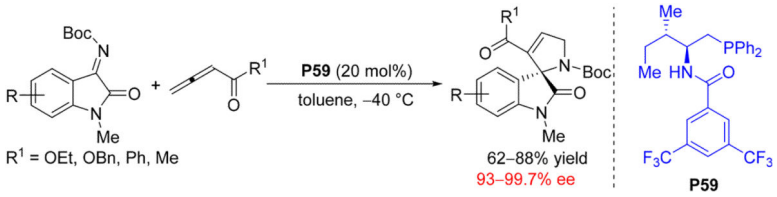
Scheme 279.

A Challenging Allene–Imine [3 + 2] Annulation



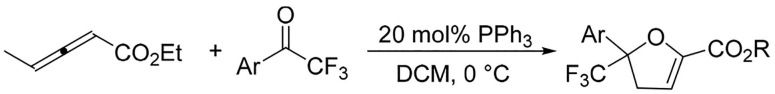
Scheme 280.

Enantioselective Phosphine-Catalyzed [3 + 2] Cycloadditions of Allenoates with Isatin-Derived Ketimines



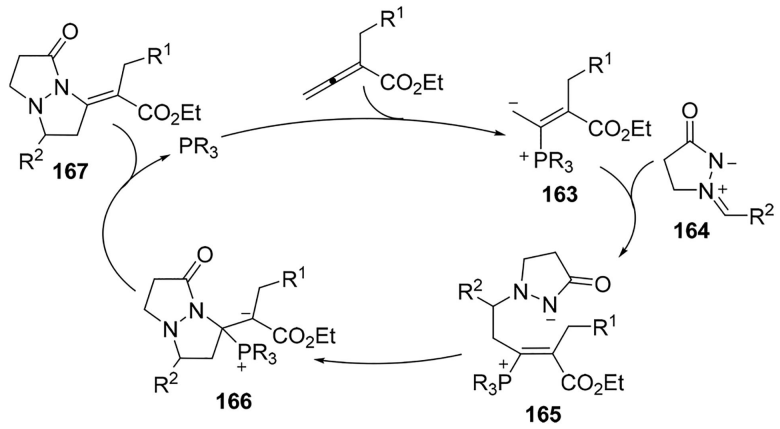
Scheme 281.

L-Isoleucine-Derived Bifunctional Phosphine-Catalyzed Asymmetric [3 + 2] Annulations of Allenyl-Esters and -Ketones with Ketimines



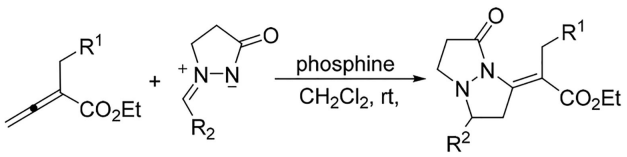
entry	R	Ar	yield (%)
1	Et	*p*-$MeOC_6H_4$	49
2	Et	*p*-ClC_6H_4	99
3	cyclohexyl	Ph	85
4	cyclohexyl	2-thienyl	54

Scheme 282.
Trifluoromethyl Ketones in Lu's [3 + 2] Annulation



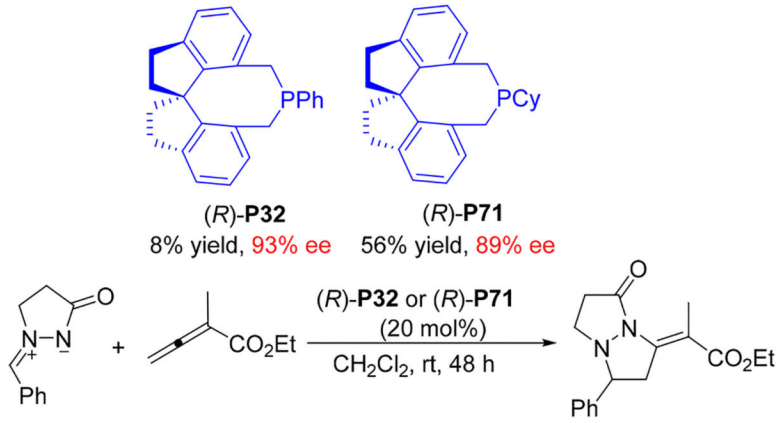
Scheme 283.

Proposed Mechanism of the Allene–Azomethine Imine [3 + 2] Annulation



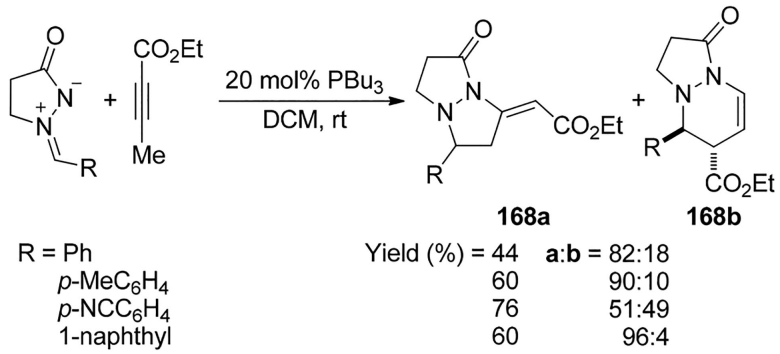
entry	R^1	R^2	phosphine	time (h)	yield (%)
1	H	*p*-$F_3CC_6H_4$	20 mol% PBu_3	24	98
2	H	*o*-$O_2NC_6H_4$	20 mol% PBu_3	24	94
3	H	2-naphthyl	20 mol% PBu_3	24	96
4	H	2-furyl	20 mol% PBu_3	20	99
5	H	cyclohexyl	20 mol% PBu_3	36	55
6	*o*-MeC_6H_4	*p*-$O_2NC_6H_4$	30 mol% PMe_3	20	95
7	*p*-FC_6H_4	*p*-$O_2NC_6H_4$	30 mol% PMe_3	15	99

Scheme 284.
Azomethine Imine–Allene [3 + 2] Annulation



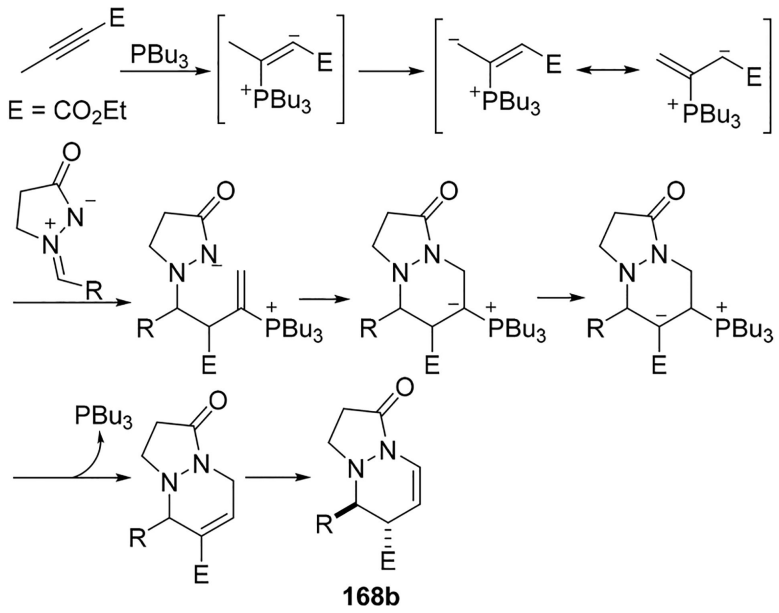
Scheme 285.

Asymmetric [3 + 2] Annulation of Azomethine Imines with Allenoates



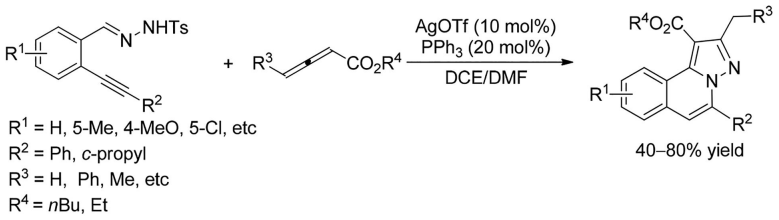
Scheme 286.

Synthesis of Functionalized Tetrahydropyrazolopyrazolones



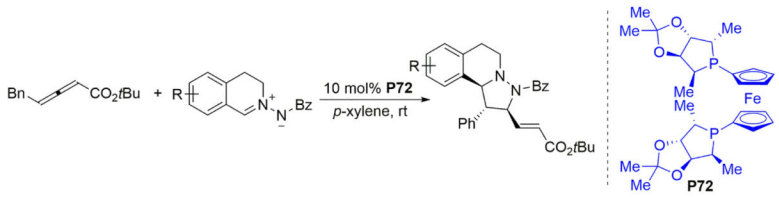
Scheme 287.

Proposed Mechanism for [3 + 3] Annulation of Azomethine Imines with Ethyl 2-Butynoate



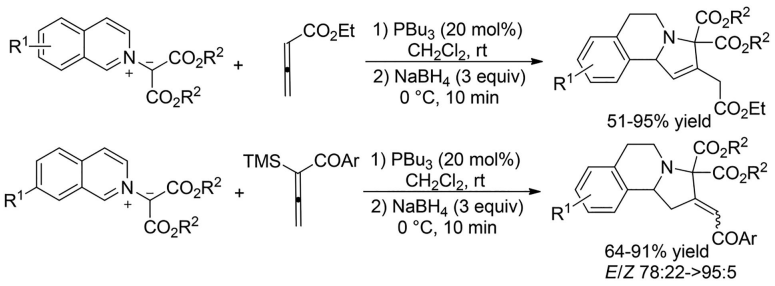
Scheme 288.

A Tandem Cyclization [3 + 2] Annulation Sequence Between *N*-(2-Alkynylbenzylidene)hydrazides and Allenoates



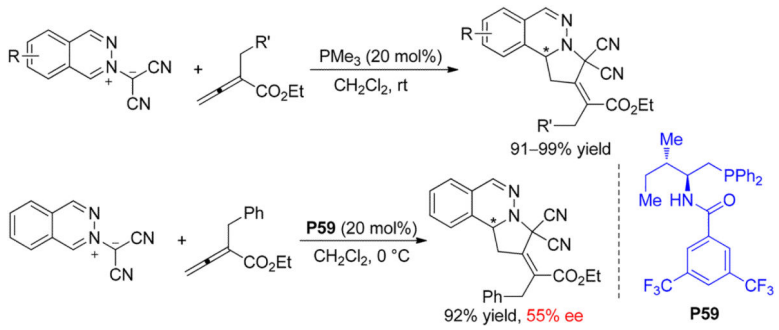
entry	R	yield (%)	ee (%)
1	H	72	82
2	7-F	92	83
3	5-Me	73	93
4	7-Br	83	80

Scheme 289.
Asymmetric Synthesis of Functionalized Polycyclic Pyrazolines



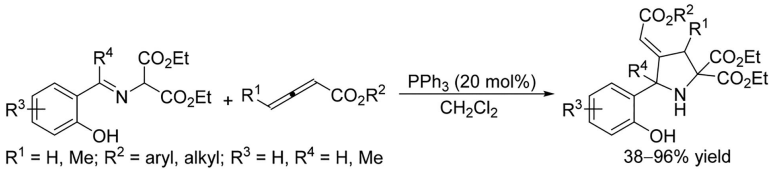
Scheme 290.

Phosphine-Catalyzed [3 + 2] Annulations of Isoquinolinium Methylides with Allenes



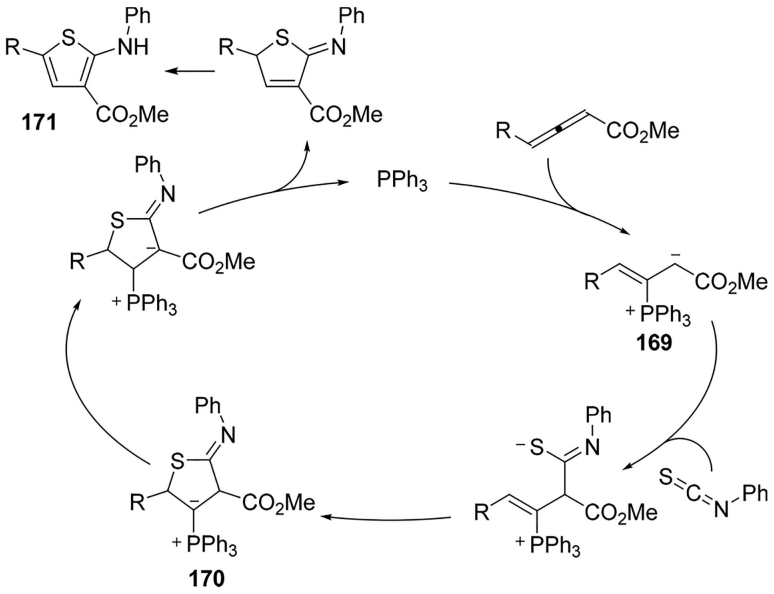
Scheme 291.

Phosphine-Catalyzed [3 + 2] Cycloadditions of Phthalazinium Dicyanomethanides with α-Substituted Allenoates



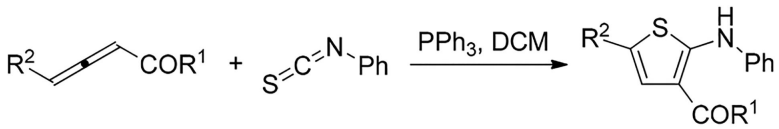
Scheme 292.

Phosphine-Catalyzed [3 + 2] Cycloadditions Between Allenoates and *o*-Hydroxyaryl Azomethine Ylides



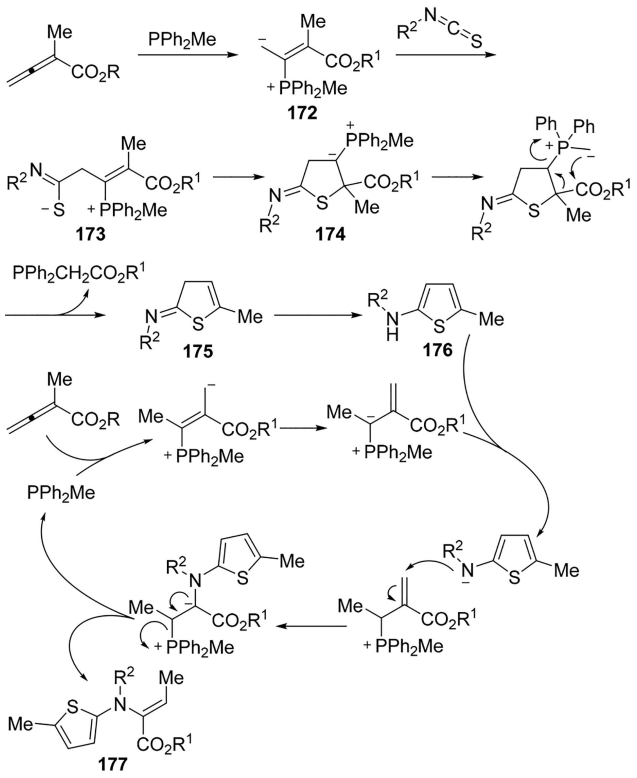
Scheme 293.

Proposed Mechanism for Phosphine-Catalyzed Thiophene Formation

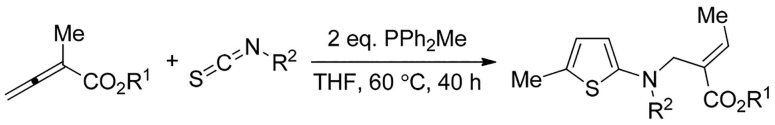


entry	R^1	R^2	mol% of PPh_3	yield (%)
1	OMe	H	100	30
2	Me	H	10	25
3	OMe	Et	50	7

Scheme 294.
Preparation of Functionalized Thiophenes

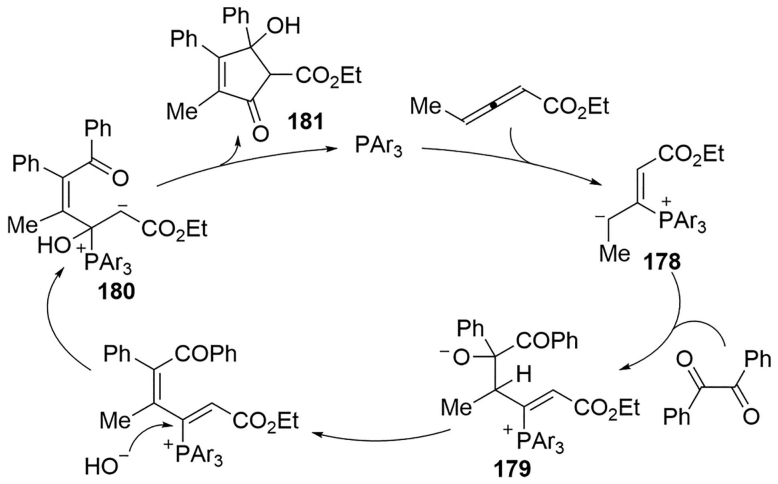


Scheme 295.
Suggested Reaction Pathway Toward 2-Aminothiophenes



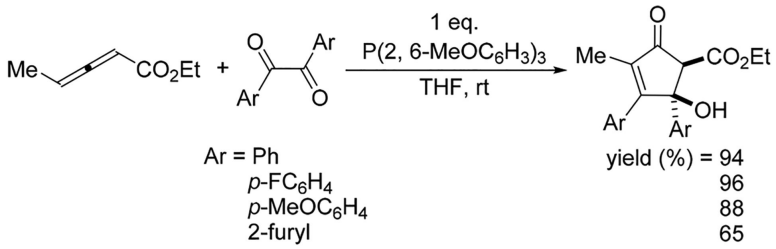
entry	R^1	R^2	yield (%)
1	Et	*p*-$MeOC_6H_4$	52
2	Et	Bn	43
3	*i*Pr	Ph	67
4	Bn	*p*-$MeOC_6H_4$	18

Scheme 296.
Synthesis of 2-Aminothiophene Derivatives



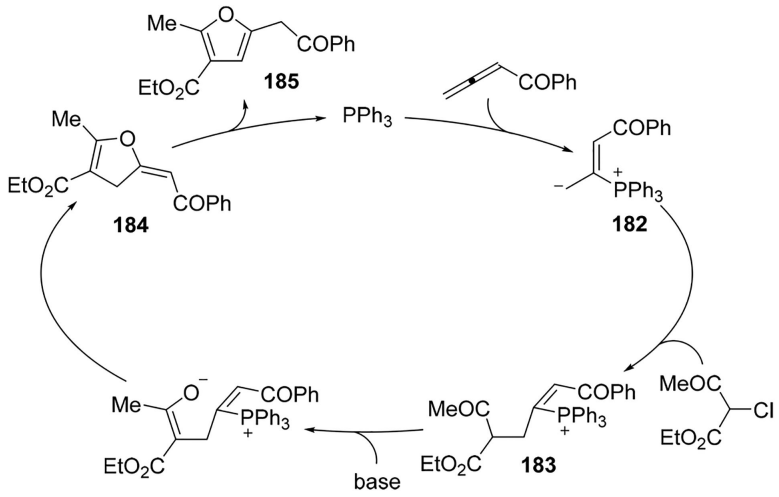
Scheme 297.

Proposed Mechanism for γ-Hydroxybutenolide Synthesis

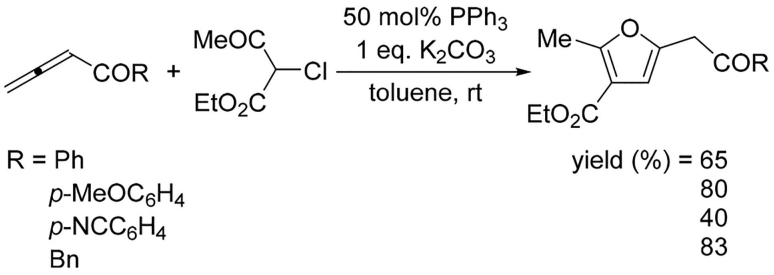


Scheme 298.

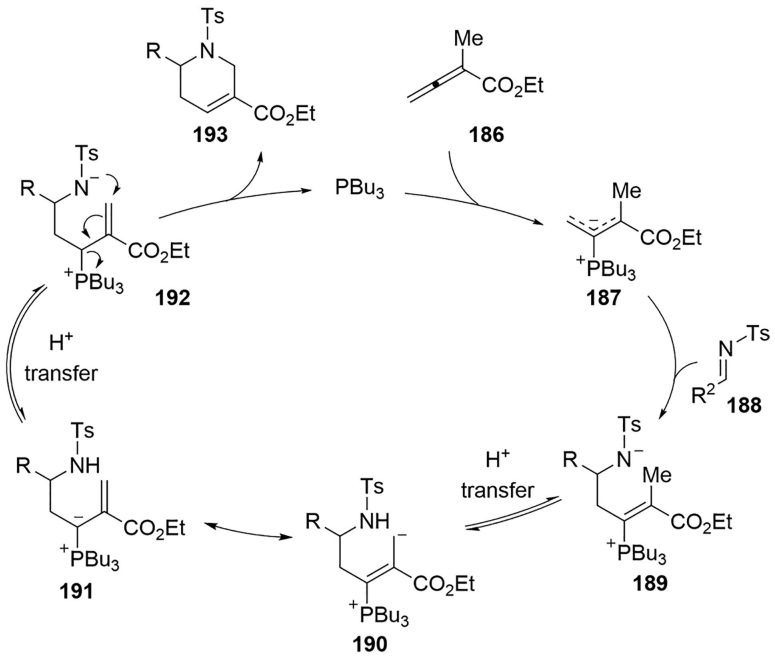
Synthesis of Functionalized γ-Hydroxybutenolides



Scheme 299.
Proposed Mechanism for the [2 + 3] Annulation

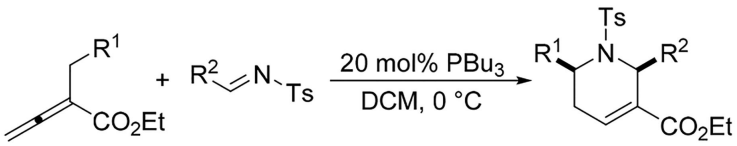


Scheme 300.
Synthesis of Functionalized Furans



Scheme 301.

Proposed Mechanism for α-Alkylallenoate–Imine [4 + 2] Annulation

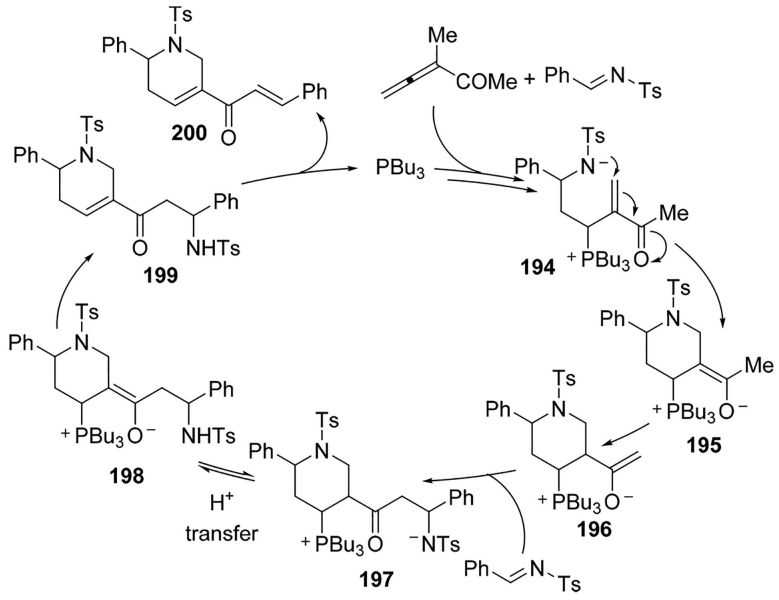


entry	R^1	R^2	yield (%)	*cis*:*trans*
1	H	Ph	98	–
2	H	*p*-$MeOC_6H_4$	99	–
3	H	*p*-$O_2NC_6H_4$	86	–
4	H	*t*Bu	86[a]	–
5	Ph	Ph	99	98:2
6	*p*-NCC_6H_4	*p*-MeC_6H_4	99	98:2
7	Ph	*p*-$O_2NC_6H_4$	90	95:5
8	*o*-MeC_6H_4	Ph	82	88:12

Scheme 302.

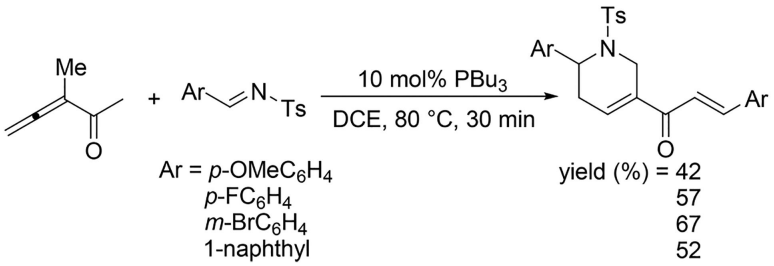
Kwon's Allene–Imine [4 + 2] Annulation

[a]Reaction performed with 3 equiv of Na_2CO_3 as additive.



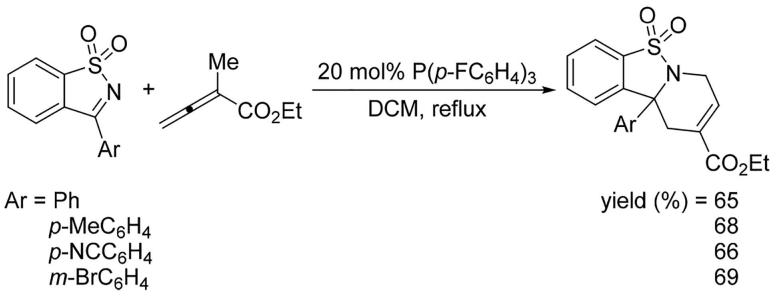
Scheme 303.

Proposed Reaction Mechanism for [4 + 2] Annulations of 3-Methyl-3,4-pentadienone with *N*-Tosyl Imines



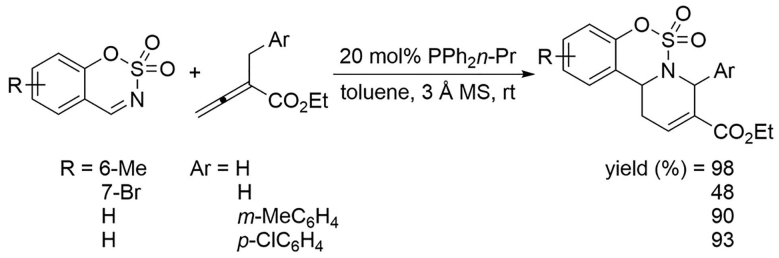
Scheme 304.

Formation of Tetrahydropyridine Derivatives



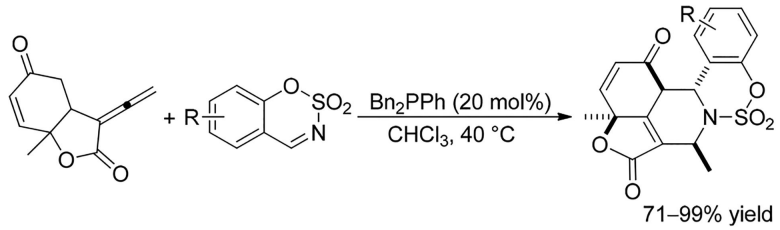
Scheme 305.

Synthesis of Functionalized Polycyclic Tetrahydropyridines



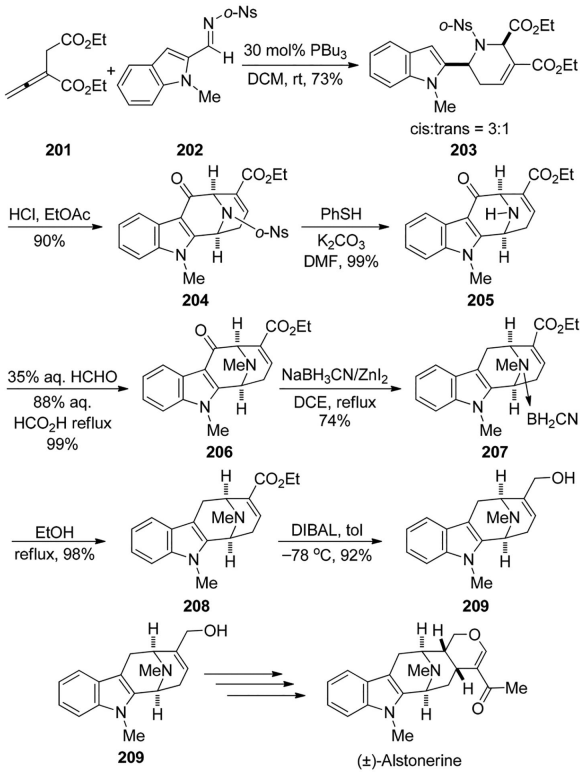
R	Ar	yield (%)
6-Me	H	98
7-Br	H	48
H	*m*-MeC_6H_4	90
H	*p*-ClC_6H_4	93

Scheme 306.
Preparation of Functionalized Tetrahydropyridines

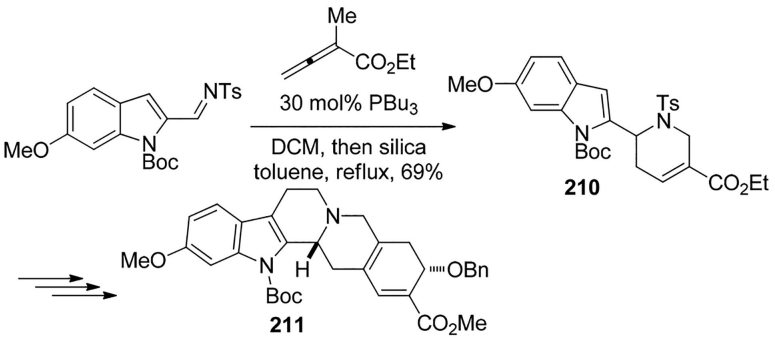


Scheme 307.

Phosphine-Catalyzed [4 + 2] Cycloadditions of Tetrahydrobenzofuranone-Derived Allenoates with Sulfamate-Derived Cyclic Imines

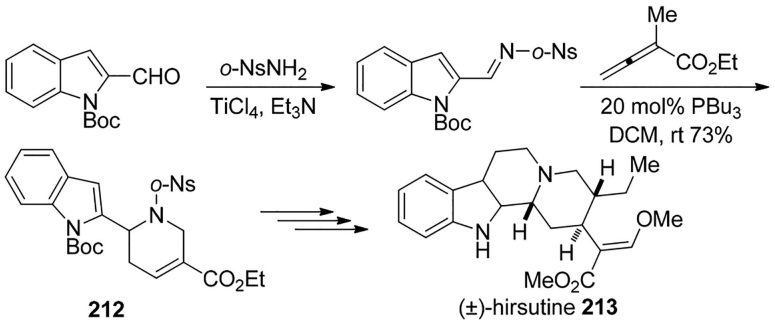


Scheme 308.
Formal Synthesis of (±)-Alstonerine

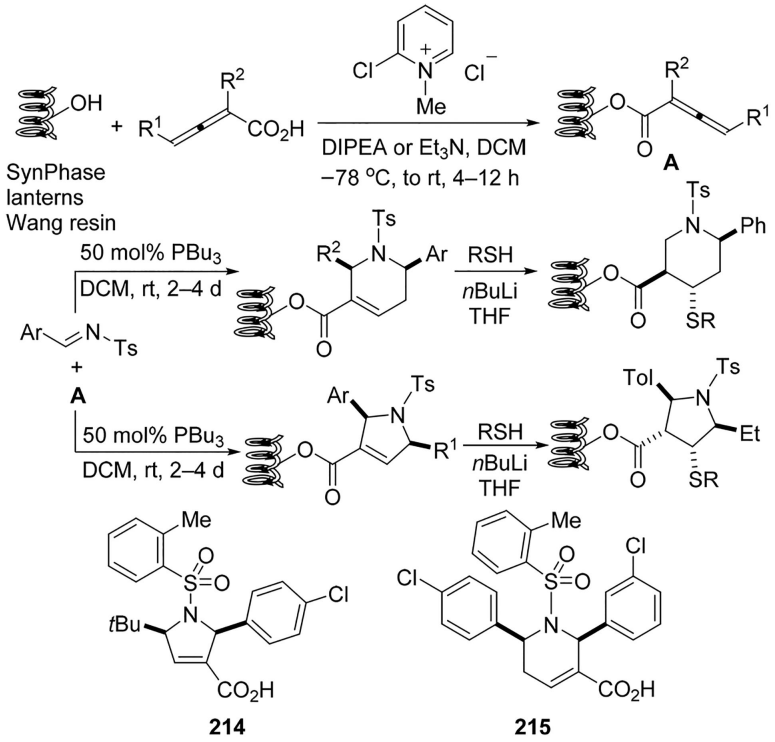


Scheme 309.

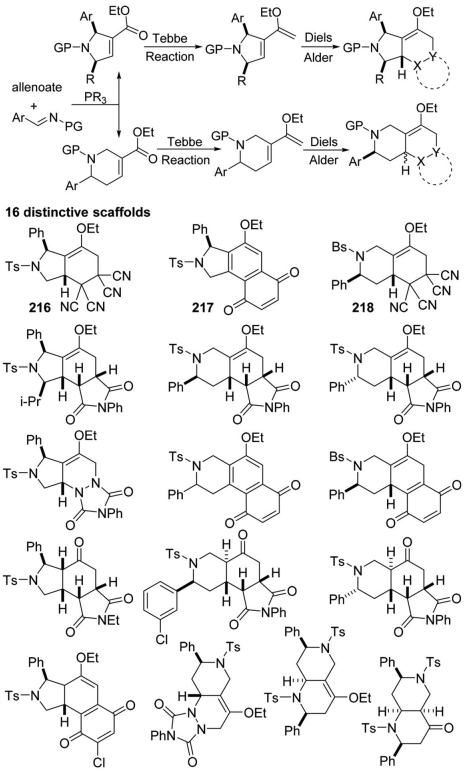
Access to the Skeletal Framework of Reserpine (211)



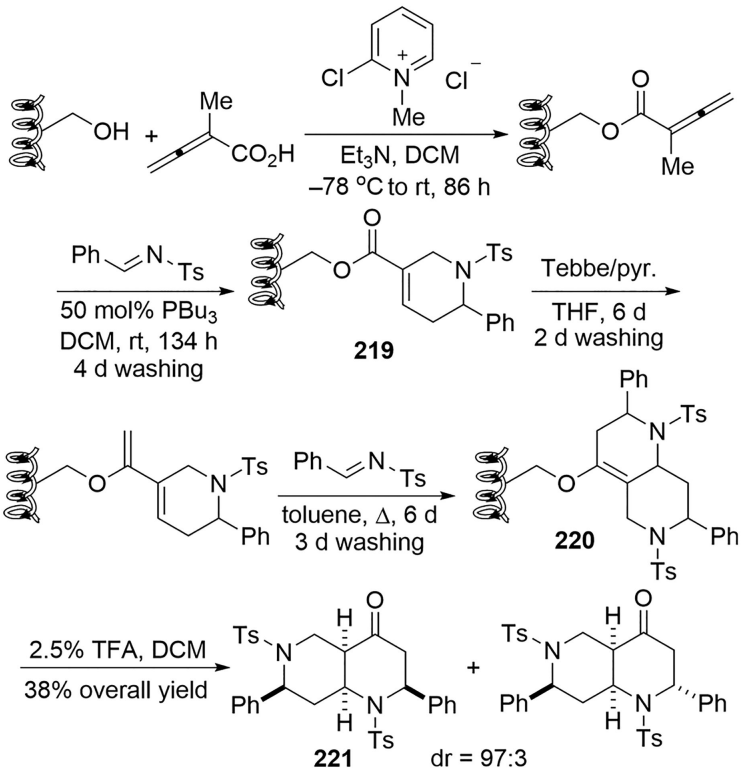
Scheme 310.
Total Synthesis of (±)-Hirsutine



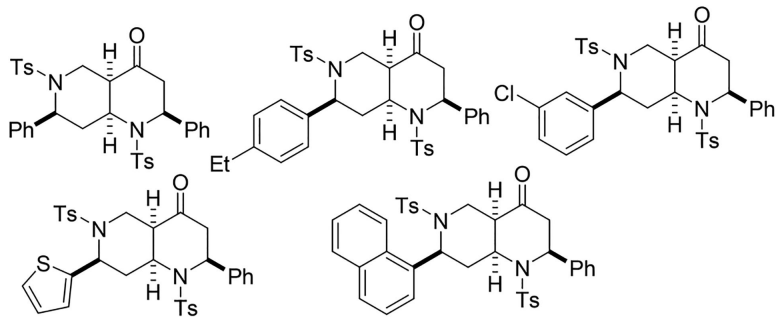
Scheme 311.
Phosphine-Catalyzed Synthesis of GGTase-I Inhibitor Libraries



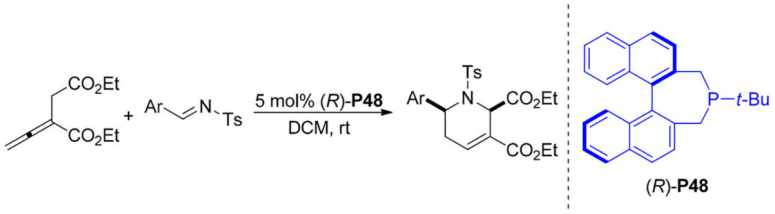
Scheme 312.
Sixteen Distinct Scaffolds in the DOS Library



Scheme 313.
Formation of Octahydro-1,6-naphthyridin-4-ones

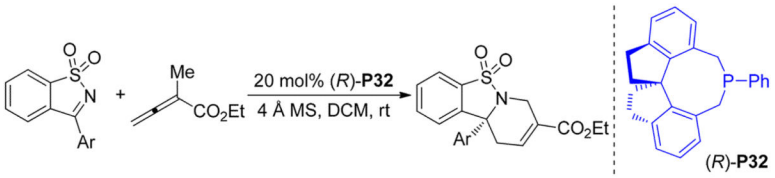


Scheme 314.
Immunoactivating Octahydro-1,6-naphthyridin-4-ones



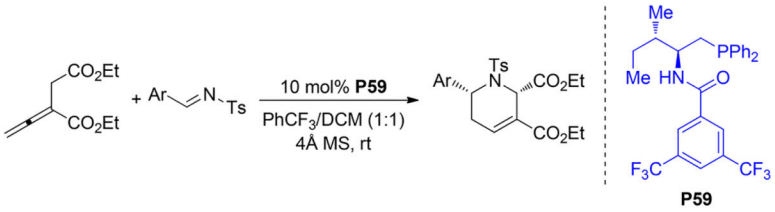
entry	Ar	yield (%)	ee (%)	*cis*:*trans*
1	Ph	93	98	91:9
2	*p*-ClC_6H_4	99	96	91:9
3	*p*-$MeOC_6H_4$	42	98	93:7
4	*o*-ClC_6H_4	75	60	76:21

Scheme 315.
Asymmetric [4 + 2] Annulations with *N*-Tosyl Imines



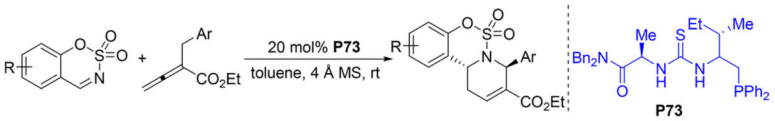
entry	Ar	yield (%)	ee (%)
1	Ph	88	90
2	*p*-$F_3CC_6H_4$	95	93
3	*m*-ClC_6H_4	87	92
4	2-pyridinyl	89	72

Scheme 316.
Asymmetric Synthesis of Functionalized Polycyclic Tetrahydropyridines



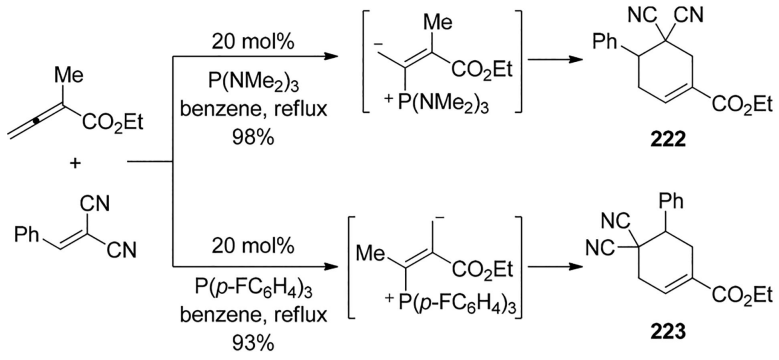
entry	Ar	dr	yield (%)	ee (%)
1	*p*-$MeOC_6H_4$	15:1	94	90
2	*o*-ClC_6H_4	4:1	88	96
3	*m*-FC_6H_4	12:1	81	95
4	2-thienyl	12:1	98	82

Scheme 317.
Enantioselective Preparation of Tetrahydropyridine Derivatives



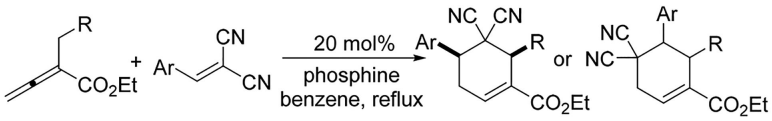
entry	R	Ar	yield (%)	ee (%)	dr
1	H	2-naphthyl	81	99	4:1
2	6-MeO	2-naphthyl	82	82	9:1
3	H	*m*-MeC_6H_4	85	81	4:1
4	H	*p*-$F_3CC_6H_4$	75	84	3:1

Scheme 318.
Asymmetric Synthesis of Functionalized Polycyclic Tetrahydropyridines



Scheme 319.

Regiodivergent α-Alkylallenoate–Alkene [4 + 2] Annulations



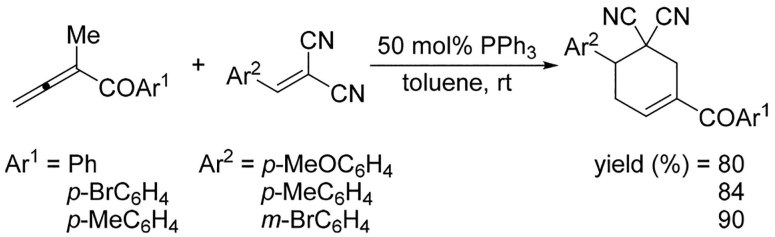
224 **225**

entry	R	Ar	phosphine	product	yield (%)
1	H	Ph	$P(NMe_2)_3$	**224**	98
2	H	*p*-$MeOC_6H_4$	$P(NMe_2)_3$	**224**	94
3	H	Ph	$P(p\text{-}FC_6H_4)_3$	**225**	93
4	H	*N*-methyl-2-indolyl	$P(p\text{-}FC_6H_4)_3$	**225**	91
5	Et	Ph	$P(NMe_2)_3$	**224**	98[a]
6	vinyl	Ph	$P(NMe_2)_3$	**224**	94[b]

Scheme 320.

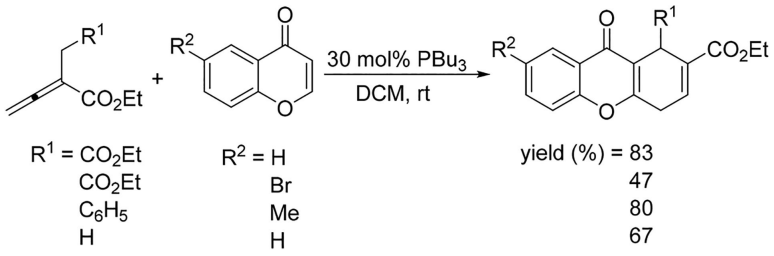
Phosphine-Catalyzed [4 + 2] Annulations Forming Cyclohexenes

[a]*cis:trans* = 92:8. [b]*cis:trans* = 91:9.

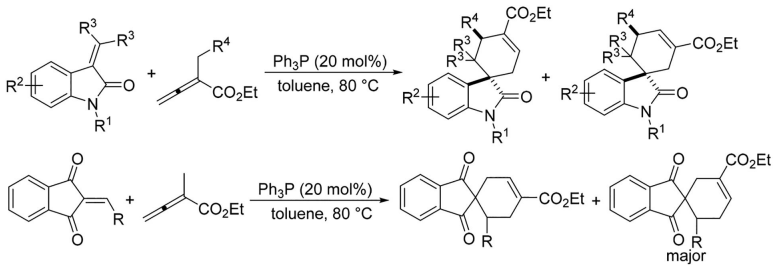


Scheme 321.

Synthesis of Cyclohexenes from Arylallenones



Scheme 322.
Formation of Tricyclic Benzopyrone Derivatives

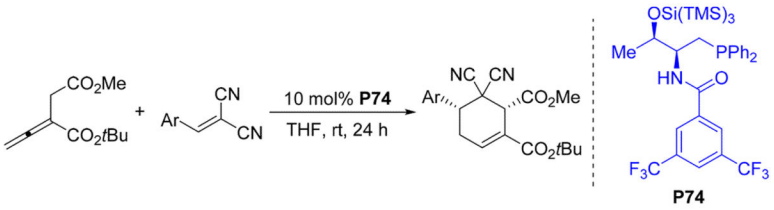


Scheme 323.

Phosphine-Catalyzed [4 + 2] Annulations of α-Substituted Allenoates with Isatin-Derived Alkenes and Indan-1,3-dione-Derived Alkenes

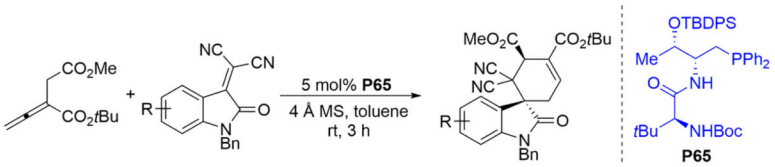
Scheme 324.

Nucleophilic Bisphosphine-Catalyzed One-Pot Sequential [4 + 2]/[4 + 2] Annulations of an Allenoate with Benzylidenepyrazolones



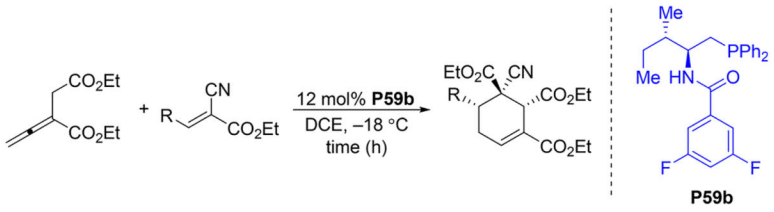
entry	Ar	yield (%)	ee (%)	cis:trans
1	*m*-ClC_6H_4	96	99	85:15
2	*p*-$MeOC_6H_4$	89	95	83:17
3	2-furyl	86	93	60:40
4	2-thienyl	93	97	79:21
5	2-naphthyl	94	97	87:13

Scheme 325.
Preparation of Optically Pure Cyclohexenes



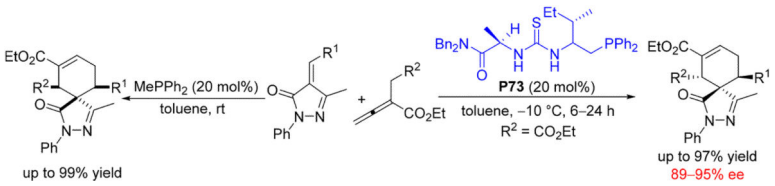
entry	R	yield (%)	ee (%)	dr
1	7-Cl	96	92	98:2
2	5-MeO	92	91	95:5
3	5-Me	91	91	96:4
4	8-Br	91	90	95:5
5	5,7-Me	95	89	99:1

Scheme 326.
Asymmetric Synthesis of 3-Spirocyclohexene-2-oxindoles



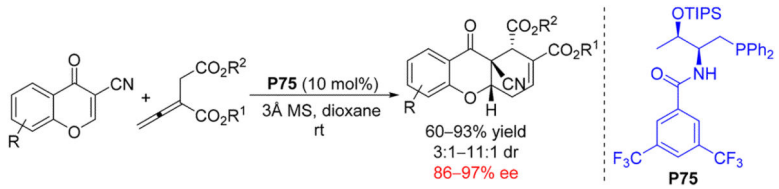
entry	R	time (h)	yield (%)	ee (%)
1	Ph	4	94	96
2	*p*-ClC_6H_4	6	99	97
3	*p*-$MeOC_6H_4$	2.5	96	95
4	2-thienyl	4	87	93
5	*i*Pr	3	92	97

Scheme 327.
Enantioselective Preparation of Tetrahydropyridines



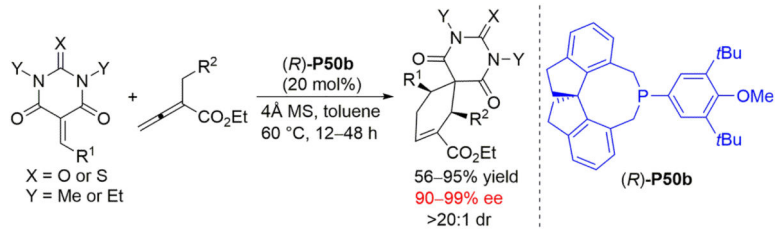
Scheme 328.

Phosphine-Catalyzed [4 + 2] Cycloadditions of Unsaturated Pyrazolones with Allenoates



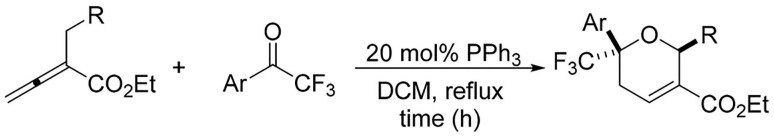
Scheme 329.

Enantioselective Phosphine-Catalyzed [4 + 2] Cycloaddition of α-Substituted Allenoates with 3-Cyano-chromones



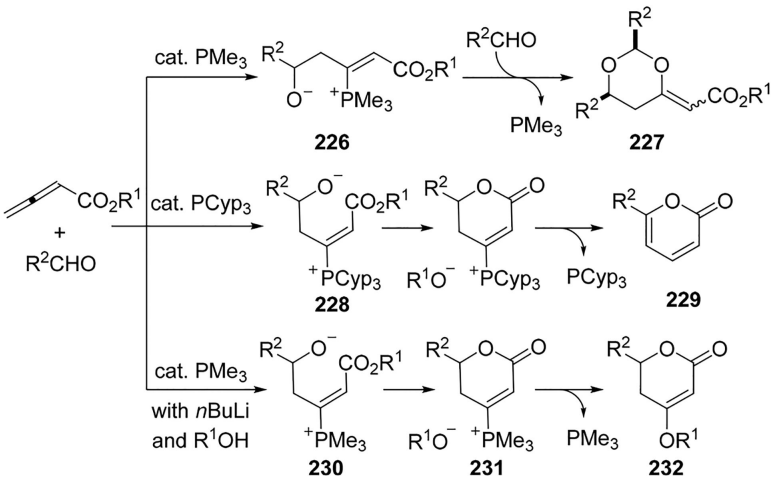
Scheme 330.

Enantioselective Phosphine-Catalyzed [4 + 2] Cycloadditions of Barbiturate-Derived Alkenes and α-Substituted Allenoates

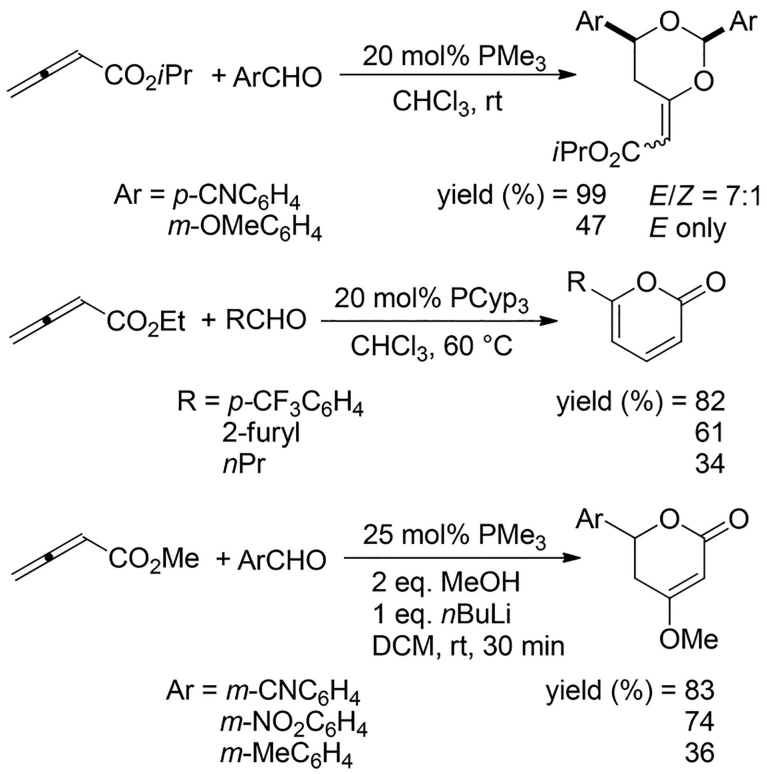


entry	R	Ar	time (h)	yield (%)
1	*p*-MeC_6H_4	Ph	66	75
2	*p*-BrC_6H_4	Ph	92	69
3	Ph	*p*-ClC_6H_4	84	85
4	Ph	2-thienyl	84	58
5	H	Ph	–	no reaction
6	CO_2Et	Ph	–	trace

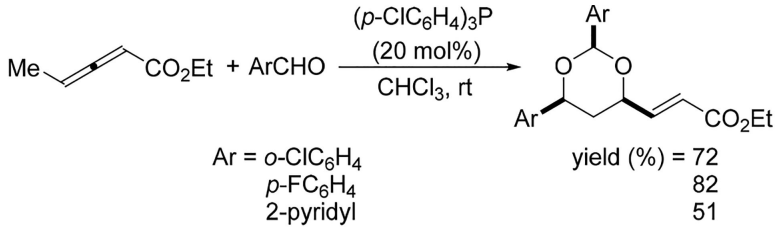
Scheme 331.
Allene–Trifluoromethyl Ketone [4 + 2] Annulation



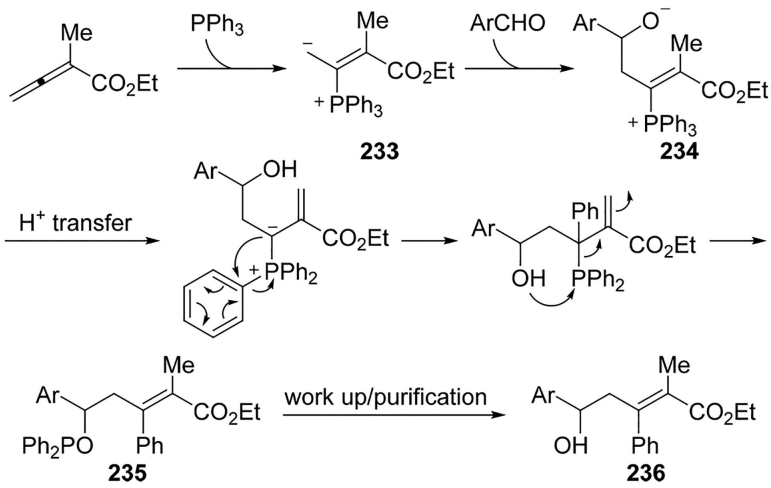
Scheme 332.
Formation of Pyrones, Dihydropyrones, and Dioxanes



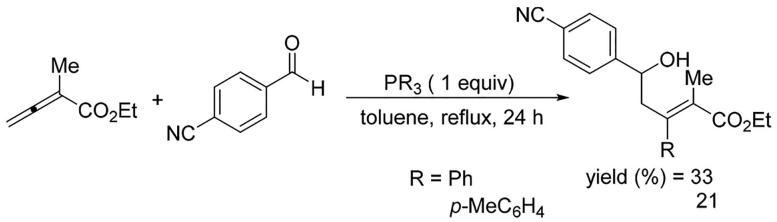
Scheme 333.
Synthesis of Pyrones, Dihydropyrones, and Dioxanes



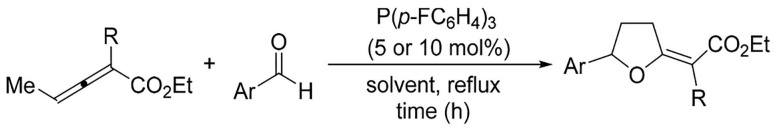
Scheme 334.
Synthesis of Functionalized Dioxanes



Scheme 335.
Speculated Phosphine-Mediated Vinylogous Aldol Pathway

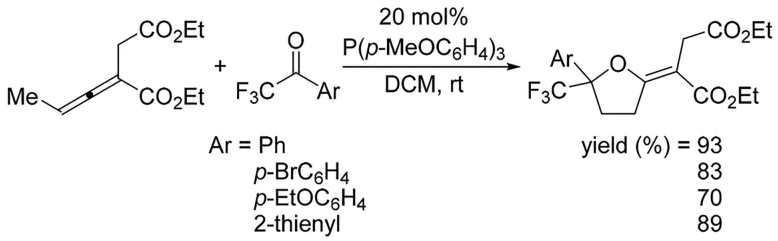


Scheme 336.
Formation of a Vinylogous Aldol Product



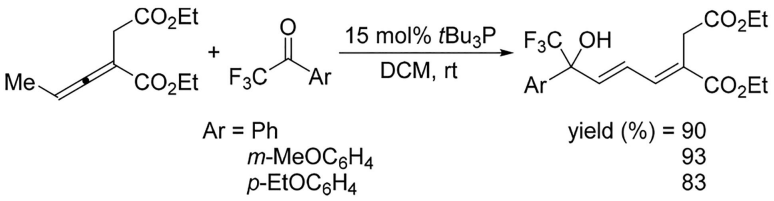
entry	R	Ar	solvent	time (h)	yield (%)	*E*/*Z*
1	H	*p*-$O_2NC_6H_4$	xylene	5	84	5:1
2	H	*p*-MeC_6H_4	xylene	48	31	2:1
3	H	*o*-$F_3CC_6H_4$	xylene	12	76	20:1
4	H	3-pyridyl	xylene	5	81	20:1
5	Me	*m*-$O_2NC_6H_4$	EtOH	35	68	1:1

Scheme 337.
Formation of Functionalized Tetrahydrofurans



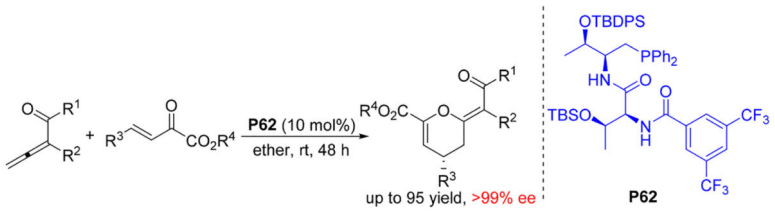
Scheme 338.

Synthesis of Functionalized Tetrahydrofurans



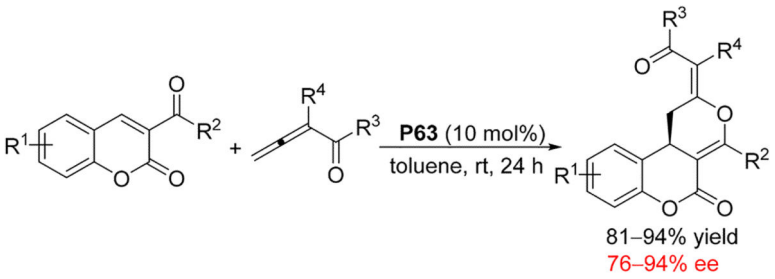
Scheme 339.

Synthesis of Functionalized 2,4-Dienoates



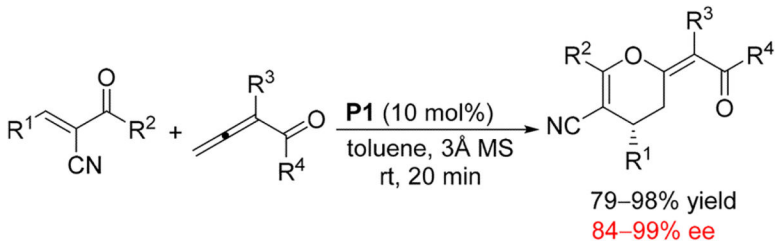
Scheme 340.

Phosphine-Catalyzed [4 + 2] Cycloadditions of Allene Ketones with β,γ-Unsaturated α-Keto Esters



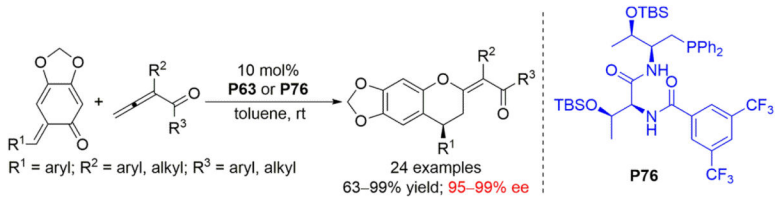
Scheme 341.

Enantioselective Phosphine-Catalyzed [4 + 2] Cycloadditions of α-Substituted Allenones with 3-Aroylcoumarins



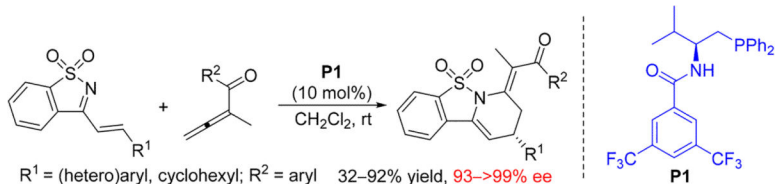
Scheme 342.

Enantioselective Phosphine-Catalyzed [4 + 2] Cycloadditions of Oxadienes with Allenones



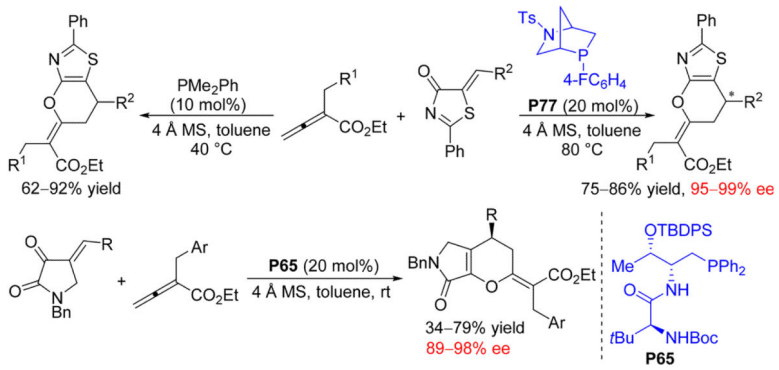
Scheme 343.

Phosphine-Catalyzed Highly Enantioselective [4 + 2] Annulations of *ortho*-Quinone Methides with Allene Ketones



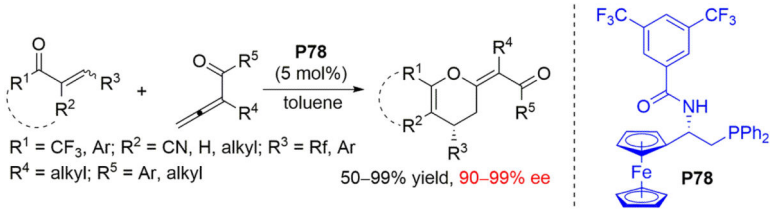
Scheme 344.

Novel Enantioselective Phosphine-Catalyzed [4 + 2] Annulations Between Allene Ketones and 1-Azadienes



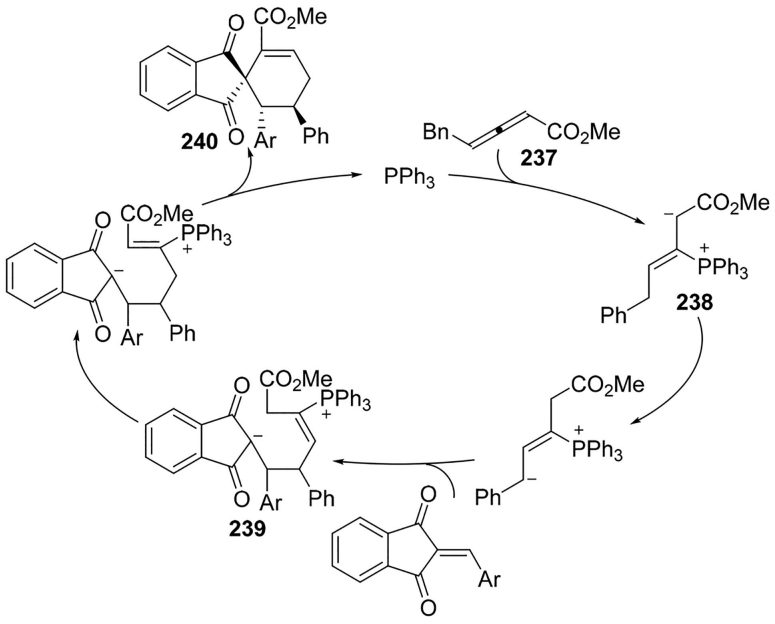
Scheme 345.

Phosphine-Catalyzed [4 + 2] Cycloadditions of Thiazolone-Derived Alkenes and (*E*)-1-Benzyl-4-olefinicpyrrolidine-2,3-diones with α-Substituted Allenoates



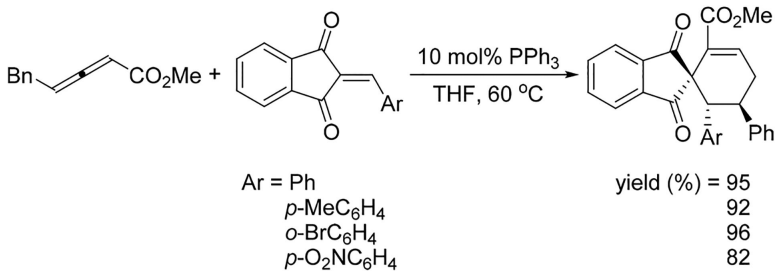
Scheme 346.

Ferrocene-Derived Bifunctional Phosphine-Catalyzed Asymmetric Oxa-[4 + 2] Cycloadditions of α-Substituted Allenones with Enones



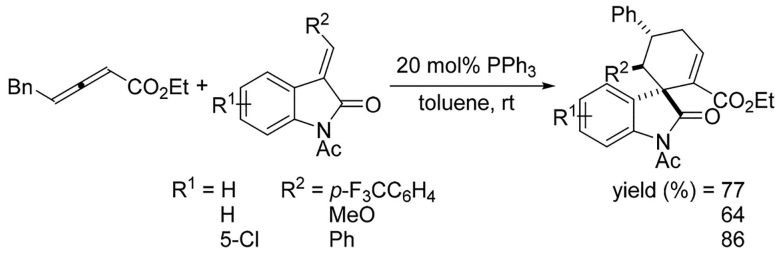
Scheme 347.

Proposed Mechanism of an Unusual Allene–Alkene [4 + 2] Annulation

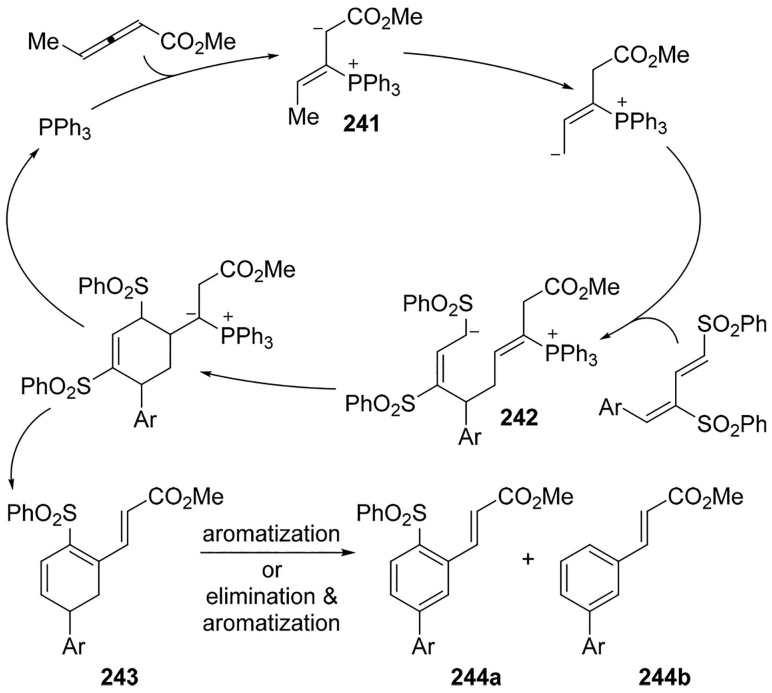


Scheme 348.

Synthesis of Functionalized Spirocyclohexenes

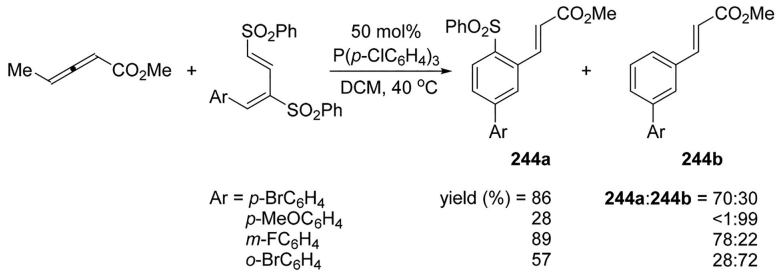


Scheme 349.
Formation of Functionalized Spirocyclohexenes



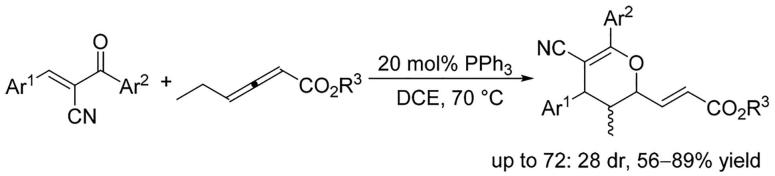
Scheme 350.

Proposed Mechanism for δ-Addition–γ-Umpolung Reaction



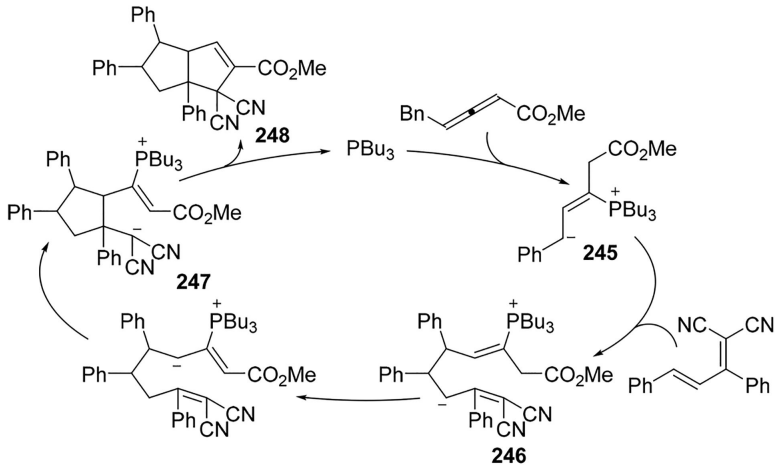
Scheme 351.

Synthesis of Functionalized Biaryl Compounds



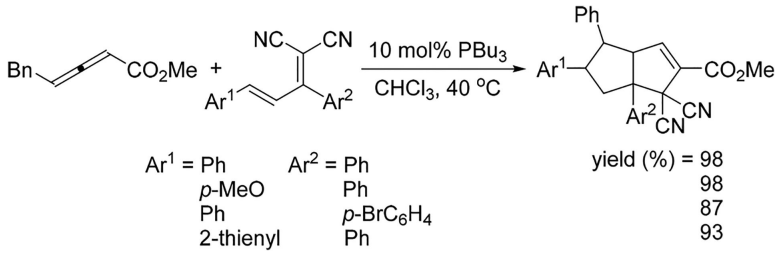
Scheme 352.

Phosphine-Catalyzed [4 + 2] Cycloadditions of α-Cyano-α,β-unsaturated Ketones with γ-Ethyl Allenoates



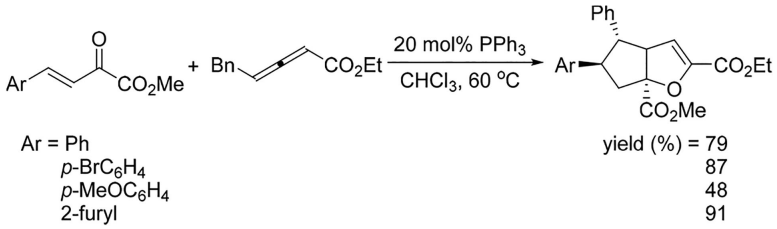
Scheme 353.

Proposed Mechanism of the [2 + 3]/[3 + 2] Domino Reaction



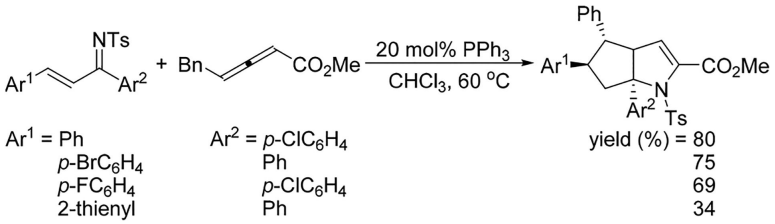
Scheme 354.

Synthesis of Functionalized Bicyclo[3.3.0]octenes



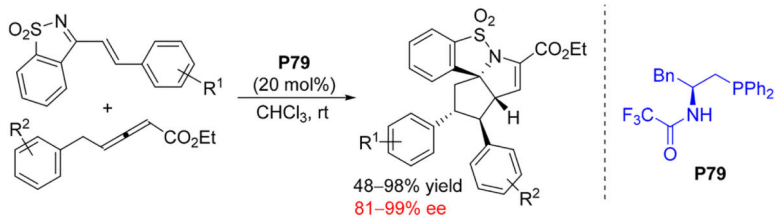
Scheme 355.

Synthesis of Functionalized Oxa-bicyclo[3.3.0]octenes



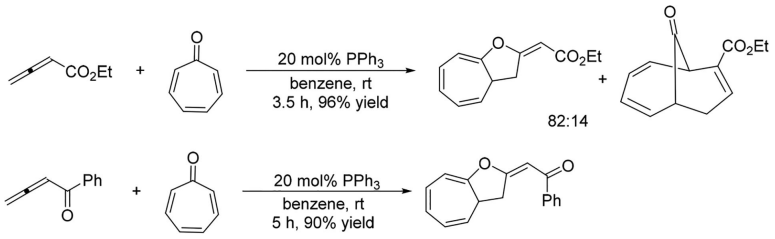
Scheme 356.

Synthesis of Functionalized Aza-bicyclo[3.3.0]octenes

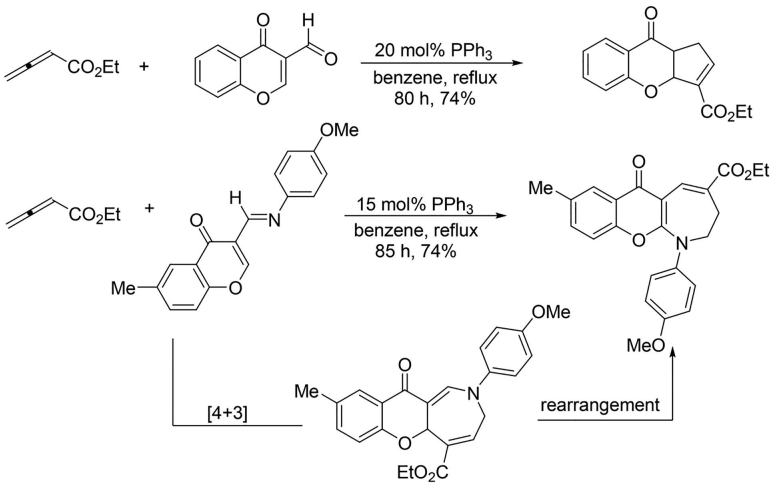


Scheme 357.

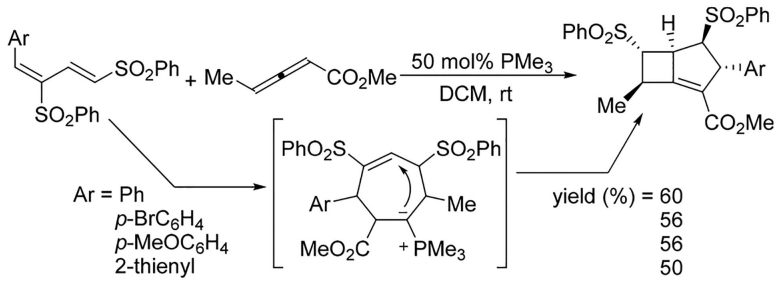
Enantioselective Phosphine-Catalyzed Sequential [3 + 2]/[3 + 2] Cycloadditions of γ-Substituted Allenoates and Saccharin-Derived Ketimines



Scheme 358.
Unusual [8 + 2] Annulations

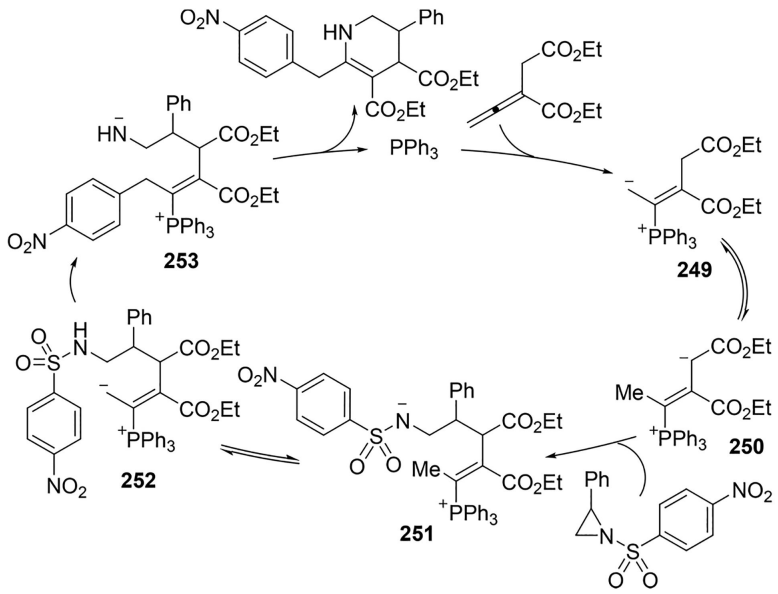


Scheme 359.
Formal [4 + 3] Annulations



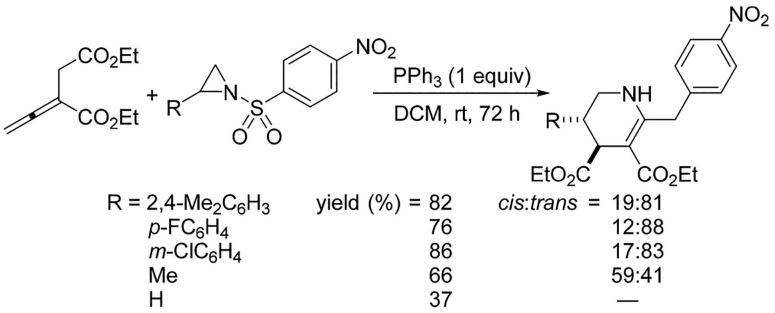
Scheme 360.

Synthesis of Functionalized Bicyclo[3.2.0]heptenes



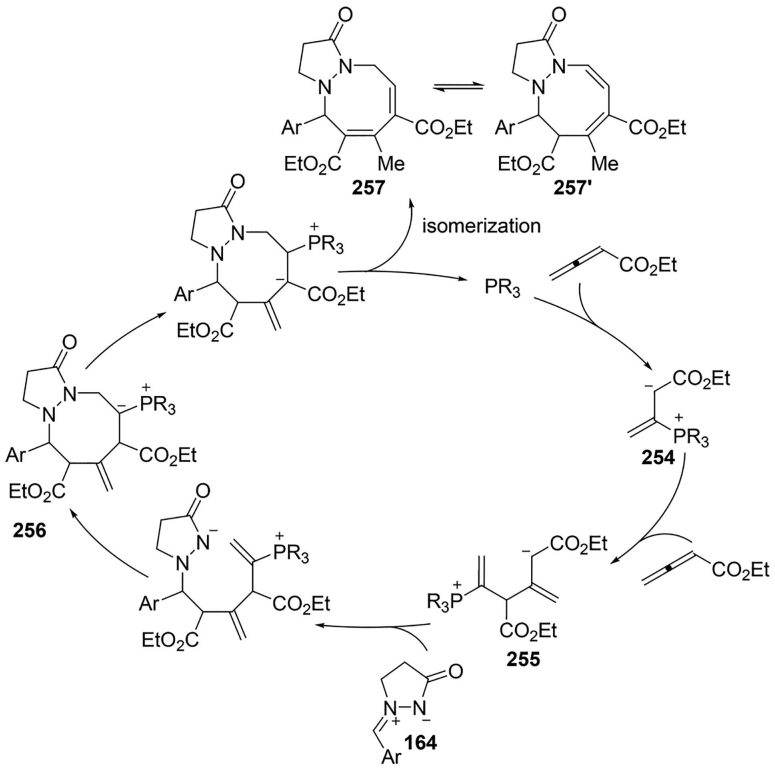
Scheme 361.

Proposed Mechanism for the Allene–Aziridine [3 + 3] Annulation

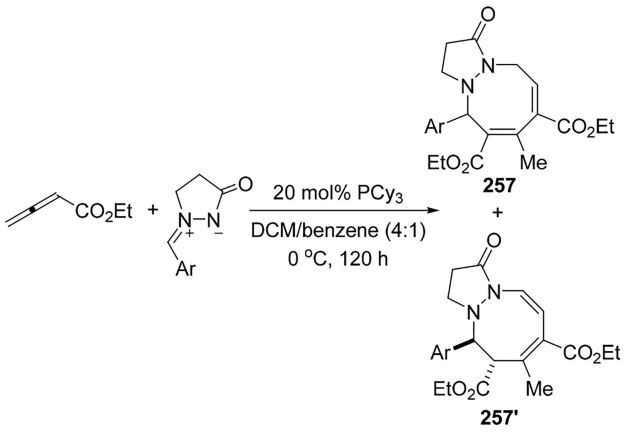


R = 2,4-$Me_2C_6H_3$	yield (%) = 82	*cis*:*trans* = 19:81
p-FC_6H_4	76	12:88
m-ClC_6H_4	86	17:83
Me	66	59:41
H	37	—

Scheme 362.
[3 + 3] Annulations of Tetrahydropyridines

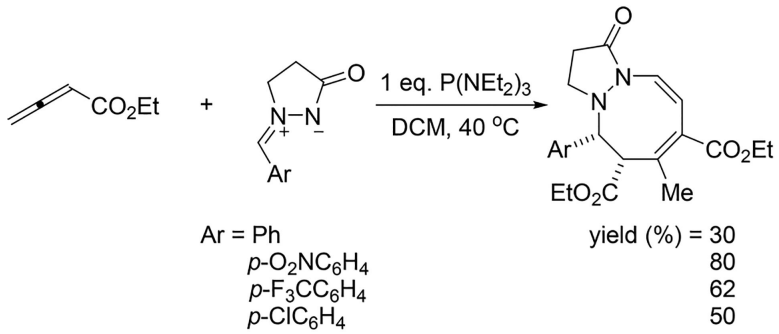


Scheme 363.
Proposed Mechanism for [3 + 2 + 3] Annulation



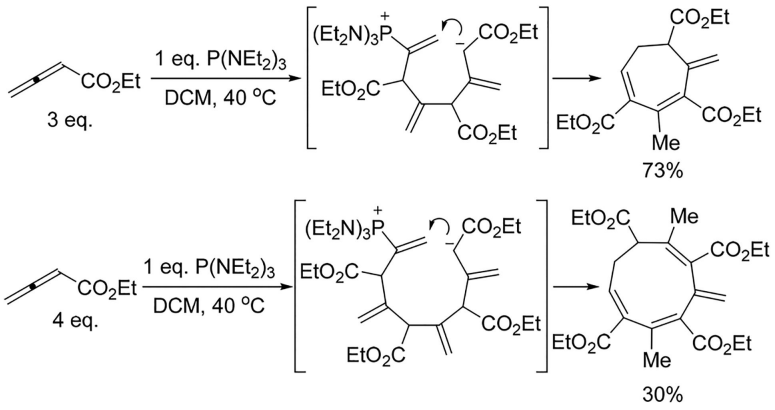
entry	Ar	yield (%)	**257**:**257'**
1	Ph	81	66:34
2	*p*-$MeOC_6H_4$	76	56:44
3	*o*-BrC_6H_4	92	72:28
4	*o*-$O_2NC_6H_4$	73	91:9
5	2-naphthyl	76	68:32

Scheme 364.
Azomethine Imine [3 + 2 + 3] Annulations

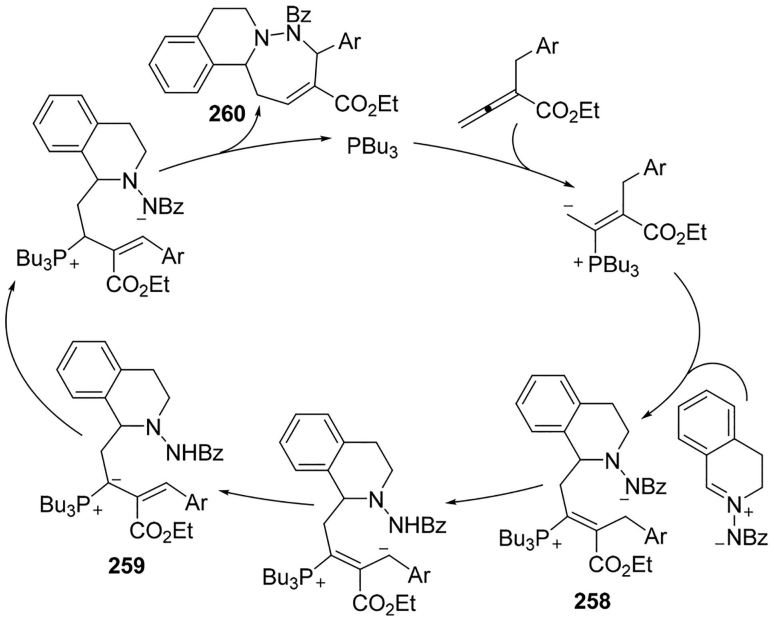


Scheme 365.

Synthesis of Functionalized Tetrahydropyrazolodiazocinones

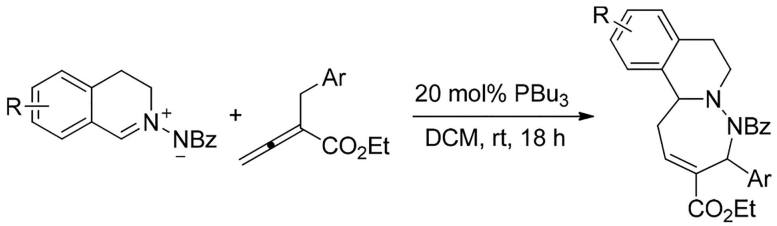


Scheme 366.
Synthesis of Allenoate Oligomers



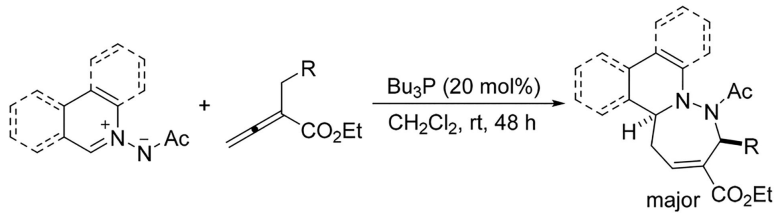
Scheme 367.

Proposed Reaction Mechanism for the Preparation of Hexahydrodiazepinoisoquinolines



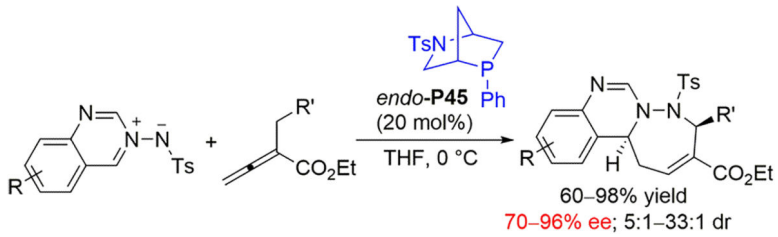
entry	R	Ar	yield (%)
1	H	Ph	90
2	H	*p*-FC_6H_4	92
3	H	*p*-MeC_6H_4	71
4	5-Me	Ph	73
5	7-Br	Ph	62

Scheme 368.
Preparation of Functionalized Hexahydrodiazepinoisoquinolines



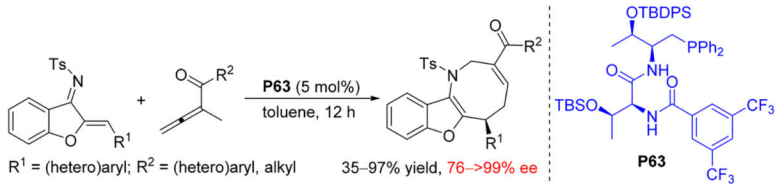
Scheme 369.

Phosphine-Catalyzed [4 + 3] Cycloaddition of *C,N*-Cyclic Aromatic Azomethine Imines with Allenoates



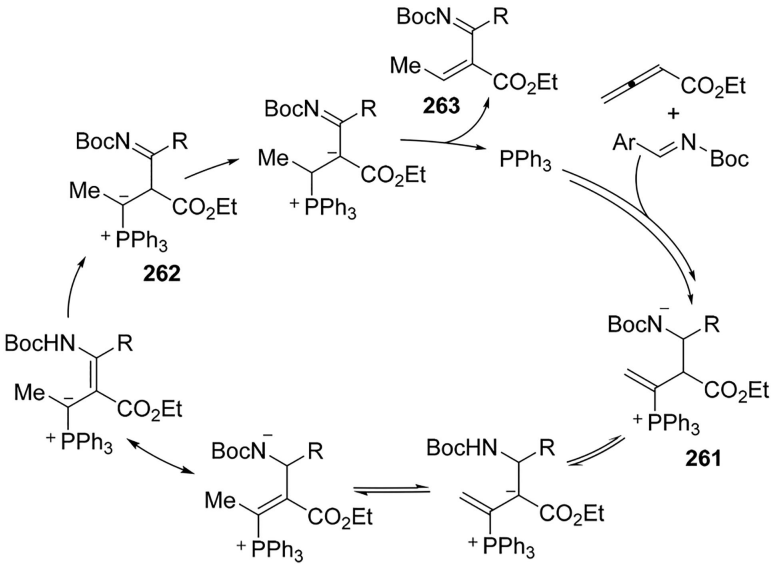
Scheme 370.

Phosphine-Catalyzed Enantioselective [4 + 3] Cycloadditions of Allenoates with Azomethine Imines

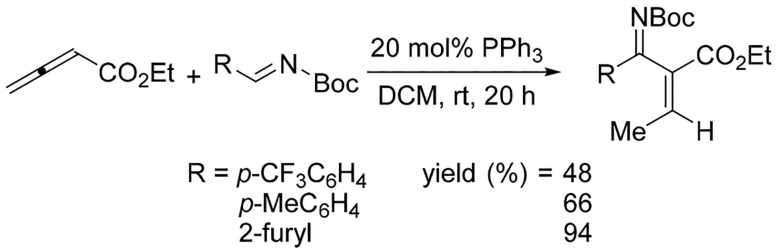


Scheme 371.

Enantioselective Phosphine-Catalyzed Formal [4 + 4] Annulation of α,β-Unsaturated Imines and Allene Ketones

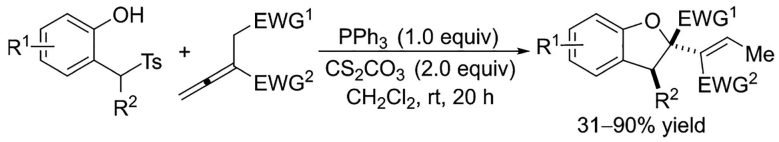


Scheme 372.
Proposed Mechanism for Azadiene Formation



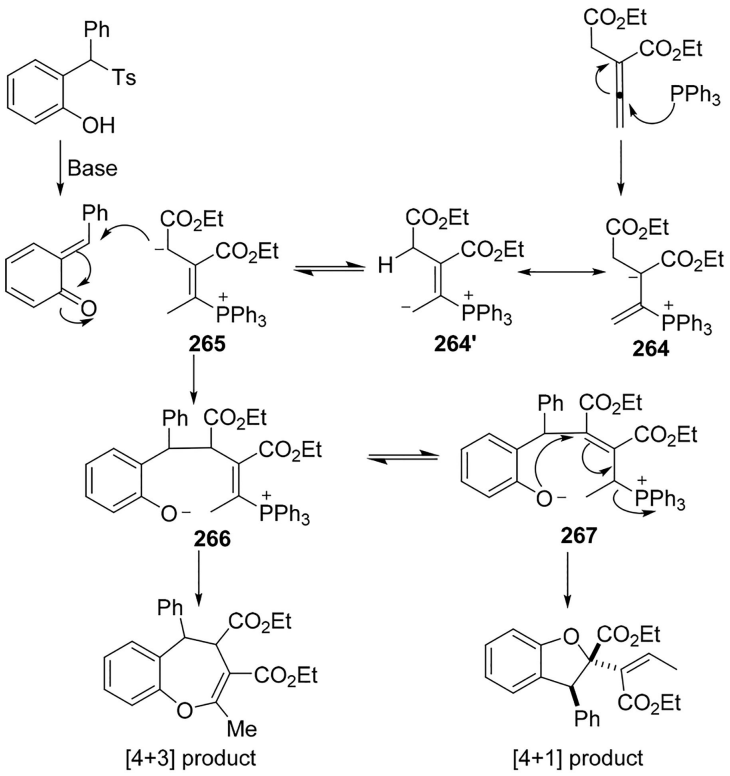
R =	yield (%) =
p-$CF_3C_6H_4$	48
p-MeC_6H_4	66
2-furyl	94

Scheme 373.
Formation of Functionalized Azadienes

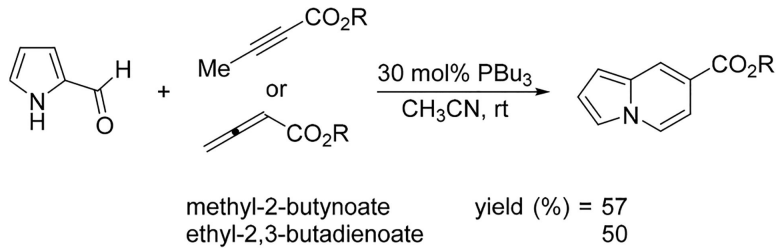


Scheme 374.

Ph_3P-Mediated [4 + 1] Annulation of Allenoates with *o*-Quinone Methides



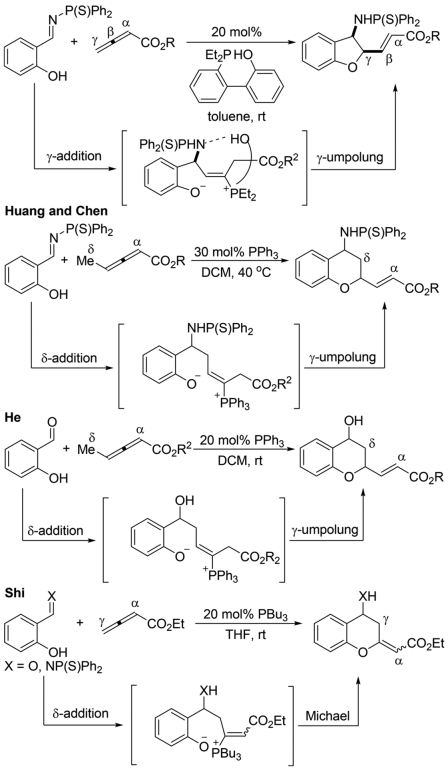
Scheme 375.
Proposed Mechanism for the [4 + 1] Annulation



methyl-2-butynoate	yield (%) = 57
ethyl-2,3-butadienoate	50

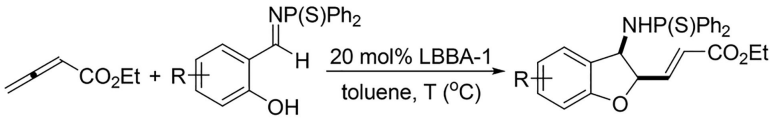
Scheme 376.

γ-Umpolung–Aldol Condensation Reactions



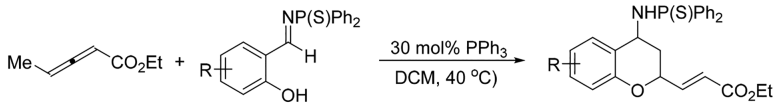
Scheme 377.

Reaction Pathways for Allene–Salicylaldehyde/Imine Annulations



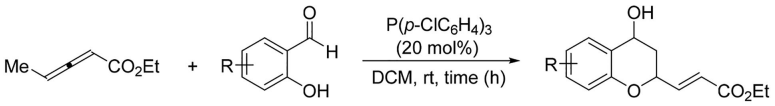
entry	R	T (°C)	time (h)	yield (%)
1	5-*t*Bu	rt	6	88
2	3,5-*t*Bu$_2$	rt	1	95
3	5-Br	50	12	72
4	3-Cl	50	12	65

Scheme 378.
Formation of Dihydrobenzofurans



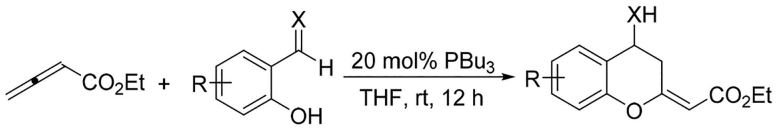
entry	R	time (h)	cis/trans	yield (%)
1	5-OMe	2	3:1	92
2	3-Cl	6	>20:1	83
3	5-NO_2	6	-	0

Scheme 379.
Formation of Aminochromans



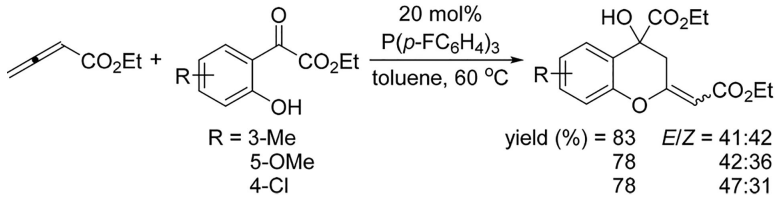
entry	R	time (h)	cis/trans	yield (%)
1	5-OMe	15	1:2.4	85
2	5-Cl	44	1:1.8	62
3	5-NO_2	148	-	trace

Scheme 380.
Formation of Hydroxychromans

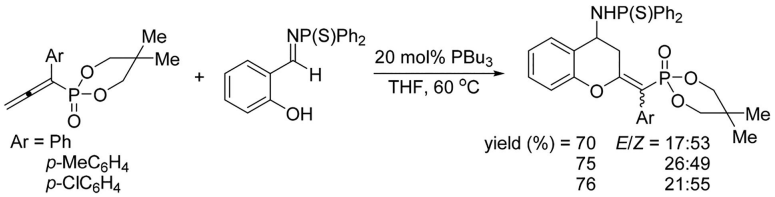


X=	R =	yield (%) =	*E*/*Z* =
NP(S)Ph$_2$	3-Me	81	61:20
O	3-OMe	95	*E* only
O	3,5-di-Br	15	*E* only
O	4-OMe	23	*E* only

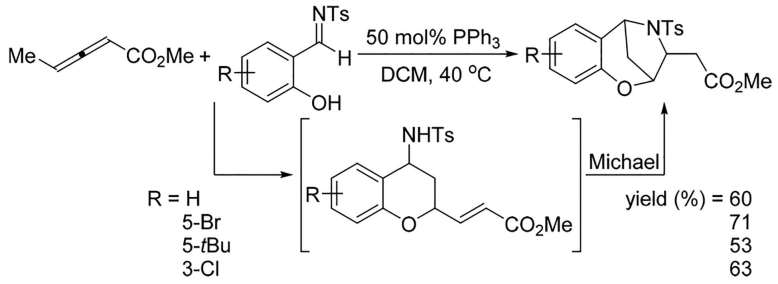
Scheme 381.
Formation of Amino- and Hydroxychromans



Scheme 382.
Synthesis of Functionalized Hydroxychromans

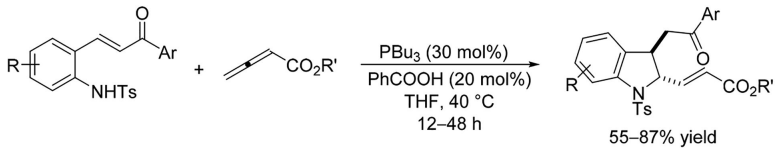


Scheme 383.
Synthesis of Functionalized Aminochromans



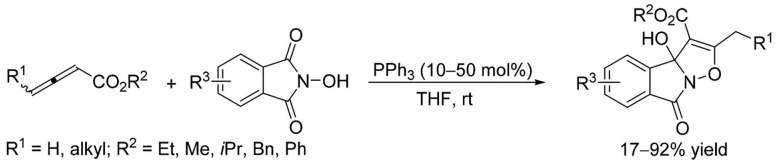
Scheme 384.

Synthesis of Functionalized Benzoxazepines



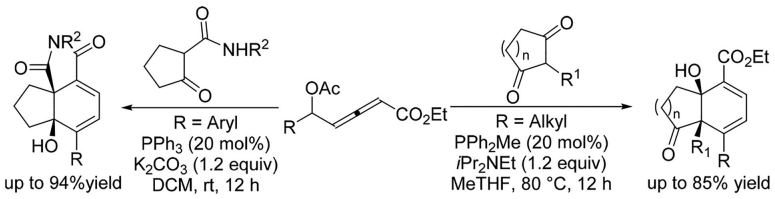
Scheme 385.

Phosphine-Catalyzed [4 + 1] Annulation of 2-Tosylaminochalcones with Allenoates



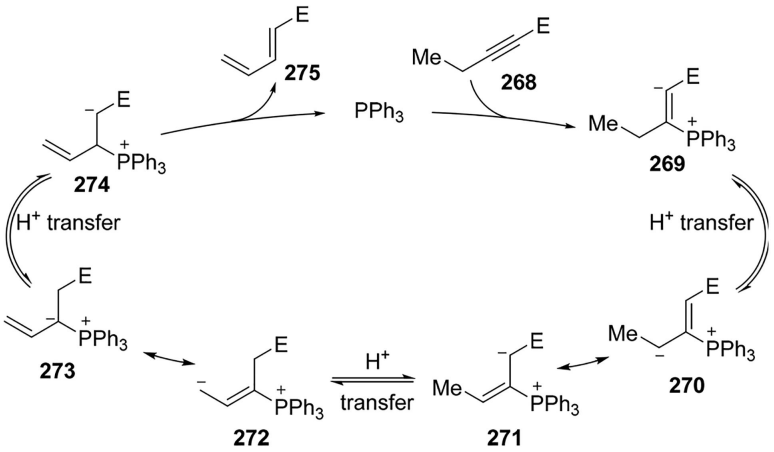
Scheme 386.

Phosphine-Catalyzed Allenoate-*N*-Hydroxyphthalimide Domino Annulation

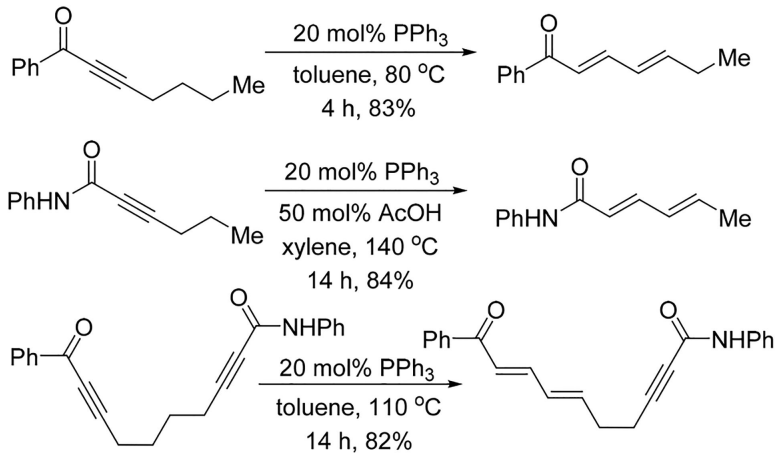


Scheme 387.

Phosphine-Catalyzed [4 + 2] Annulations of *δ*-Acetoxy Allenoates and Ketones

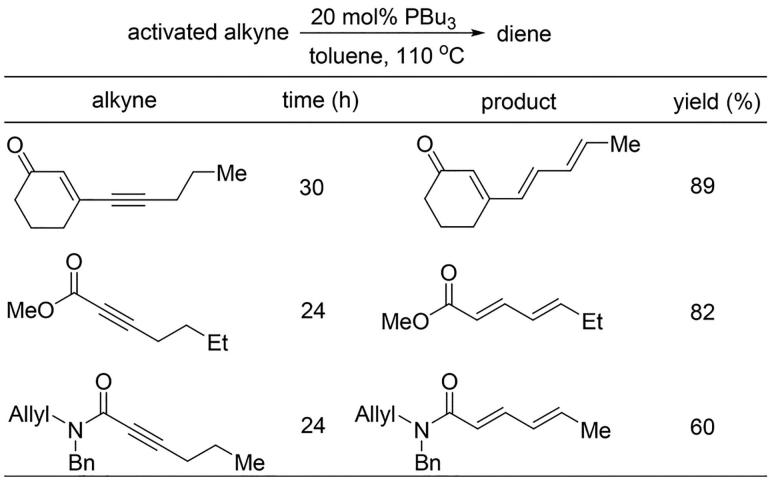


Scheme 388.
Proposed Mechanism for Alkyne Isomerization



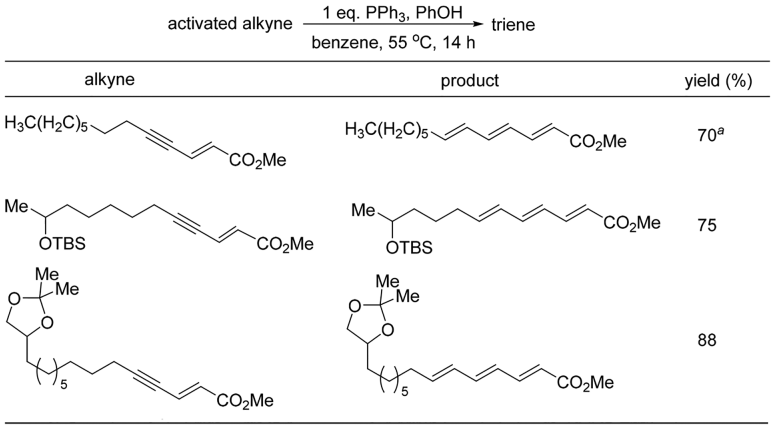
Scheme 389.

Phosphine-Catalyzed Isomerizations of Alkynes



Scheme 390.

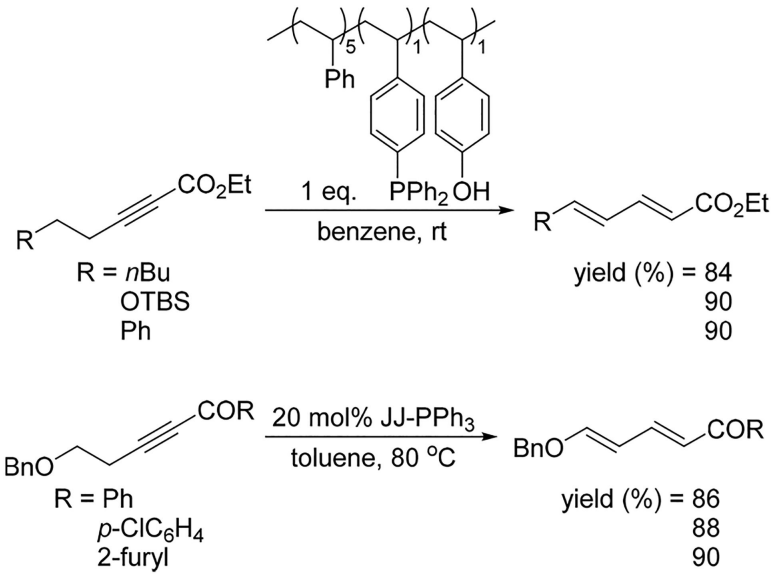
Isomerization of Less Reactive Alkynes



Scheme 391.

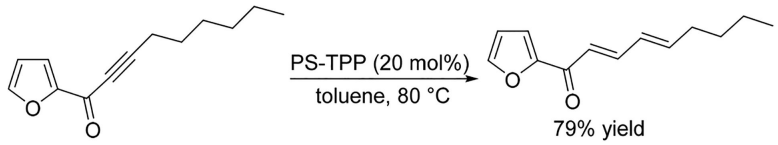
Mild Conditions for Alkynoate Isomerizations

[a]Reaction was complete within 12 h.

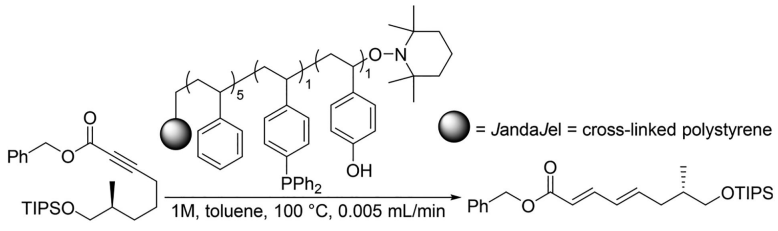


Scheme 392.

Solid-Supported Phosphine-Catalyzed Alkyne Isomerizations

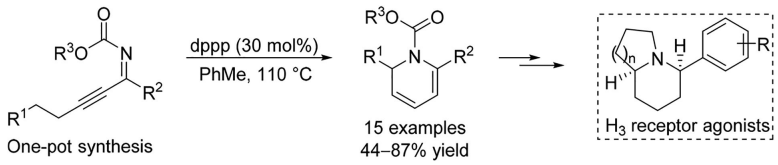


Scheme 393.
Phosphine-Catalyzed Isomerization of Ynones



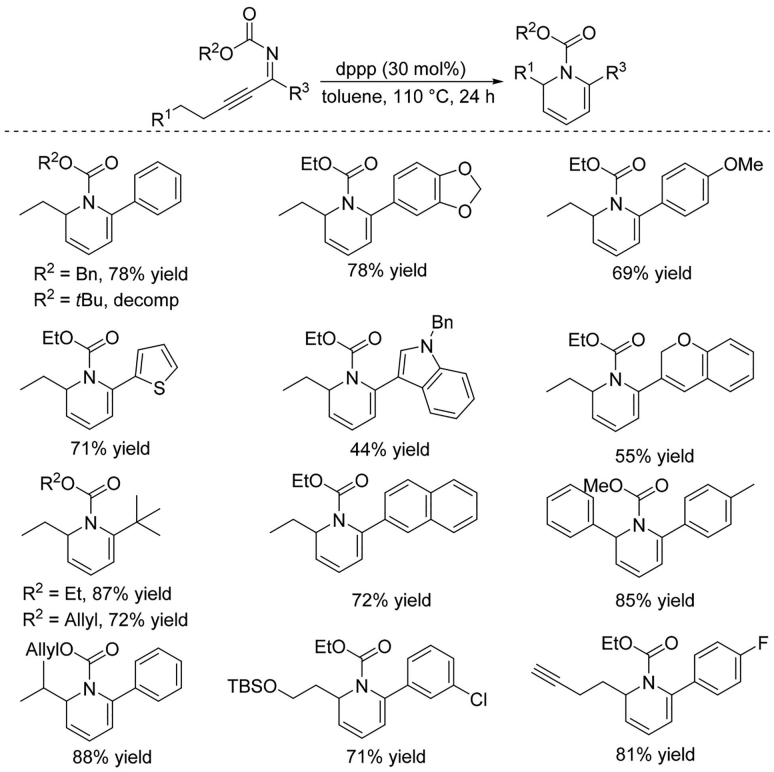
Scheme 394.

Isomerization of Activated Alkynes Catalyzed by Polymer-Supported Phosphine



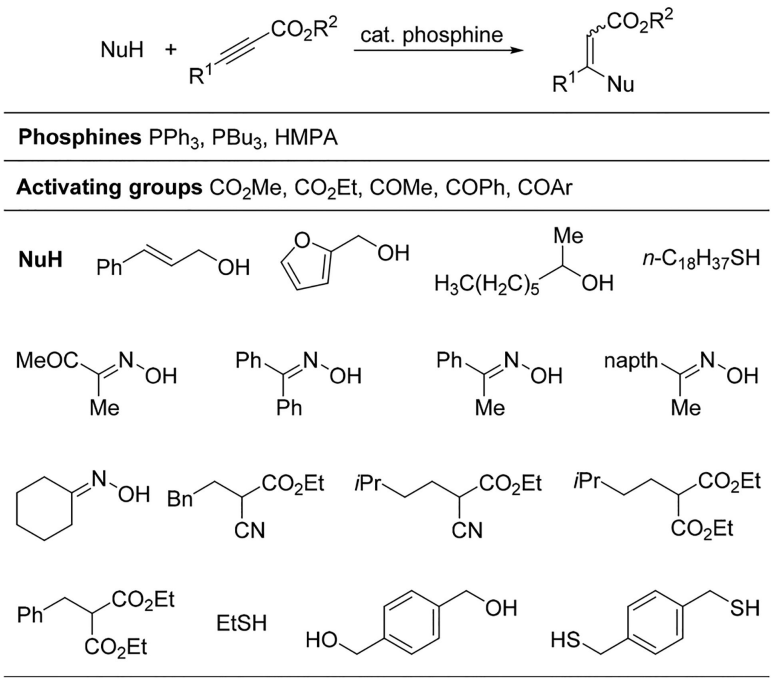
Scheme 395.

Phosphine-Catalyzed Cycloisomerization of Propargylidenecarbamates and its Synthetic Applications



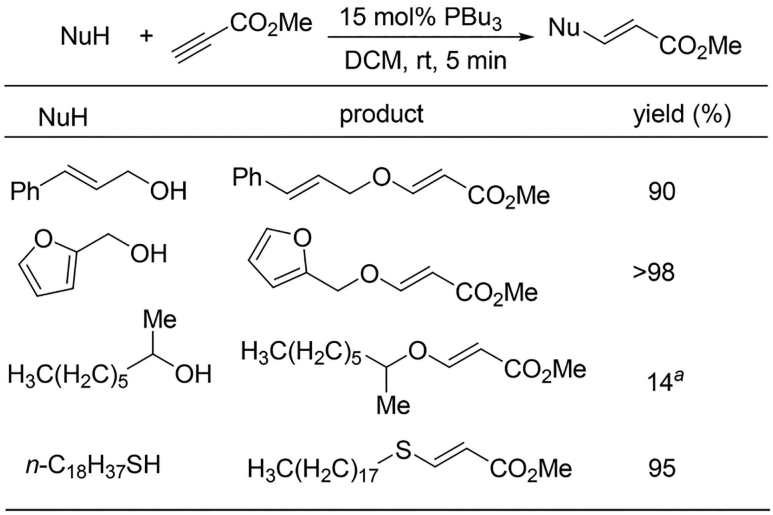
Scheme 396.

Examples for Phosphine-Catalyzed Cycloisomerization of Propargylidenecarbamates



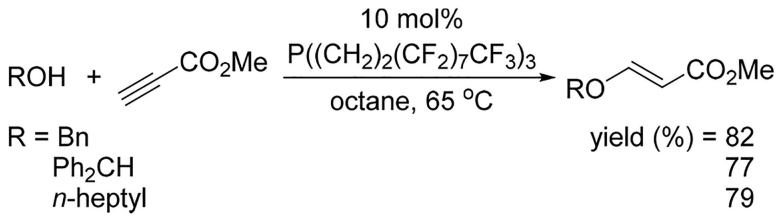
Scheme 397.

Scope of Pronucleophiles, Activating Groups, and Phosphines

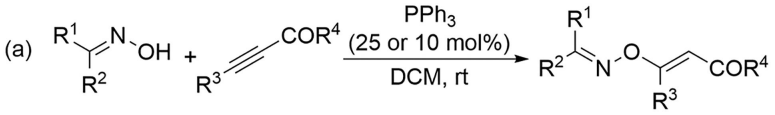


Scheme 398.

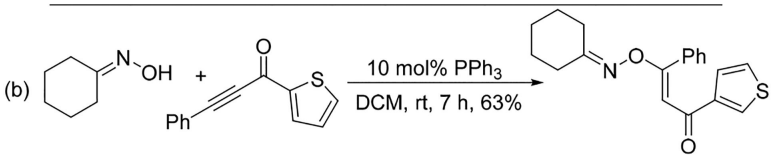
Phosphine-Catalyzed Michael Addition of Alcohols and Thiols



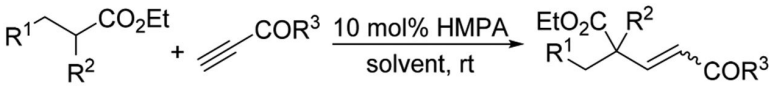
Scheme 399.
Michael Additions Catalyzed by a Fluorous Phosphine



entry	R^1	R^2	R^3	R^4	time (h)	yield (%)
1	COMe	Me	H	OEt	10	70
2	Ph	Ph	H	OEt	10	83
3	Ph	Me	Ph	2-furyl	7	83
4	1-naphthyl	Me	Ph	Ph	7	82

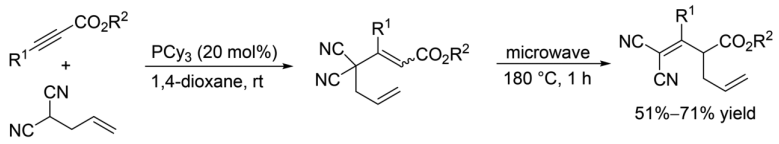


Scheme 400.
Phosphine-Catalyzed Michael Additions of Oximes



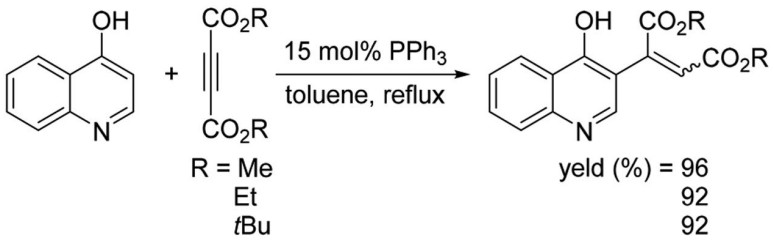
entry	R^1	R^2	R^3	solvent	yield (%)	*E*/*Z*
1	Bn	CN	Me	CH_3CN	83	30:70
2	CH_2*i*Pr	CN	OEt	CH_3CN	89	75:25
3	CH_2*i*Pr	CO_2Et	Me	CH_3CN	oligomer	–
4	Ph	CO_2Et	OEt	Neat	79	85:15

Scheme 401.
HMPA-Catalyzed Michael Additions of Carbon Pronucleophiles

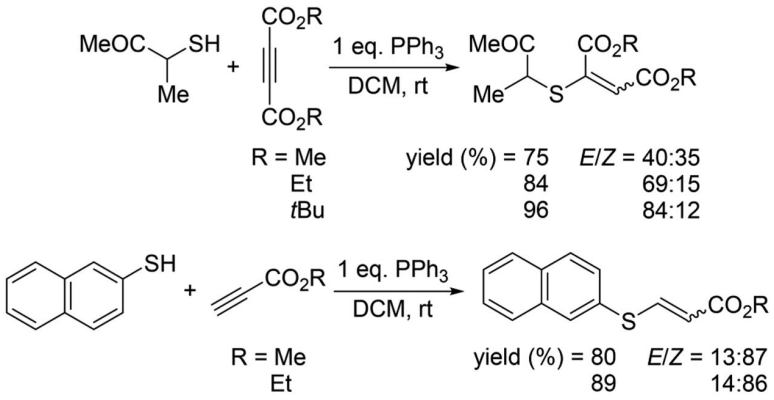


Scheme 402.

Phosphine-Catalyzed Coupling of Allyl Malononitrile with Alkynoates

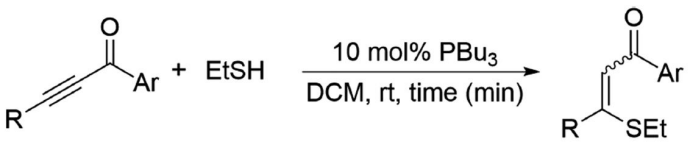


Scheme 403.
Synthesis of Functionalized Fumarates



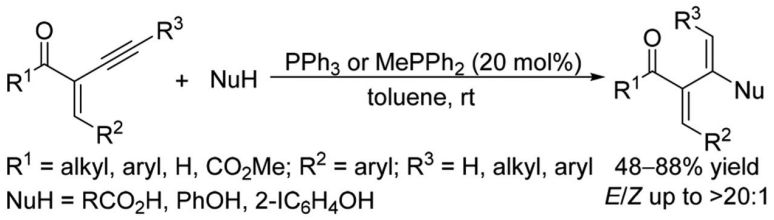
Scheme 404.

Synthesis of Functionalized β-Mercaptoacrylates



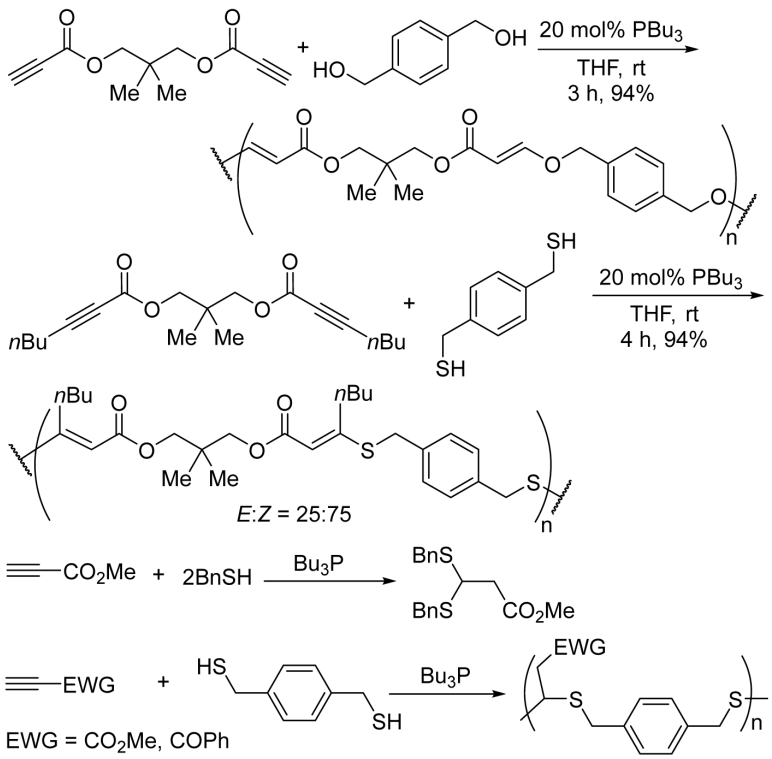
entry	R	Ar	time (min)	yield (%)	*E*/*Z*
1	Ph	*p*-FC_6H_4	15	99	33:67
2	Ph	*p*-$MeOC_6H_4$	60	96	32:68
3	H	Ph	35	90	19:81

Scheme 405.
Formation of Mercapto-Chalcone Derivatives



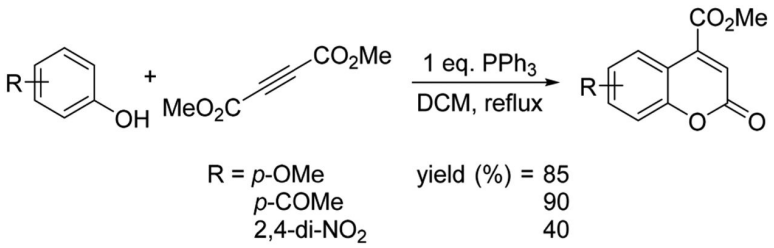
Scheme 406.

Phosphine-Catalyzed Regio- and Stereoselective Hydrocarboxylation of Enynes



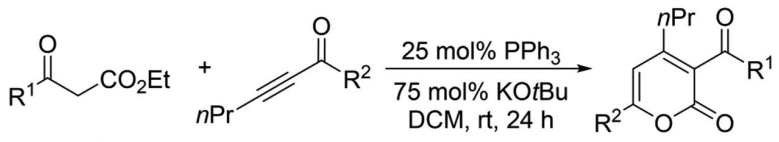
Scheme 407.

Michael Addition as an Efficient Means of Polymerization



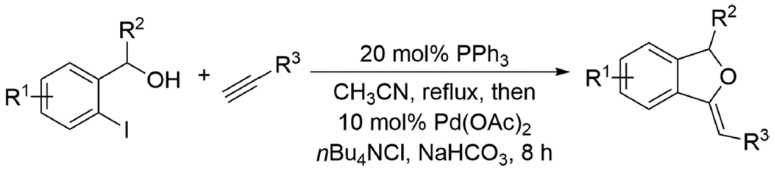
Scheme 408.

Tandem Electrophilic Aromatic Substitution/Lactonization



entry	R^1	R^2	yield (%)
1	Me	*p*-FC_6H_4	84
2	*p*-BrC_6H_4	*p*-ClC_6H_4	82
3	*t*Bu	*p*-BrC_6H_4	75
4	OEt	Ph	53

Scheme 409.
Synthesis of 2-Pyrone Derivatives

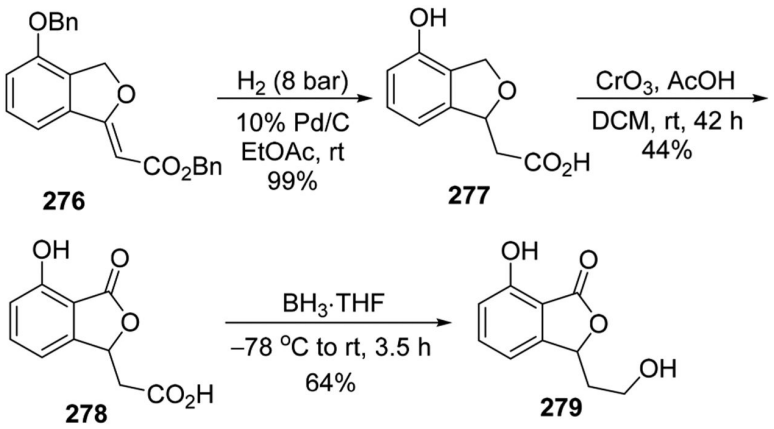


entry	R^1	R^2	R^3	yield (%)[a]	E:Z[b,c]
1	H	H	CO_2Me	74	1:3
2	4-CF_3	H	CO_2Me	60	1:3
3	3-Me	H	CO_2Me	94	1:16
4	H	cyclopropyl	CO_2Me	72	1:3
5	6-OBn	H	CO_2Bn	62	1:5
6	4,5-$(OBn)_2$	H	COMe	69	1:3
7	H	H	Ts	51	1:3

Scheme 410.

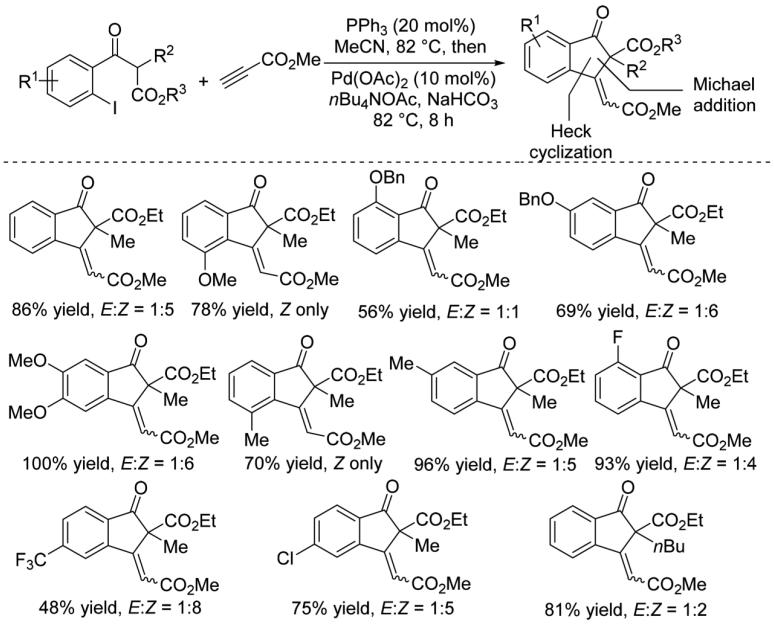
Preparation of Phthalan Derivatives through Michael–Heck Reactions

[a]Major *Z*-phthalan isolated. [b]Ratio determined from the ^{1}H NMR spectrum of the crude product. [c]Purification and characterization of E-isomers was difficult, due to other byproducts.



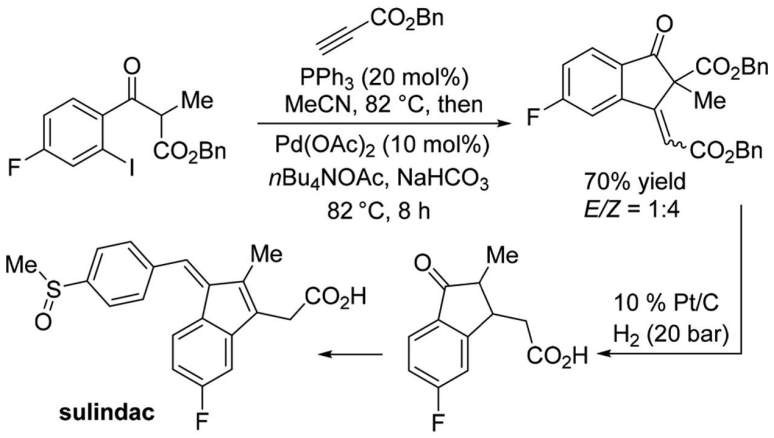
Scheme 411.

Syntheses of 3-Deoxyisoochracinic Acid, Isoochracinic Acid, and Isoochracinol



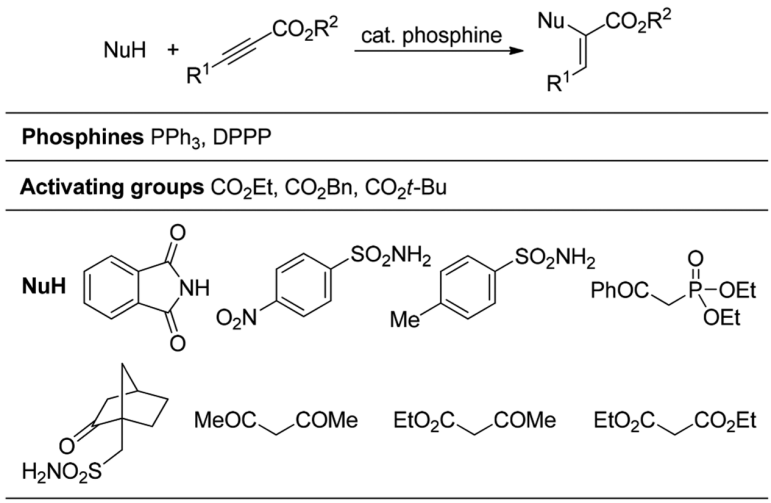
Scheme 412.

Synthesis of Alkylidene Indanes and Indanones Through Phosphine-Catalyzed Michael Addition and Palladium-Catalyzed Heck Cyclization



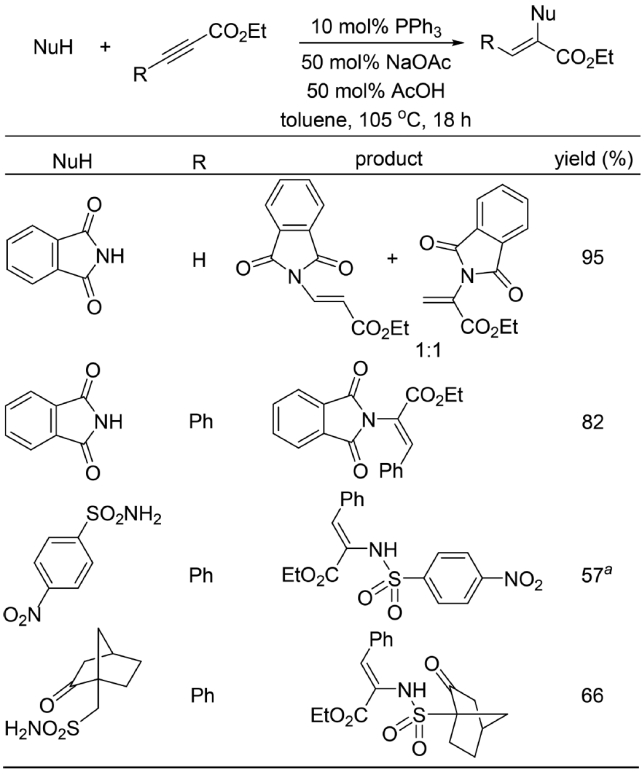
Scheme 413.

Synthetic Application of the Michael Addition–Heck Cyclization



Scheme 414.

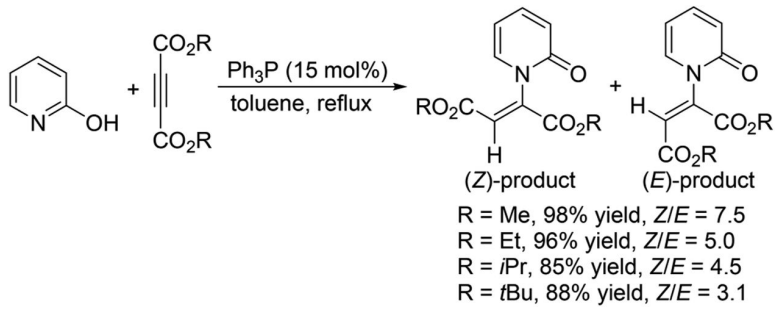
Scope of Pronucleophiles, Activating Groups, and Phosphines for Phosphine-Catalyzed α-Umpolung Additions



Scheme 415.

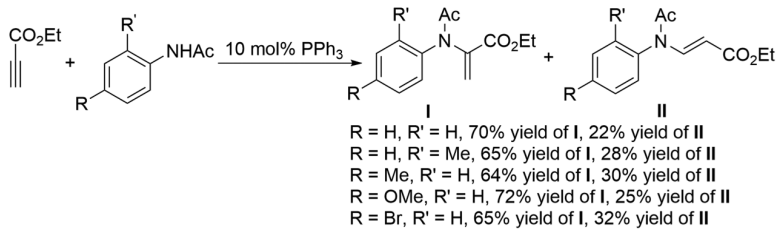
α-Umpolung Additions of Phthalimide and Sulfonamides

[a]Reaction was complete within 5 h.



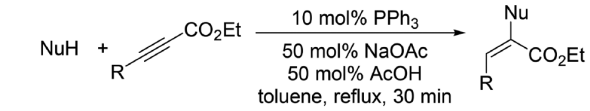
Scheme 416.

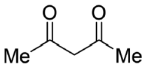
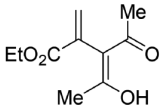
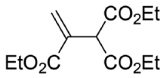
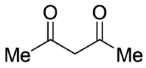
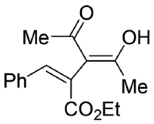
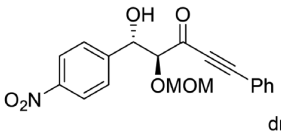
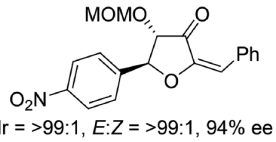
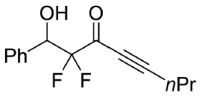
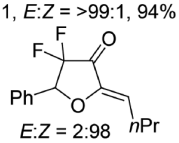
Phosphine-Catalyzed α-Addition of 2-Hydroxypyridine to Dialkyl Acetylenedicarboxylates



Scheme 417.

Phosphine-Catalyzed α-Additions of Acetanilides or Arylsulfonylanilides to Ethyl Propiolate

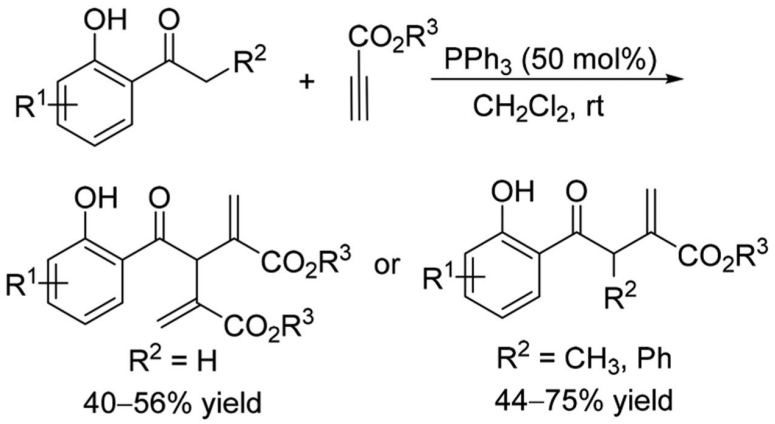


entry	NuH	R	product	yield (%)
1		H		88
2		H		60[a]
3		Ph	 mixture of E/Z isomers	62[b]
4			 dr = >99:1, *E*:*Z* = >99:1, 94% ee	90[c]
5			 *E*:*Z* = 2:98	11[d]

Scheme 418.

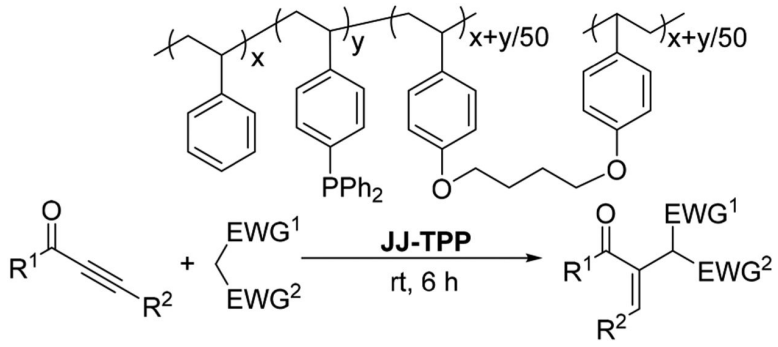
α-Umpolung Reactions of Carbon and Oxygen Pronucleophiles

[a]30 mol % PPh_3 was used. [b]Reaction with 20 mol % PPh_3 was complete within 19 h. [c]Reaction with 10 mol % DPPP and 40 mol % AcOH at 60 °C was complete within 3 h. [d]Reaction with 10 mol % DPPP and 40 mol % AcOH at 60 °C was complete wihtin 5 h.



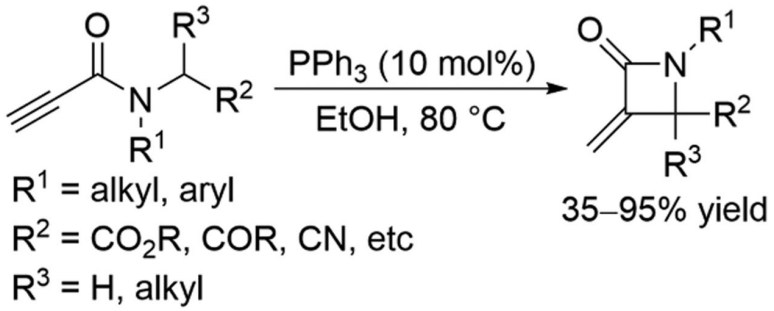
Scheme 419.

Ph_3P-Mediated Double α-Additions of *o*-Hydroxyacetophenones to Ethyl Propiolates

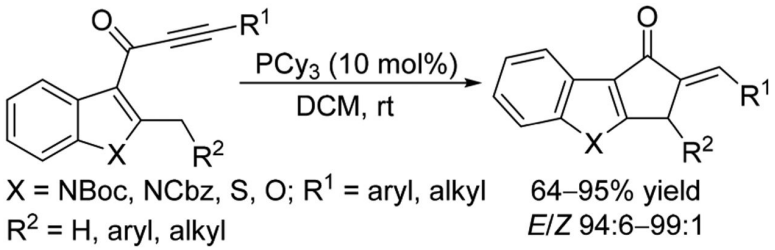


Scheme 420.

Polymer-Supported Phosphine-Promoted α-Additions of Carbon Nucleophiles to α,β-Unsaturated Compounds

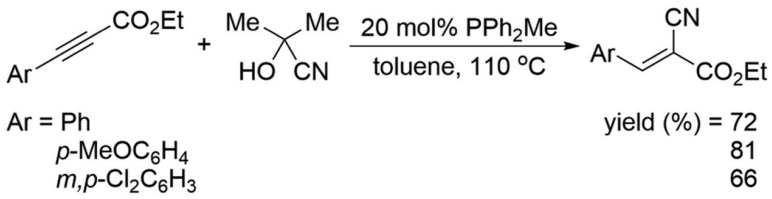


Scheme 421.
PPh_3-Catalyzed Umpolung Cyclizations of Propiolamides

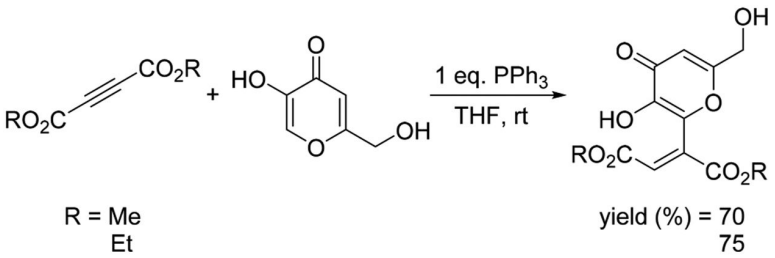


Scheme 422.

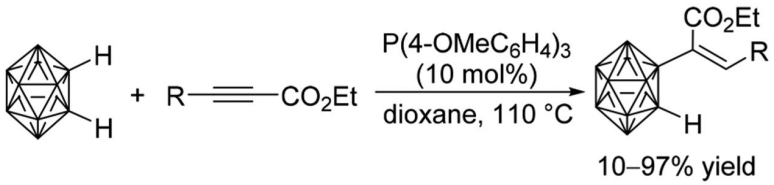
Cyclopenta[*b*]annulation of Heteroarenes Through Organocatalytic γ'[C(sp^3)-H] Functionalization of Ynones



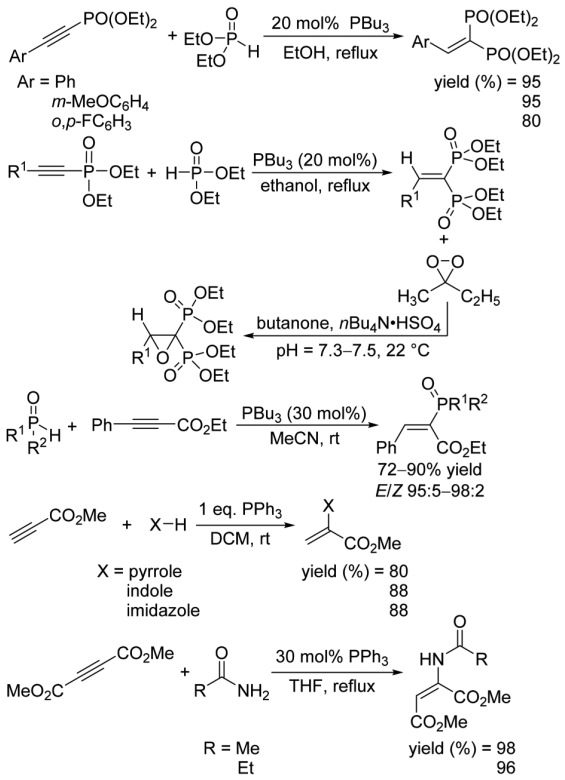
Scheme 423.
Synthesis of Functionalized α-Cyanoacrylates



Scheme 424.
Vinylation of Kojic Acid Through α-Umpolung Additions

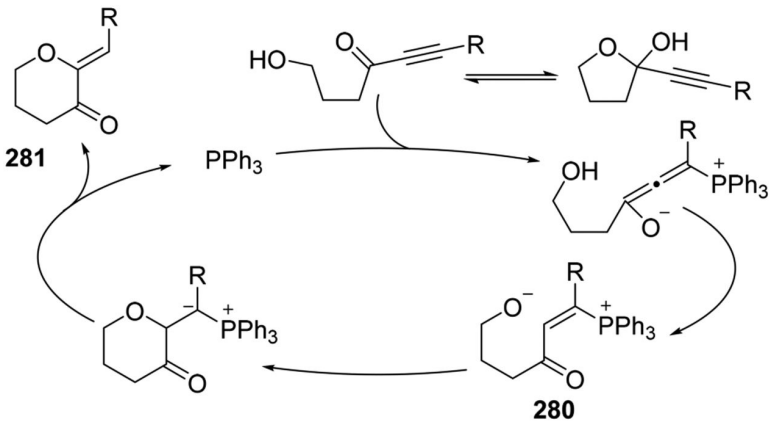


Scheme 425.
Phosphine-Catalyzed *α*-Additions of *o*-Carborane to Alkynoates



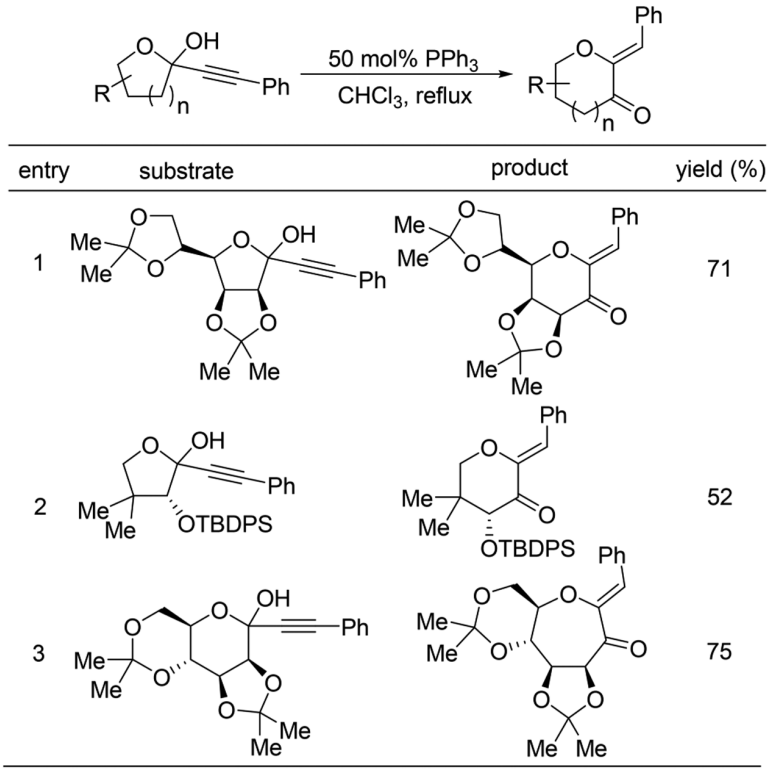
Scheme 426.

α-Umpolung Additions of Phosphorus and Nitrogen Pronucleophiles

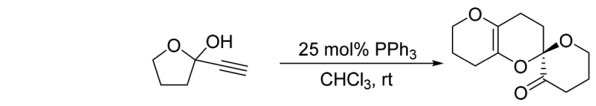


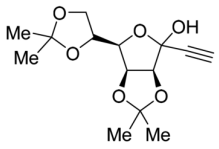
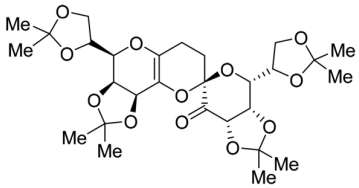
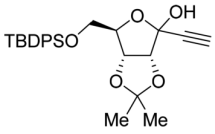
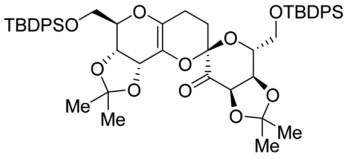
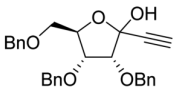
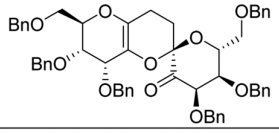
Scheme 427.

Suggested Mechanism for the Formation of 3-Oxanones from Alkynyl Hemiketals

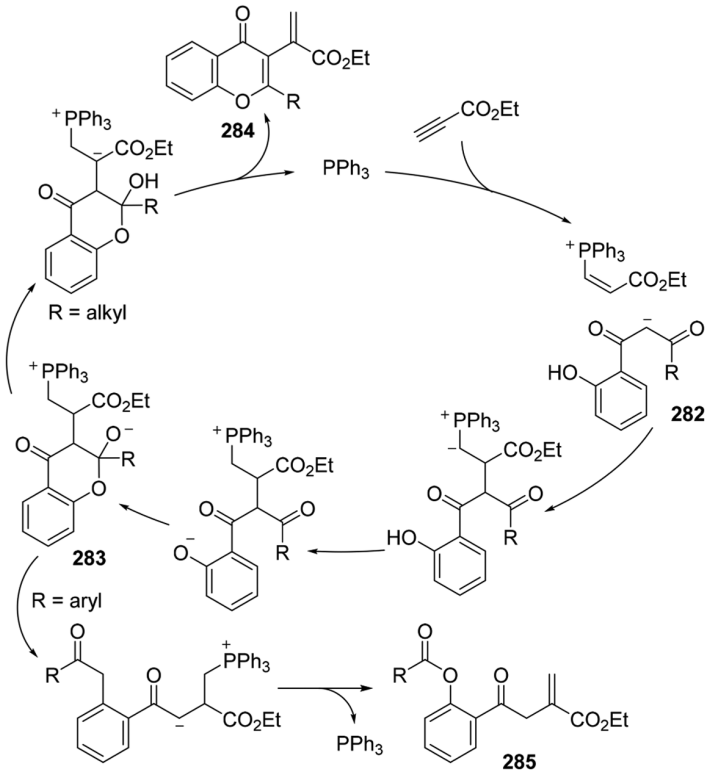


Scheme 428.
Preparation of Functionalized 3-Oxanones and 3-Oxepanones



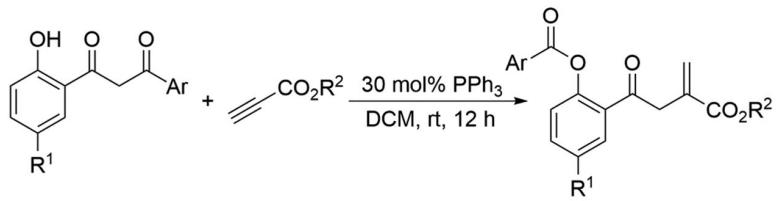
entry	substrate	product	yield (%)
1			80
2			71
3			55

Scheme 429.
Synthesis of Spiroketal Derivatives Through Dimerization



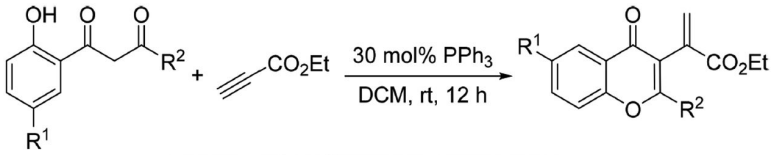
Scheme 430.

Proposed Reaction Pathway for α-Umpolung Addition of 1-(2-Hydroxyaryl)-3-arylpropane-1,3-dione Into Alkyl Propiolates



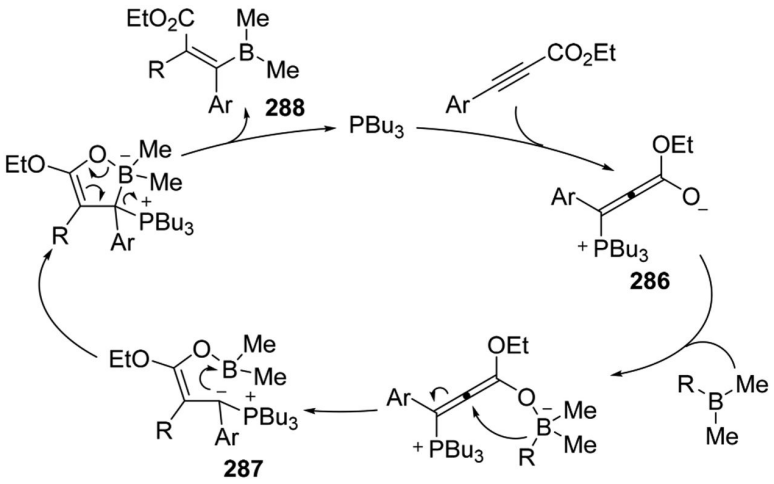
entry	R^1	R^2	Ar	yield (%)
1	Me	Et	3,4-$(MeO)_2C_6H_3$	78
2	H	Et	*p*-FC_6H_4	40
3	H	Me	Ph	46
4	H	Bn	Ph	55

Scheme 431.
Formation of Vinyl Esters from 1-(2-Hydroxyaryl)-3-arylpropane-1,3-diones

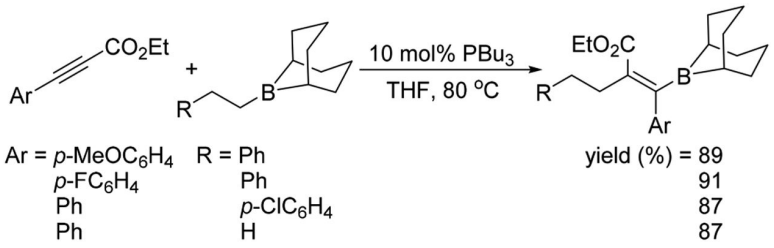


entry	R^1	R^2	yield (%)
1	H	Me	59
2	H	CH_2Bn	46
3	H	cyclohexyl	38
4	Cl	Me	39

Scheme 432.
Formation of Chromones Through Phosphine Catalysis

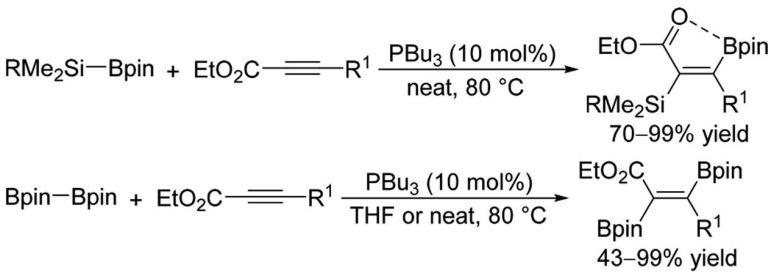


Scheme 433.
Proposed Mechanism of *anti*-Carboboration

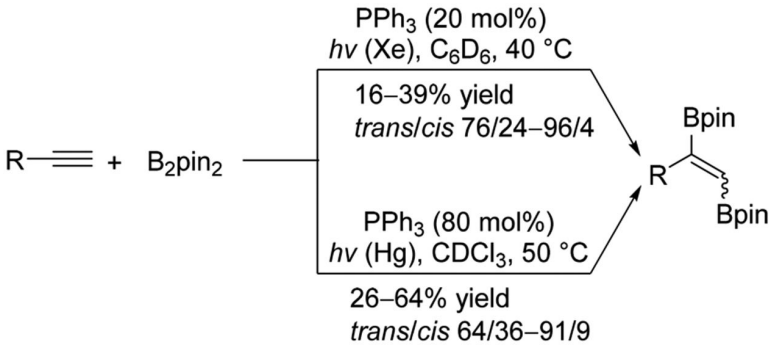


Scheme 434.

Synthesis of Functionalized β-Borylacrylates

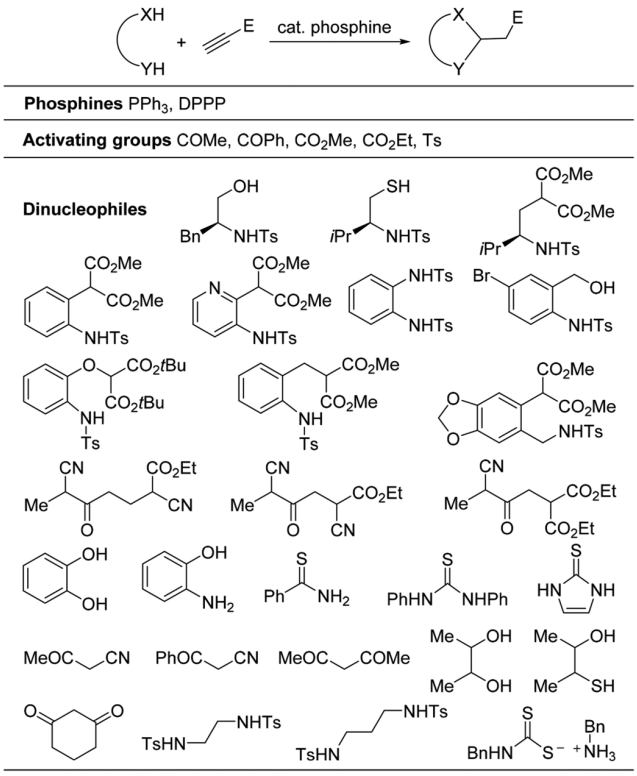


Scheme 435.
Phosphine-Catalyzed *anti*-Selective Vicinal Silaboration and Diboration of Alkynoates



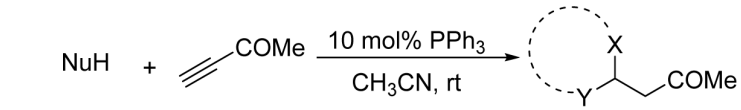
Scheme 436.

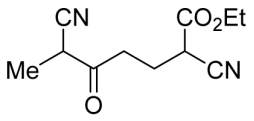
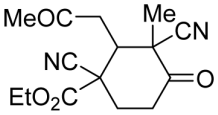
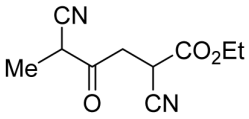
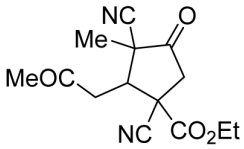
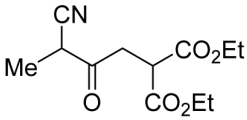
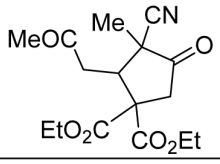
Phosphine-Catalyzed Diboration of Alkynes in the Presence of Alkynes



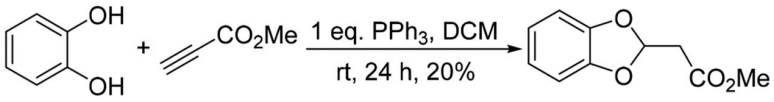
Scheme 437.

Scope of Dinucleophiles, Alkynes, and Phosphines for Catalytic Annulations

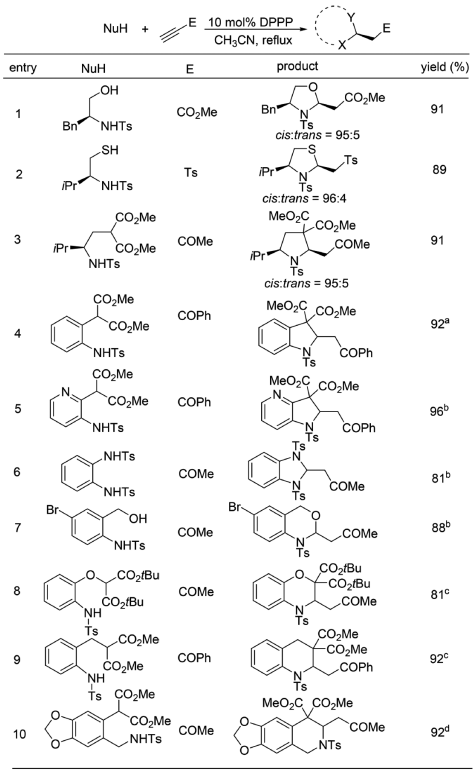


entry	NuH	product	yield (%)
1			83
2			55
3			46

Scheme 438.
Formation of Cyclohexanones and Cyclopentanones



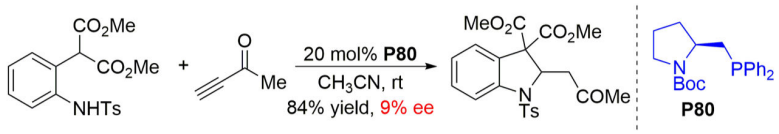
Scheme 439.
A Double-Michael Reaction of Catechol



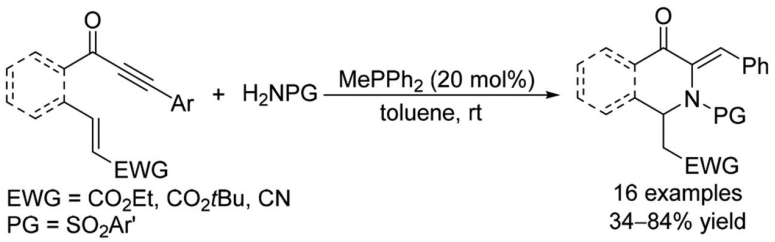
Scheme 440.

Phosphine-Catalyzed Mixed Double-Michael Additions

[a]Reaction performed with 20 mol % DPP, 50 mol % AcOH, and 50 mol % NaOAc at rt. [b]Reaction performed with 20 mol % DPPP, 50 mol % AcOH, and 50 mol % NaOAc under reflus. [c]Reaction performed with 20 mol % DPPP. [d]Reaction performed with 20 mol % DPPP at rt.

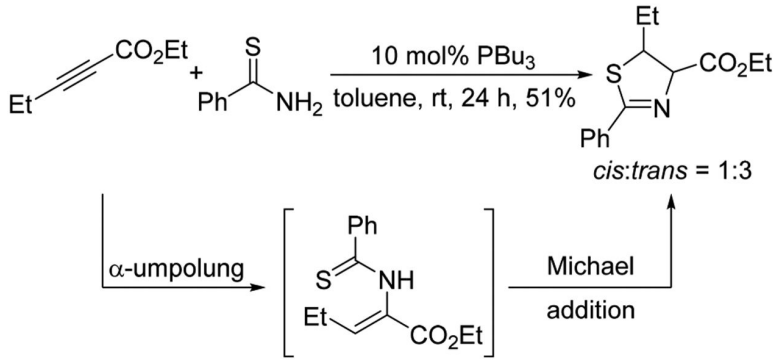


Scheme 441.
Asymmetric Double-Michael Addition

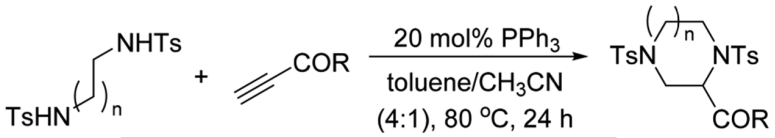


Scheme 442.

Phosphine-Catalyzed [5 + 1] Annulations of Ynones/Michael Acceptors with Sulfonamides

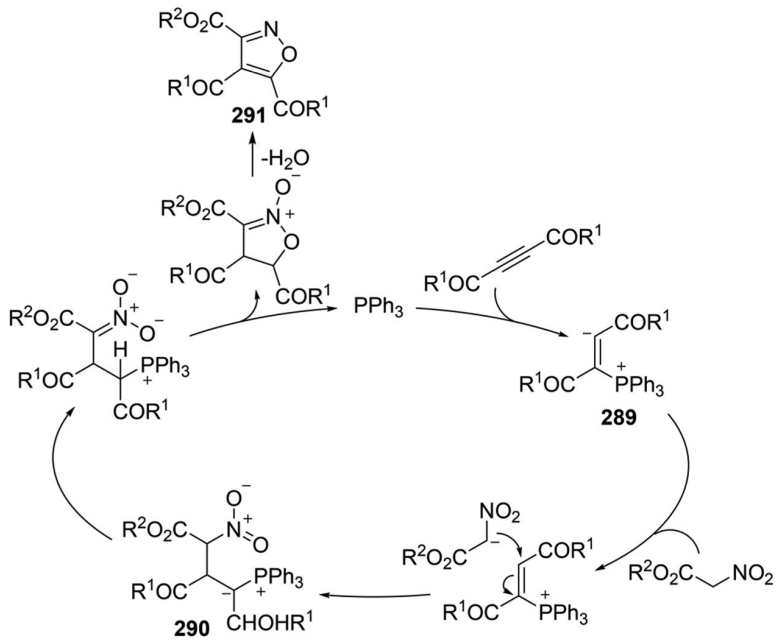


Scheme 443.
Proposed α-Umpolung–Michael Pathway

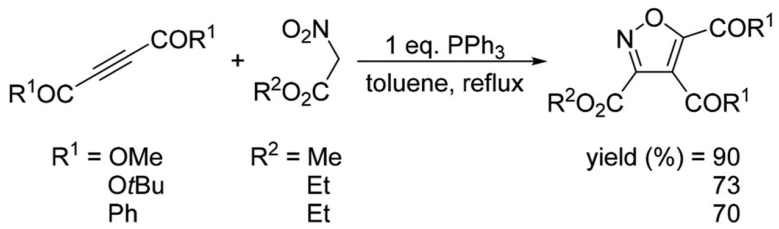


entry	n	R	yield (%)
1	1	OEt	86
2	1	*n*Pr	83
3	2	OEt	88

Scheme 444.
Formation of Piperazines and 1,4-Diazepanes

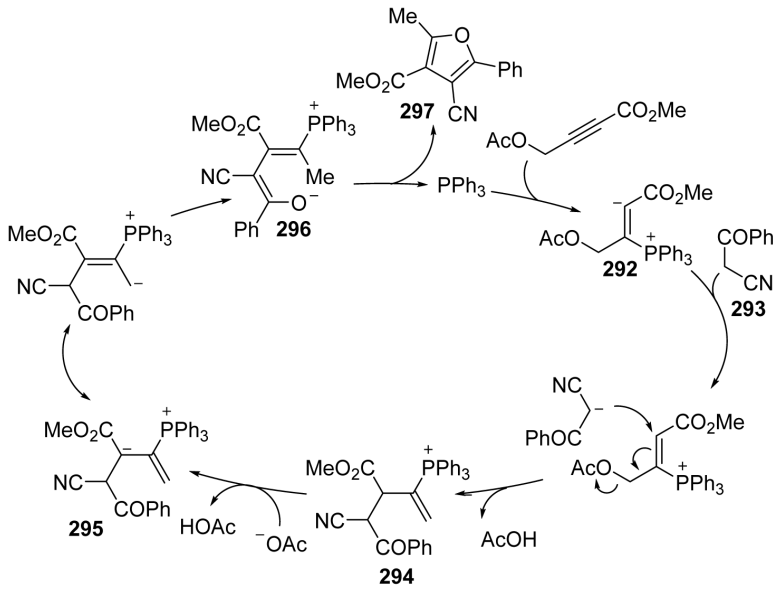


Scheme 445.
Proposed Mechanism for Isoxazole Formation



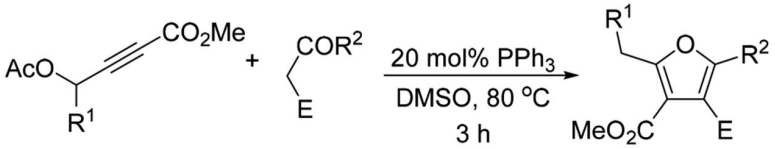
R^1 =	R^2 =	yield (%) =
OMe	Me	90
O*t*Bu	Et	73
Ph	Et	70

Scheme 446.
Synthesis of Functionalized Isoxazoles



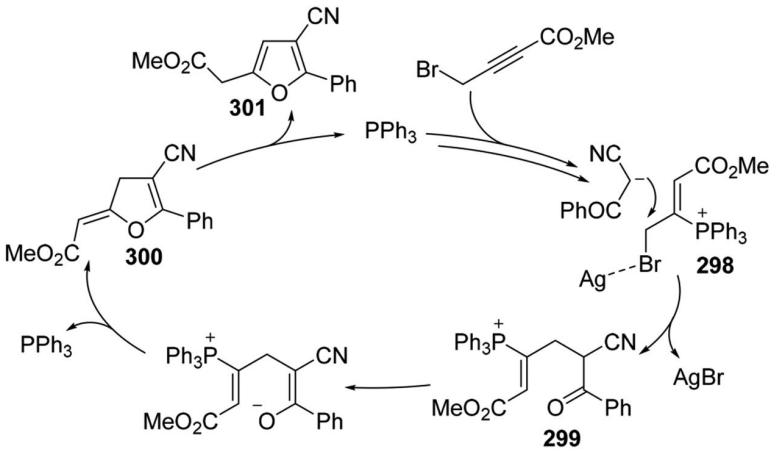
Scheme 447.

Proposed Reaction Mechanism for the Formation of Functionalized Furans



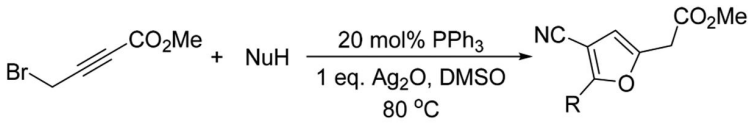
entry	R^1	R^2	E	yield (%)
1	H	Ph	CN	91
2	H	*p*-ClC_6H_4	CN	94
3	H	Me	COMe	63
4	Ph	Ph	CN	56

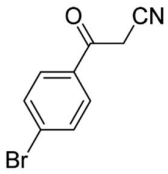
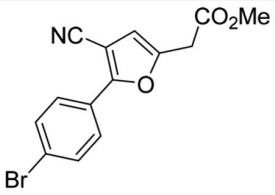
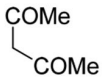
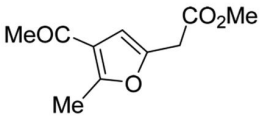
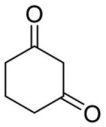
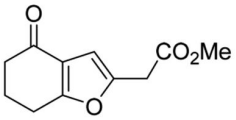
Scheme 448.
Formation of Functionalized Furans



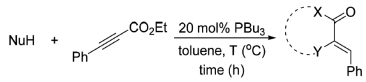
Scheme 449.

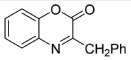
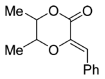
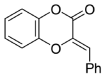
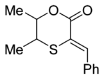
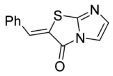
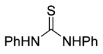
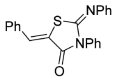
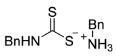
Alternative Reaction Mechanism for the γ-Umpolung–Michael Process



entry	NuH	product	yield (%)
1			92
2			63
3			44

Scheme 450.
Formation of Trisubstituted Furans



entry	NuH	T (°C)	time (h)	product	yield (%)
1		rt	24		75[a]
2		rt	14		75
3		reflux	2		61
4		rt	12		77
5		70	8		91
6		90	4		62
7		reflux	12		83[b]

Scheme 451.

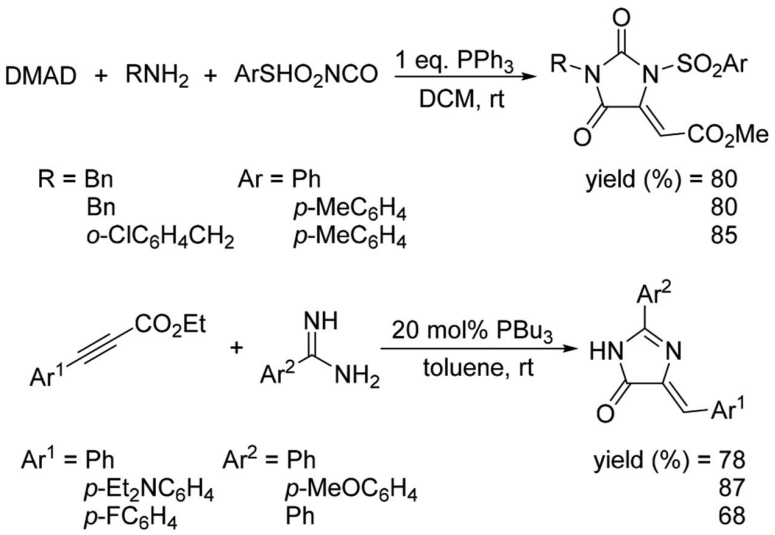
Annulation Through α-Umpolung–Lactonization

[a]Reaction performed using 1 equiv of PPh_3 in DCM. [b]Reaction performed in *i*PrOH.

302 **303**

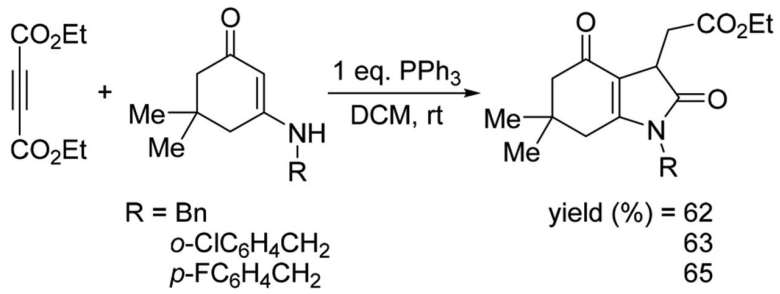
entry	R^1	R^2	**302**:**303**	yield (%)
1	Me	Bn	100:0	73
2	Me	cyclohexyl	100:0	68
3	Me	*p*-$MeOC_6H_4CH_2$	85:15	73
4	Me	Ph	70:30	67
5	cyclohexyl	*p*-$MeOC_6H_4$	0:100	51

Scheme 452.
Generation of Thiohydantoin Derivatives



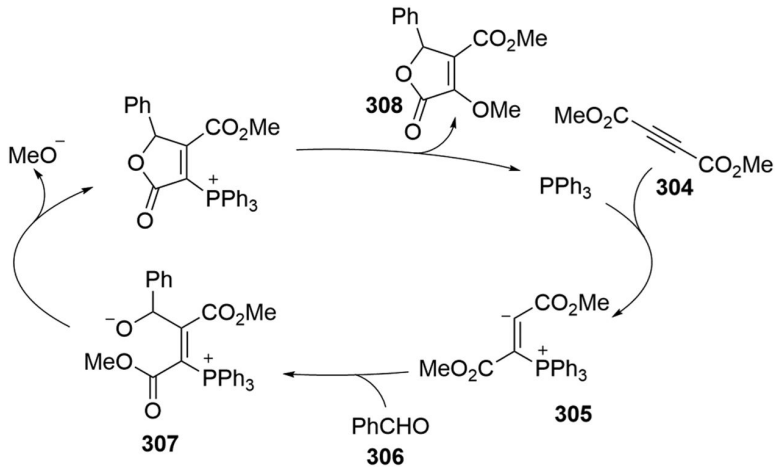
Scheme 453.

Synthesis of Functionalized Hydatoins and Imidazolones

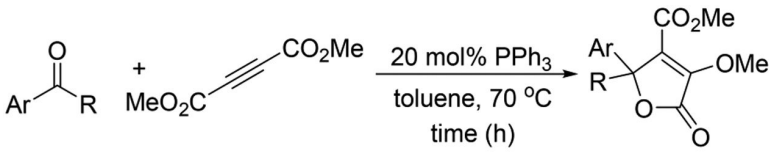


Scheme 454.

Synthesis of Functionalized Tetrahydroindole-2,4-diones

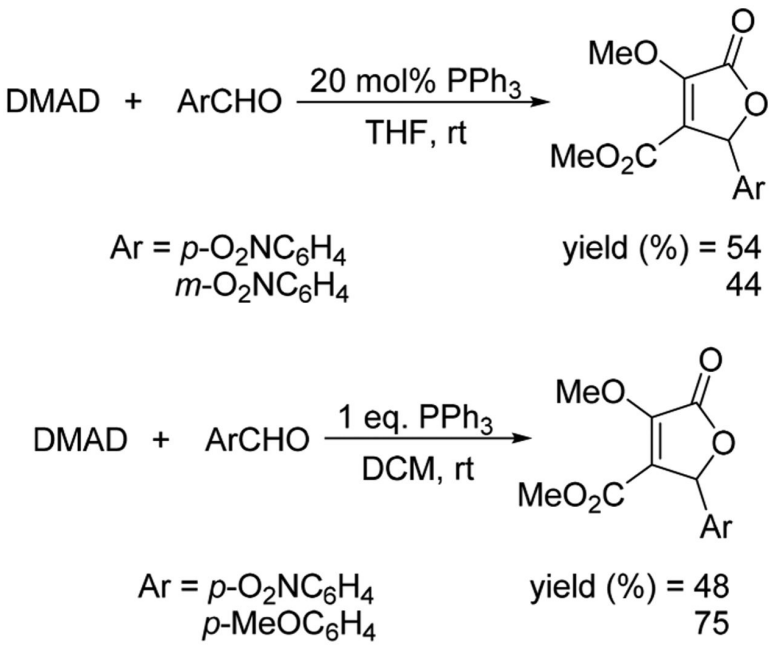


Scheme 455.
Formation of a Butenolide

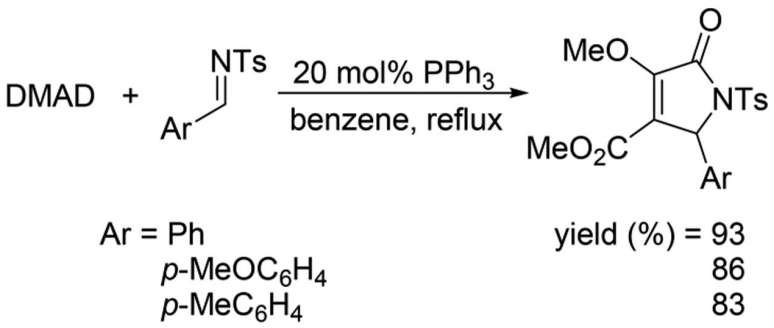


entry	Ar	R	time (h)	yield (%)
1	*p*-$O_2NC_6H_4$	CO_2Me	22	94
2	Ph	CO_2Me	8	11
3	*p*-$MeOC_6H_4$	CN	19	67
4	*p*-ClC_6H_4	CN	22	30
5	Ph	CF_3	17	75

Scheme 456.
Phosphine-Catalyzed Formation of Butenolides

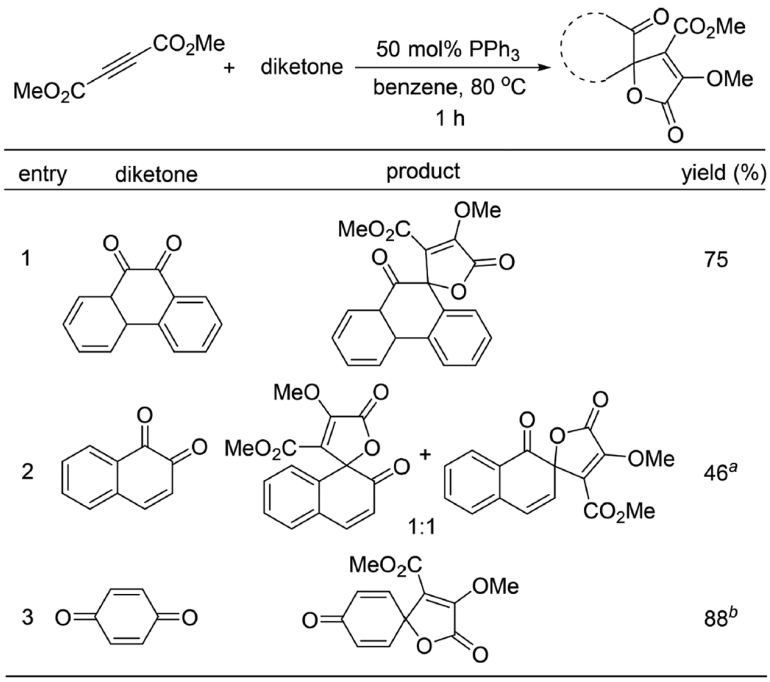


Scheme 457.
Synthesis of Functionalized γ-Butenolides



Ar =	yield (%) =
Ph	93
p-$MeOC_6H_4$	86
p-MeC_6H_4	83

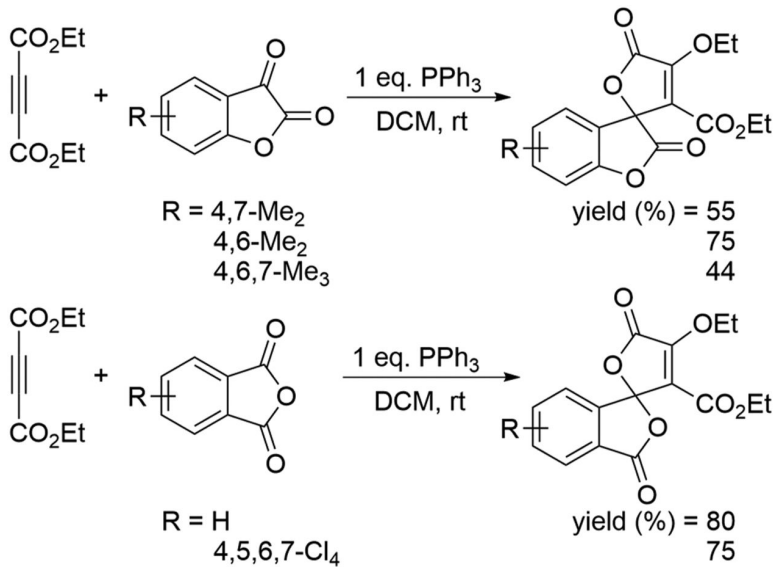
Scheme 458.
Synthesis of Functionalized Pyrroline-2-ones



Scheme 459.

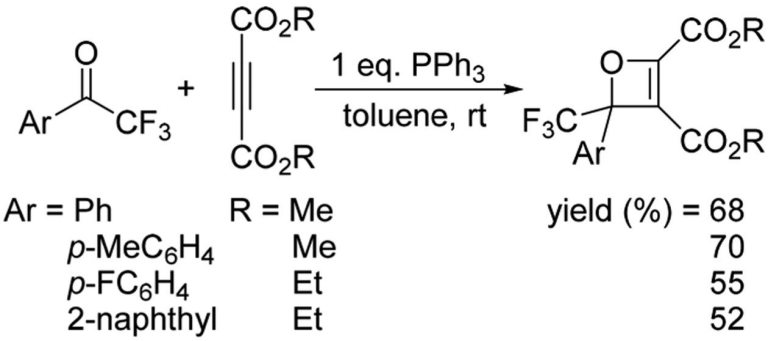
Formation of Butenolides from Diketones

[a]Reaction was complete within 8 h. [b]Reaction was complete within 12 h at rt.



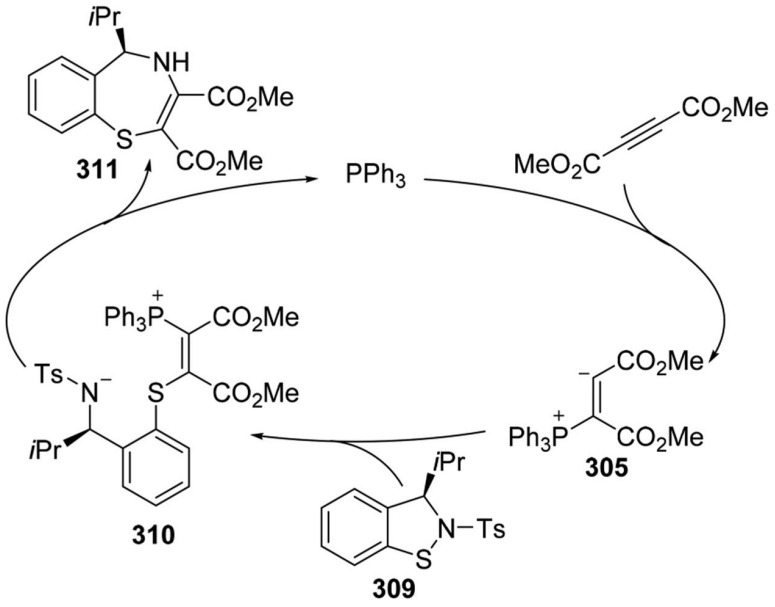
Scheme 460.

Synthesis of Functionalized Spirobenzofuran-2-ones and Spirophthalans



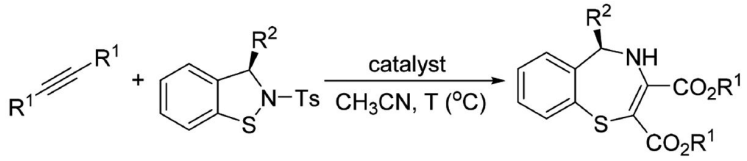
Ar =	R =	yield (%) =
Ph	Me	68
p-MeC_6H_4	Me	70
p-FC_6H_4	Et	55
2-naphthyl	Et	52

Scheme 461.
Synthesis of Functionalized Oxetenes



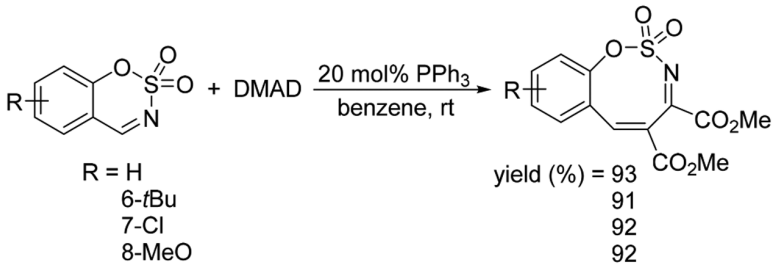
Scheme 462.

Proposed Annulation Pathway for Phosphine Catalysis of DMAD and an Isobenzothiazoline



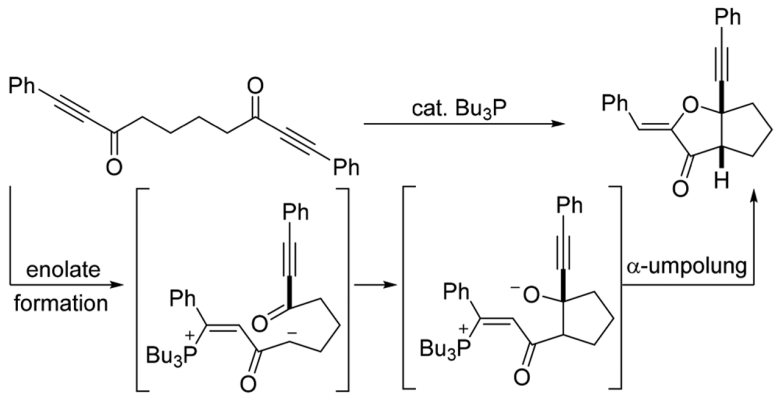
entry	R^1	R^2	Catalyst	T (°C)	yield (%)
1	CO_2Me	*i*Pr	1 eq. PPh_3	40	70[a]
2	CN	*m*-BrC_6H_4	10 mol% CsF	60	85
3	SO_2tBu	*i*Pr	10 mol% CsF	60	No reaction

Scheme 463.
Formation of Benzothiazepines
[a]Reaction performed in DCM.

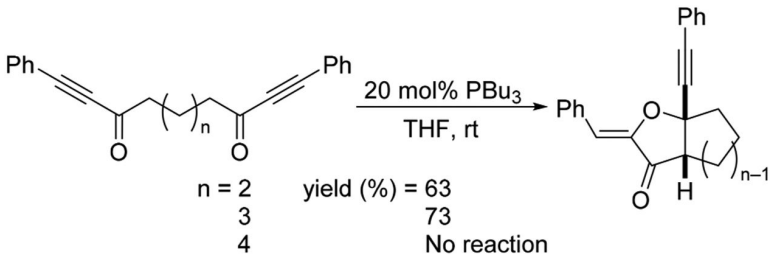


Scheme 464.

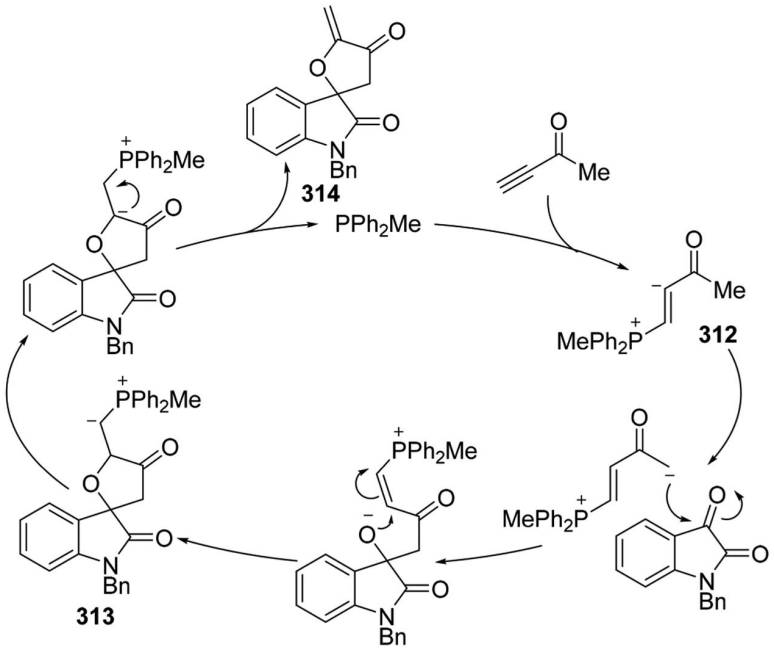
Synthesis of Functionalized Benzo[*g*][1,2,3]oxathiazocines



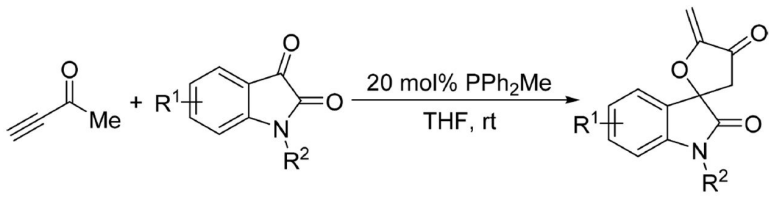
Scheme 465.
Proposed Pathway for Formation of Bicyclic Ketones



Scheme 466.
Formation of Diquinanes and Hydrindanes

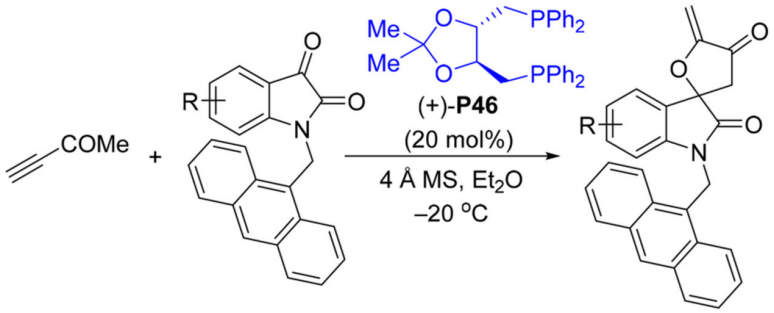


Scheme 467.
Suggested Annulation Mechanism



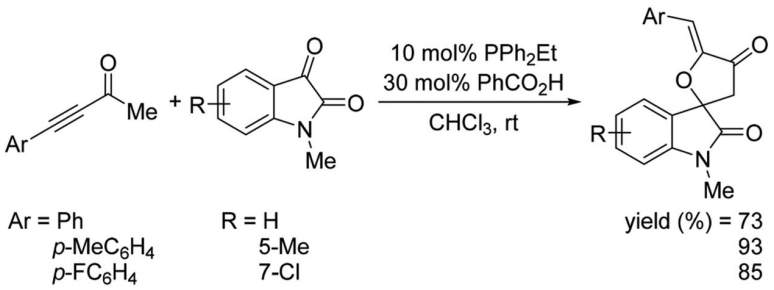
entry	R^1	R^2	yield (%)
1	5-OMe	Bn	98
2	7-Br	Bn	65
3	H	Boc	90
4	H	Tr	64

Scheme 468.
Synthesis of Functionalized 3-Spirotetrahydrofuran-3-one-2-oxindoles

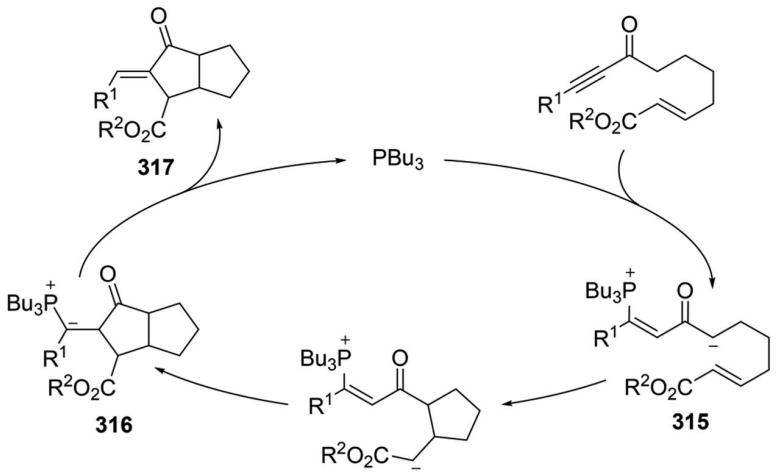


entry	R	yield (%)	ee (%)
1	5-F	47	68
2	5-Me	62	68
3	5-MeO	54	84
4	6-Cl	55	81

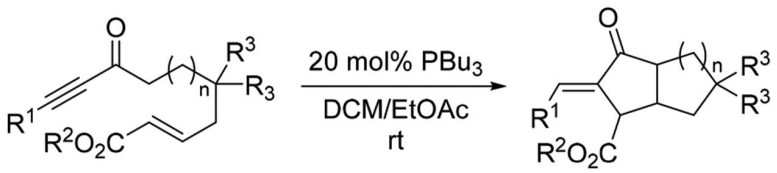
Scheme 469.
Asymmetric Synthesis of Functionalized Spirooxindoles



Scheme 470.
Synthesis of Functionalized Spirooxindoles

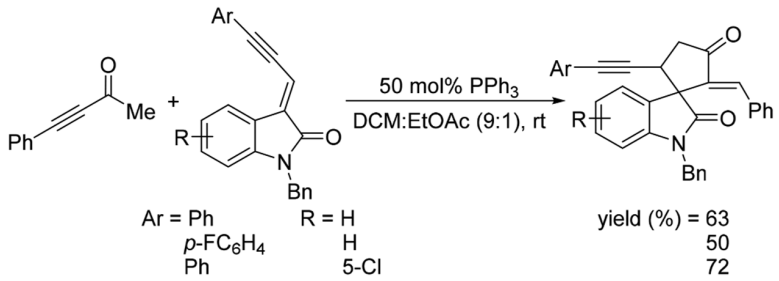


Scheme 471.
Proposed Reaction Pathway Toward Functionalized Diquinanes



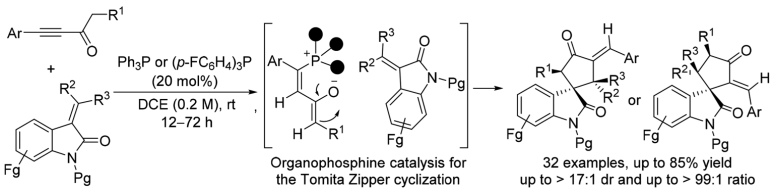
entry	R^1	R^2	R^3	*n*	yield (%)
1	Ph	Et	H	1	89
2	cyclohexyl	Me	CO_2Et	1	74
3	Me	Me	CO_2Et	1	56
4	Ph	Me	CO_2Et	2	60

Scheme 472.
Preparation of Functionalized Diquinanes and Hydrindanes



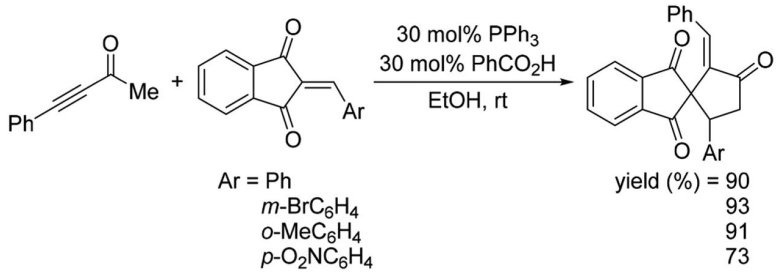
Scheme 473.

Synthesis of Functionalized Spirooxindoles



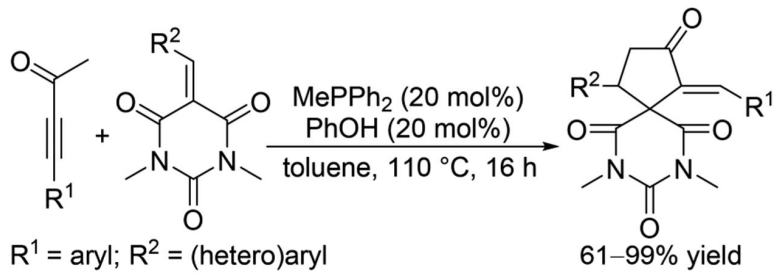
Scheme 474.

Phosphine-Catalyzed Formal [3 + 2] Cycloaddition of Ynones with Isatin-Derived Olefins



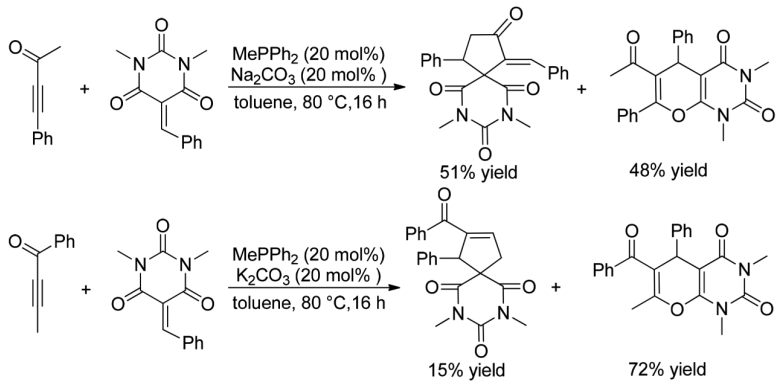
Scheme 475.

Synthesis of Functionalized Spiroindan-1,3-diones



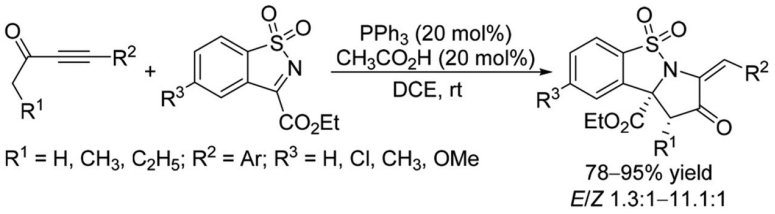
Scheme 476.

Phosphine-Catalyzed [3 + 2] Annulations of Ynones and Barbiturate-Derived Alkenes



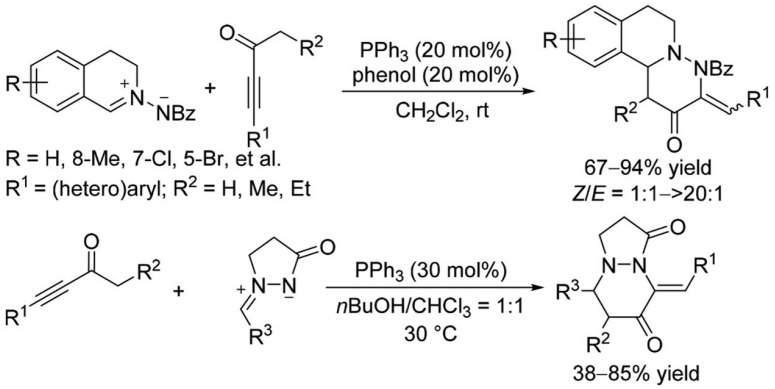
Scheme 477.

Phosphine-Catalyzed [4 + 2] Annulations of Ynones and Barbiturate-Derived Alkenes



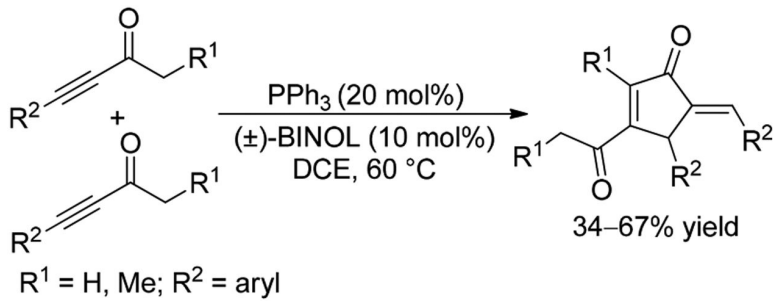
Scheme 478.

Organophosphine-Catalyzed Intermolecular Tomita Zipper-Cyclization of Ynone and Cyclic *N*-Sulfonyl-Iminoester

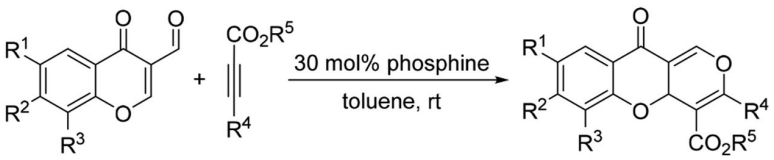


Scheme 479.

Phosphine-Catalyzed [3 + 3] Annulations of Azomethine Imines with Ynones

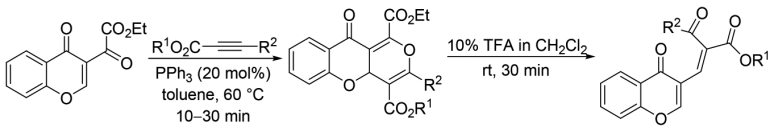


Scheme 480.
Phosphine-Catalyzed Umpolung Annulative Dimerization of Ynones



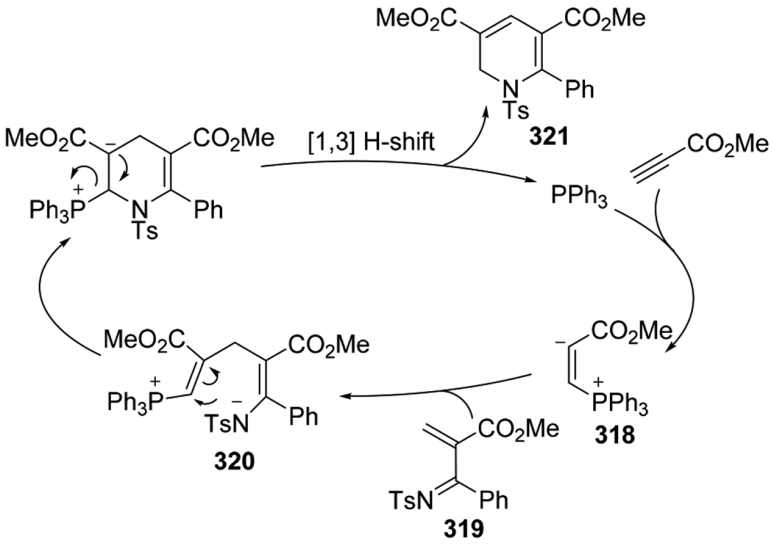
entry	R^1	R^2	R^3	R^4	R^5	phosphine	yield (%)
1	H	H	H	CO_2Me	Me	PPh_3	92
2	*i*Pr	H	H	CO_2Et	Et	PBu_3	99
3	H	OBn	Me	H	Me	PPh_3	60

Scheme 481.
Preparation of Functionalized Tricyclic Chromones



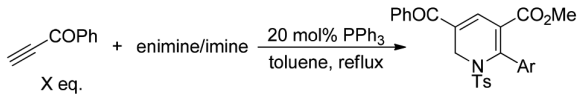
Scheme 482.

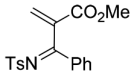
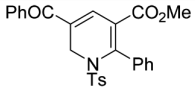
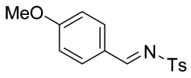
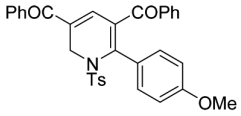
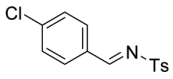
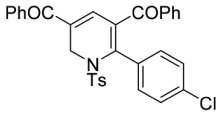
Synthesis of Chromone-Fused Dienes Through Phosphine-Catalyzed [4 + 2] Cycloadditions of α-Chromonyl Ketoester with 2-Alkynoates



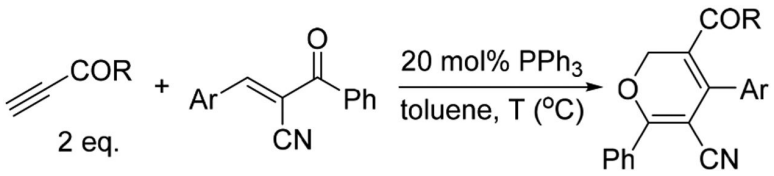
Scheme 483.

Proposed Mechanism for Annulation of Enimines and Propiolates Into Functionalized Dihydropyridines



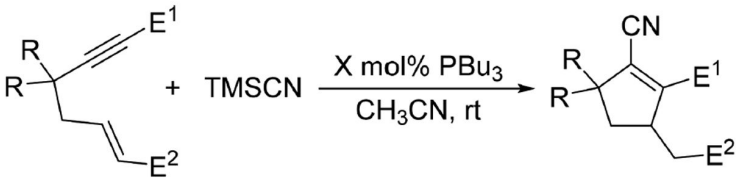
entry	X	enimine/imine	Product	yield (%)
1	2			59
2	3			90
3	3			67

Scheme 484.
Formation of Functionalized Dihydropyridines



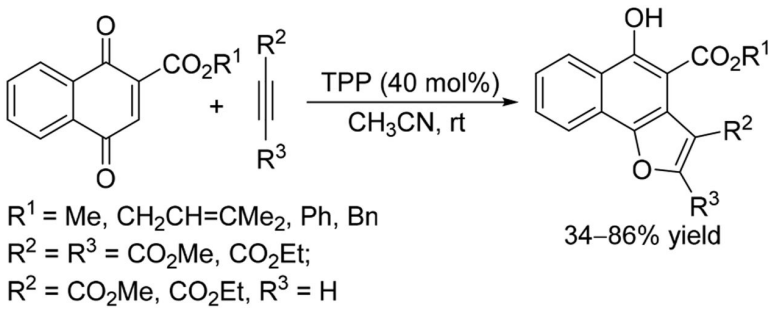
entry	R	Ar	T (°C)	yield (%)
1	Ph	2-furyl	rt	99
2	OMe	Ph	80	96
3	OMe	*p*-BrC_6H_4	80	37

Scheme 485.
Formation of Functionalized Dihydropyrans



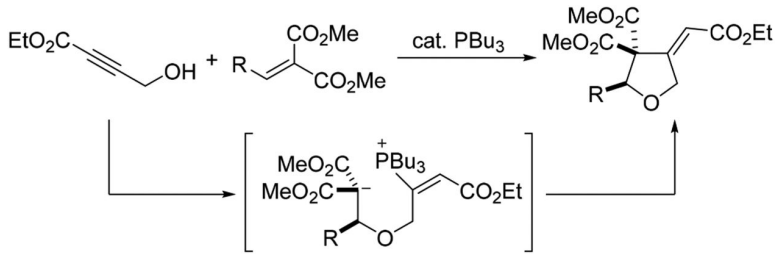
entry	R	E^1	E^2	X (mol%)	yield (%)
1	H	CO_2Me	CO_2Me	10	61
2	Me	CO_2Me	CO_2Me	50	61
3	H	CO_2Me	CN	15	41
4	Me	SO_2Ph	CN	15	50

Scheme 486.
Synthesis of Functionalized 2-Cyanocyclopentenes



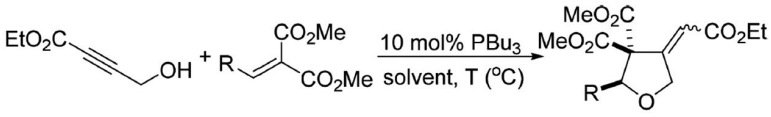
Scheme 487.

Phosphine-Catalyzed [3 + 2] Annulations of Activated 1,4-Naphthoquinones and Acetylenecarboxylates

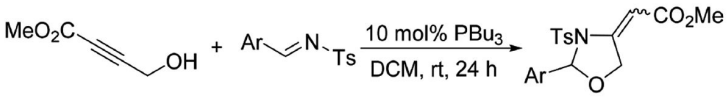


Scheme 488.

Proposed Mechanistic Pathway toward Functionalized Tetrahydrofurans

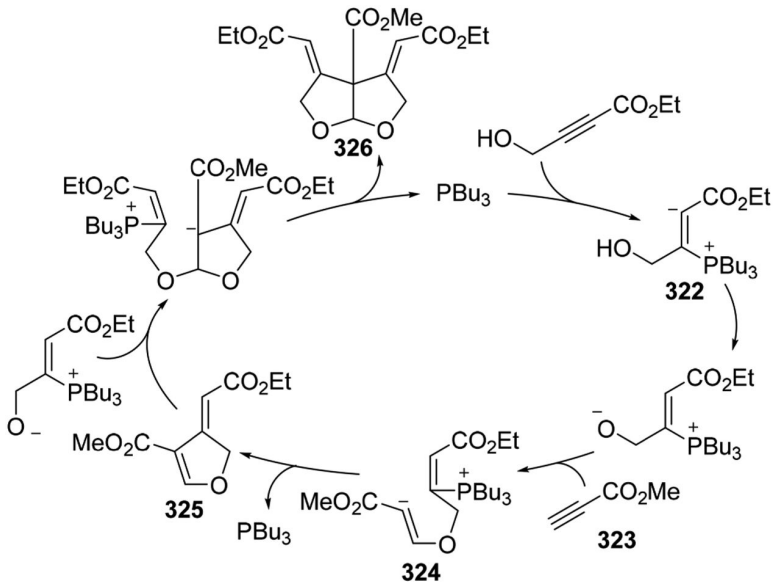


entry	R	solvent	T (°C)	time (h)	yield (%)	*E*/*Z*
1	*i*Bu	Neat	rt	8	92	1:2
2	*p*-BrC_6H_4	Toluene	80	6	85	1:5.1



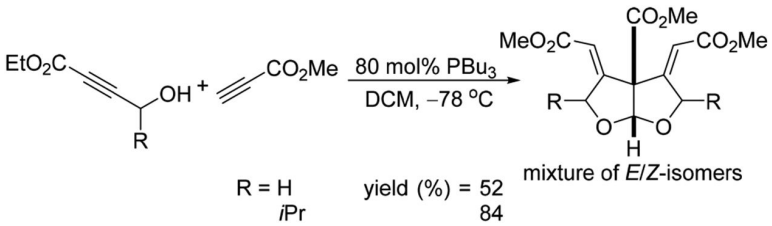
entry	Ar	yield (%)	*E*/*Z*
1	*p*-$O_2NC_6H_4$	95	3:2
2	*p*-$MeOC_6H_4$	<5	—

Scheme 489.
Formation of Tetrahydrofurans and Oxazolidines



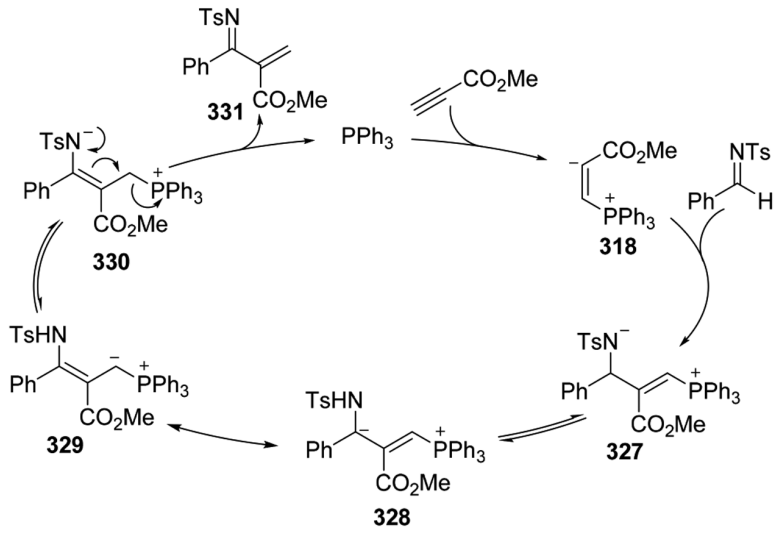
Scheme 490.

Proposed Route toward a 5,5-Fused Bicyclic Ring System

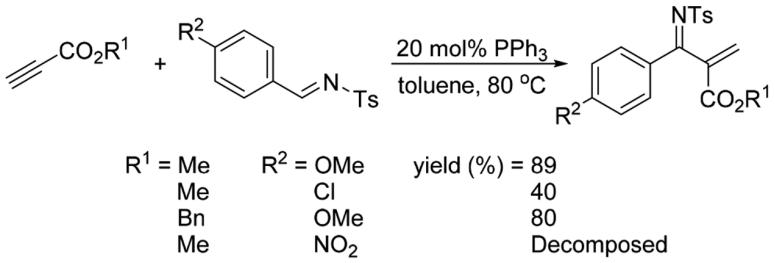


Scheme 491.

Formation of 5,5-Fused Bicyclic Furans

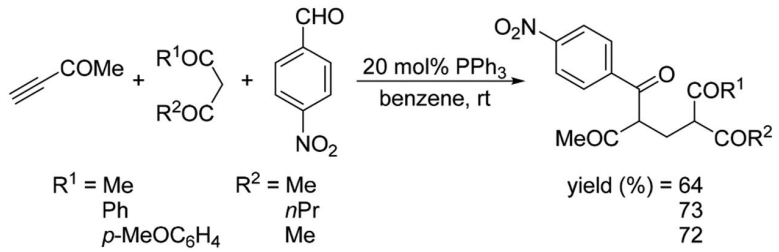


Scheme 492.
Proposed Mechanism of Enimine Formation



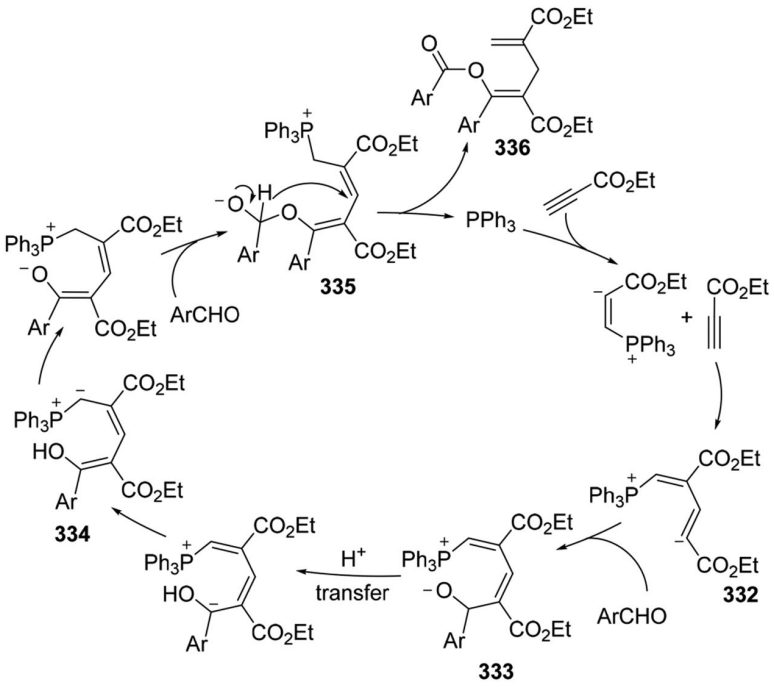
R^1 =	R^2 =	yield (%) =
Me	OMe	89
Me	Cl	40
Bn	OMe	80
Me	NO_2	Decomposed

Scheme 493.
Formation of Functionalized Enimines

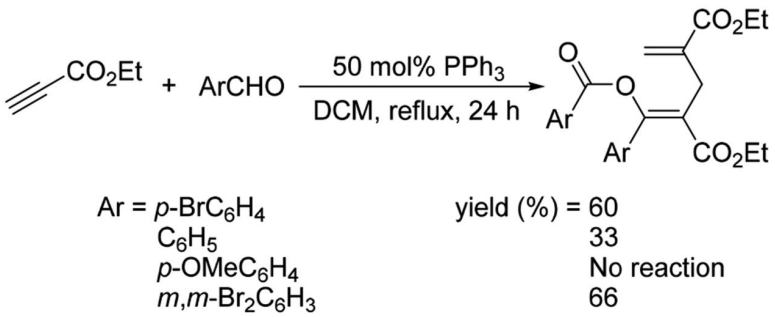


Scheme 494.

Synthesis of Functionalized 2,4-Diketopentane-1,5-diones

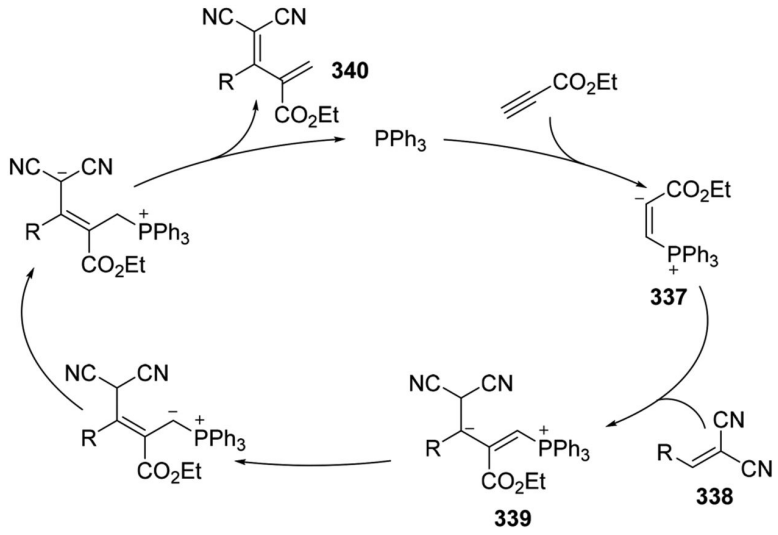


Scheme 495.
Proposed Mechanistic Pathway toward Vinyl Esters



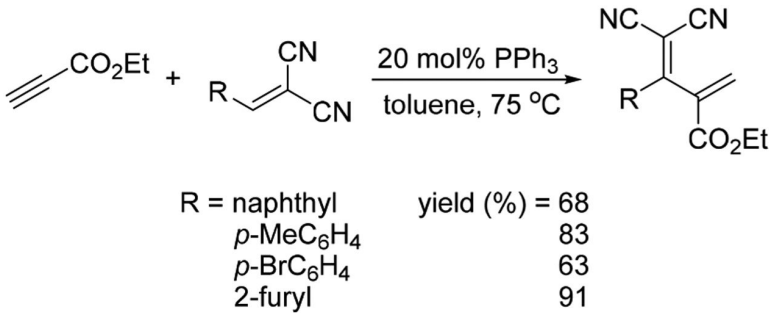
Ar =	yield (%) =
p-BrC_6H_4	60
C_6H_5	33
p-$OMeC_6H_4$	No reaction
m,*m*-$Br_2C_6H_3$	66

Scheme 496.
Formation of Functionalized Vinyl Esters



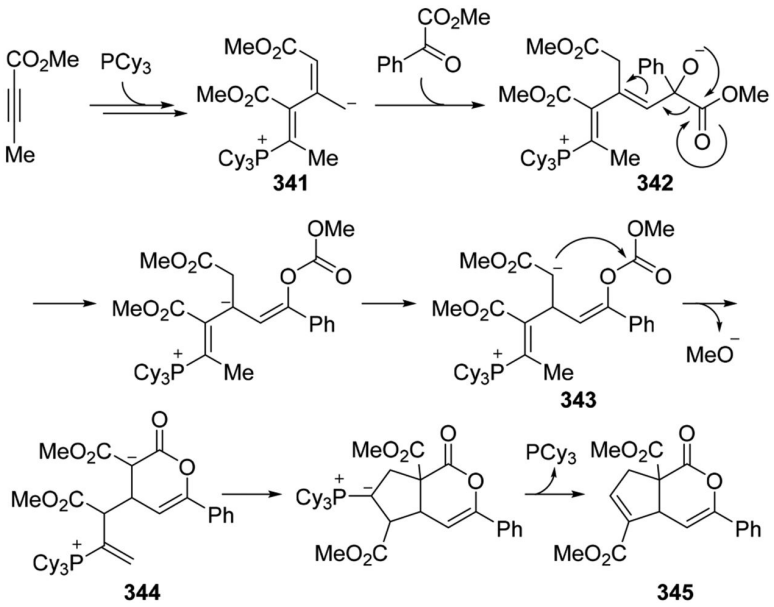
Scheme 497.

Proposed Mechanism for the Formation of Derivatized 1,3-Butadienes

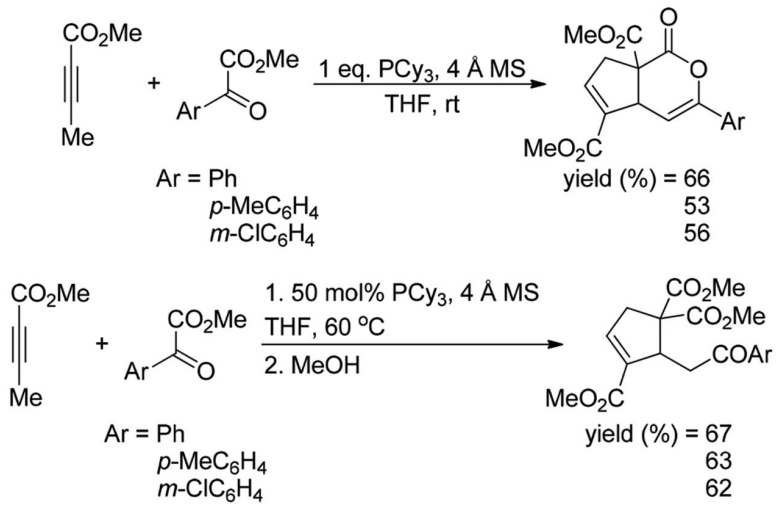


R =	yield (%) =
naphthyl	68
p-MeC_6H_4	83
p-BrC_6H_4	63
2-furyl	91

Scheme 498.
Formation of Functionalized 1,3-Butadienes

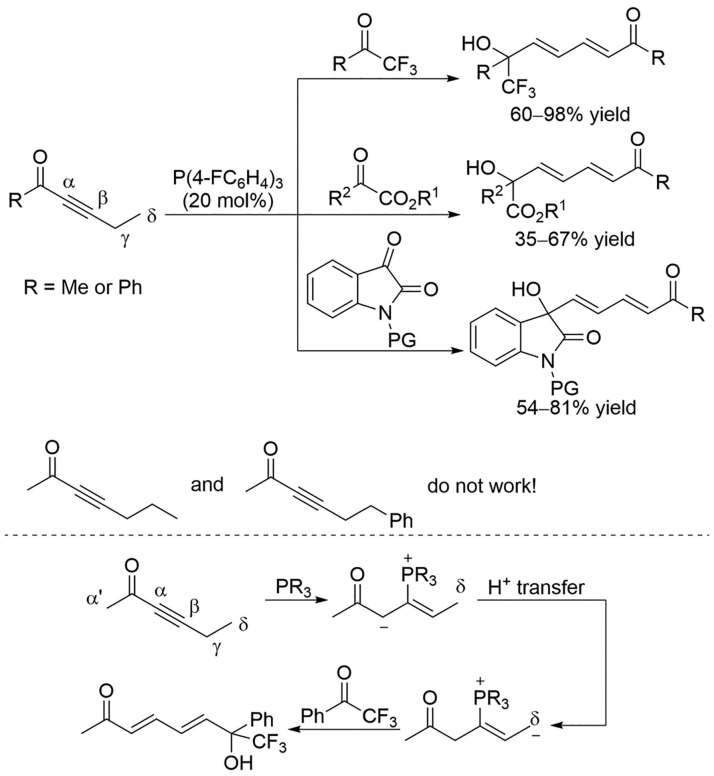


Scheme 499.
Proposed Mechanism for Cyclopentene Formation



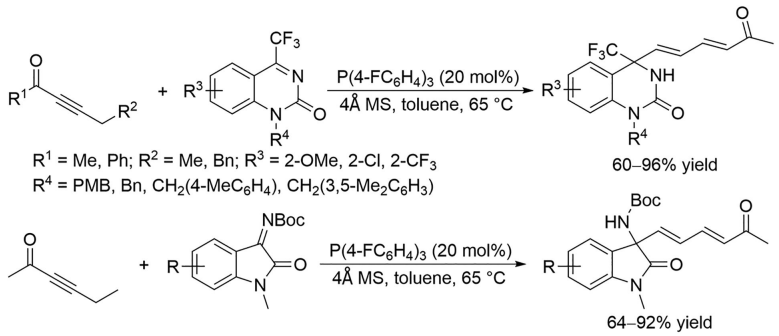
Scheme 500.

Synthesis of Functionalized Bicyclic Cyclopentenes



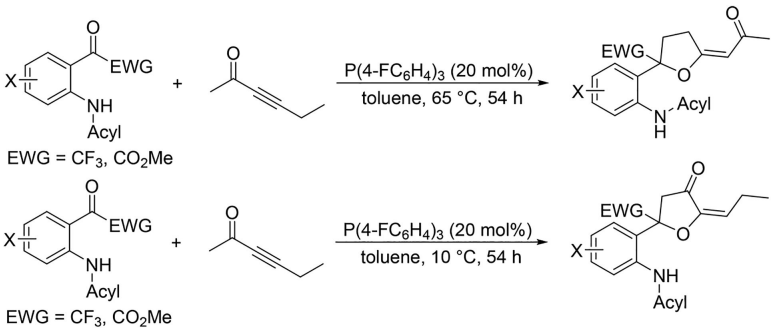
Scheme 501.

Phosphine-Catalyzed Nucleophilic Additions of the *δ*-Carbon of Alkynones to Electron-Deficient Carbonyl-Containing Compounds



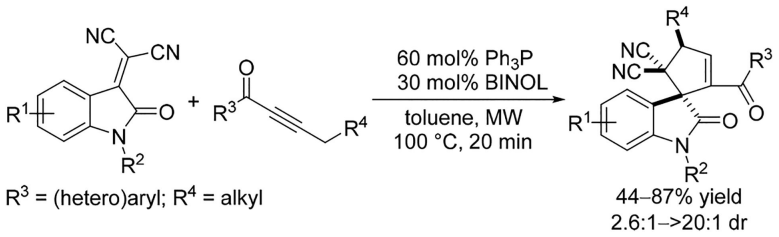
Scheme 502.

Phosphine-Catalyzed *δ*-Carbon Addition and Isomerization of Alkynones to Ketimines



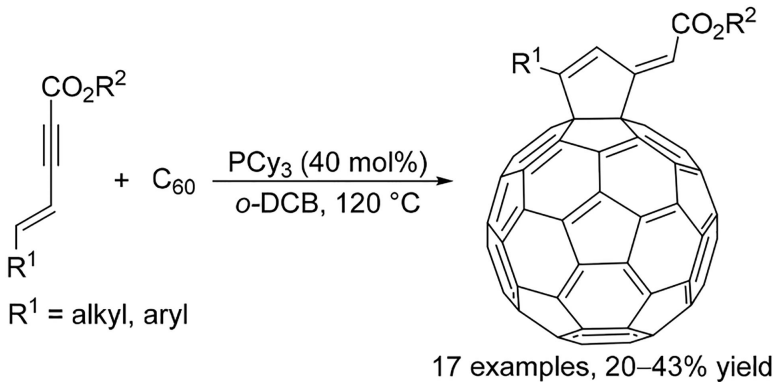
Scheme 503.

Phosphine-Catalyzed [3 + 2] Cycloadditions of Alkynones and Trifluoroacetyl Phenylamides



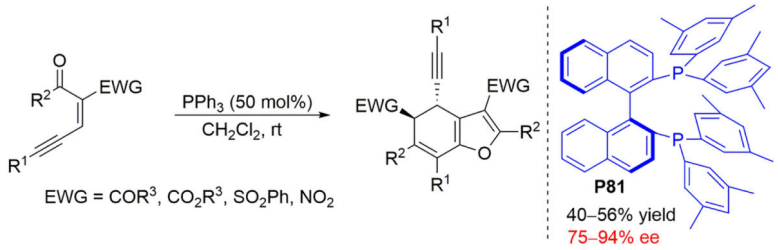
Scheme 504.

Microwave-Assisted Phosphine-Catalyzed Tomita Zipper Cyclization of Dicyanomethylideneoxindoles and Ynones



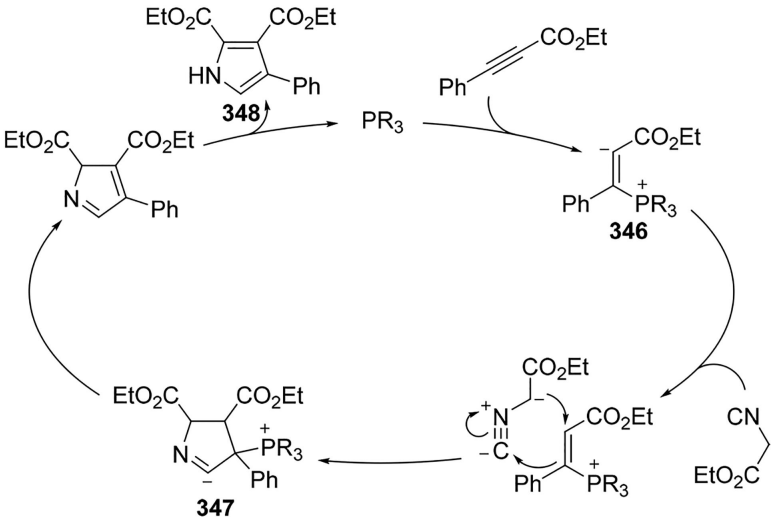
Scheme 505.

Tricyclohexylphosphine-Catalyzed [3 + 2] Cycloaddition of Enynoates with [60]Fullerene

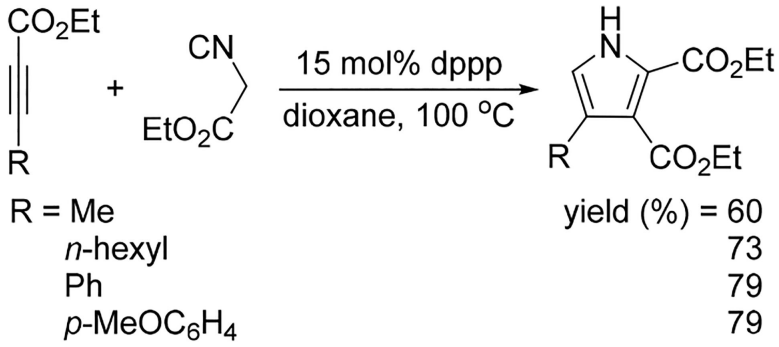


Scheme 506.

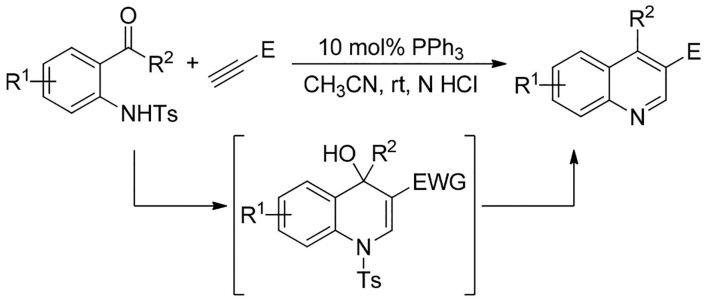
Phosphine-Mediated Dimerization of Conjugated Ene-Yne Ketones



Scheme 507.
Proposed Mechanism of Pyrrole Formation

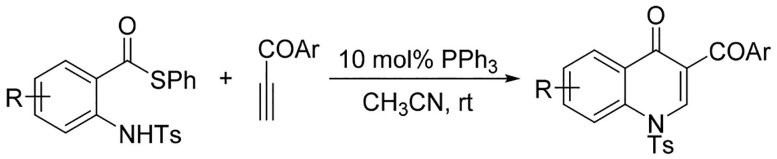


Scheme 508.
Synthesis of Functionalized Pyrroles



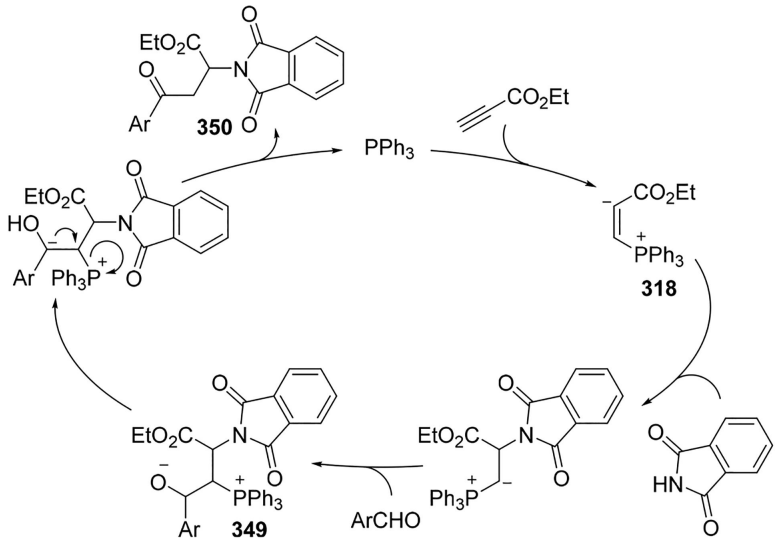
entry	R^1	R^2	E	yield (%)
1	4-F	H	COMe	96
2	4,5-MeO	H	COMe	99
3	H	H	COPh	95
4	H	H	Ts	30
5	H	Me	COPh	79
6	H	Ph	COPh	72

Scheme 509.
Synthesis of Functionalized Quinolines

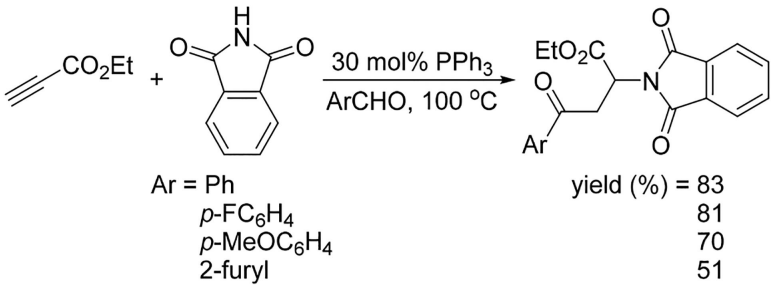


entry	R	Ar	yield (%)
1	H	*p*-FC_6H_4	75
2	H	2-thienyl	79
3	4,5-F	Ph	69
4	4,5-MeO	Ph	41
5	5-Br	Ph	87

Scheme 510.
Synthesis of Functionalized Quinolones

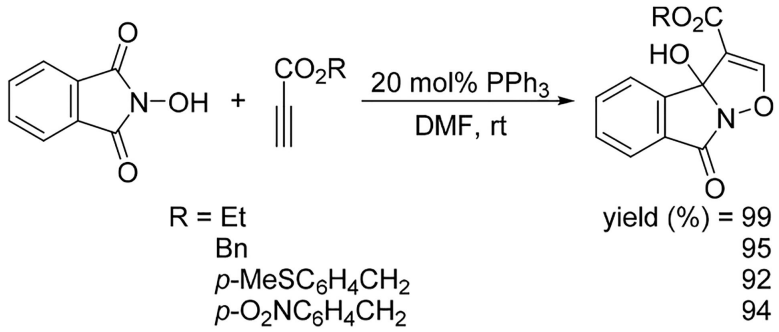


Scheme 511.
Proposed Mechanism of α-Amino-γ-ketoester Synthesis

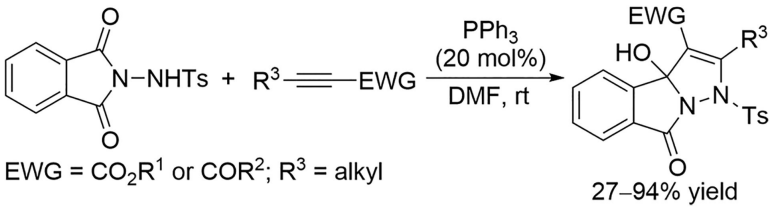


Ar	yield (%)
Ph	83
p-FC_6H_4	81
p-$MeOC_6H_4$	70
2-furyl	51

Scheme 512.
Synthesis of Functionalized α-Amino-γ-ketoesters

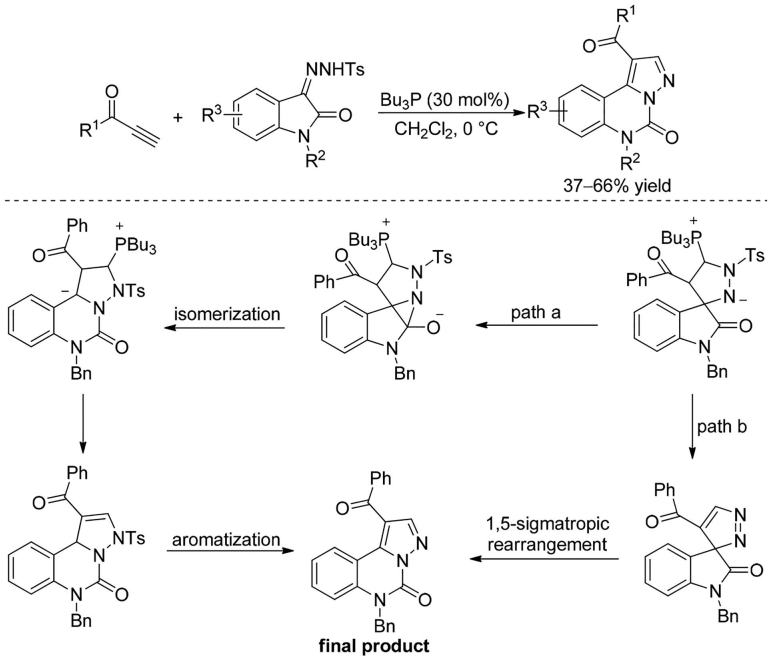


Scheme 513.
Synthesis of Functionalized Hydroxyisoxazoloisooxindoles



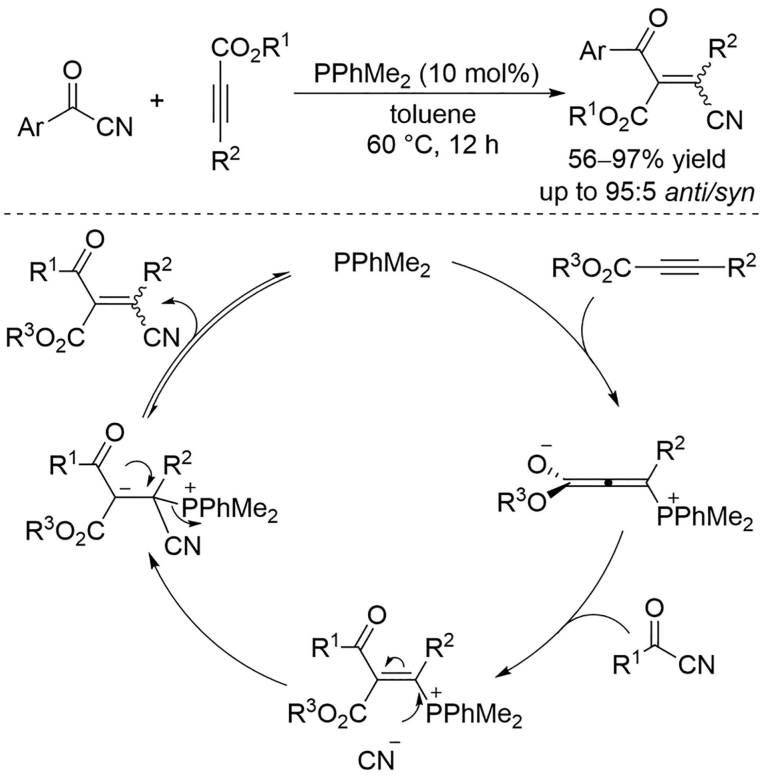
Scheme 514.

Phosphine-Catalyzed [3 + 2] Cyclization of *N*-Tosylaminophthalimides with Alkynoates or Alkynyl Ketones

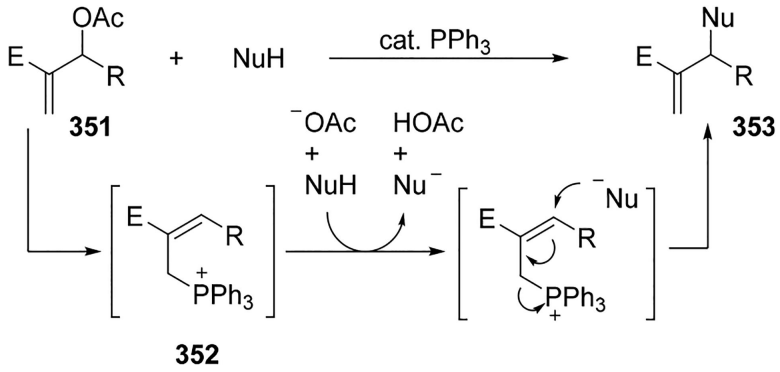


Scheme 515.

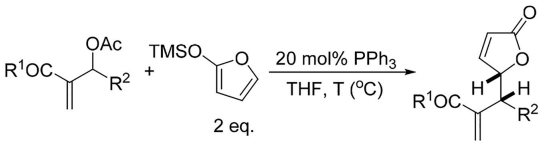
Phosphine-Catalyzed Cyclizations of Sulfonylhydrazones and Alkynyl Ketones



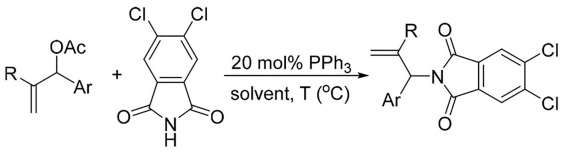
Scheme 516.
Phosphine-Catalyzed Acylcyanation of Alkynoates with Acyl Cyanides



Scheme 517.
Proposed Mechanism for the S_N2'–S_N2' Process

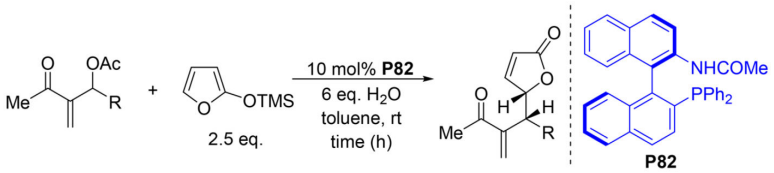


entry	R^1	R^2	T (°C)	yield (%)	cis:trans
1	Me	*p*-$O_2NC_6H_4$	0	88	>95:5
2	Me	*n*Pr	50	63	>95:5
3	Me		rt	45	>95:5
4	OMe	*n*Pr	80	67	2.8:1



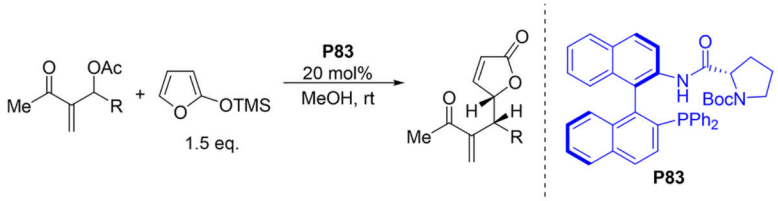
entry	R	Ar	solvent	T (°C)	yield (%)
1	COMe	Ph	THF	rt	95
2	P(O)$(OEt)_2$	*p*-$O_2NC_6H_4$	dioxane	110	90

Scheme 518.
Phosphine-Catalyzed Allylic Alkylations and Aminations



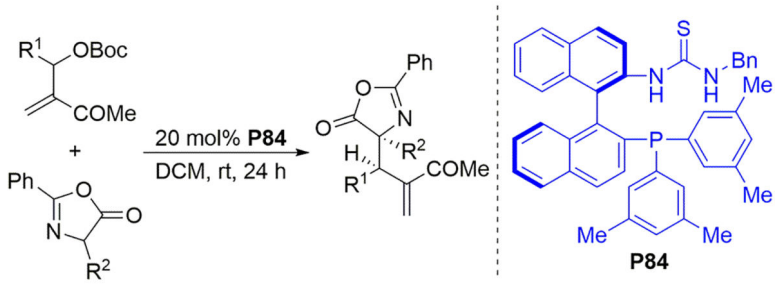
entry	R	time (h)	yield (%)	ee (%)
1	*p*-MeC_6H_4	36	94	96
2	*p*-$O_2NC_6H_4$	24	98	91
3	*n*Pr	96	60	71
4	Ph	72	45	84

Scheme 519.
Asymmetric Formation of γ-Butenolides



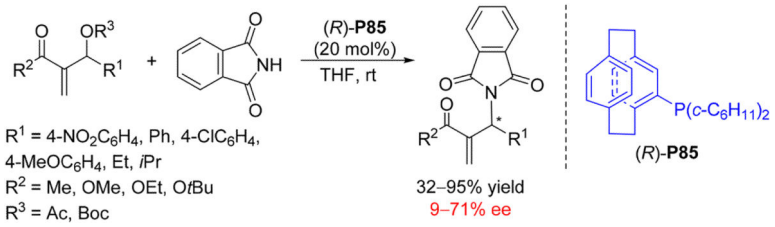
entry	R	time (h)	yield (%)	ee (%)
1	*p*-$O_2NC_6H_4$	5	92	97
2	*m*-ClC_6H_4	5	95	97
3	Ph	24	65	97
4	*p*-MeC_6H_4	60	75	98

Scheme 520.
Improved Procedure for 2-Trimethylsilyloxyfuran Addition



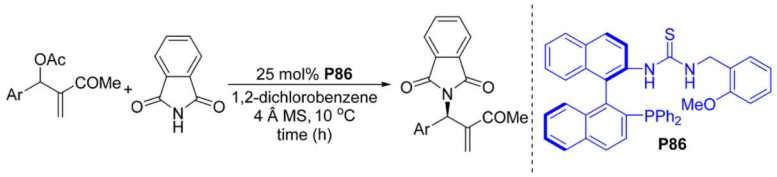
entry	R^1	R^2	yield (%)	ee (%)	dr
1	*p*-$O_2NC_6H_4$	*i*Pr	95	98	4:1
2	*p*-MeC_6H_4	*i*Pr	91	96	20:1
3	2-thienyl	*i*Pr	95	95	12:1
4	Et	*i*Pr	96	85	7:1
5	*p*-MeC_6H_4	Me	90	96	10:1

Scheme 521.
Asymmetric Formation of Functionalized Oxazolones



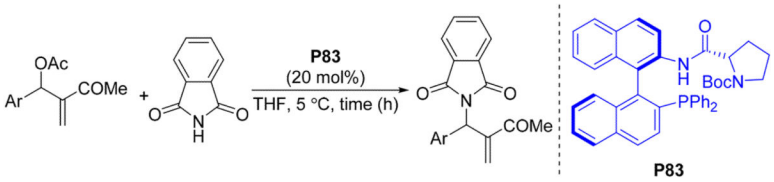
Scheme 522.

Chiral Phosphine-Catalyzed Allylic Amination of MBH Adducts



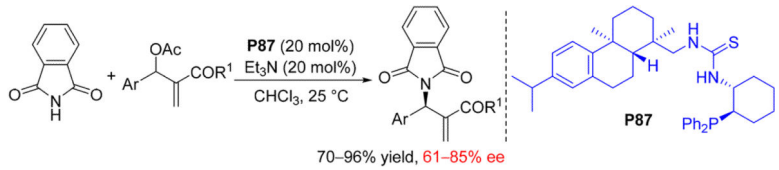
entry	Ar	time (h)	yield (%)	ee (%)
1	*p*-$O_2NC_6H_4$	61	91	90
2	*p*-MeC_6H_4	118	83	85
3	*p*-NCC_6H_4	87	>99	85
4	*p*-$F_3CC_6H_4$	85	78	87
5	Ph	111	72	81

Scheme 523.
Asymmetric Amination of MBHADs



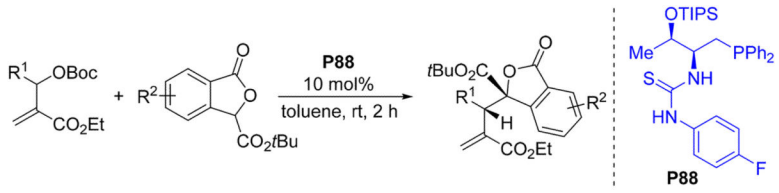
entry	Ar	time (h)	yield (%)	ee (%)
1	*p*-NCC_6H_4	36	91	58
2	*p*-MeC_6H_4	72	75	45
3	Ph	72	75	34
4	*m*-$O_2NC_6H_4$	24	79	50

Scheme 524.
Enantioselective Amination of MBHADs



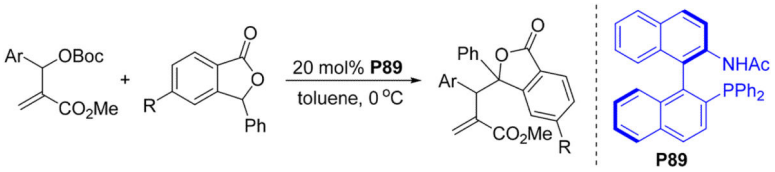
Scheme 525.

Chiral Phosphine-Catalyzed Allylic Amination of MBH Acetates with Phthalimide



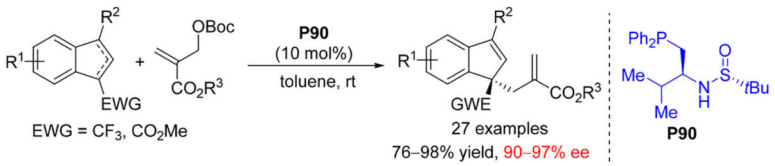
entry	R^1	R^2	yield (%)	ee (%)
1	Ph	H	96	98
2	*p*-$O_2NC_6H_4$	H	91	98
3	Ph	5-CN	92	98
4	*i*Bu	H	92	98

Scheme 526.
Asymmetric Synthesis of Functionalized Acrylates



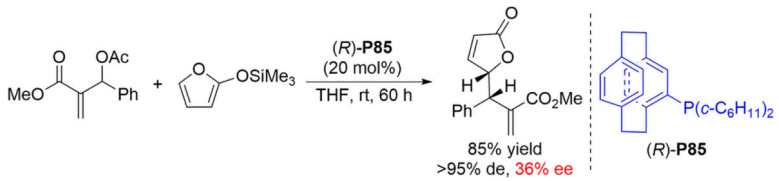
entry	Ar	R	yield (%)	ee (%)	dr
1	Ph	Cl	93	92	56:44
2	Ph	*t*Bu	91	94	64:37
3	*m*-NCC_6H_4	H	84	90	56:44
4	*p*-FC_6H_4	H	93	92	64:36

Scheme 527.
Asymmetric Formation of Functionalized Acrylates



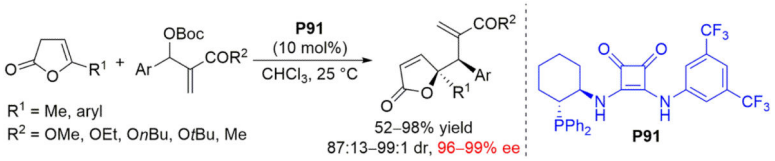
Scheme 528.

Chiral Sulfinamide Phosphine-Catalyzed Allylic Alkylation of Indenes with MBH Carbonates



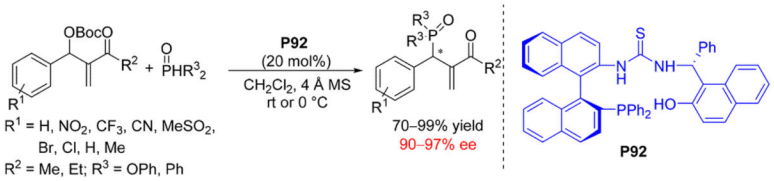
Scheme 529.

Chiral Phosphine-Catalyzed Preparation of an Enanthioenriched γ-Butenolide



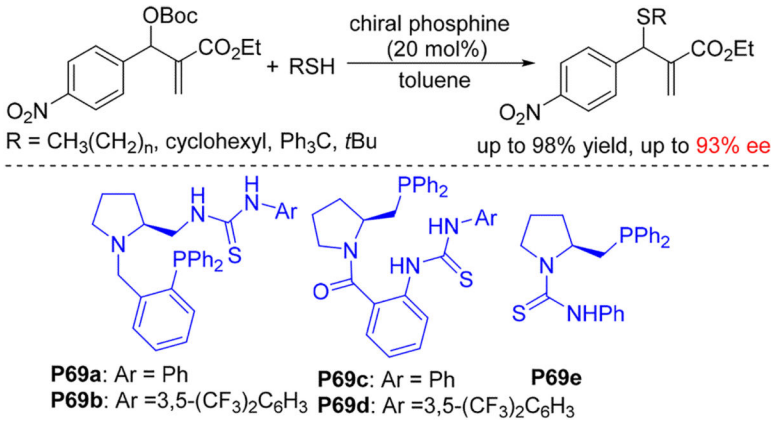
Scheme 530.

Chiral Squaramide-Phosphine-Catalyzed Enantioselective Allylic Alkylations of MBH Carbonates with β,γ-Butenolides



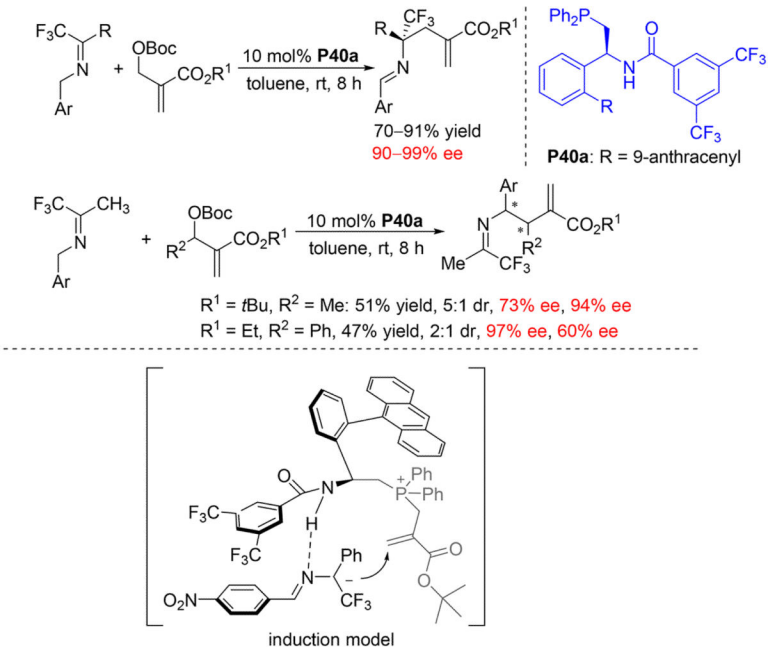
Scheme 531.

Chiral Phosphine-Catalyzed Allylic Substitution of MBH Adducts by Phosphites or Phosphane Oxides



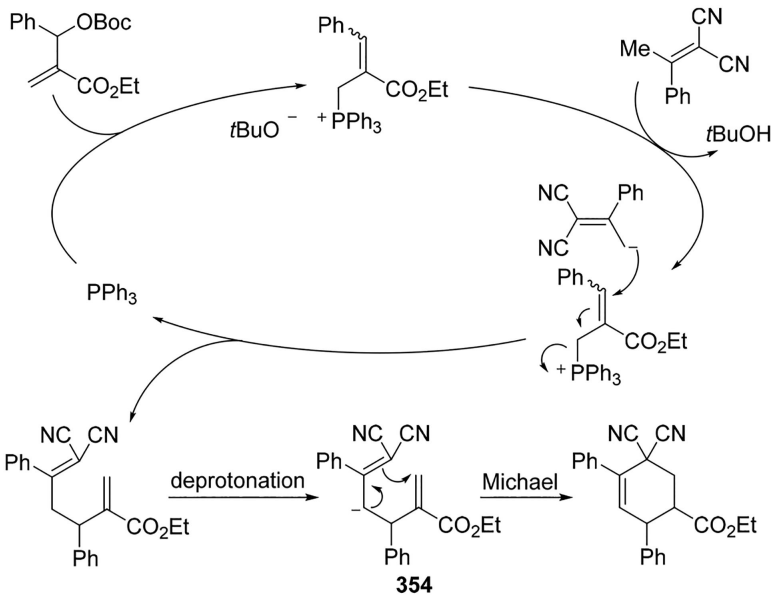
Scheme 532.

Asymmetric Allylic Substitutions of MBH Adducts with Alkyl Thiols Resulting in C–S Bond Formation



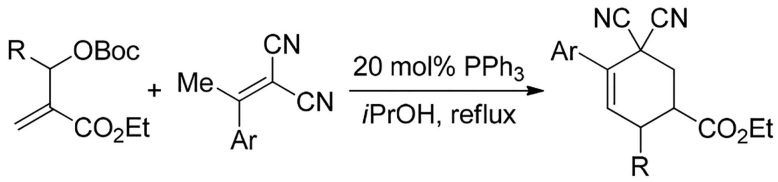
Scheme 533.

Phosphine-Catalyzed Enantioselective Umpolung Addition of Trifluoromethyl Ketimines to MBH Carbonates



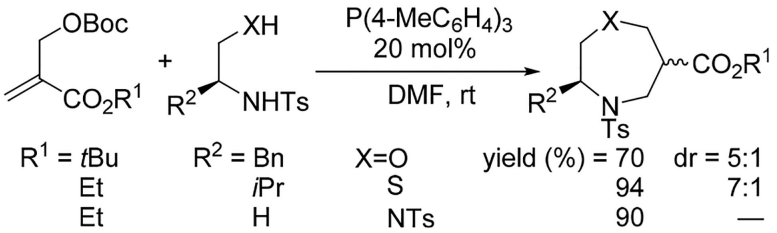
Scheme 534.

Proposed Reaction Pathway for Phosphine Catalysis of MBHADs with Alkylidenemalononitriles



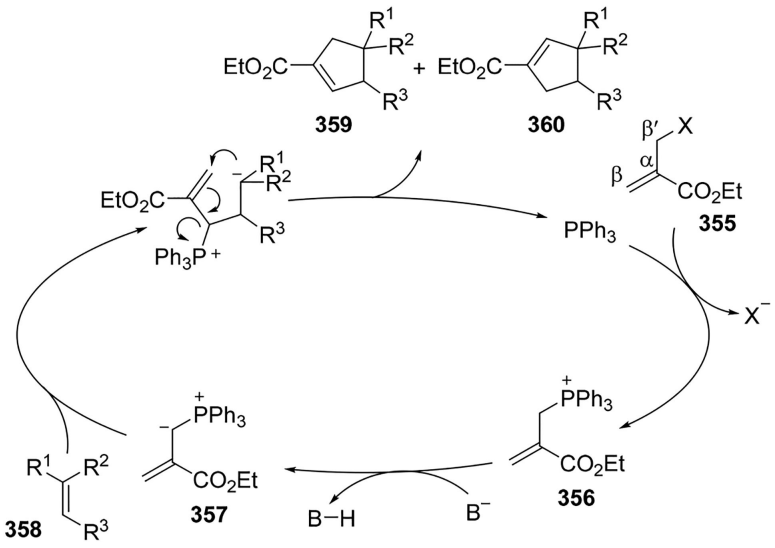
entry	R	Ar	yield (%)	trans:cis
1	Ph	Ph	89	5.1:1
2	*p*-$O_2NC_6H_4$	Ph	74	>10:1
3	Me	*p*-BrC_6H_4	100	>10:1
4	Me	*t*Bu	75	>10:1

Scheme 535.
Formation of Cyclohexenes Using MBHADs

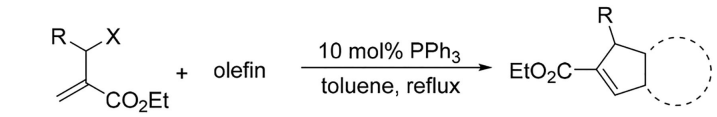


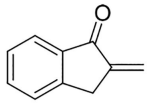
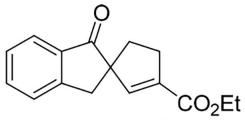
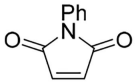
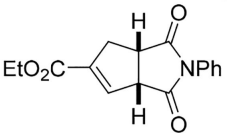
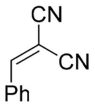
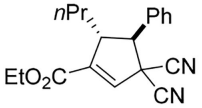
Scheme 536.

Synthesis of Functionalized 1,4-Oxazepanes, 1,4-Thiazepanes, and 1,4-Diazepanes



Scheme 537.
Proposed Mechanism of [3 + 2] Annulations with MBHADs

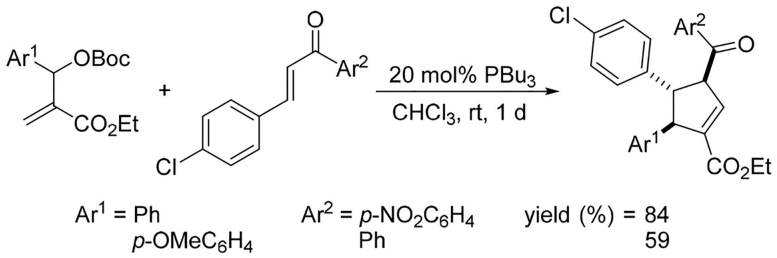


entry	R	X	time (h)	olefin	product	yield (%)
1	H	Br	20			72[a]
2	H	OBoc	2			74
3	*n*Pr	OBoc	1			90[b]

Scheme 538.

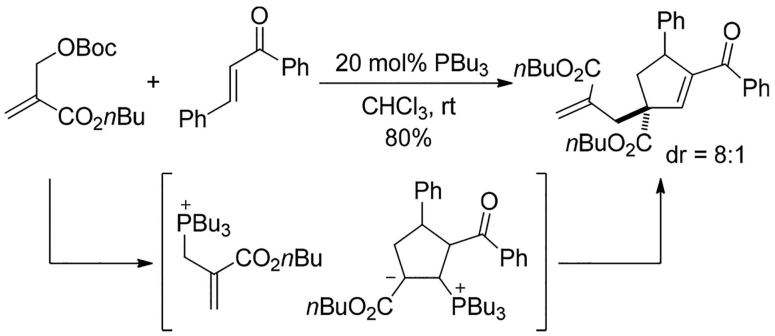
Phosphine-Catalyzed [3 + 2] Annulations with MBHADs

[a]1.5 equiv K_2CO_3 is used as additive. [b]Reaction performed at rt.



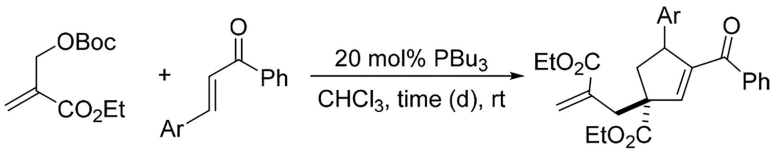
Ar^1	Ar^2	yield (%)
Ph	*p*-$NO_2C_6H_4$	84
p-$OMeC_6H_4$	Ph	59

Scheme 539.
Synthesis of Functionalized Cyclopentenes



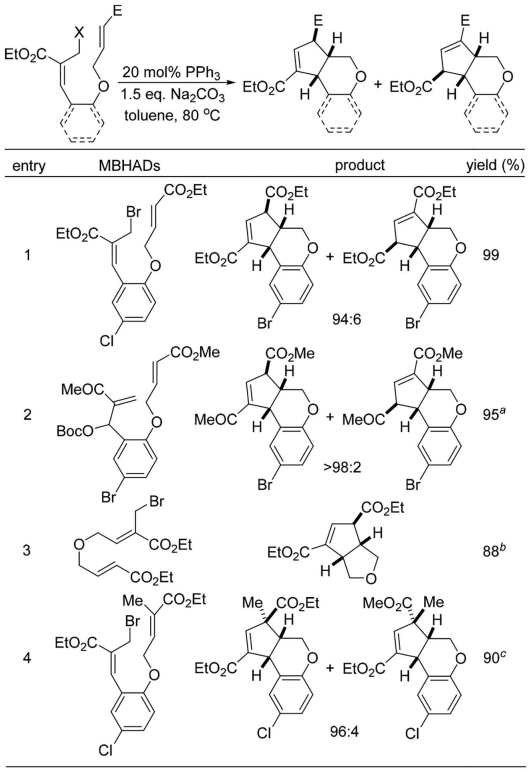
Scheme 540.

Proposed Cascade [3 + 2] Cyclization–Allylic Alkylation Pathway



entry	Ar	time (days)	dr	yield (%)
1	*p*-FC_6H_4	1	10:1	80
2	*p*-ClC_6H_4	2	7:1	91
3	*m*-$O_2NC_6H_4$	3	7:1	83
4	*p*-$MeOC_6H_4$	2	11:1	49

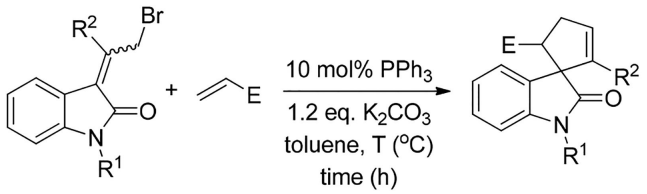
Scheme 541.
Generation of Alkylated Cyclopentenes



Scheme 542.

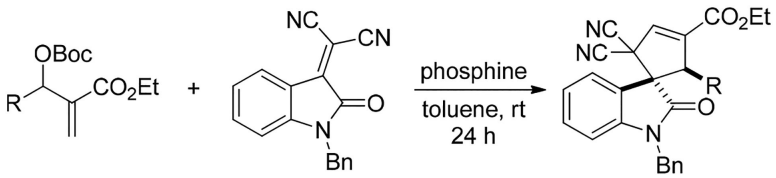
Intramolecular [3 + 2] Annulation with MBHADs

[a]Reaction performed with 10 mol % PBu_3 and 20 mol % $Ti(OiPr)_4$ at rt. [b]1.5 equiv of Cs_2CO_3 was used instead of Na_2CO_3 at 90 °C. [c]Reaction performed at 90 °C.



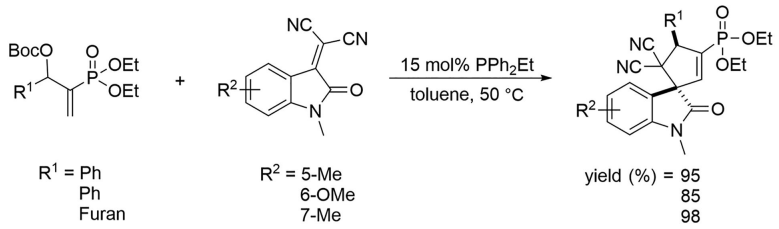
entry	R^1	R^2	E	T (°C)	time (h)	yield (%)
1	Me	CO_2Me	CO_2Me	80	12	65
2	Bn	CO_2Me	COMe	60	2	48
3	Propargyl	CN	CO_2Me	60	6	66

Scheme 543.
[3 + 2] Annulations of Isatin-Derived MBHADs

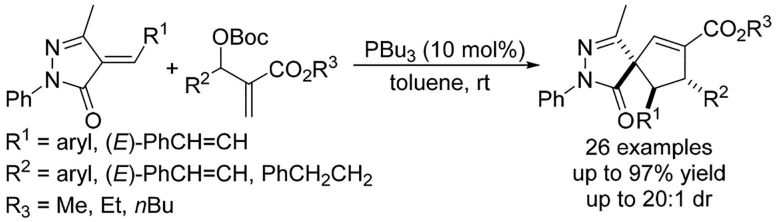


entry	R	phosphine	dr	yield (%)
1	*p*-$O_2NC_6H_4$	20 mol% PPh_3	>99:1	86
2	*p*-NCC_6H_4	20 mol% PPh_3	>99:1	98
3	*p*-$MeOC_6H_4$	10 mol% dppb	19:1	89
4	H	10 mol% dppb	12:1	81
5	Me	10 mol% dppb	2:1	56

Scheme 544.
Formation of Functionalized Spirocyclopenteneoxindoles

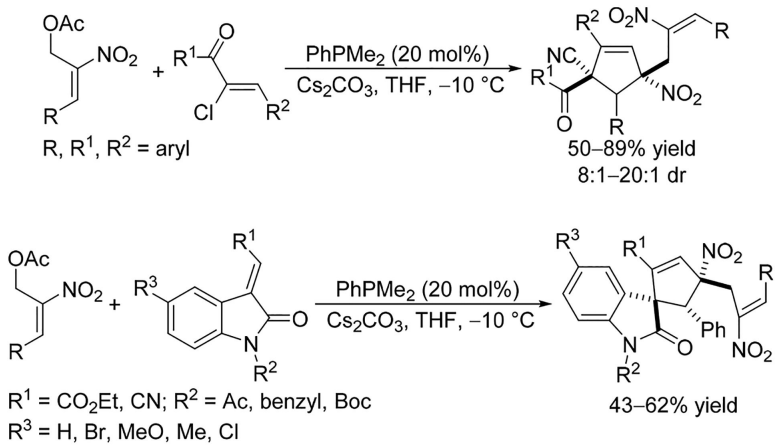


Scheme 545.
Synthesis of Functionalized Spirooxindoles



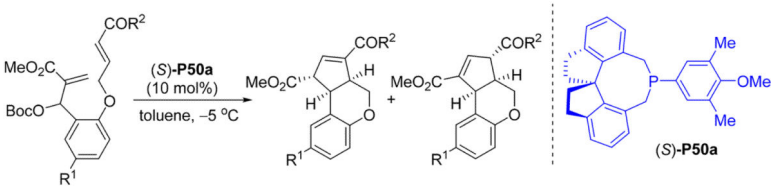
Scheme 546.

Phosphine-Catalyzed [3 + 2] Annulations of MBH Carbonates with Pyrazolone-Derived Alkenes



Scheme 547.

Lewis Base-Catalyzed Annulations of Nitroallylic Acetates with Electron-Deficient Alkenes

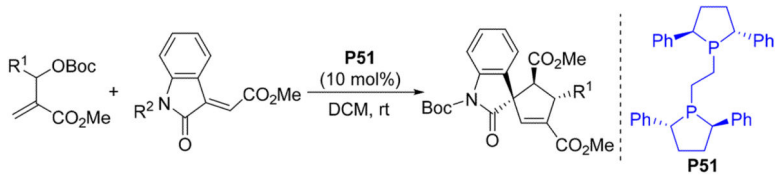


entry	R^1	R^2	yield (%)	ee (%)	dr
1	Cl	OMe	91	86	80:20
2	Cl	OMe	99[a]	86	93:7
3	H	Me	75[a]	77	>95:5

Scheme 548.

Asymmetric Intramolecular [3 + 2] Annulations

[a]$Ti(OiPr)_4$ was added.

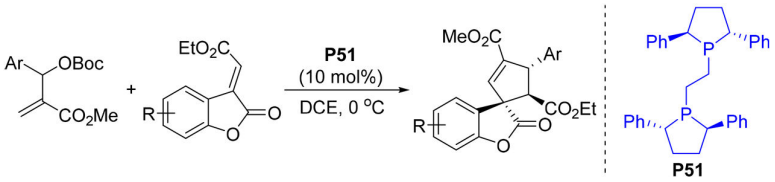


entry	R^1	R^2	yield (%)	ee (%)
1	Ph	C(O)NHPh	85	99
2	*p*-$O_2NC_6H_4$	C(O)NHPh	81	96
3	Me	C(O)NHPh	47	46
4	Ph	Boc	91[a]	95

Scheme 549.

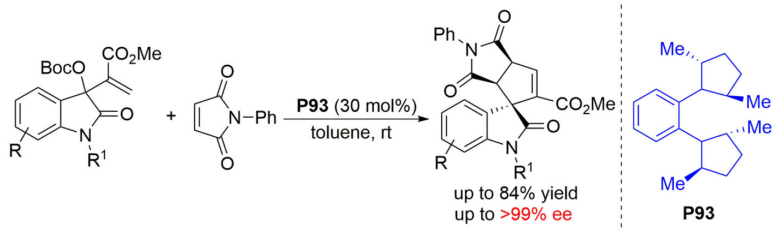
Asymmetric [3 + 2] Annulations with Methyleneindolinones

[a]Reaction performed at −20 °C with 20 mol % catalyst.



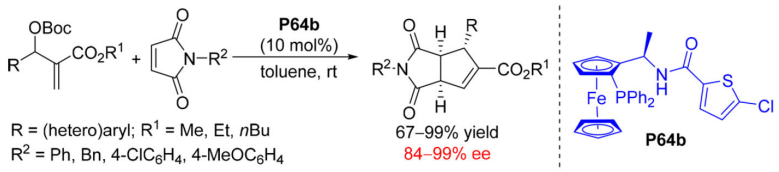
entry	Ar	R	yield (%)	ee (%)
1	Ph	H	95	97
2	*p*-NCC$_6$H$_4$	H	94	92
3	2-furyl	H	86	81
4	Ph	6-MeO	94	96

Scheme 550.
Asymmetric Synthesis of Functionalized Spirobenzofuranones



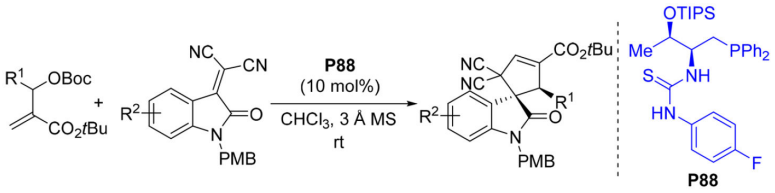
Scheme 551.

Enantioselective Phosphine-Catalyzed [3 + 2] Cycloadditions of MBH Carbonates of Isatins with *N*-Phenylmaleimide



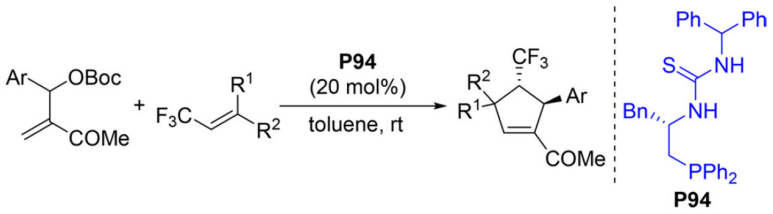
Scheme 552.

Chiral Bifunctional Ferrocenylphosphine-Catalyzed Asymmetric [3 + 2] Cycloadditions of MBH Carbonates with Maleimides



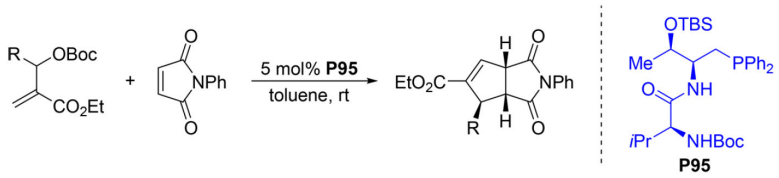
entry	R^1	R^2	yield (%)	ee (%)	α:γ
1	Ph	H	93	96	1:13
2	*p*-NCC_6H_4	H	92	93	1:14
3	*p*-MeC_6H_4	H	94	94	1:12
4	2-naphthyl	H	94	94	1:16
5	2-thienyl	H	91	90	1:1
6	Ph	5,7-di-Me	86	96	1:10
7	Ph	7-F	85	94	1:7

Scheme 553.
Asymmetric [3 + 2] Annulations with MBHADs



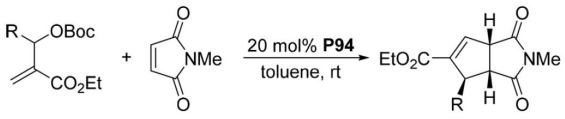
entry	Ar	R^1	R^2	yield (%)	ee (%)
1	*m*-$O_2NC_6H_4$	CO_2Me	CO_2Me	>99	90
2	*p*-BrC_6H_4	CO_2Me	CO_2Me	98	96
3	Ph	CO_2Me	CO_2Me	76	95
4	*p*-BrC_6H_4	CO_2Et	CO_2Et	98	96
5	*p*-BrC_6H_4	H	CO_2Et	trace	–

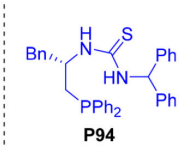
Scheme 554.
Synthesis of Functionalized Cyclopentenes



entry	R	yield (%)	ee (%)	dr
1	Ph	93	99	>25:1
2	*p*-$O_2NC_6H_4$	93	98	>25:1
3	2-thienyl	95	>99	18:1
4	CO_2Et	95	>99	12:1

Scheme 555.
Asymmetric Synthesis of Functionalized Cyclic Imides

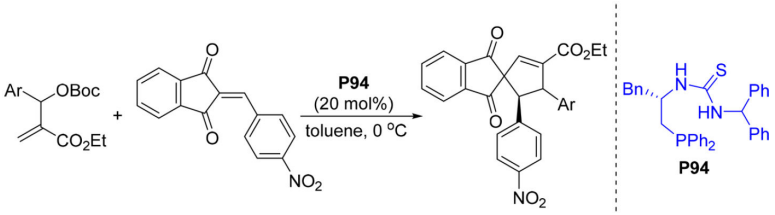




P94

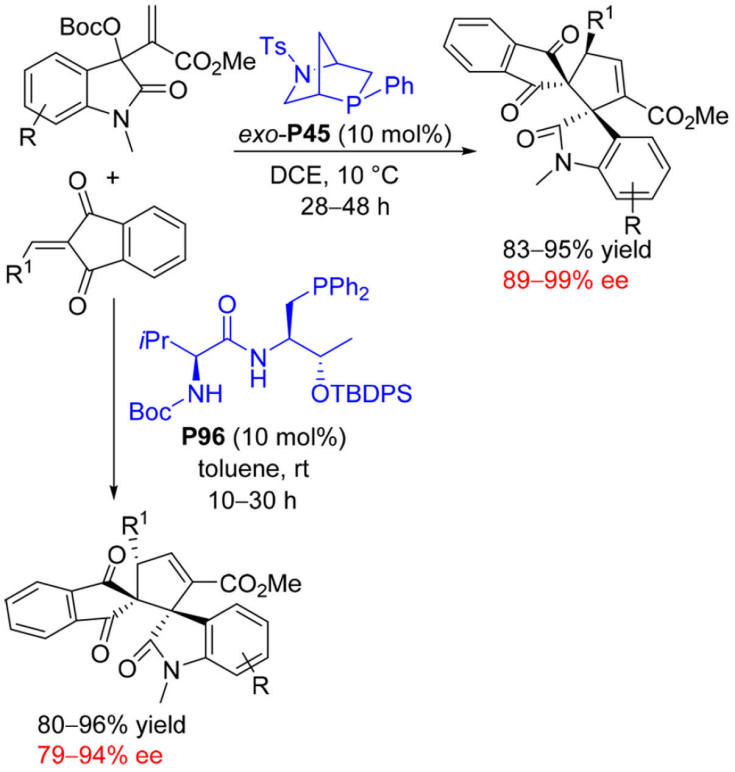
entry	R	yield (%)	ee (%)
1	Ph	74	94
2	*p*-BrC_6H_4	79	95
3	*p*-$MeOC_6H_4$	55	98
4	2-furyl	69	96

Scheme 556.
Enantioselective Synthesis of Functionalized Cyclic Imides



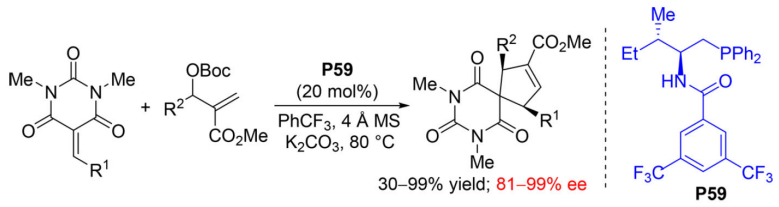
entry	Ar	yield (%)	ee (%)
1	*o*-BrC_6H_4	50	97
2	*m*-$O_2NC_6H_4$	75	87
3	*o*,*m*-$Cl_2C_6H_3$	67	98
4	*p*-MeC_6H_4	trace	–

Scheme 557.
Asymmetric Synthesis of Functionalized Spiroindan-1,3-diones



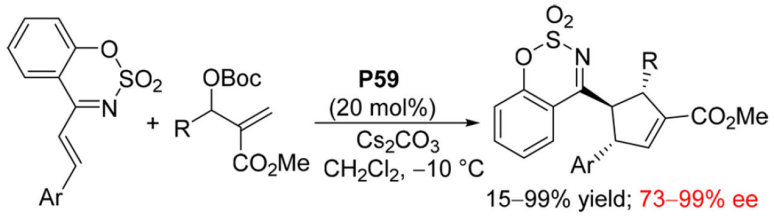
Scheme 558.

Chiral Phosphine–Catalyzed Asymmetric [3 + 2] Annulations of MBH Carbonates Derived from Isatins and 2-Alkylidene-1*H*-indene-1,3(2*H*)-diones



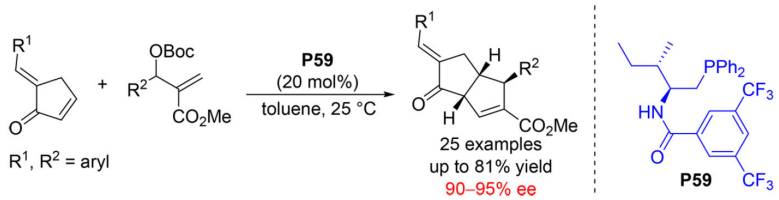
Scheme 559.

Enantioselective Phosphine-Catalyzed [3 + 2] Cycloadditions of MBH Cycloadducts with Barbiturate-Derived Alkenes



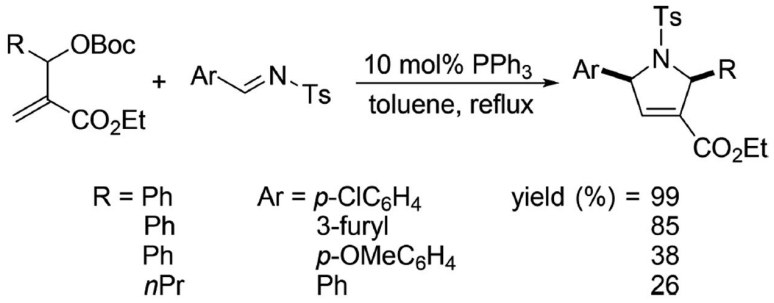
Scheme 560.

Phosphine-Catalyzed Asymmetric [3 + 2] Cycloadditions of MBH Cycloadducts with Cyclic 1-Azadienes



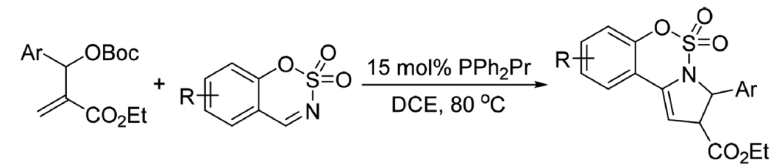
Scheme 561.

Multifunctional Chiral Phosphine-Catalyzed Asymmetric [3 + 2] Annulations of 5-Arylmethylenecyclopent-2-enones and MBH Carbonates



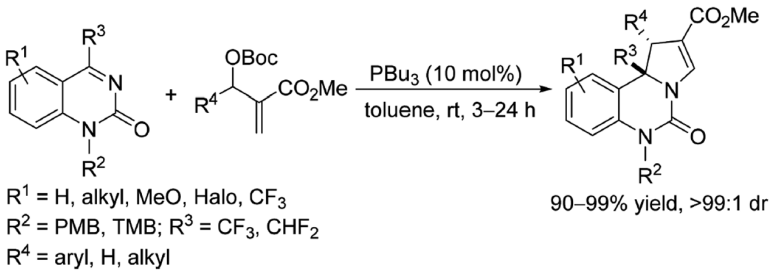
R = Ph	Ar = *p*-ClC$_6$H$_4$	yield (%) = 99
Ph	3-furyl	85
Ph	*p*-OMeC$_6$H$_4$	38
*n*Pr	Ph	26

Scheme 562.
Formation of Pyrrolines Using MBHADs



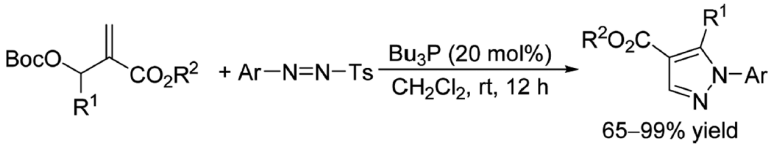
Ar	R	yield (%)
Ar = *p*-FC_6H_4	R = H	= 70
p-$MeOC_6H_4$	H	72
Ph	6-Cl	71
Ph	6-*t*Bu	61

Scheme 563.
Synthesis of Functionalized Cyclic Sulfamidates



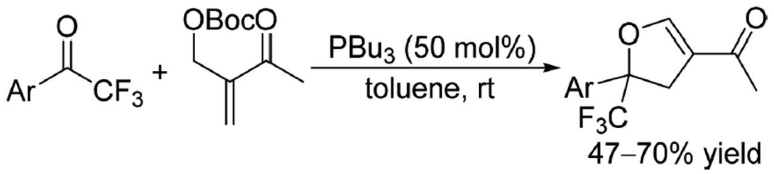
Scheme 564.

Phosphine-Catalyzed [3 + 2] Cycloadditions of MBH Carbonates with Cyclic N-Acyl-Substituted Ketimines



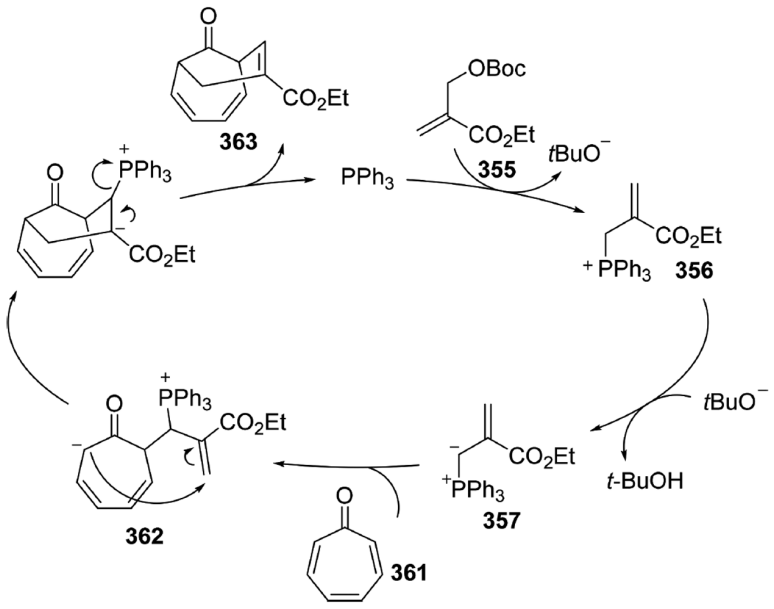
Scheme 565.

Phosphine-Catalyzed [3 + 2] Cycloadditions of MBH Adducts With Arylazosulfones

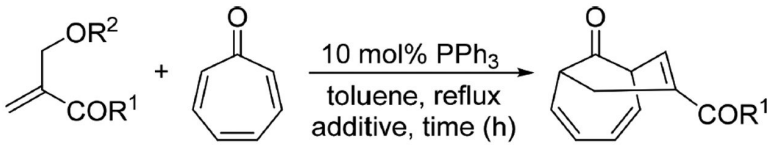


Scheme 566.

Phosphine-Promoted [3 + 2] Cycloadditions Between Nonsubstituted MBH Carbonates and Trifluoromethyl Ketones

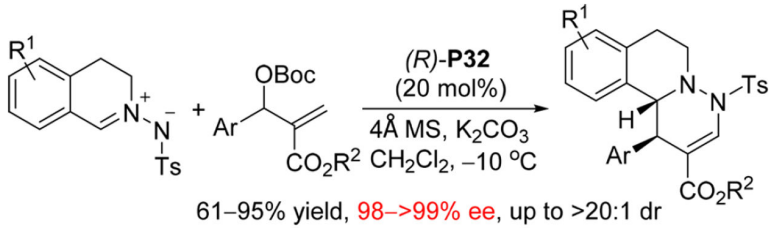


Scheme 567.
Proposed Mechanism for the [6 + 3] Annulation



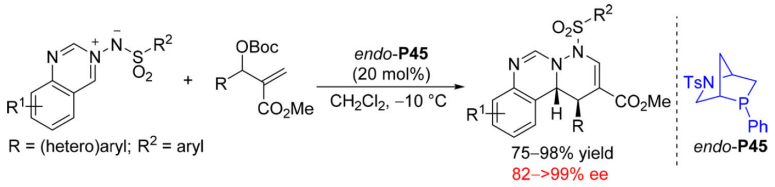
entry	R^1	R^2	additive	time (h)	yield (%)
1	OEt	Boc	–	3	90
2	Ph	Ac	K_2CO_3	1	85
3	*p*-BrC_6H_4	Ac	K_2CO_3	1	95

Scheme 568.
Synthesis of Functionalized [4.5.1]-Bicyclic Adducts



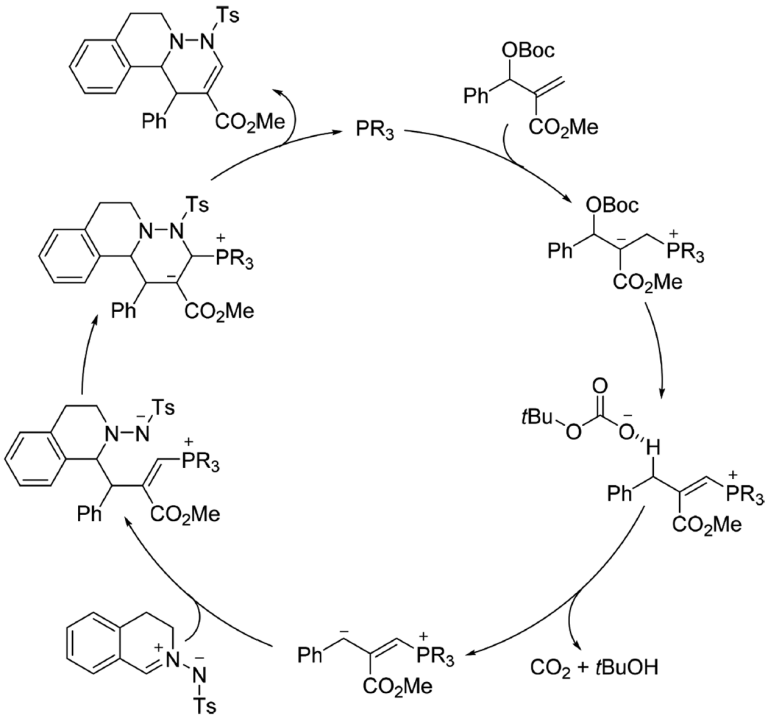
Scheme 569.

Enantioselective Phosphine-Catalyzed [3 + 3] Cycloadditions of MBH Adducts and Azomethine Imines



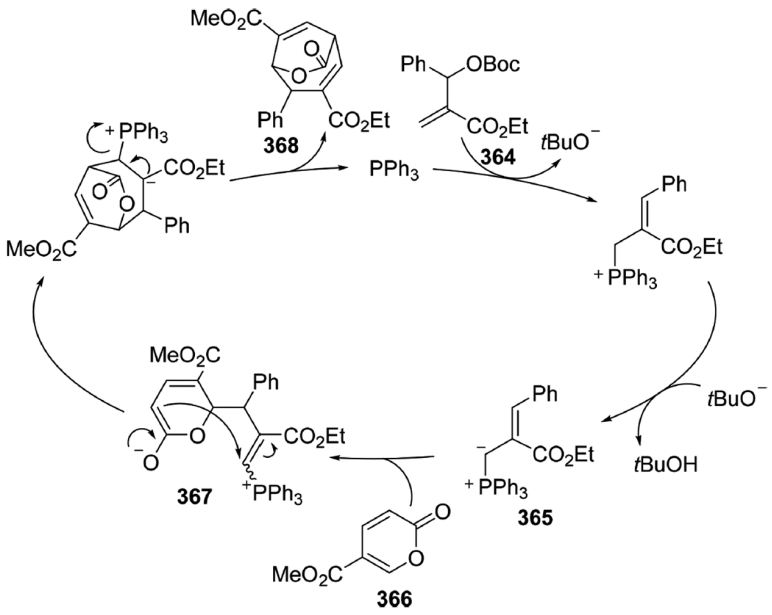
Scheme 570.

Phosphine-Catalyzed Enantioselective [3 + 3] Cycloadditions of MBH Carbonates with Quinazoline-Based 1,3-Dipoles

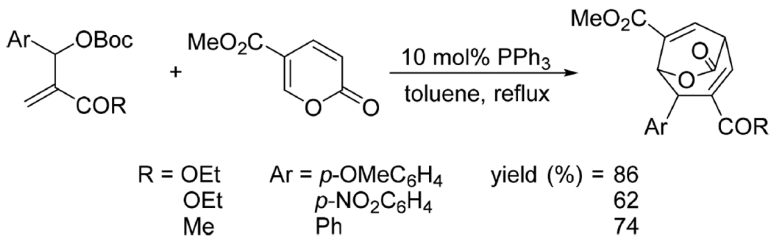


Scheme 571.

Mechanism of Phosphine-Catalyzed Annulations of MBH Carbonates with *C,N*-Cyclic Azomethine Imines

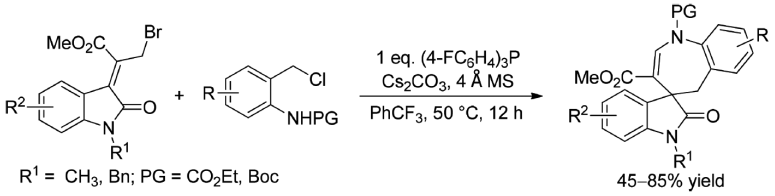


Scheme 572.
Proposed Mechanism for [4 + 3] Annulation



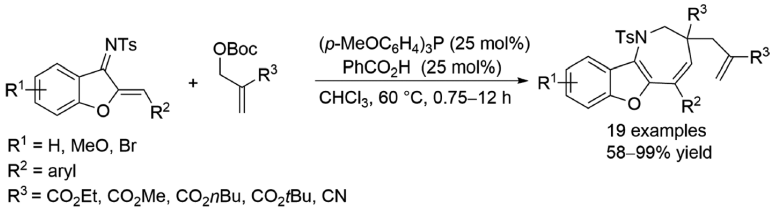
R = OEt	Ar = *p*-$OMeC_6H_4$	yield (%) = 86
OEt	*p*-$NO_2C_6H_4$	62
Me	Ph	74

Scheme 573.
Formation of Bicyclo[3.2.2.]nonadienes



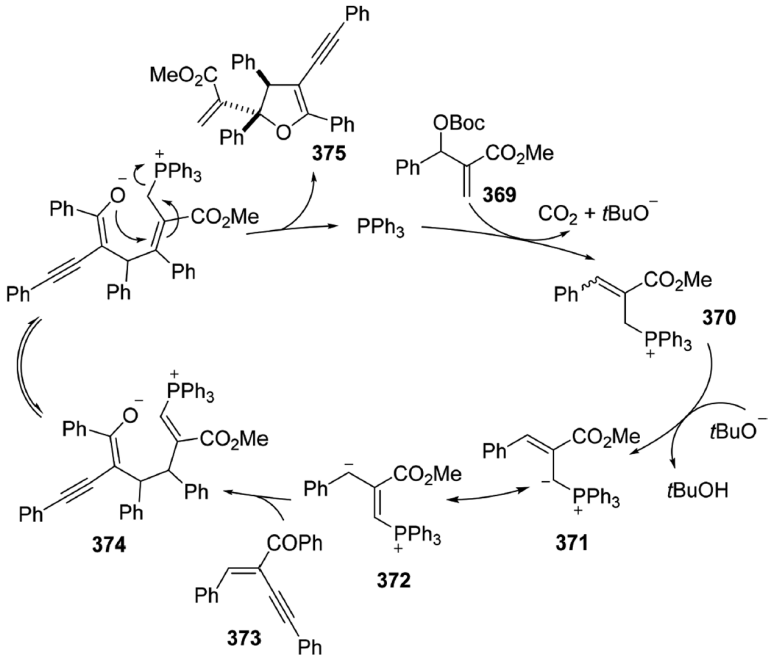
Scheme 574.

[4 + 3] Cycloadditions between Bromo-Substituted MBH Adducts Derived from Isatins and *N*-(*o*-Chloromethyl)aryl Amides

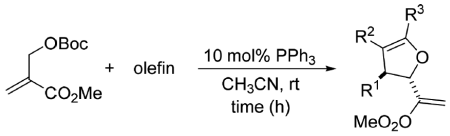


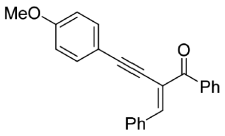
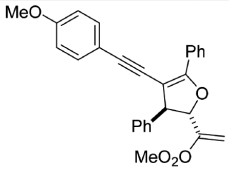
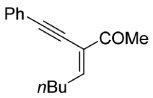
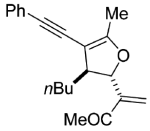
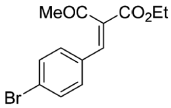
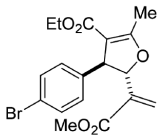
Scheme 575.

Phosphine-Catalyzed Intermolecular Sequential [4 + 3] Domino Annulation/Allylic Alkylation of MBH Carbonates and *N*-Tosyl Azadienes

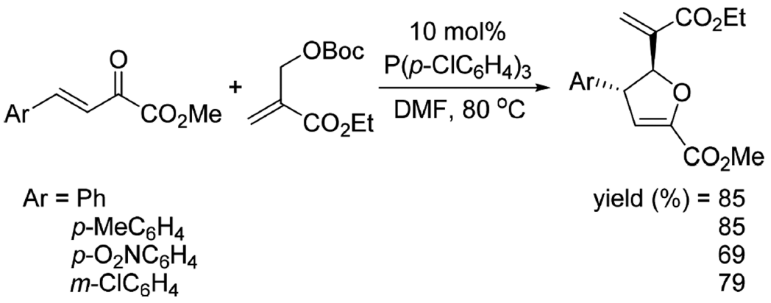


Scheme 576.
Proposed Mechanism for [4 + 1] Annulation

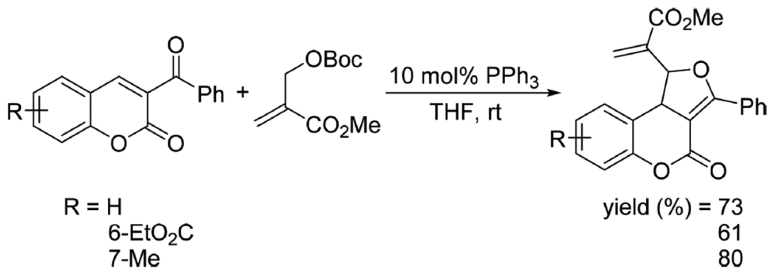


entry	olefin	time (h)	product	yield (%)
1		18	 *cis*:*trans* = 1:30	70
2		20	 *cis*:*trans* = 1:20	40
3		11	 *cis*:*trans* = 1:15	62

Scheme 577.
Formation of Dihydrofurans

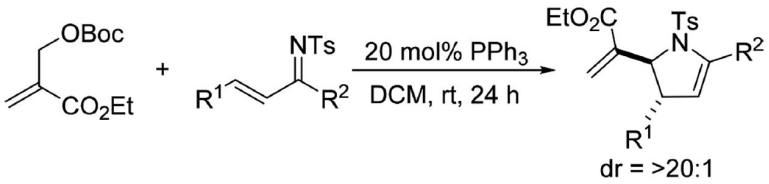


Scheme 578.
Synthesis of Functionalized Dihydrofurans



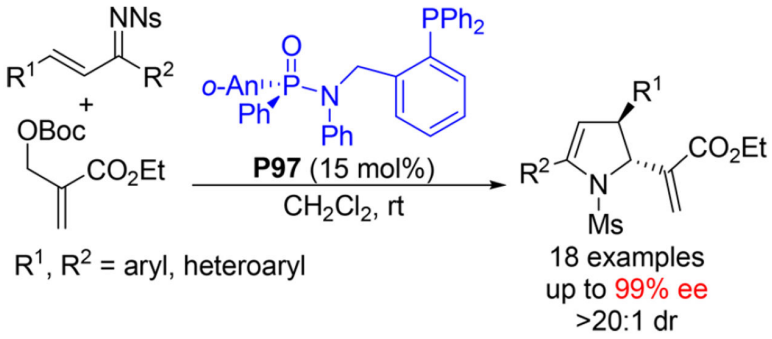
Scheme 579.

Synthesis of Functionalized Chromenone-Fused Dihydrofurans



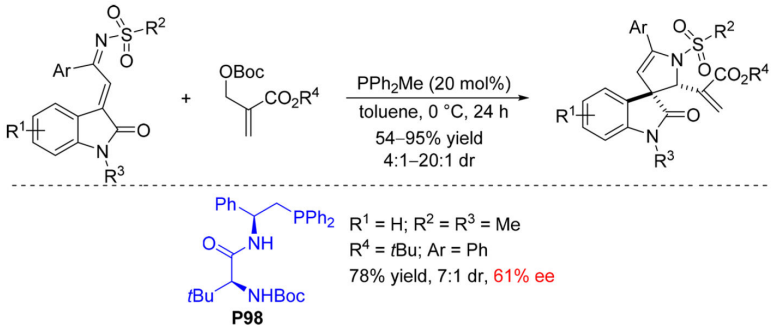
entry	R^1	R^2	yield (%)
1	Ph	Ph	99
2	*p*-$MeOC_6H_4$	Ph	80
3	*p*-$F_3CC_6H_4$	Ph	99
4	Ph	*p*-$NO_2C_6H_4$	85

Scheme 580.
Formation of Functionalized 2-Pyrrolines



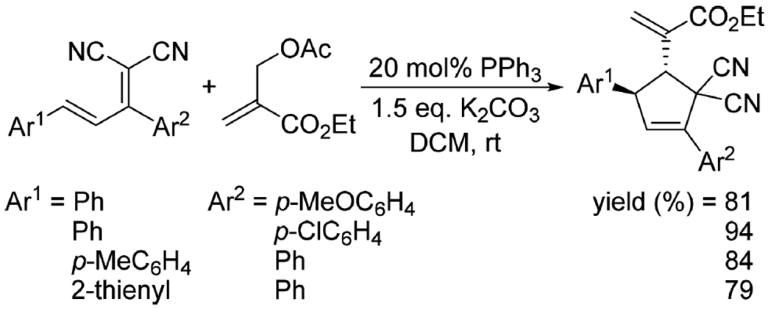
Scheme 581.

Phosphine-Catalyzed [4 + 1] Annulations of α,β-Unsaturated Imines and Allylic Carbonates



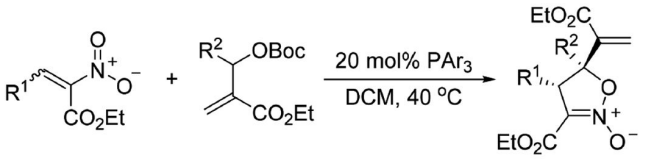
Scheme 582.

Phosphine-Catalyzed Regio- and Diastereoselective [4 + 1] Annulations of MBH Carbonates with Oxindole-Derived α,β-Unsaturated Imines



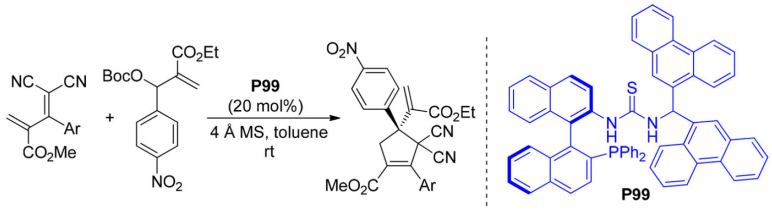
Ar^1 =	Ar^2 =	yield (%) =
Ph	*p*-$MeOC_6H_4$	81
Ph	*p*-ClC_6H_4	94
p-MeC_6H_4	Ph	84
2-thienyl	Ph	79

Scheme 583.
Synthesis of Functionalized Cyclopentenes



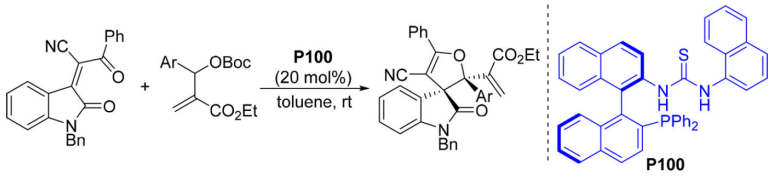
entry	R^1	R^2	PAr_3	yield (%)	trans:cis
1	*p*-MeC_6H_4	H	P(*p*-$F_3CC_6H_4$)$_3$	89	20:1
2	*p*-$F_3CC_6H_4$	H	P(*p*-$F_3CC_6H_4$)$_3$	41	14:1
3	Ph	*p*-$O_2NC_6H_4$	PPh_3	89	1:5
4	Ph	*p*-ClC_6H_4	PPh_3	94	1:20

Scheme 584.
Synthesis of Functionalized Nitronates



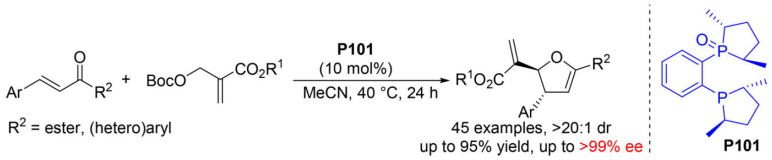
entry	Ar	yield (%)	ee (%)
1	*p*-MeC_6H_4	86	90
2	2-furyl	81	91
3	2-naphthyl	84	90
4	Ph	85	89

Scheme 585.
Asymmetric Synthesis of Functionalized Dicyanocyclopentenes



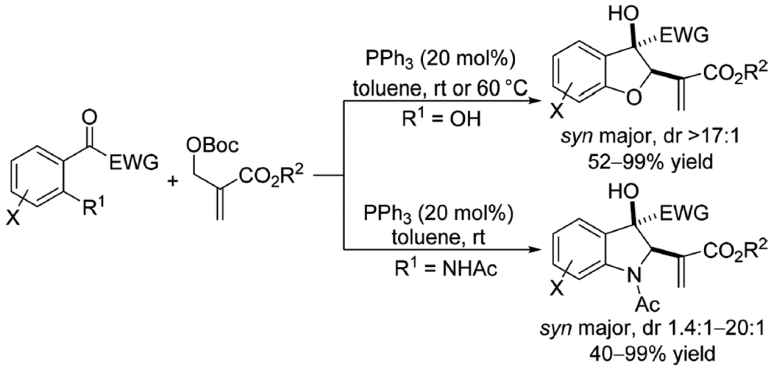
entry	Ar	yield (%)	ee (%)	dr
1	*p*-ClC_6H_4	90	97	3:1
2	*p*-NCC_6H_4	98	98	3:1
3	*m*,*p*-$Cl_2C_6H_3$	85	81	1:1
4	*m*,*m*-$Cl_2C_6H_3$	89	96	2:1

Scheme 586.
Asymmetric Synthesis of Functionalized Spirooxindoles



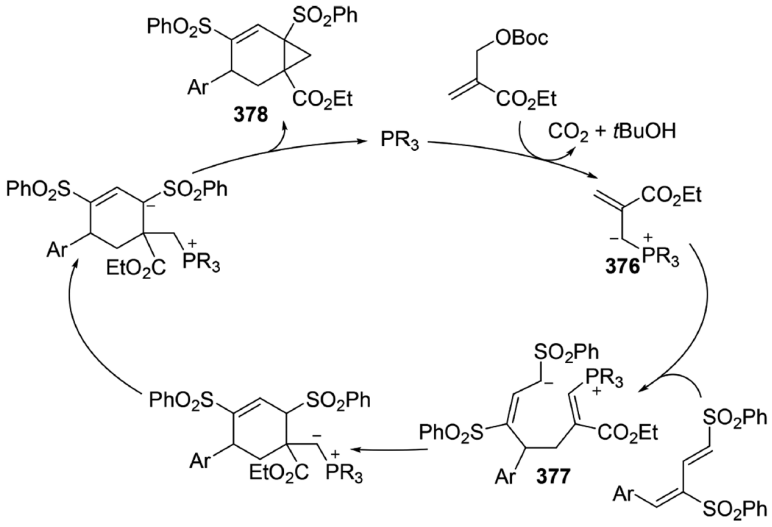
Scheme 587.

Chiral Phosphine-Catalyzed Enantioselective [4 + 1] Annulations of MBH Carbonates with Electron-Deficient Olefins



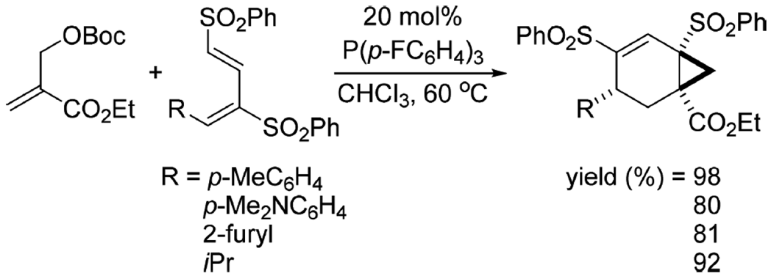
Scheme 588.

Phosphine-Catalyzed [4 + 1] Annulations of MBH Adducts with *o*-Hydroxylphenyl or *o*-Aminophenyl Ketones



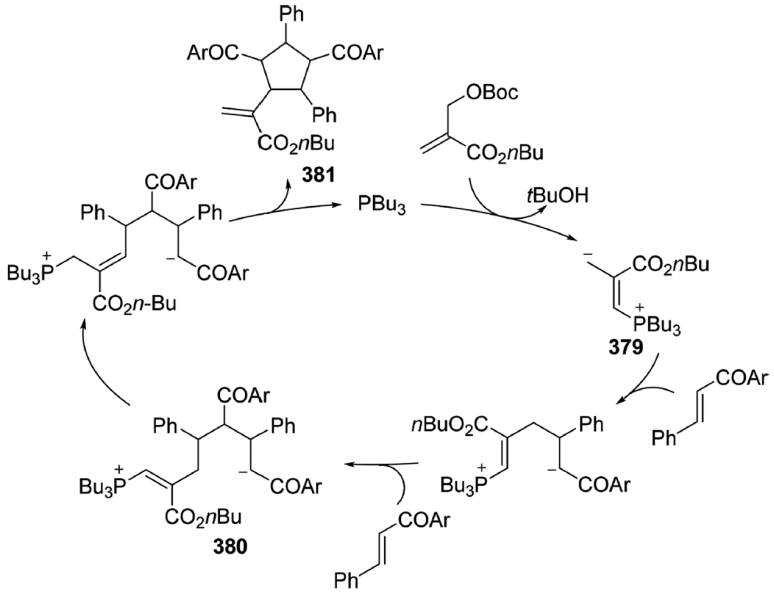
Scheme 589.

Proposed Mechanism for the Synthesis of Bicyclo[4.1.0]heptenes

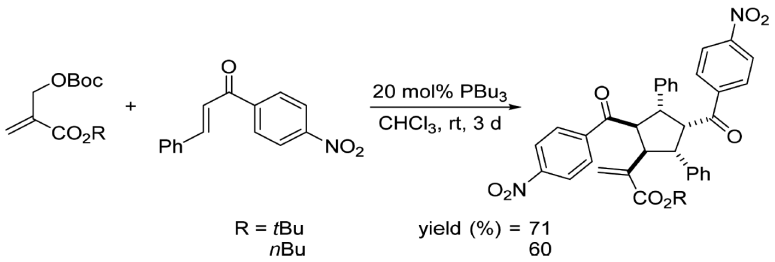


Scheme 590.

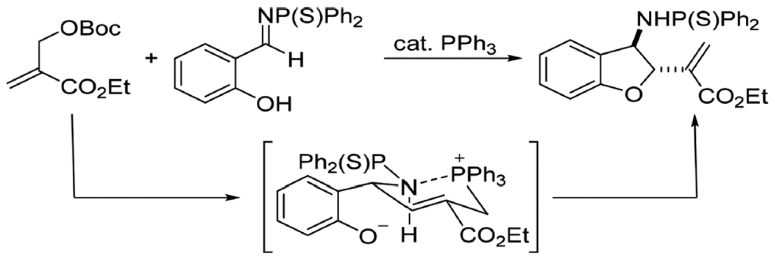
Synthesis of Functionalized Bicyclo[4.1.0]heptenes



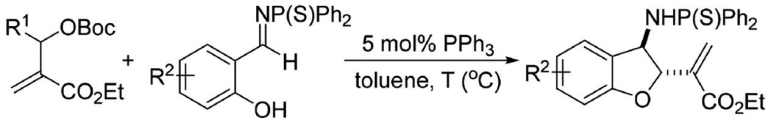
Scheme 591.
Suggested Mechanism for Enone–MBHAD [2 + 2 + 1] Annulation



Scheme 592.
Formation of Highly Substituted Cyclopentanes

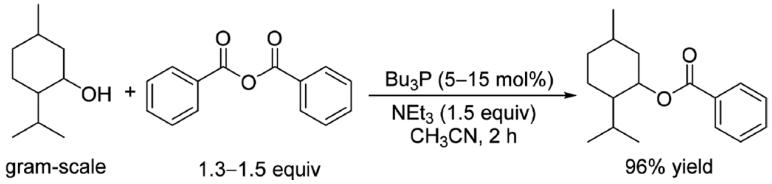


Scheme 593.
Proposed Reaction Pathway Toward Dihydrobenzofurans



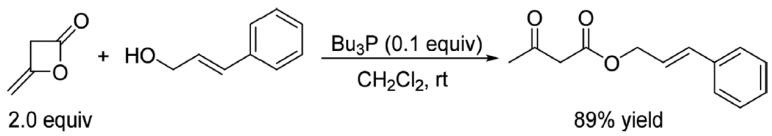
entry	R^1	R^2	T (°C)	yield (%)	cis:trans
1	H	H	reflux	99	3:97
2	H	4,6-di-*t*Bu	reflux	83	3:97
3	H	4-NO_2	reflux	88	24:76
4	*p*-MeC_6H_4	6-Ph	130	76	1:>99

Scheme 594.
Phosphine-Catalyzed Formation of Dihydrobenzofurans



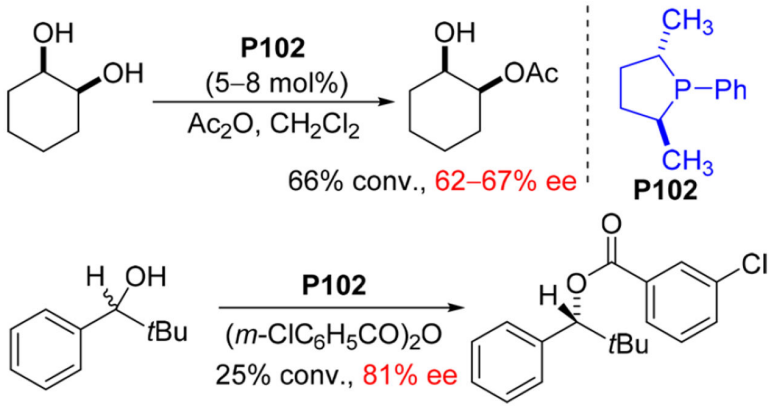
Scheme 595.

Bu_3P-Catalyzed Acylation of Menthol by Benzoic Anhydrides

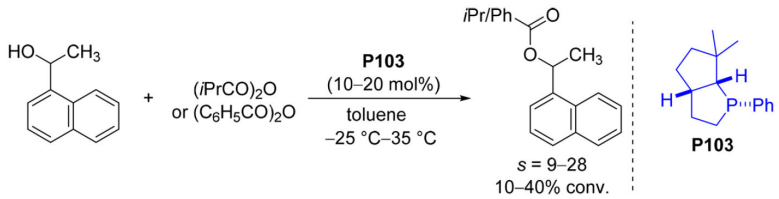


Scheme 596.

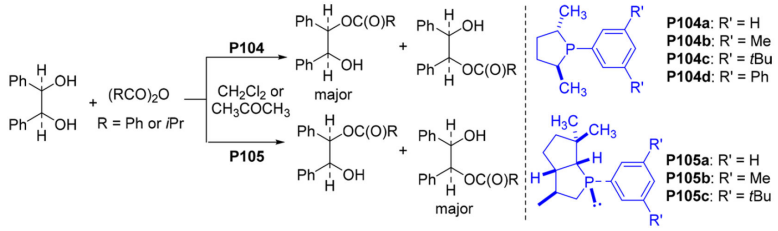
Bu_3P-Catalyzed Acylation of Cinnamyl Alcohol by Diketene



Scheme 597.
Chiral Phosphine-Catalyzed Acylation of Alcohols

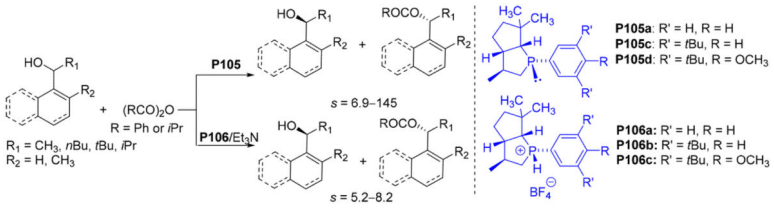


Scheme 598.
Bicyclic Phospholane-Catalyzed Acylation of Alcohols



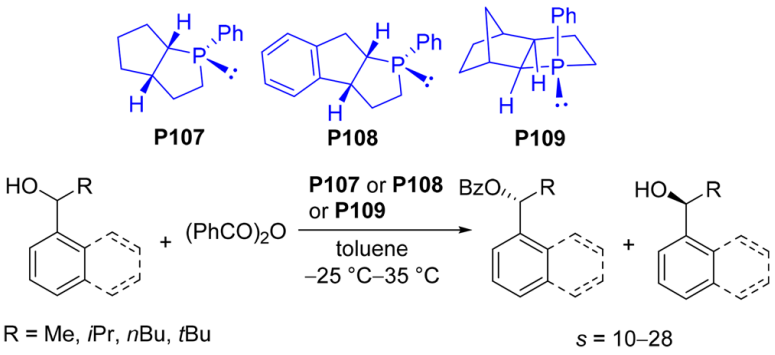
Scheme 599.

Phosphine-Catalyzed Acylation Leading to Kinetic Resolution of Diols



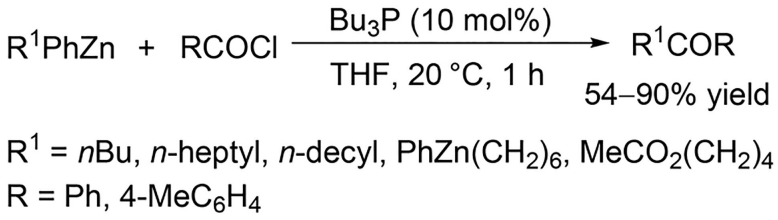
Scheme 600.

Chiral Phosphine-Catalyzed Acylation of Alcohols and Corresponding Kinetic Resolution

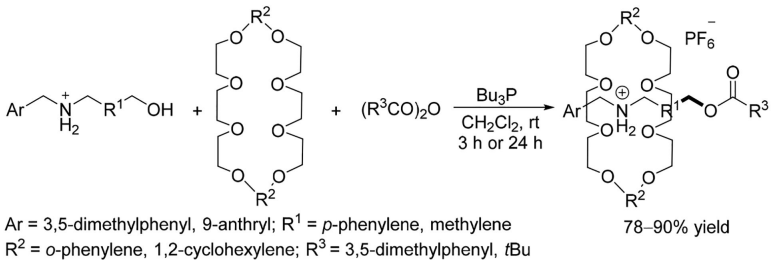


Scheme 601.

Chiral Phosphine-Catalyzed Acylation of Alcohols and Corresponding Kinetic Resolution

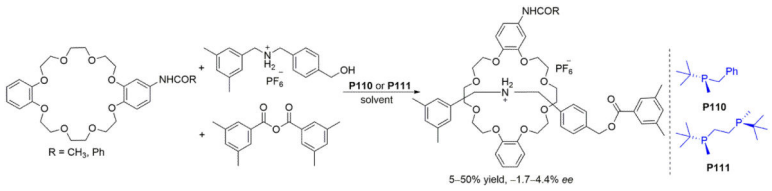


Scheme 602.
Chiral Phosphine–Catalyzed Acylation of Alkylphenylzincs



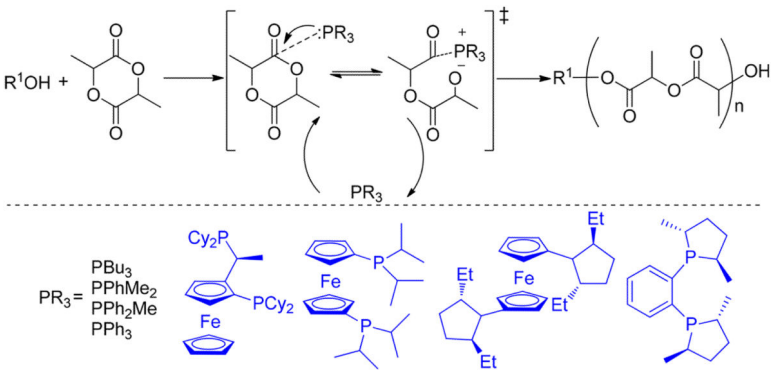
Scheme 603.

Phosphine-Catalyzed Construction of [2]Rotaxanes

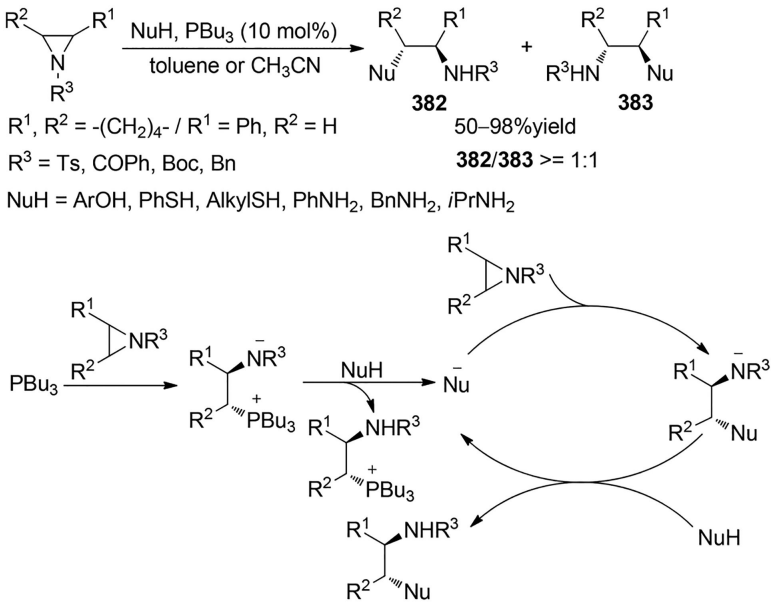


Scheme 604.

Chiral Phosphine-Catalyzed Construction of Planar Chiral [2]Rotaxanes

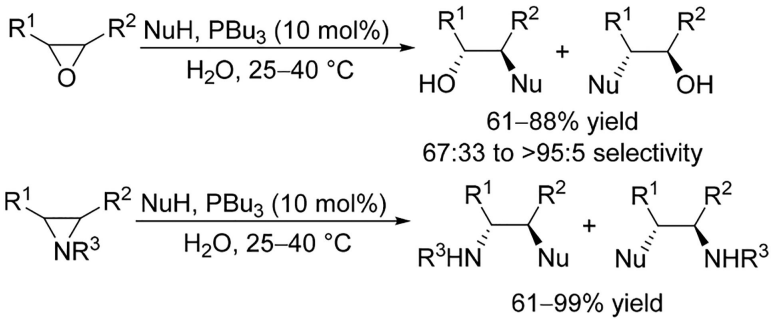


Scheme 605.
Phosphine-Promoted Ring-Opening Polymerization of Lactides



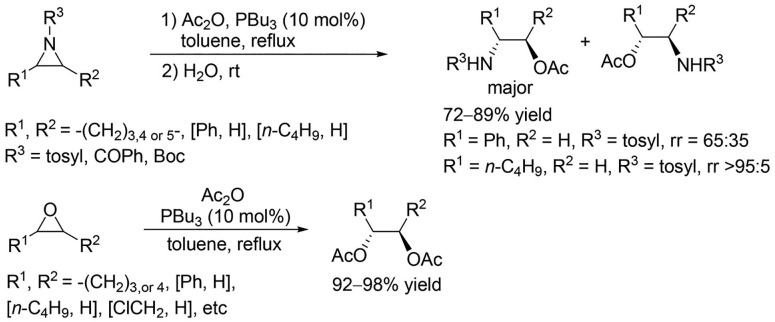
Scheme 606.

Proposed Mechanism for Phosphine-Catalyzed Ring-Opening Reactions of Aziridines



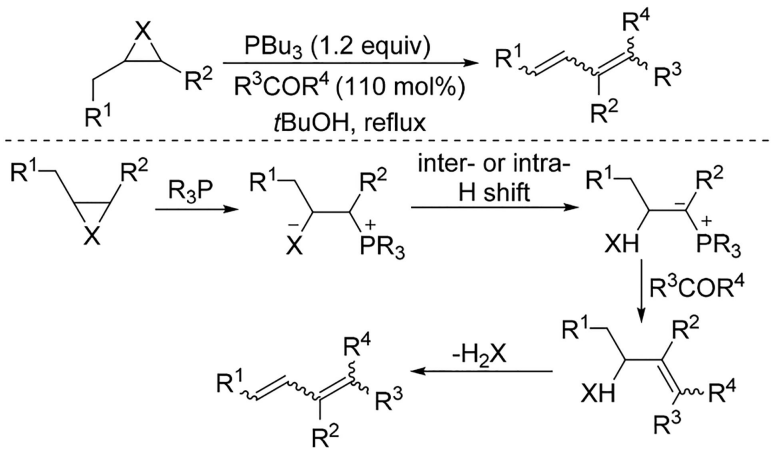
Scheme 607.

Phosphine-Catalyzed Ring-Opening Reactions of Epoxides and Aziridines with Nucleophiles



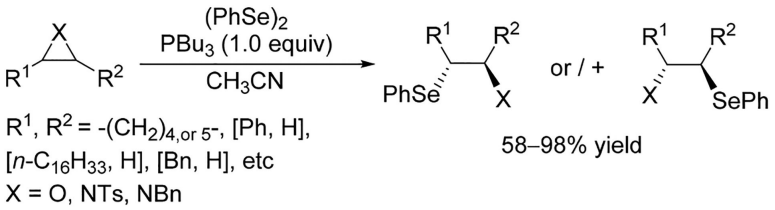
Scheme 608.

Phosphine-Catalyzed Ring-Opening Reactions of Epoxides and Aziridines with Acetic Anhydride



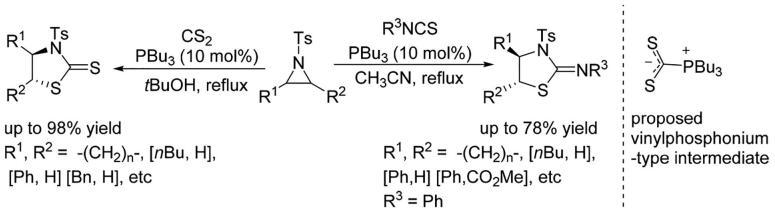
Scheme 609.

Phosphine-Mediated Reaction of Aziridines or Epoxides with Ketones or Aldehydes



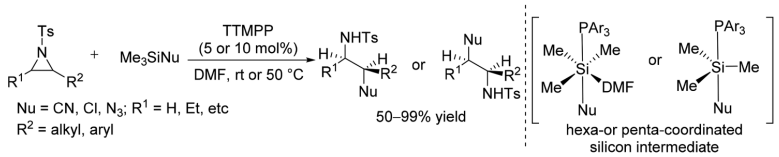
Scheme 610.

Phosphine-Mediated Ring-Opening Reactions of Aziridines and Epoxides with Diphenyl Diselenide



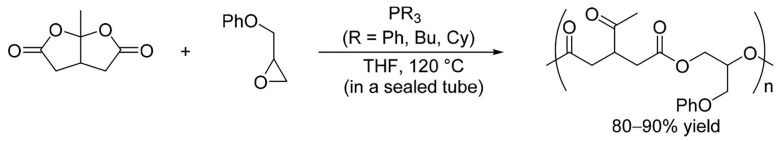
Scheme 611.

Phosphine-Catalyzed [3 + 2] Cycloadditions of Aziridines with Carbon Disulfide or Isothiocyanate



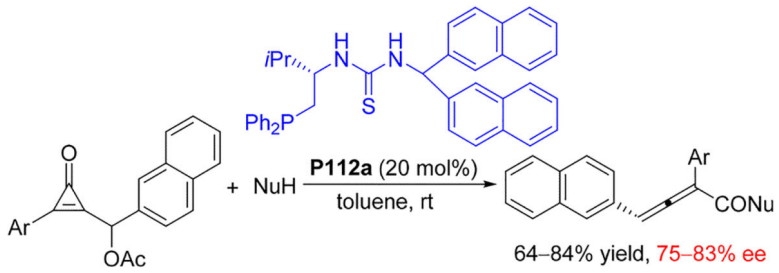
Scheme 612.

Phosphine-Catalyzed Ring-Opening Reactions of Aziridines with Silylated Nucleophiles



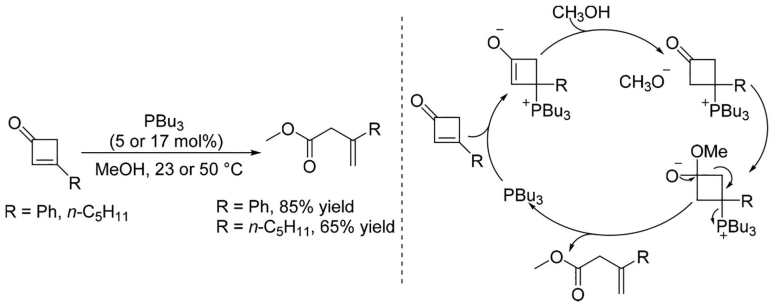
Scheme 613.

Phosphine-Initiated Copolymerization of a Bis(lactone) and an Epoxide



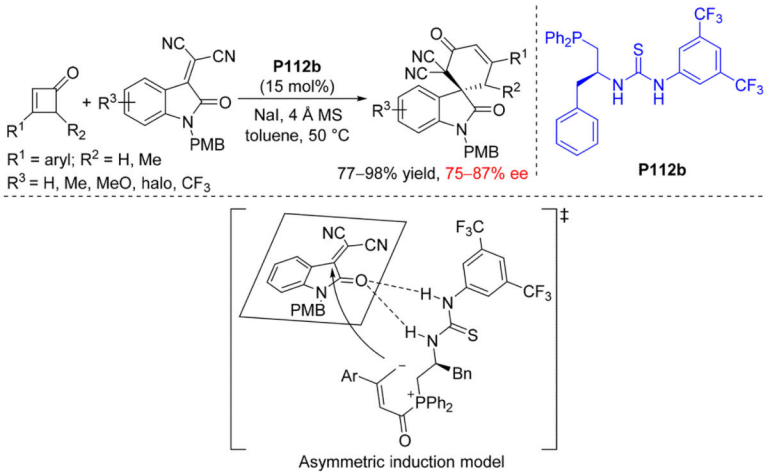
Scheme 614.

Lewis Base-Catalyzed Reactions of Cyclopropenones with Alcoholic Nucleophiles



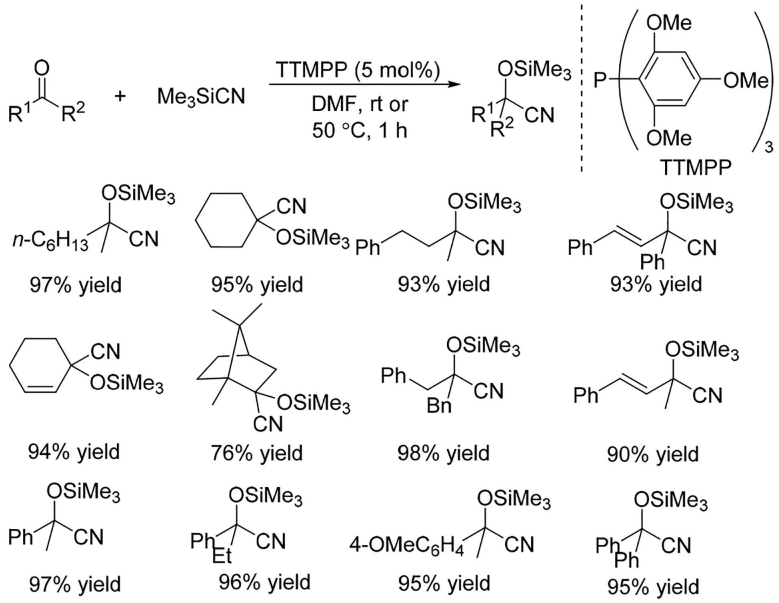
Scheme 615.

Phosphine-Catalyzed Ring-Opening Reactions of Substituted Cyclobutenones



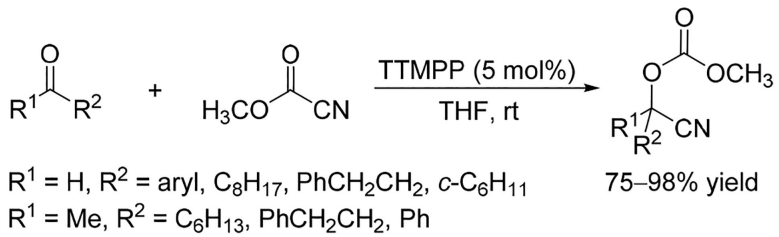
Scheme 616.

Enantioselective Phosphine-Catalyzed [4 + 2] Cycloadditions of Cyclobutenones with Isatylidenemalononitriles

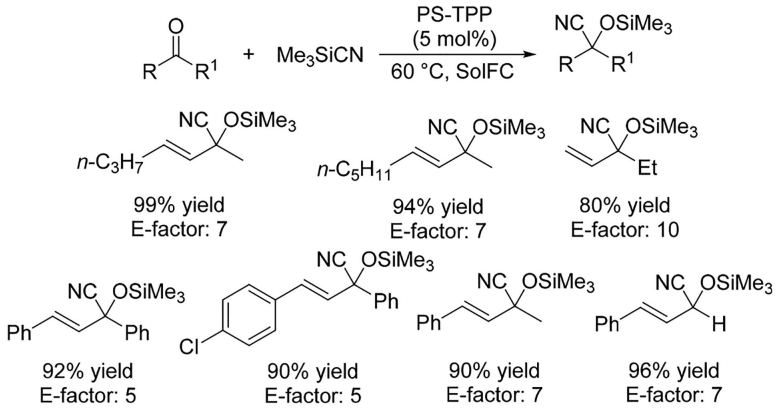


Scheme 617.

TTMPP-Catalyzed Preparation of Cyanohydrin Silyl Ethers

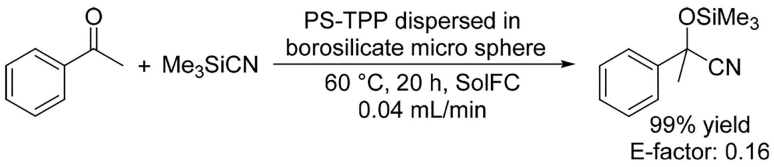


Scheme 618.
TTMPP-Catalyzed Preparation of Cyanohydrin Carbonates



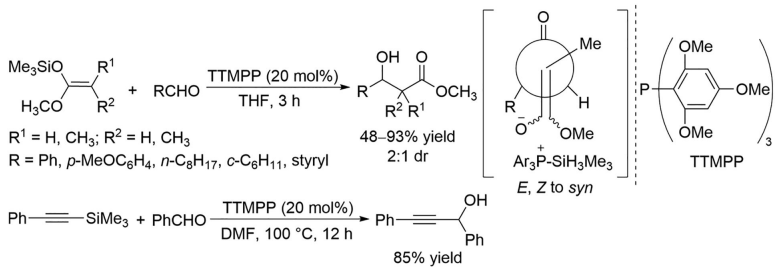
Scheme 619.

Cyanosilylation of α,β-Unsaturated Carbonyl Compounds

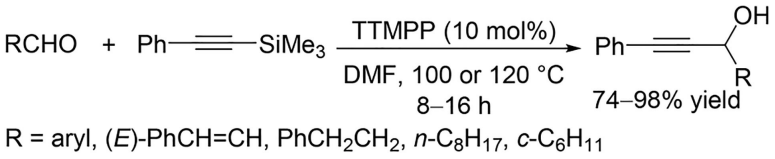


Scheme 620.

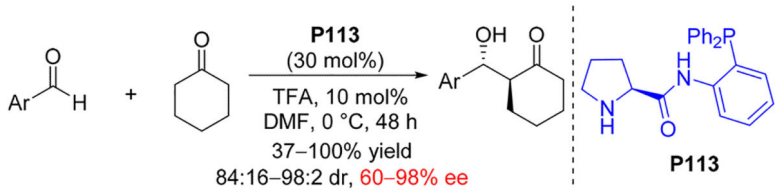
Cyanosilylation of Acetophenone Using a Continuous Flow Reactor



Scheme 621.
TTMPP-Catalyzed Mukaiyama Aldol Reactions

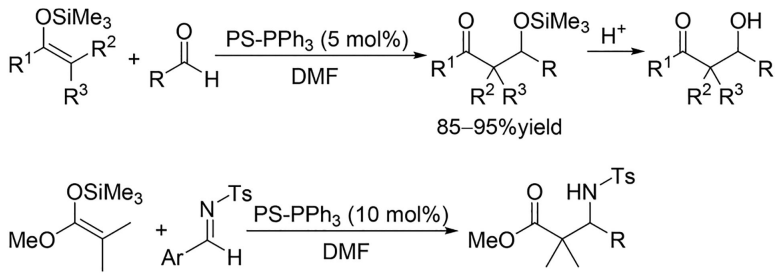


Scheme 622.
TTMPP-Catalyzed Alkynylation of Aldehydes



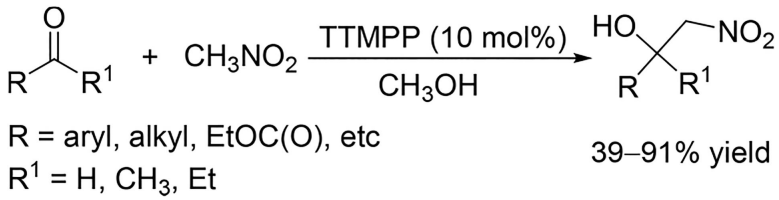
Scheme 623.

Chiral Phosphine-Catalyzed Asymmetric Aldol Reactions

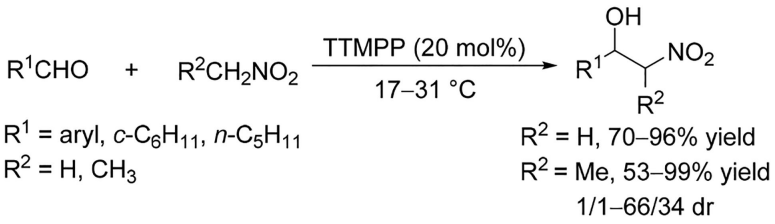


Scheme 624.

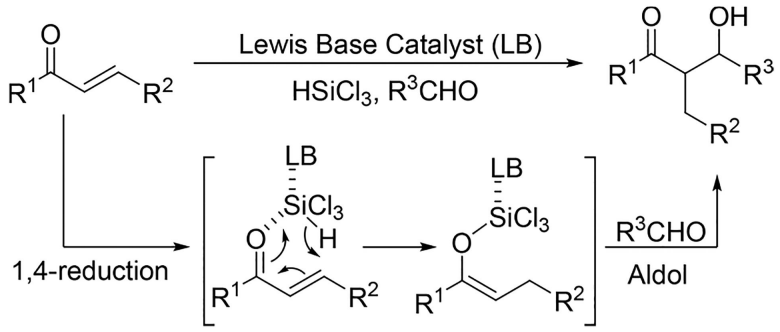
Polymer-Supported Phosphine-Catalyzed Aldol Reactions of Aldehydes and Mannich Reactions of Imines



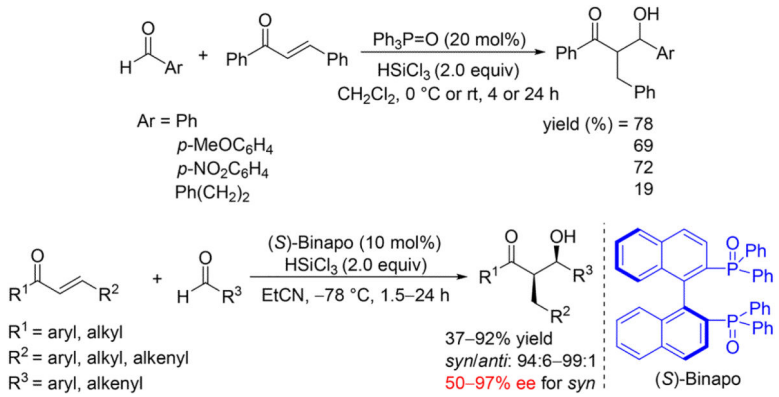
Scheme 625.
TTMPP-Catalyzed Nitroaldol Reactions



Scheme 626.
TTMPP-Catalyzed Nitroaldol Reactions

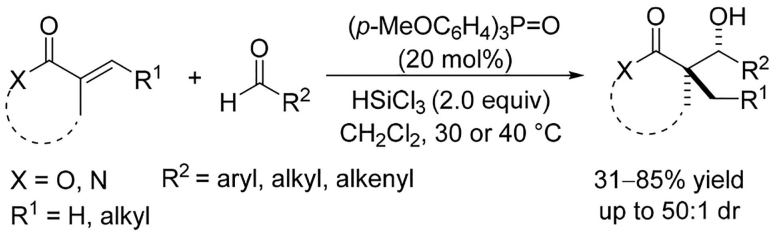


Scheme 627.
Ph_3P=O- or HMPA-Catalyzed Reductive Aldol Reaction



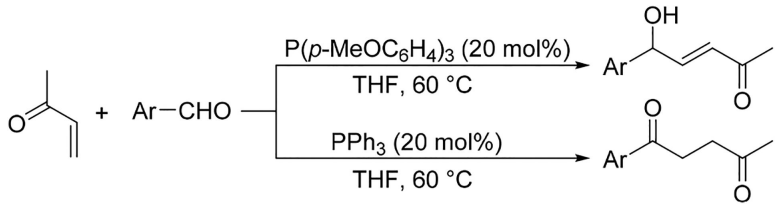
Scheme 628.

Reductive Aldol Reaction of Enones and Aldehydes



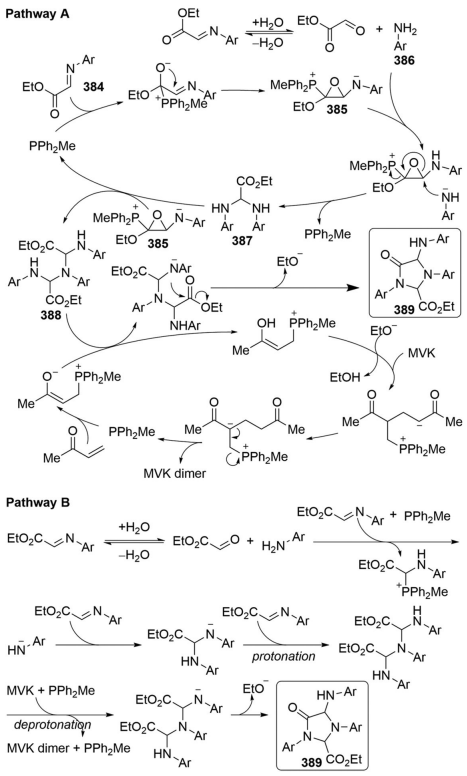
Scheme 629.

Reductive Aldol Reaction to Access β-Hydroxylactones, Lactams, and Morpholine Amides

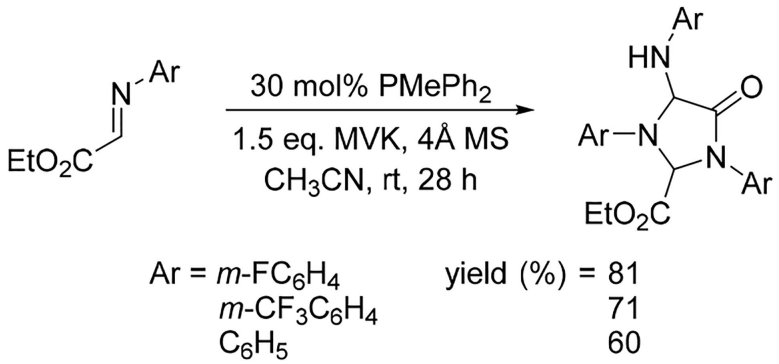


Scheme 630.

Phosphine-Dependent Formation of 1-Phenylpentane-1,4-diones and (*E*)-5-Hydroxy-5-phenylpent-3-en-2-ones from Aromatic Aldehydes and But-3-en-2-one

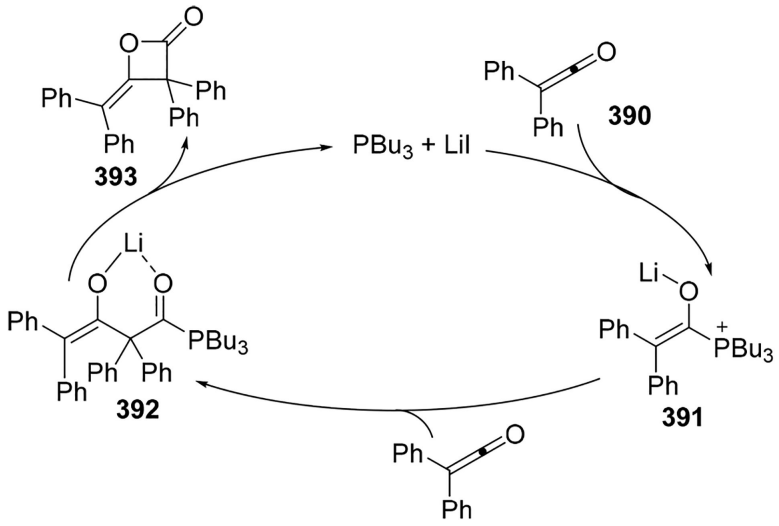


Scheme 631.
Proposed Reaction Pathways for Imidazolidinone Formation.

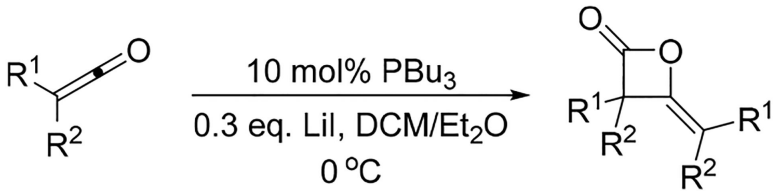


Ar =	yield (%) =
m-FC_6H_4	81
m-$CF_3C_6H_4$	71
C_6H_5	60

Scheme 632.
Formation of Functionalized Oxoimidazolidines.

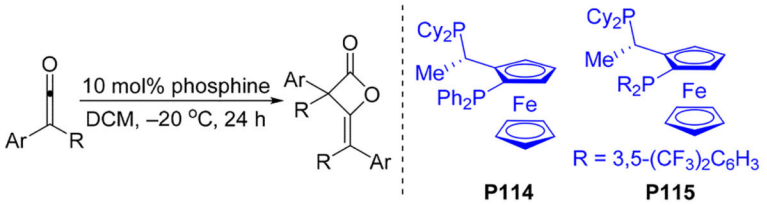


Scheme 633.
Proposed Mechanistic Pathway for Ketoketene Dimerization



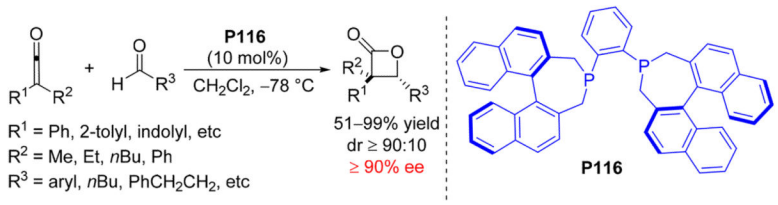
entry	R^1	R^2	yield (%)	*E*/*Z*
1	Ph	Me	78	1:>16
2	*p*-MeC_6H_4	Me	90	1:39
3	3-thienyl	Et	78	1:20

Scheme 634.
Formation of Functionalized *β*-Lactones



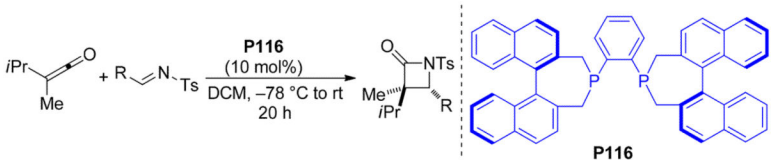
entry	Ar	R	phosphine	yield (%)	ee (%)	abs. config.
1	Ph	*n*Bu	(*R*,*S*p)-**P114**	90	89	*R*
2	*o*-MeC_6H_4	Me	(*R*,*S*p)-**P115**	80	94	*R*
3	*o*-ClC_6H_4	Me	(*S*,*R*p)-**P115**	45	96	*S*
4	3-thienyl	Et	(*S*,*R*p)-**P114**	68	46	*S*

Scheme 635.
Asymmetric Dimerizations of Ketoketenes



Scheme 636.

Chiral Phosphine-Catalyzed [2 + 2] Annulations of Arylketoketenes and Aldehydes

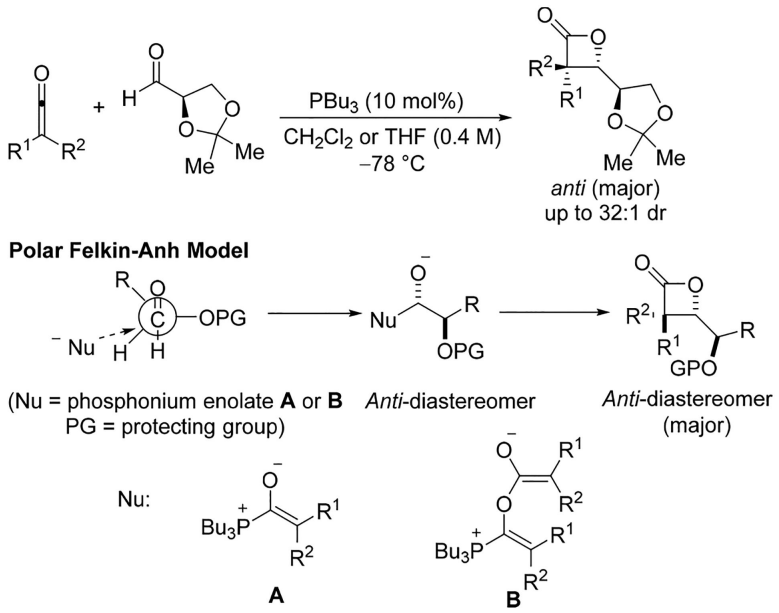


entry	R	yield (%)	ee (%)	dr
1	*o*-ClC_6H_4	91[a]	98	87:13
2	*p*-$O_2NC_6H_4$	>99[a]	67	90:10
3	*o*-FC_6H_4	87	91	99:1
4	*p*-BrC_6H_4	93	85	95:5
5	*p*-ClC_6H_4	68	90	94:6
6	*p*-$CF_3C_6H_4$	90	73	93:7

Scheme 637.

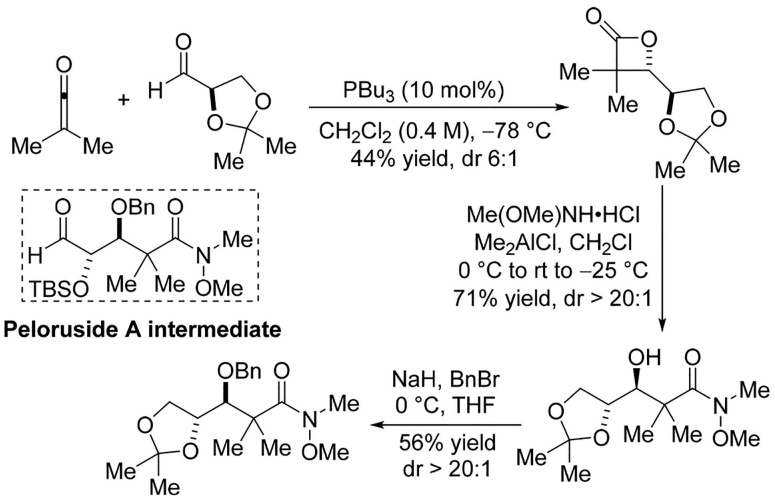
Synthesis of Optically Active β-Lactams.

[a]15 mol % BINAPHANE was used.



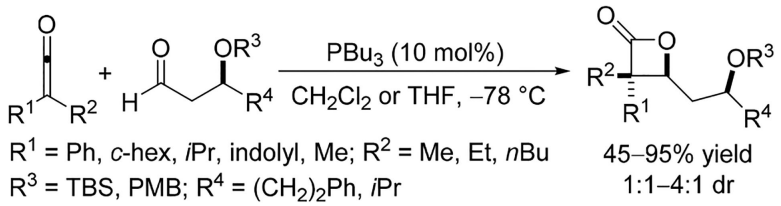
Scheme 638.

Phosphine-Catalyzed [2 + 2] Cycloadditions of Disubstituted Ketenes with α-Chiral Oxyaldehydes, and Their Selectivity



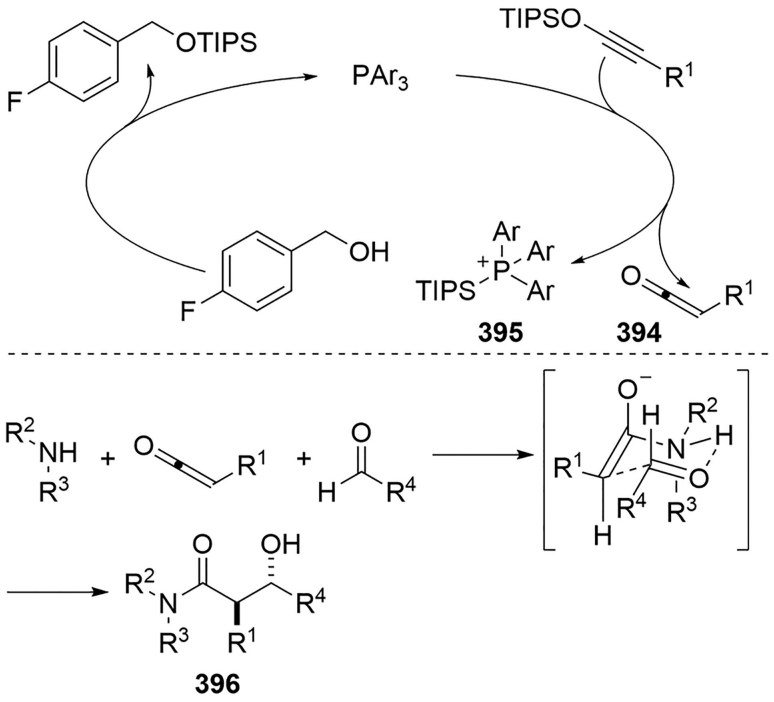
Scheme 639.

Example of the Synthetic Utility of Phosphine-Catalyzed [2 + 2] Cycloaddition of a Disubstituted Ketene with an α-Chiral Oxyaldehyde



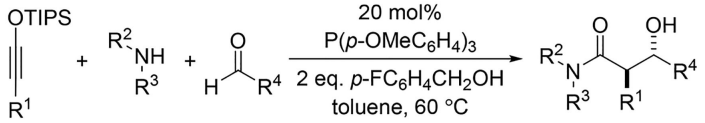
Scheme 640.

Phosphine-Catalyzed [2 + 2] Cycloadditions of Disubsituted Ketenes and Chiral *β*-Oxyaldehydes



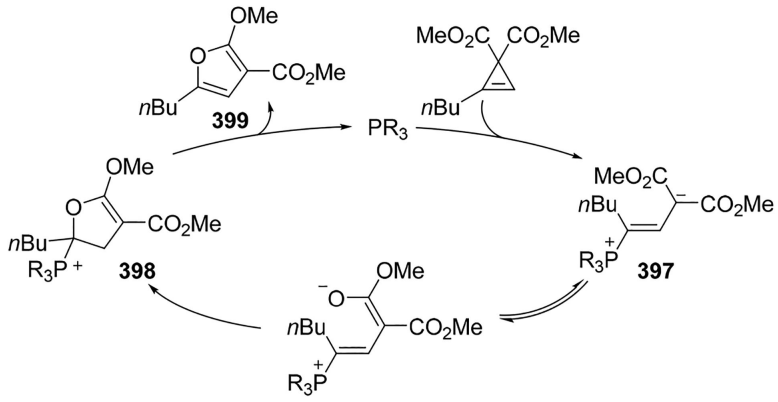
Scheme 641.

Suggested Mechanism for Three-Component Condensation

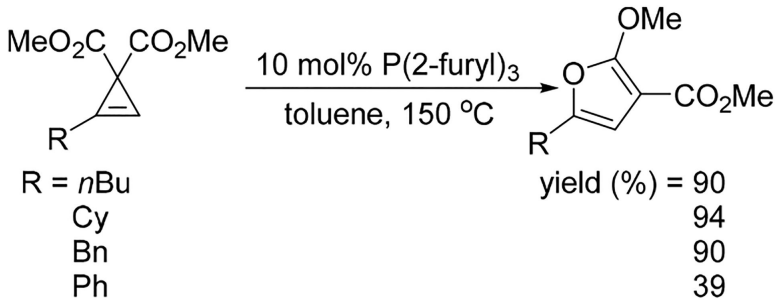


entry	R^1	R^2	R^3	R^4	yield (%)	dr
1	*n*Bu	*p*-$MeOC_6H_4$	Me	*p*-$F_3CC_6H_4$	87	91:9
2	*n*Bu	*p*-$MeOC_6H_4$	Me	2-furyl	59	88:12
3	cyclohexyl	*p*-$MeOC_6H_4$	Me	*p*-$F_3CC_6H_4$	80	91:9
4	*n*Bu	Ph	allyl	*p*-$F_3CC_6H_4$	57	89:11
5	*n*Bu	*i*Pr	*i*Pr	*p*-$F_3CC_6H_4$	30	63:37

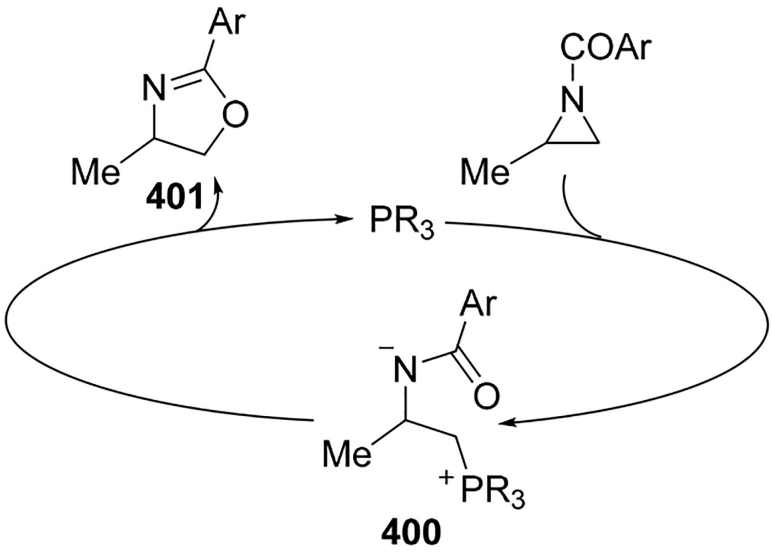
Scheme 642.
Preparation of Functionalized β-Hydroxyamides



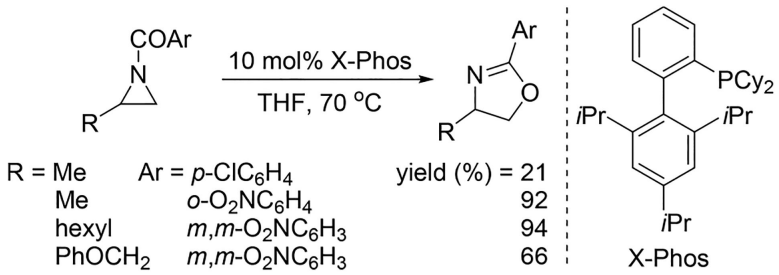
Scheme 643.
Proposed Cycloisomerization Mechanism



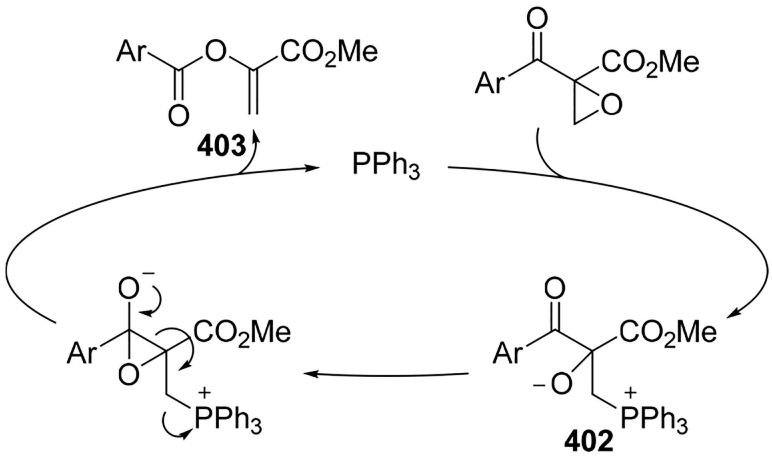
Scheme 644.
Synthesis of Substituted Furans



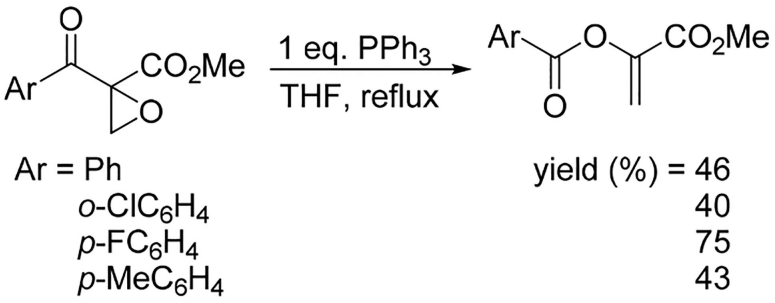
Scheme 645.
Proposed Mechanism for the Phosphine-Catalyzed Heine Reaction



Scheme 646.
Synthesis of Functionalized Oxazolines

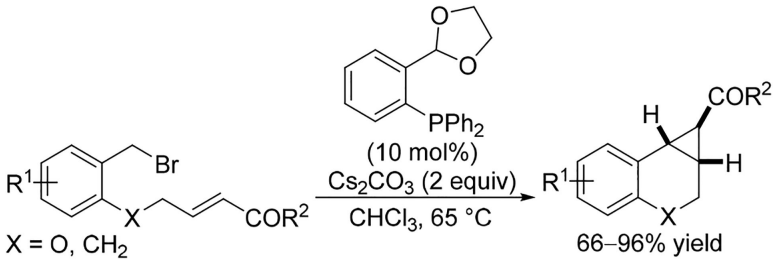


Scheme 647.
Proposed Rearrangement Mechanism

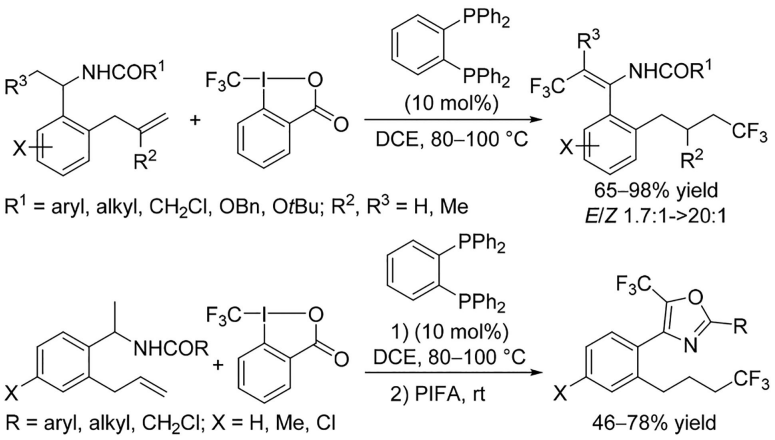


Ar =	yield (%) =
Ph	46
o-ClC_6H_4	40
p-FC_6H_4	75
p-MeC_6H_4	43

Scheme 648.
Synthesis of Functionalized α-Aroylacrylates

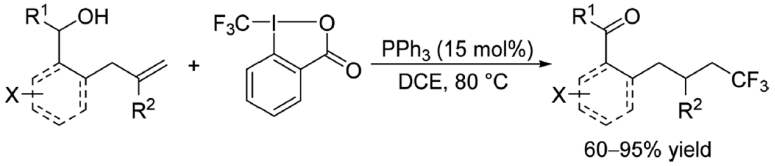


Scheme 649.
Phosphine-Catalyzed Cyclopropanation



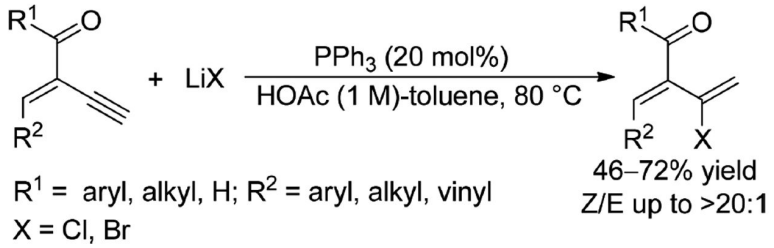
Scheme 650.

Phosphine-Catalyzed Remote β-C–H Functionalization of Amines Triggered by Trifluoromethylation of Alkenes



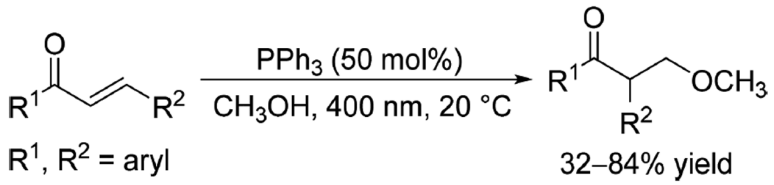
Scheme 651.

Phosphine-Catalyzed Remote α-C–H Bond Activation of Alcohols Triggered by Radical Trifluoromethylation of Alkenes



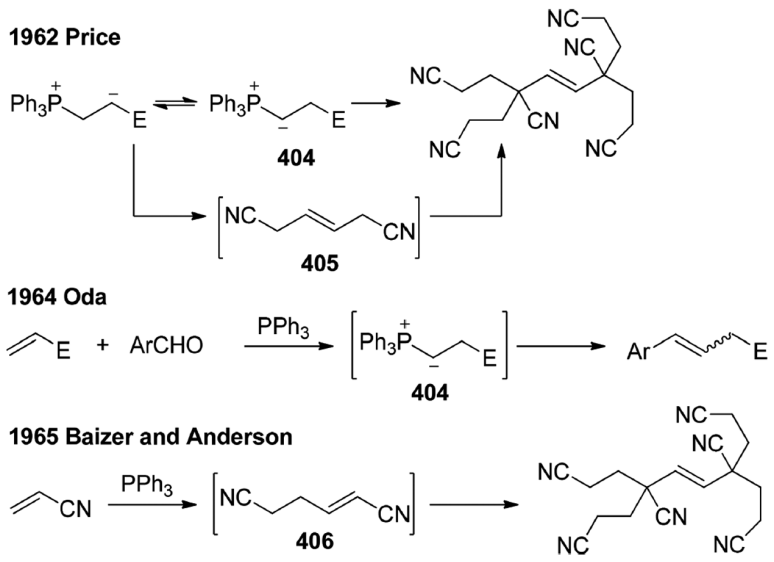
Scheme 652.

Phosphine-Catalyzed Regioselective and Stereoselective Hydrohalogenation of 2-(1-Alkynyl)-2-alken-1-ones

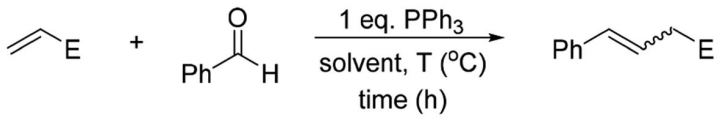


Scheme 653.

Ph_3P-Mediated Photo-Rearrangement and Methanol Addition of Aryl Chalcones to 1-Propanones

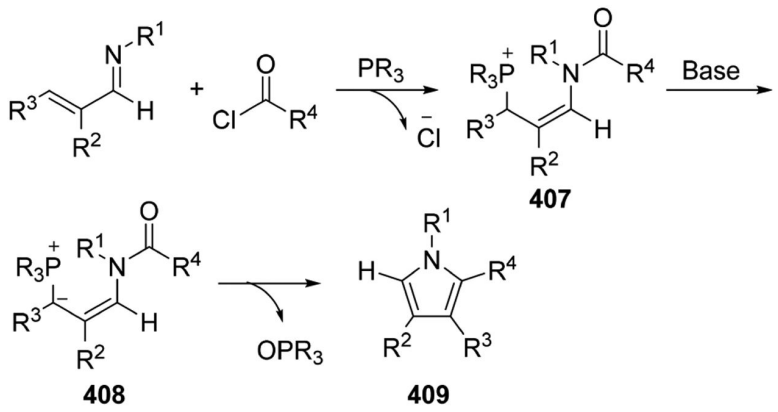


Scheme 654.
Formation of Phosphonium Ylides



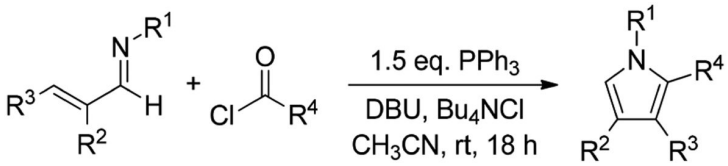
entry	E	solvent	T (°C)	time (h)	yield (%)
1	CN	EtOH	140	8	23
2	$CONH_2$	EtOH	135	8	10
3	CO_2Et	$nC_6H_{13}OH$	135	9	45

Scheme 655.
Formation of Functionalized Styrenes



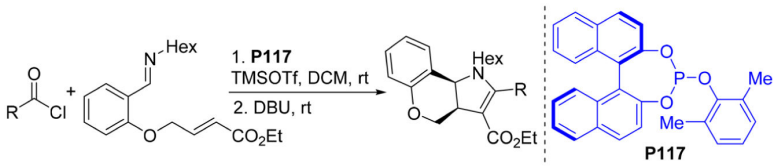
Scheme 656.

Suggested Pyrrole Formation via Intramolecular Wittig Reaction



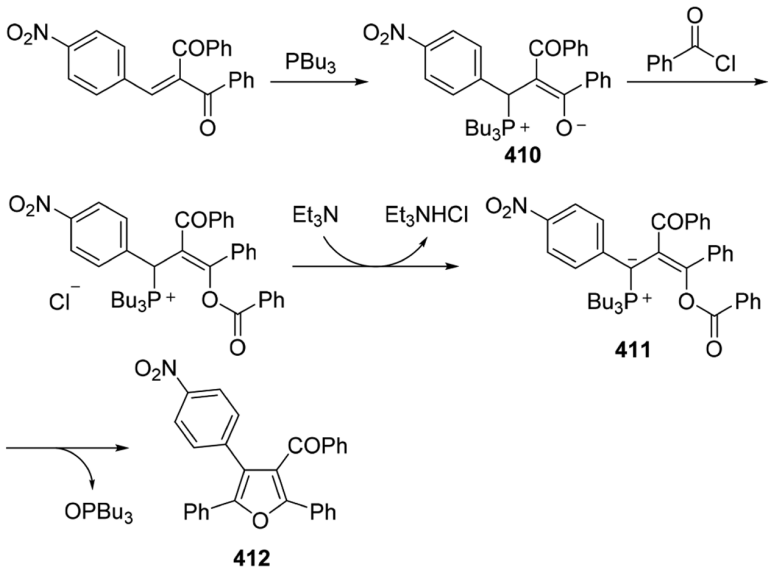
entry	R^1	R^2	R^3	R^4	yield (%)
1	Ph	H	*p*-MeC_6H_4	*p*-$O_2NC_6H_4$	82
2	Et	Me	3-pyridinyl	*p*-ClC_6H_4	70
3	Et	Ph	*p*-$F_3CC_6H_4$	OEt	59[a]
4	Bn	CN	*p*-$MeOC_6H_4$	CO_2Et	68

Scheme 657.
Synthesis of Pyrrole Derivatives
[a]Reaction performed at 65 °C.



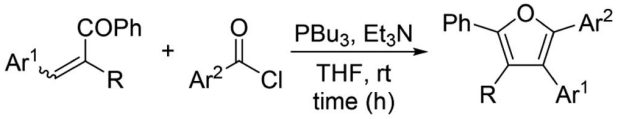
entry	R	yield (%)	ee (%)
1	*p*-MeC_6H_4	77	95
2	*p*-$MeOC_6H_4$	85	95
3	*i*Pr	64	87

Scheme 658.
Asymmetric Synthesis of Functionalized Polycyclic Dihydropyrroles



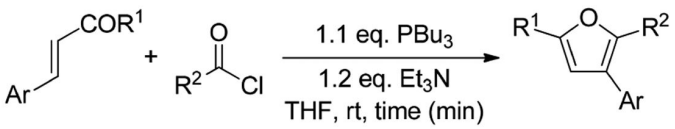
Scheme 659.

Proposed Mechanism of the Intramolecular Wittig Reaction for Furan Synthesis



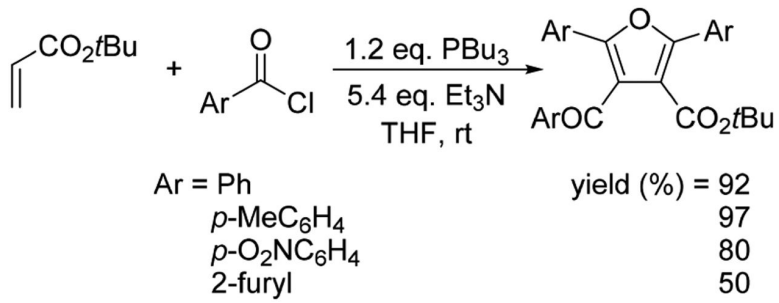
entry	Ar^1	Ar^2	R	time (h)	yield (%)
1	*p*-$O_2NC_6H_4$	*p*-$O_2NC_6H_4$	COPh	1.5	91
2	*p*-ClC_6H_4	2-furyl	COPh	21	71
3	*p*-$O_2NC_6H_4$	Ph	CO_2Et	2	93
4	*p*-NCC_6H_4	*p*-ClC_6H_4	CN	0.16	95

Scheme 660.
Formation of Functionalized Furans

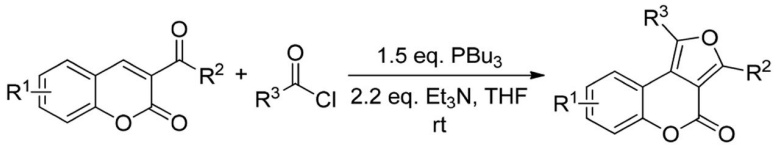


entry	Ar	R^1	R^2	time (min)	yield (%)
1	*p*-$F_3CC_6H_4$	Ph	Ph	10	93
2	2-furyl	Ph	Ph	10	60
3	*p*-NCC_6H_4	*p*-BrC_6H_4	Ph	10	83
4	*p*-NCC_6H_4	cyclohexyl	Ph	60	51
5	*p*-NCC_6H_4	Ph	*i*Pr	60	52

Scheme 661.
Preparation of Functionalized Furans

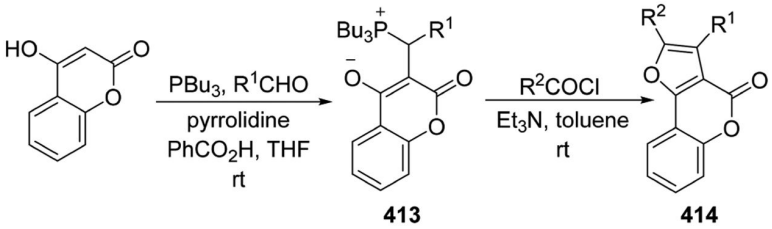


Scheme 662.
Synthesis of Functionalized Furans



entry	R^1	R^2	R^3	yield (%)
1	6-NO_2	Ph	Ph	89
2	6-Br	*p*-$O_2NC_6H_4$	Ph	86
3	6-Br	Ph	cyclohexyl	65
4	6-NO_2	Ph	*p*-ClC_6H_4	91

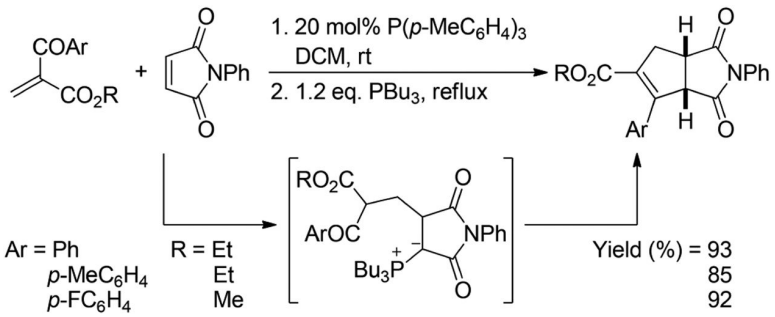
Scheme 663.
Synthesis of Furocoumarin Derivatives



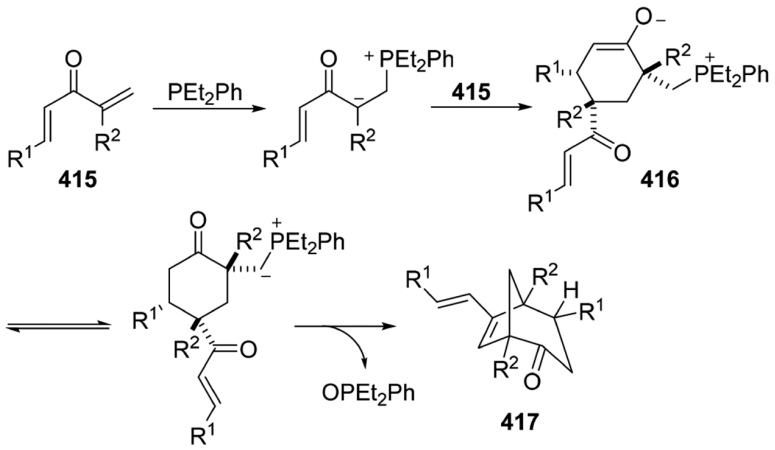
413 414

entry	R^1	R^2	yield of **413**	yield of **414**
1	*p*-$F_3CC_6H_4$	*p*-BrC_6H_4	90	90
2	*p*-$MeOC_6H_4$	*o*-BrC_6H_4	91	90
3	2-thienyl	*p*-BrC_6H_4	97	97
4	*p*-$OCHC_6H_4$	Ph	50	85
5	CO_2Et	Ph	69	89

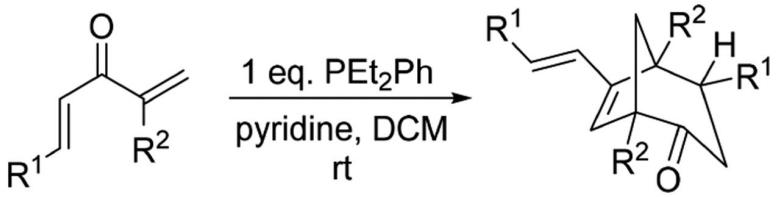
Scheme 664.
Formation of Furo[3,2-*c*]coumarin Derivatives



Scheme 665.
Synthesis of Functionalized Cyclic Imides



Scheme 666.
Proposed Formal [4 + 2] Cycloaddition–Wittig Pathway

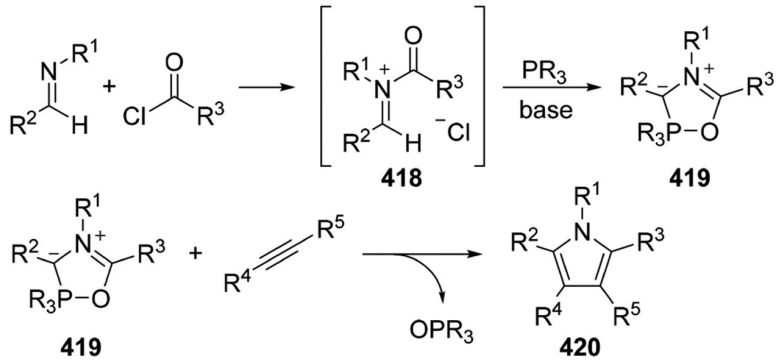


entry	R^1	R^2	yield (%)
1	Ph	Me	76
2	2-furyl	Me	75
3	Ph	Et	41[a]
4	*n*-heptyl	Me	60[b]

Scheme 667.

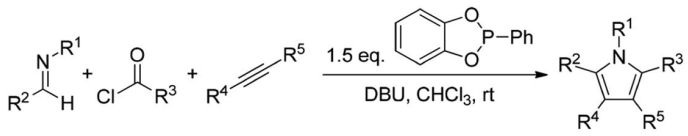
Formation of Functionalized Bicyclo[3.2.1]octane Derivatives

[a]Reaction run in $CHCl_3$ at 50 °C. [b]PBu_3 was added over 6 h at 0 °C.



Scheme 668.

Proposed Pathway toward the Mesoionic Intermediate

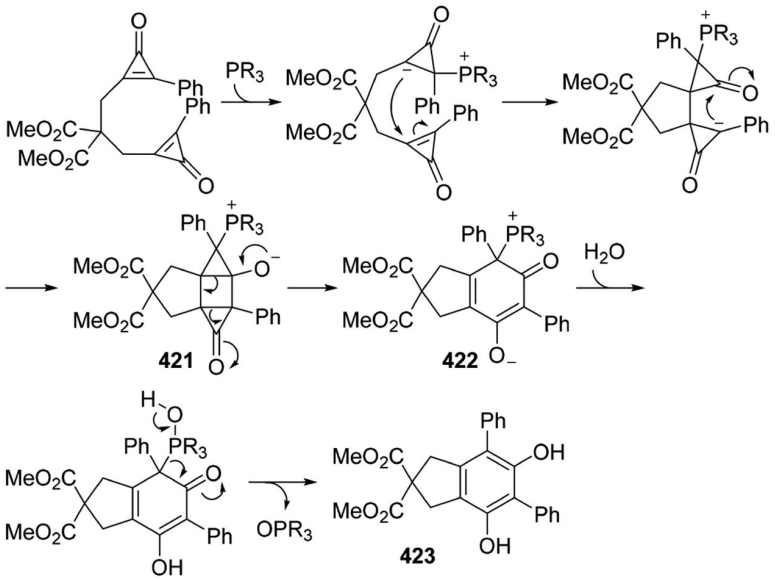


entry	R^1	R^2	R^3	R^4	R^5	yield (%)
1	Bn	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	CO_2Me	CO_2Me	85
2	Allyl	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	H	CO_2Me	89
3	Bn	H	Ph	CO_2Me	CO_2Me	44[a,b]
4	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	Ph	H	H	42[c]
5	Bn	Ph	*i*Pr	H	CO_2Me	67[b]
6	Bn	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	H	CO_2Me	91

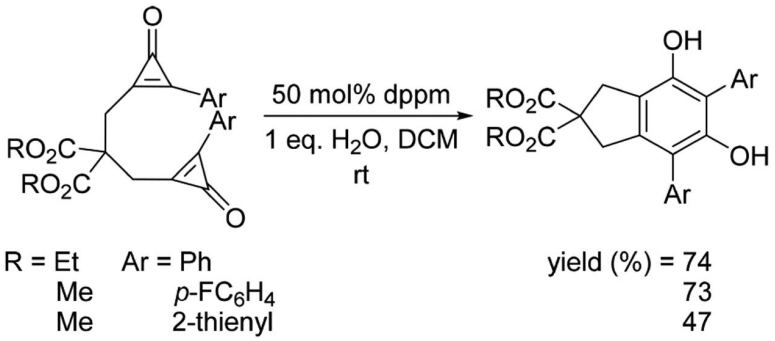
Scheme 669.

Preparation of Functionalized Pyrroles

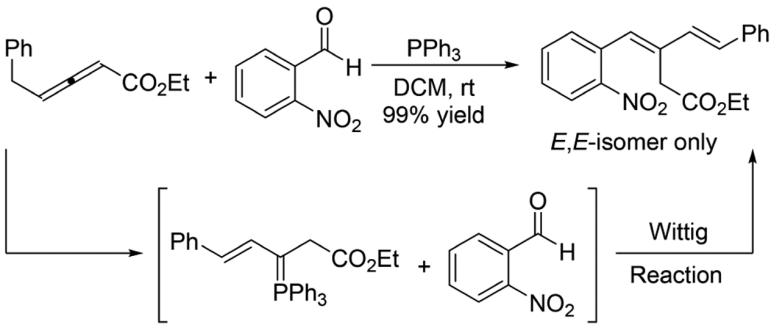
[a]Mixture stirred for 16 h prior to addition of base. [b]LiHMDS at −78 °C. [c]Reaction performed at 50 °C.



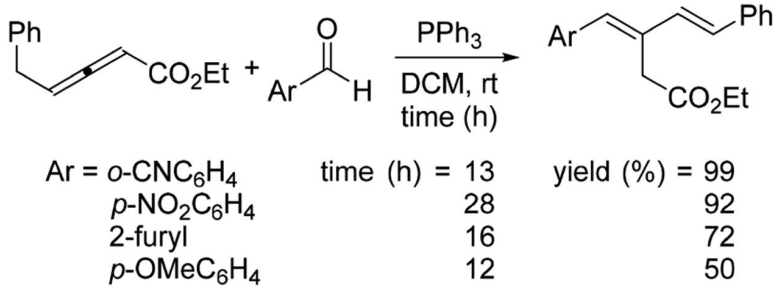
Scheme 670.
Proposed Mechanism for Indane Formation



Scheme 671.
Synthesis of Functionalized Indanes

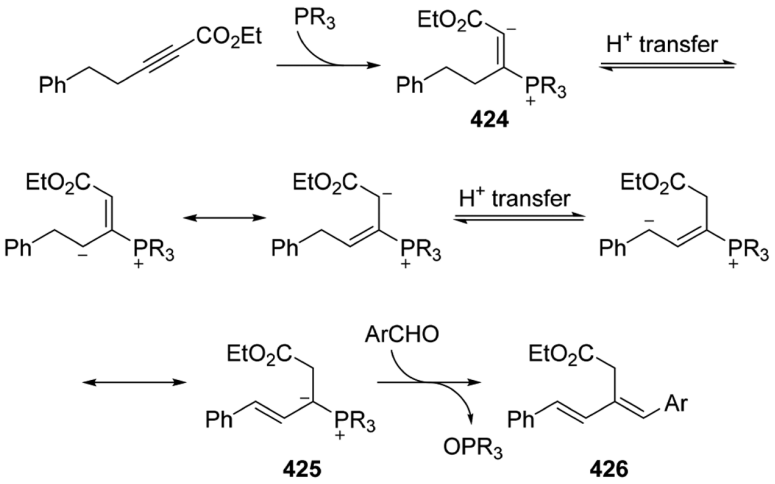


Scheme 672.
Formation of Functionalized Dienes with Allenoates



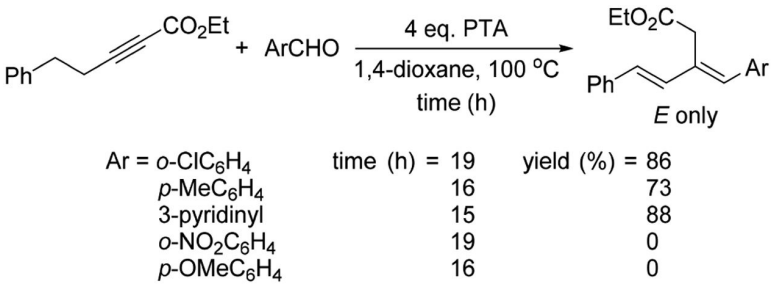
Ar =	time (h) =	yield (%) =
o-CNC_6H_4	13	99
p-$NO_2C_6H_4$	28	92
2-furyl	16	72
p-$OMeC_6H_4$	12	50

Scheme 673.
Formation of Functionalized Dienes



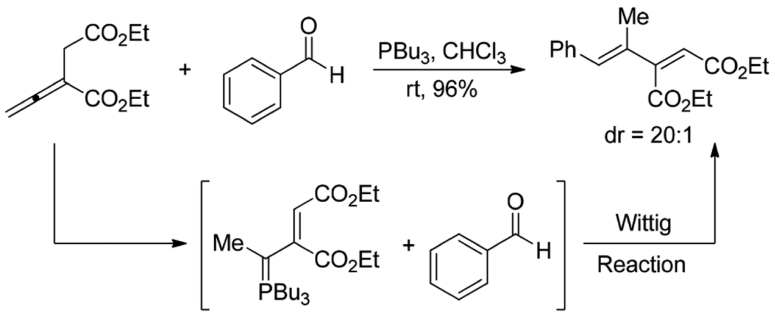
Scheme 674.

Mechanism for the Wittig Reaction of 5-Phenyl-2-pentynoate

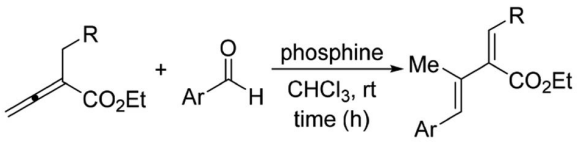


Ar = *o*-ClC_6H_4	time (h) = 19	yield (%) = 86
p-MeC_6H_4	16	73
3-pyridinyl	15	88
o-$NO_2C_6H_4$	19	0
p-$OMeC_6H_4$	16	0

Scheme 675.
Formation of Functionalized 1,3-Dienes

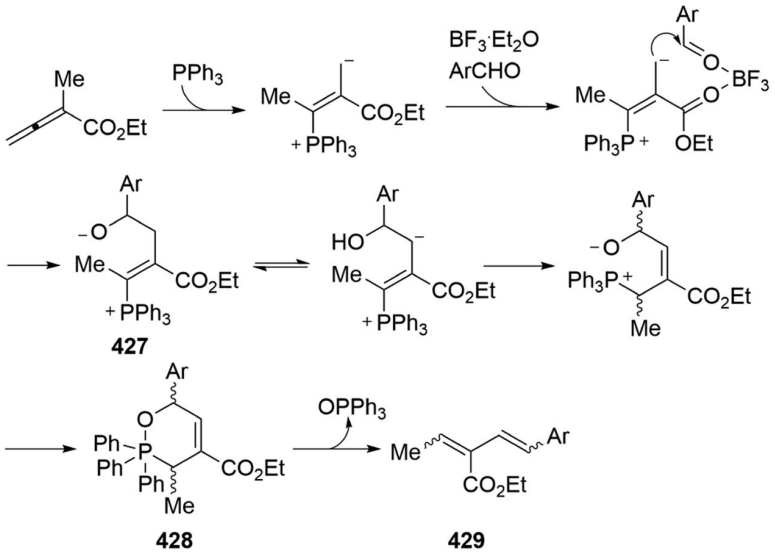


Scheme 676.
Wittig Olefination with a Vinylidenesuccinate



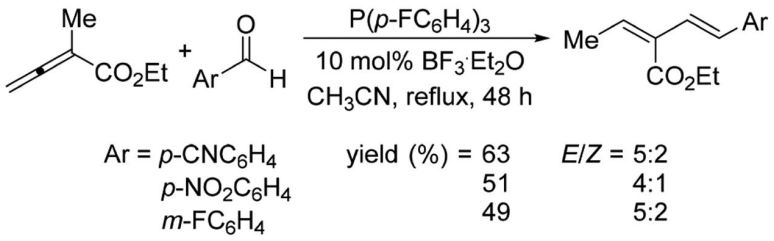
entry	R	Ar	phosphine	time (h)	yield (%)	dr
1	CO_2Et	*p*-$MeOC_6H_4$	PBu_3	24	87	20:1
2	CO_2Et	*p*-$F_3CC_6H_4$	$PMePh_2$	6	95	20:1
3	CO_2Et	*p*-$O_2NC_6H_4$	$PMePh_2$	1	63	8:1
4	Ph	Ph	PBu_3	24	91	17:1

Scheme 677.
Formation of Derivatized Dienes

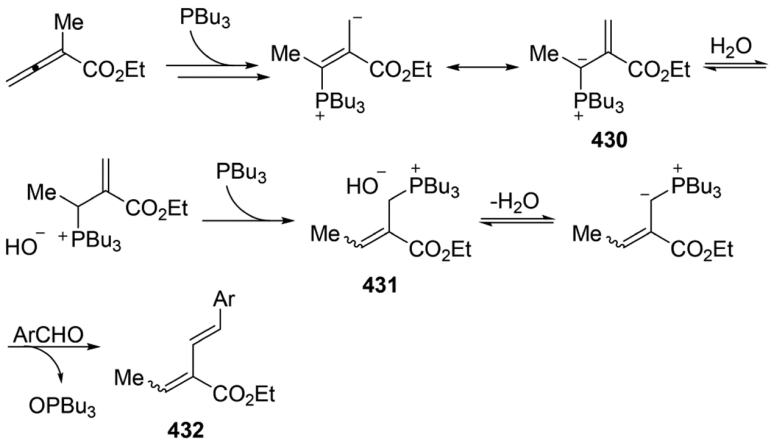


Scheme 678.

Mechanism for Kwon's Vinylogous Wittig Reaction of α-Methylallenoate

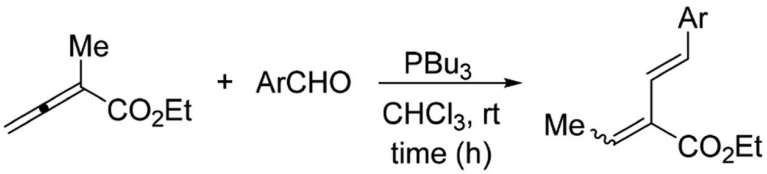


Scheme 679.
Formation of Functionalized Dienes



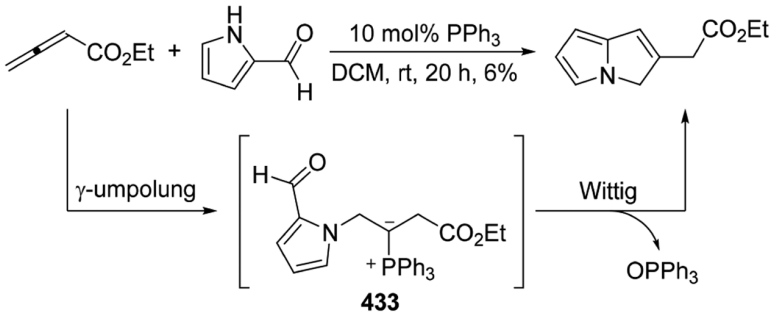
Scheme 680.

Mechanism for He's Vinylogous Wittig Reaction of α-Methylallenoate



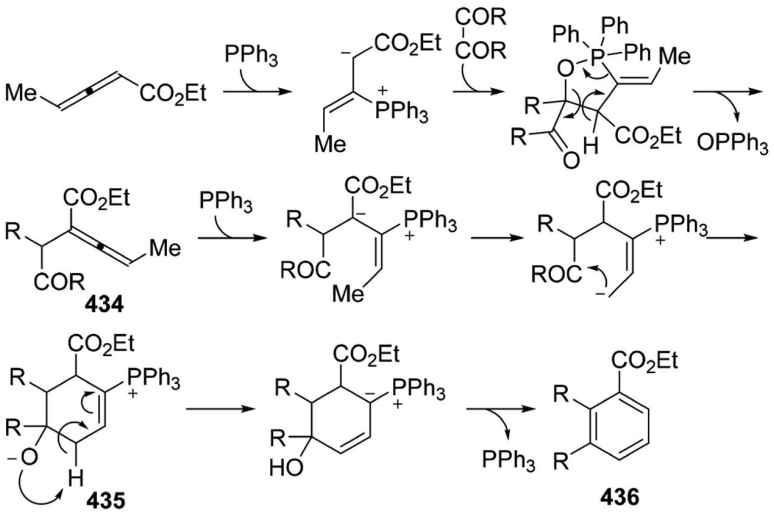
entry	Ar	time (h)	yield (%)	*E*/*Z*
1	*m*-ClC_6H_4	12	99	5:1
2	*p*-FC_6H_4	24	96	4:1
3	*o*-$F_3CC_6H_4$	24	44	4:1
4	1-naphthyl	36	98	4:1
5	2-furyl	24	87	5:1

Scheme 681.
Preparation of Functionalized 1,3-Dienes



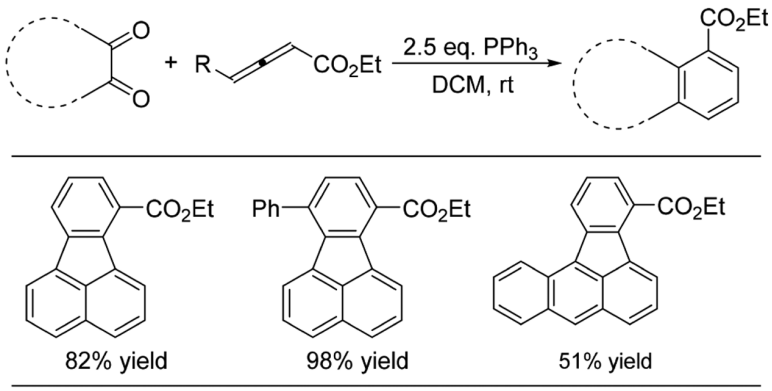
Scheme 682.

Proposed Reaction Pathway for the Formation of a Pyrrolizine



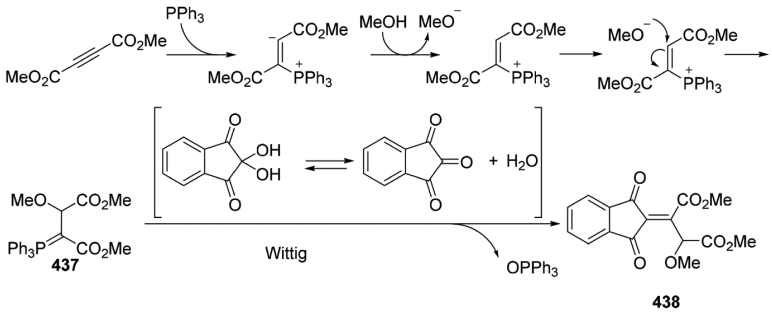
Scheme 683.

Proposed Mechanism of Benzo[*a*]aceanthrylene Formation

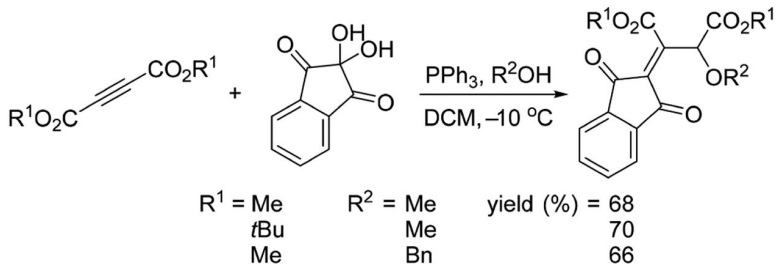


Scheme 684.

Synthesis of Functionalized Fluoranthenes and Benzo[*a*]aceanthrylenes

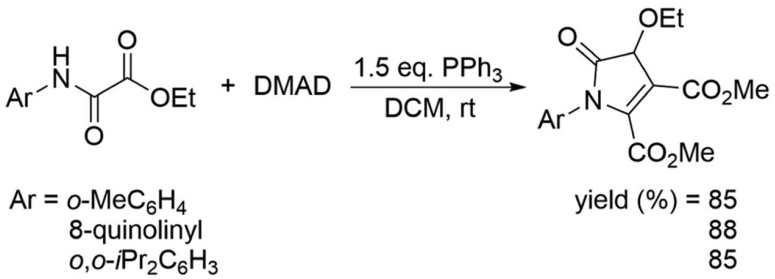


Scheme 685.
Proposed Reaction Mechanism for the Wittig Reaction of DMAD

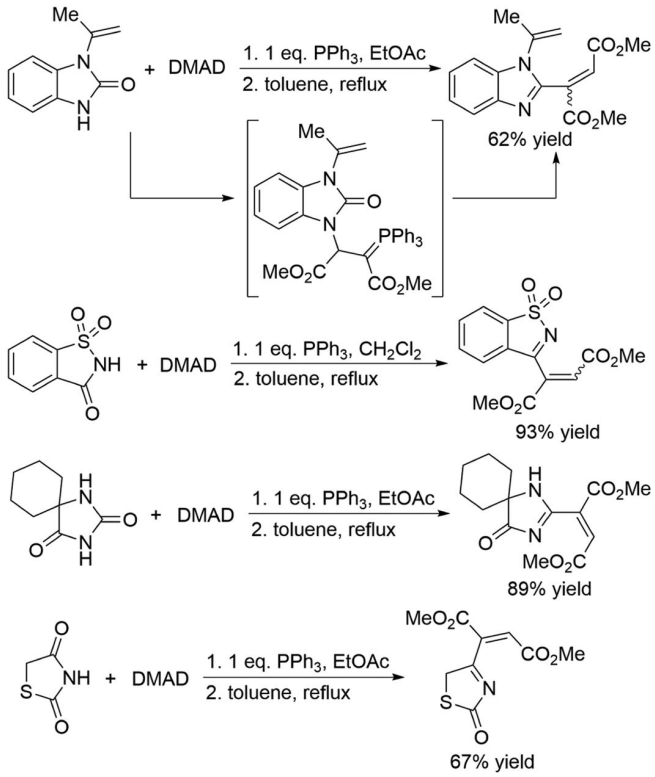


R^1 =	R^2 =	yield (%) =
Me	Me	68
*t*Bu	Me	70
Me	Bn	66

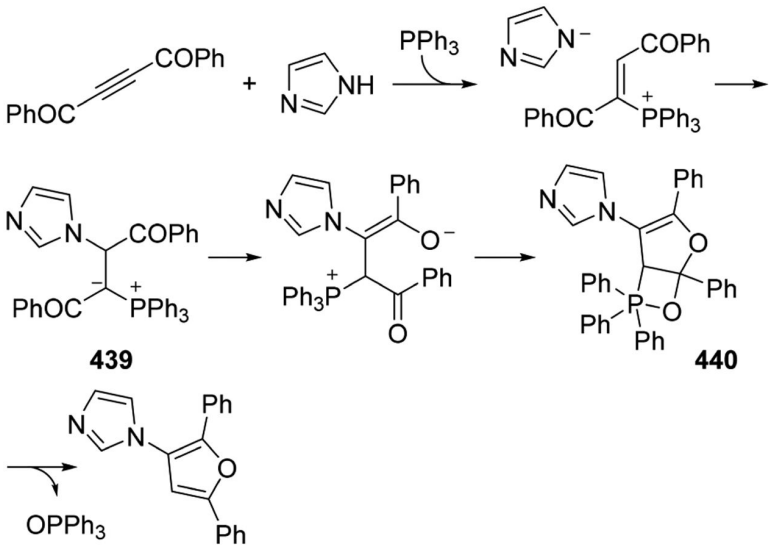
Scheme 686.
Wittig Reactions Involving DMAD



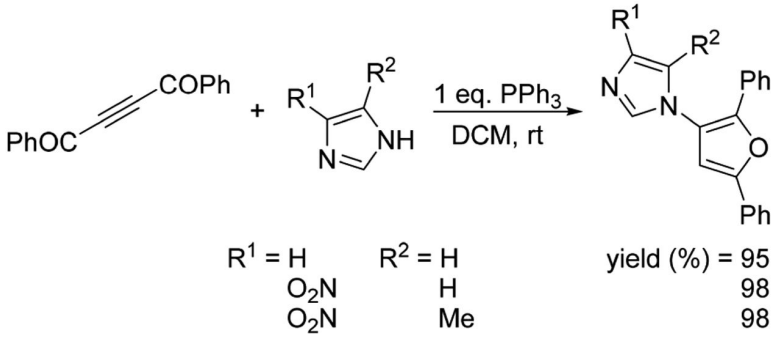
Scheme 687.
Synthesis of Functionalized Dihydropyrrolones



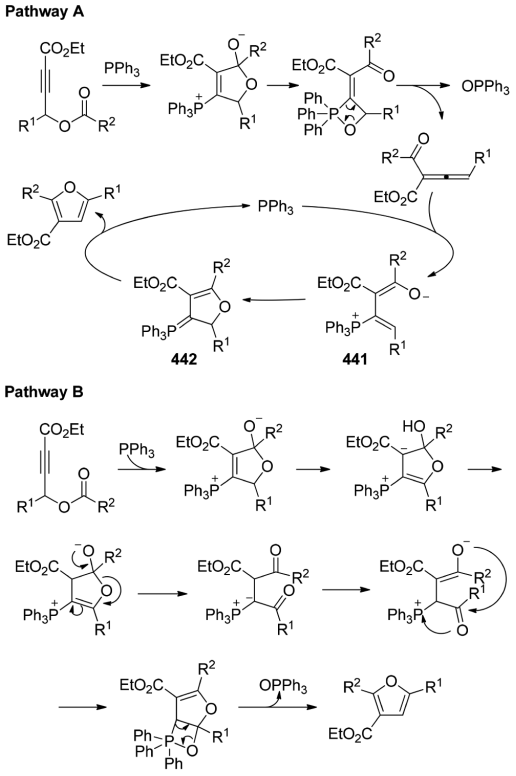
Scheme 688.
Synthesis of Functionalized Azadienoates



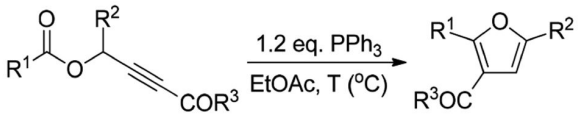
Scheme 689.
Proposed Mechanism of Furan Formation

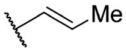
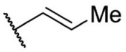


Scheme 690.
Synthesis of Functionalized Furans

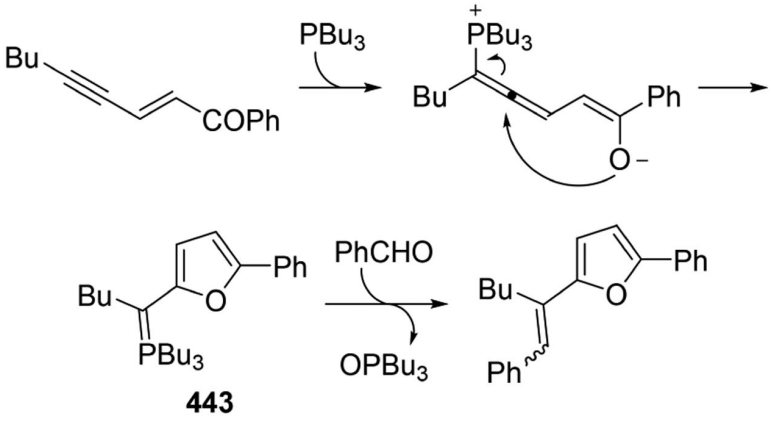


Scheme 691.
Possible Reaction Mechanisms for the Formation of Furans from 4-Acyloxy-2-butynoates



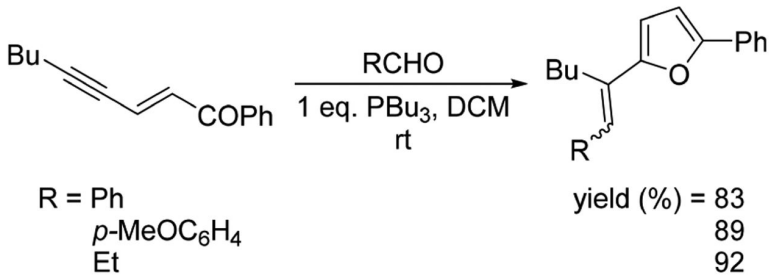
entry	R^1	R^2	R^3	T (°C)	yield (%)
1	3,5-$(O_2N)_2C_6H_3$	H	OEt	110	91
2	*p*-$O_2NC_6H_4$	H	Me	rt	73
3	C_6F_5	H	OEt	rt	71[a]
4	2-furyl	H	OEt	110	73
5		H	OEt	110	83
6	3,5-$(O_2N)_2C_6H_3$		OEt	110	86

Scheme 692.
Formation of Functionalized Furans
[a]Reaction conducted with (*m*-tolyl)$_3$P.

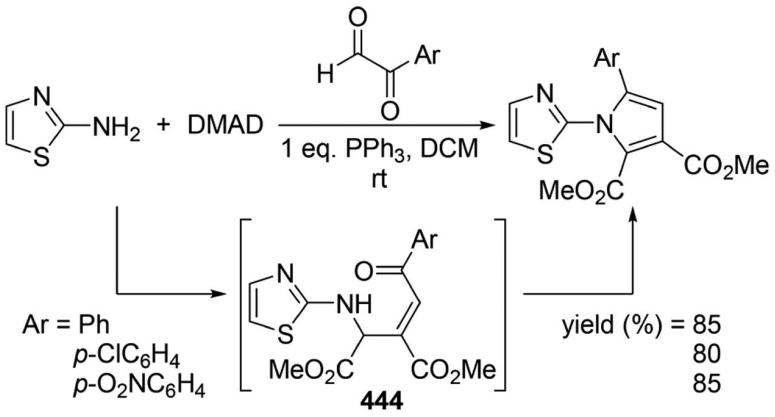


Scheme 693.

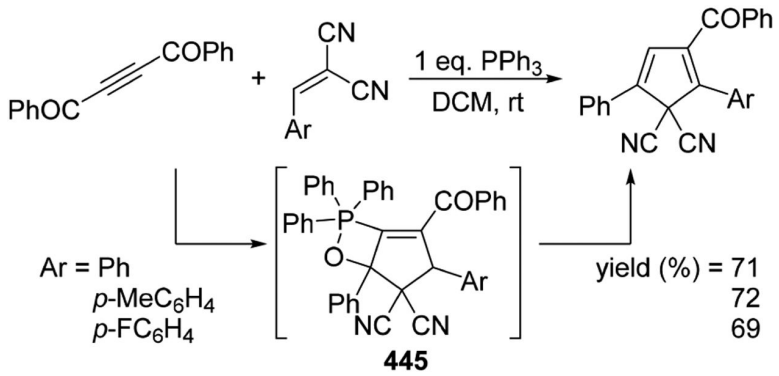
Mechanism for the Formation of an Ylide from a Conjugated Enynone



Scheme 694.
Preparation of Functionalized Furans

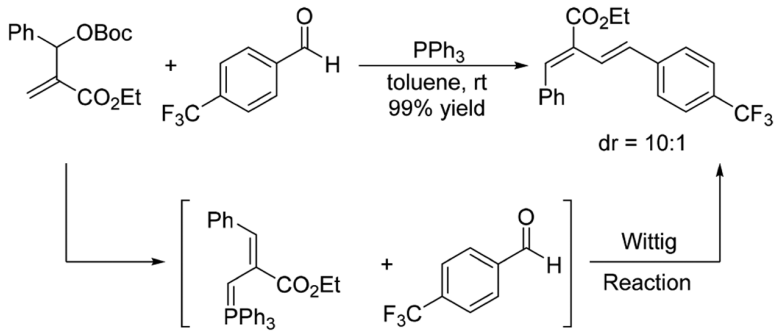


Scheme 695.
Synthesis of Functionalized Pyrroles

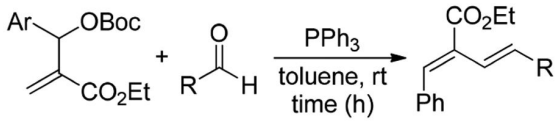


Scheme 696.

Synthesis of Functionalized Cyclopentadienes

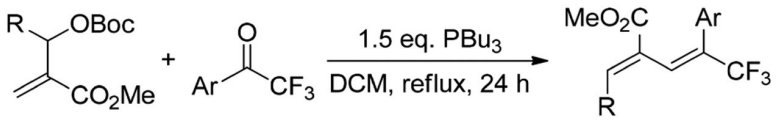


Scheme 697.
Formation of Functionalized Dienes



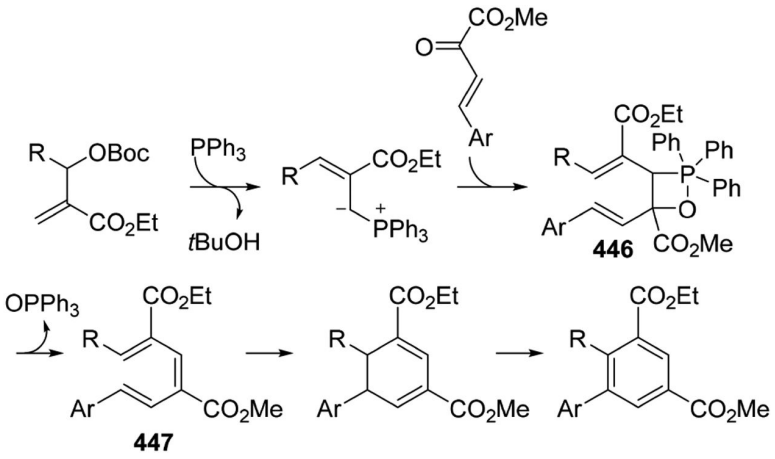
entry	Ar	R	time (h)	yield (%)	Dr
1	Ph	2-furyl	25	84	>20:1
2	*p*-$MeOC_6H_4$	*p*-$O_2NC_6H_4$	29	96	20:1
3	2-furyl	*p*-$O_2NC_6H_4$	22	80	20:1
4	Ph	*n*Pr	3	90[a]	5:1

Scheme 698.
Formation of Trisubstituted Dienes
[a]PBu_3 used as catalyst.

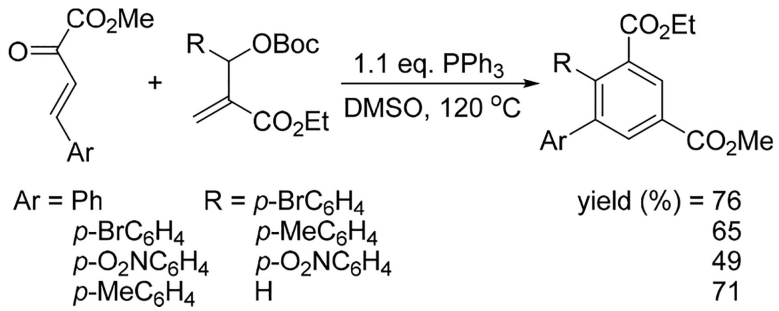


entry	R	Ar	yield (%)
1	Ph	*p*-$MeOC_6H_4$	69
2	Ph	2-thienyl	58
3	*o*-ClC_6H_4	Ph	76
4	*p*-MeC_6H_4	Ph	67

Scheme 699.
Synthesis of Functionalized Diene Derivatives

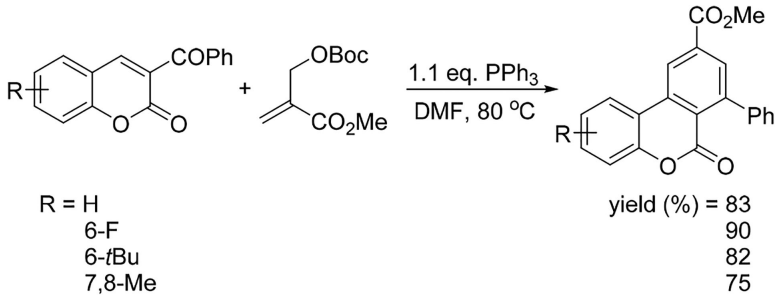


Scheme 700.
Proposed Reaction Mechanism for the Benzannulation

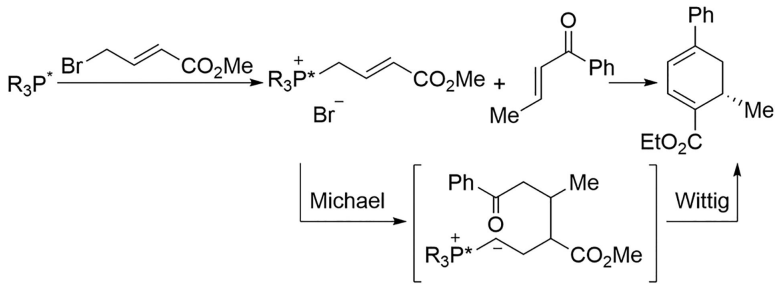


Ar = Ph	R = *p*-BrC_6H_4	yield (%) = 76
p-BrC_6H_4	*p*-MeC_6H_4	65
p-$O_2NC_6H_4$	*p*-$O_2NC_6H_4$	49
p-MeC_6H_4	H	71

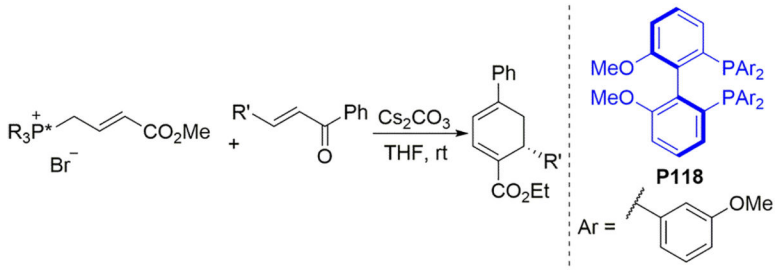
Scheme 701.
Synthesis of Functionalized Benzenes



Scheme 702.
Synthesis of Functionalized Benzchromenones

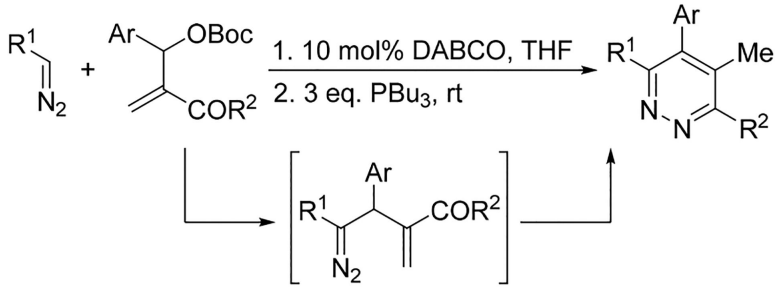


Scheme 703.
An Asymmetric Michael–Wittig Reaction



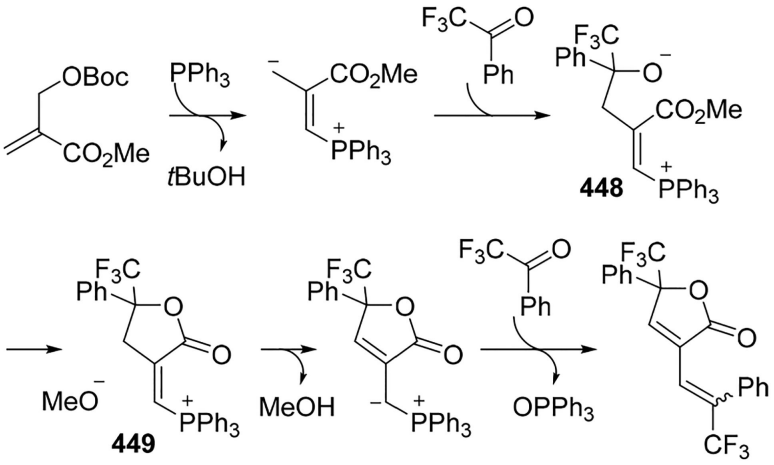
entry	R′	yield (%)	ee (%)
1	Ph	62	83
2	*p*-MeOC$_6$H$_4$	65	90
3	Me	67	25

Scheme 704.
Asymmetric Michael–Wittig Reactions

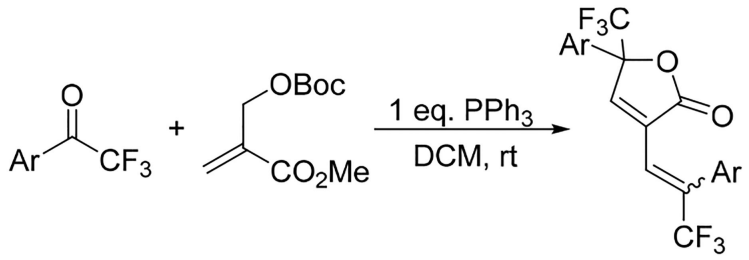


entry	R^1	R^2	Ar	yield (%)
1	CO_2Et	EtO	*p*-FC_6H_4	70
2	CO_2Et	Me	Ph	65
3	F_3C	MeO	*p*-$F_3CC_6H_4$	64
4	F_3C	Me	Ph	68

Scheme 705.
Synthesis of Functionalized Pyridazines

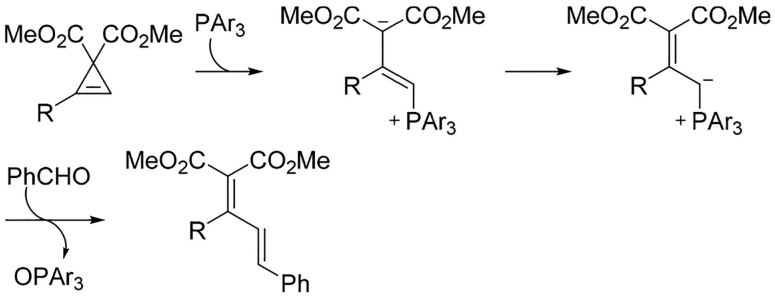


Scheme 706.
Synthesis of Functionalized Pyridazines

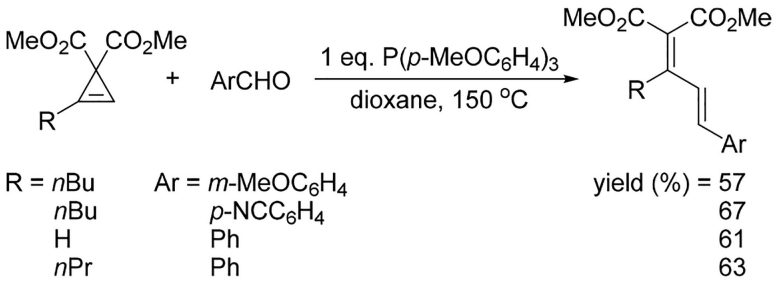


Ar = Ph	yield (%) = 82	*Z*/*E* = 6:1
p-BrC_6H_4	71	4:1
p-$MeOC_6H_4$	60	>15:1
2-thienyl	63	>15:1

Scheme 707.
Synthesis of Functionalized Butenolides

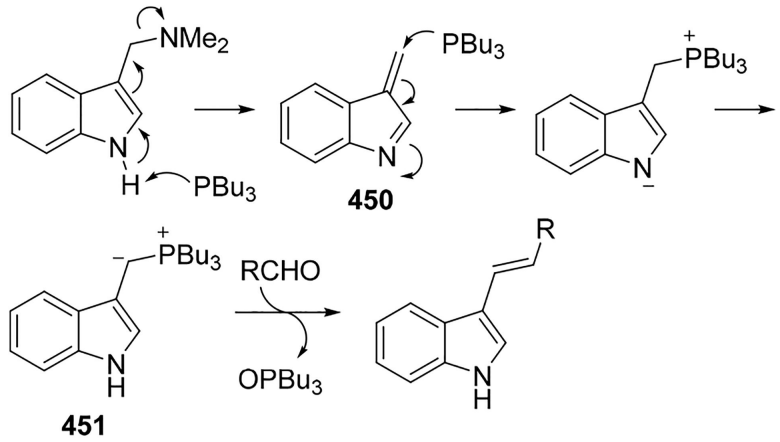


Scheme 708.
Wittig Reaction of Ylides From Cyclopropane-1,1-dicarboxylates

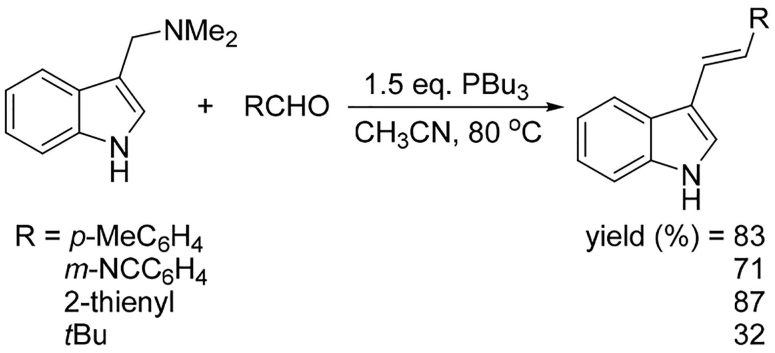


R =	Ar =	yield (%) =
*n*Bu	*m*-MeOC$_6$H$_4$	57
*n*Bu	*p*-NCC$_6$H$_4$	67
H	Ph	61
*n*Pr	Ph	63

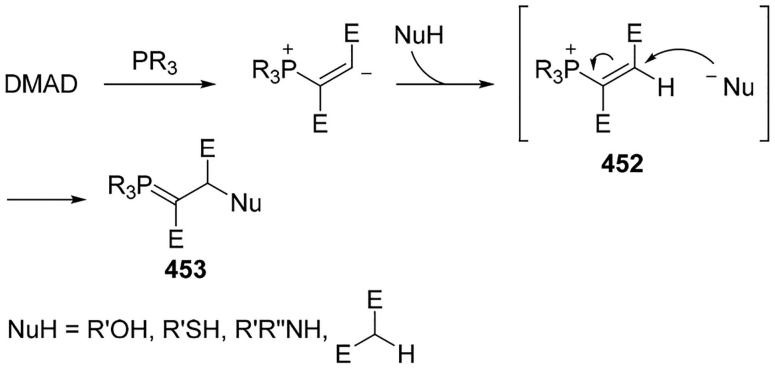
Scheme 709.
Synthesis of Functionalized Dienes



Scheme 710.
Wittig Reaction of an Ylide Formed from Gramine

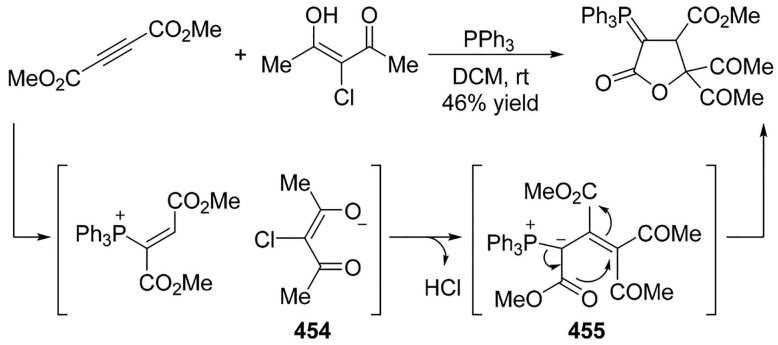


Scheme 711.
Synthesis of Functionalized Indoles

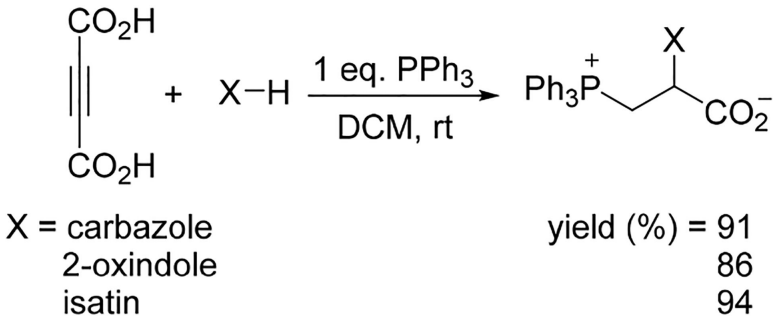


Scheme 712.

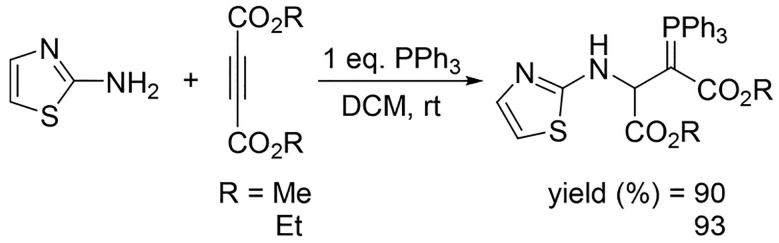
General Mechanism for Phosphorus Ylide Formation with Nucleophiles



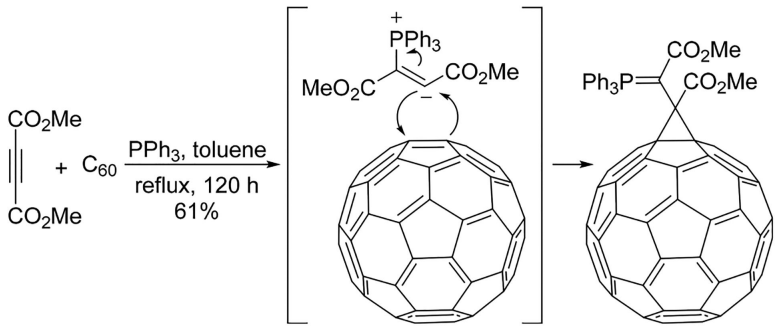
Scheme 713.
Phosphorane Formation with DMAD



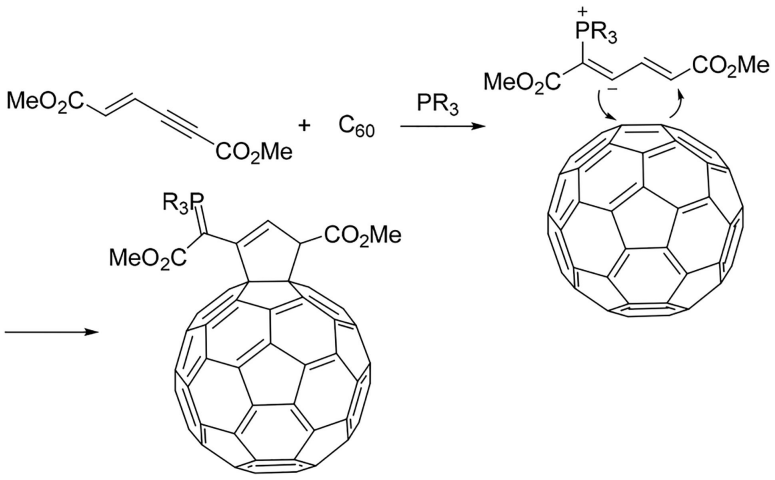
Scheme 714.
Synthesis of *Phospho*-betaines



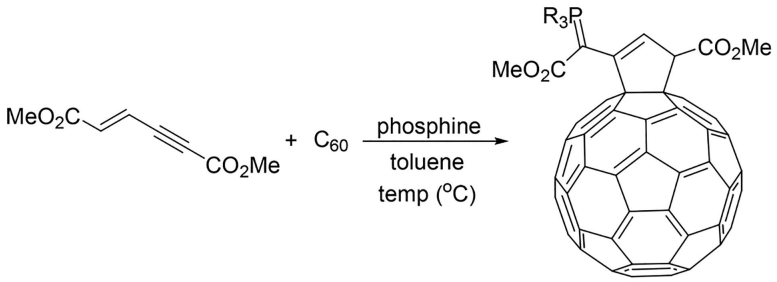
Scheme 715.
Synthesis of 2-Aminothiazole-Derived Ylides



Scheme 716.
Cyclopropanation of Fullerene

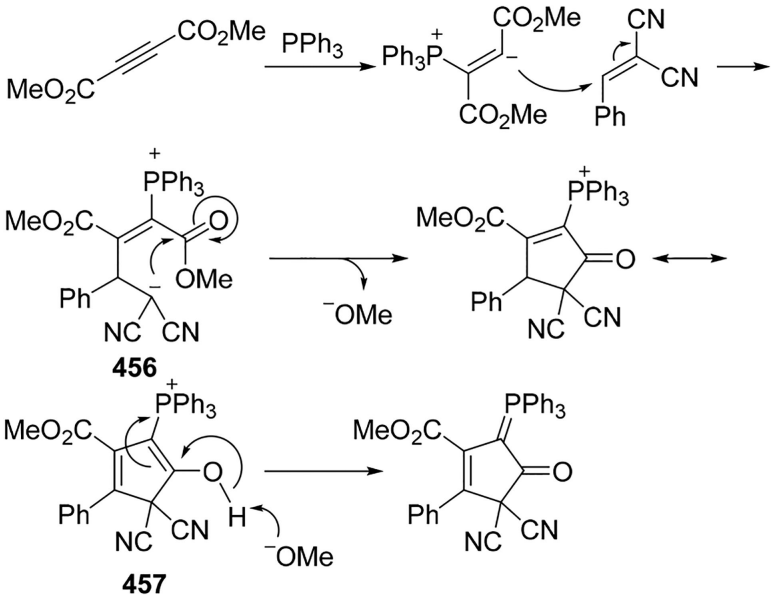


Scheme 717.
Proposed Reaction Pathway Toward Fullerene Derivatives



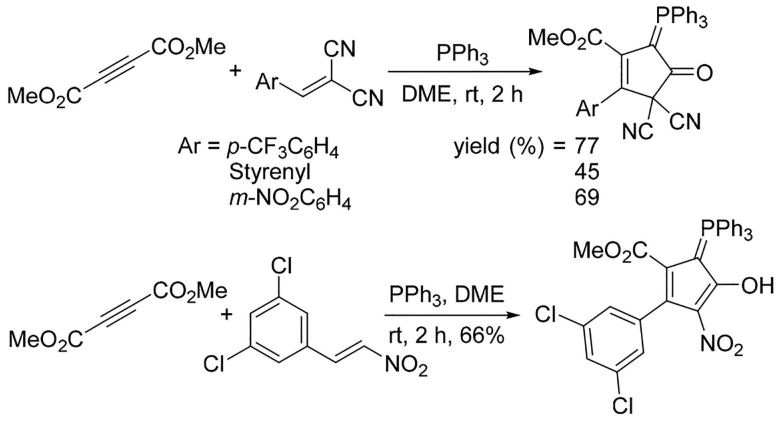
entry	phosphine	T (°C)	yield (%)
1	P(*p*-MeOC$_6$H$_4$)$_3$	25	57
2	PPh$_3$	50	52
3	P(*p*-ClC$_6$H$_4$)$_3$	110	16
4	P(NEt$_2$)$_3$	110	33

Scheme 718.
Formation of Fullerene Derivatives

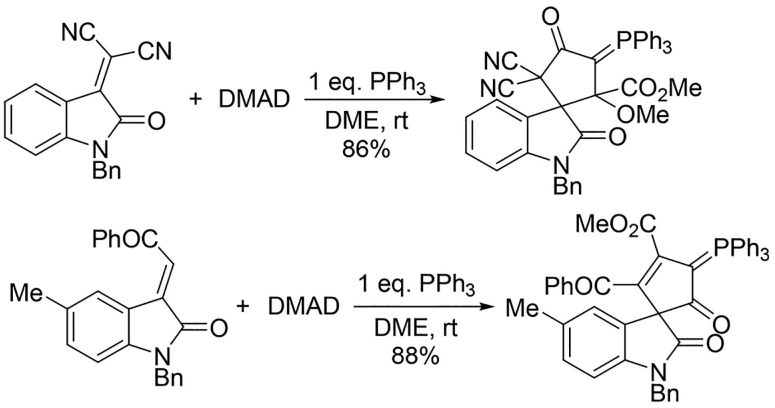


Scheme 719.

Ylide Formation from Triphenylphosphine, DMAD, and Benzylidenemalononitrile

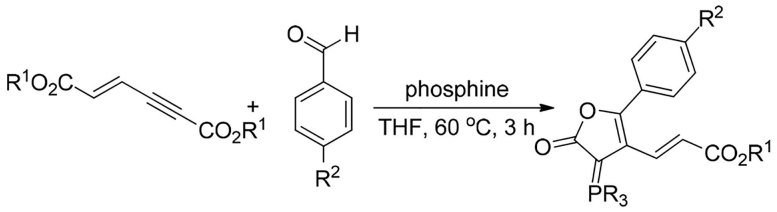


Scheme 720.
Formation of Phosphoranes



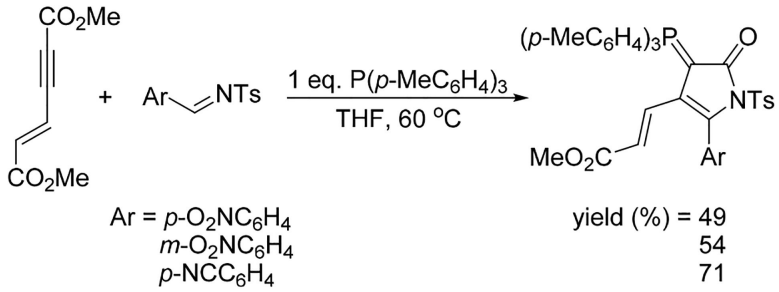
Scheme 721.

Synthesis of Functionalized Spirooxindole-Derived Ylides



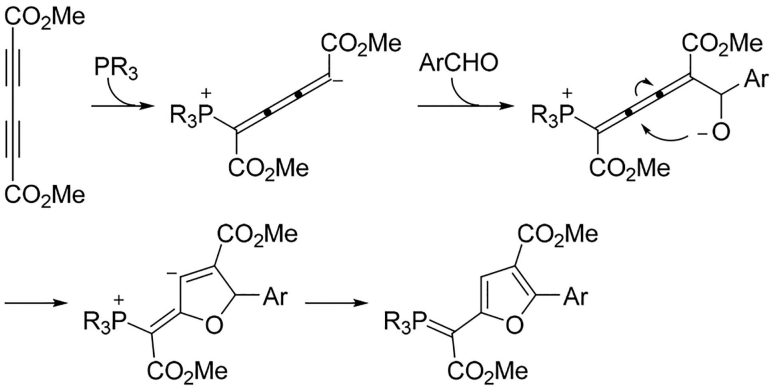
entry	R^1	R^2	phosphine	yield (%)
1	Me	NO_2	P(*p*-$MeOC_6H_4$)$_3$	77
2	Et	NO_2	PPh_3	68
3	Me	CN	P(*p*-$MeOC_6H_4$)$_3$	72

Scheme 722.
Formation of Cyclic Phosphoranes



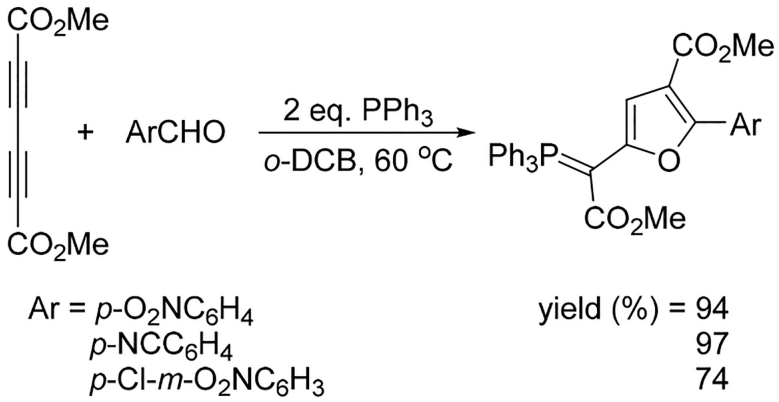
Scheme 723.

Synthesis of Functionalized Ylide-Containing Dihydropyrrolones

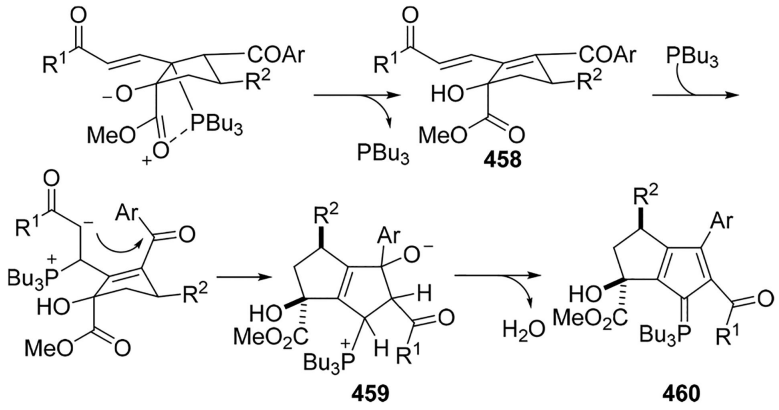


Scheme 724.

Ylide Formation from PR_3, a Diynedioate, and an Aldehyde

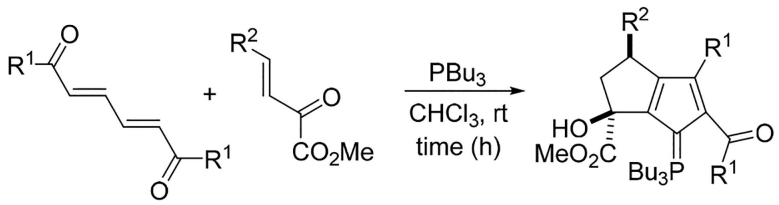


Scheme 725.
Synthesis of Ylide-Containing Furans



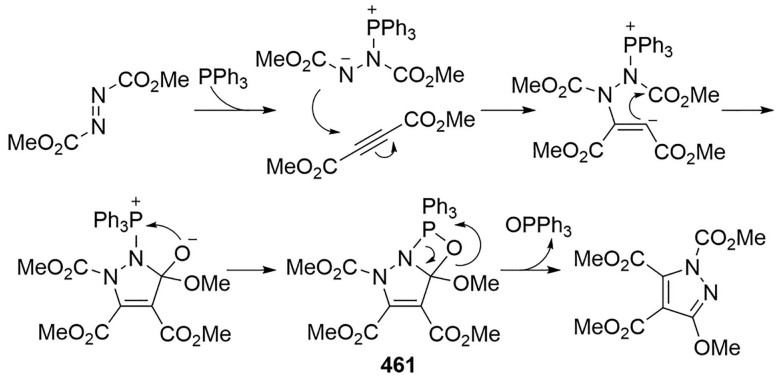
Scheme 726.

Ylide Formation from PBu_3, an Enone–Enoate, and an Enoylester

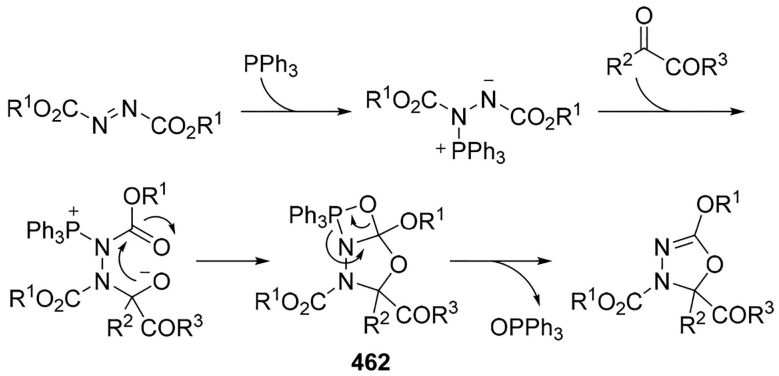


entry	R^1	R^2	time (h)	yield (%)
1	Ph	*p*-BrC_6H_4	5	85
2	*p*-FC_6H_4	*p*-MeC_6H_4	6	79
3	*m*-$MeOC_6H_4$	*p*-MeC_6H_4	5	81
4	*p*-FC_6H_4	2-naphthyl	12	65

Scheme 727.
Formation of Functionalized Phosphoranes



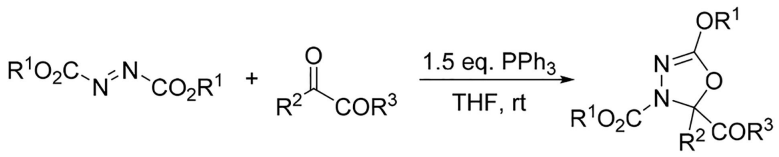
Scheme 728.
Proposed Annulation Mechanism



462

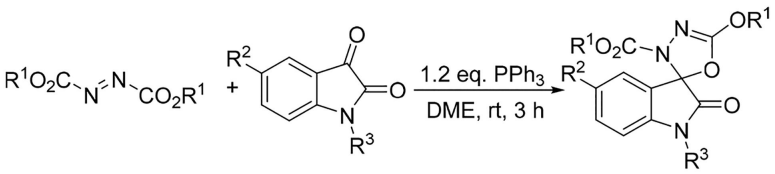
Scheme 729.

Proposed Mechanistic Pathway Toward Oxadiazolines



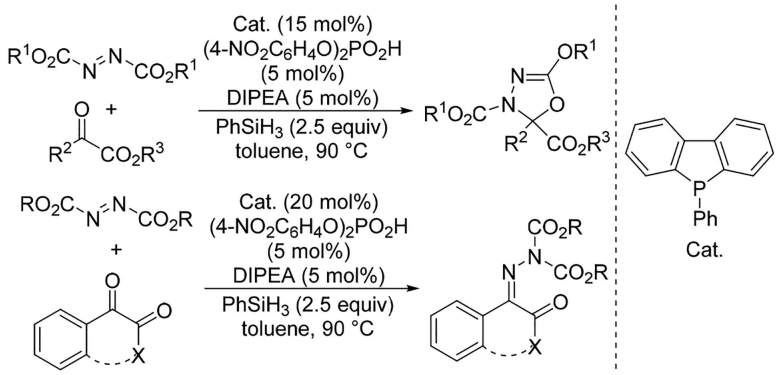
entry	R^1	R^2	R^3	yield (%)
1	*i*Pr	Ph	OMe	90
2	Bn	Me	OMe	83
3	*i*Pr	$(CH_2)_2CO_2Me$	OMe	93
4	Bn	Me	Me	55

Scheme 730.
Formation of Functionalized 1,3,4-Oxadiazolines



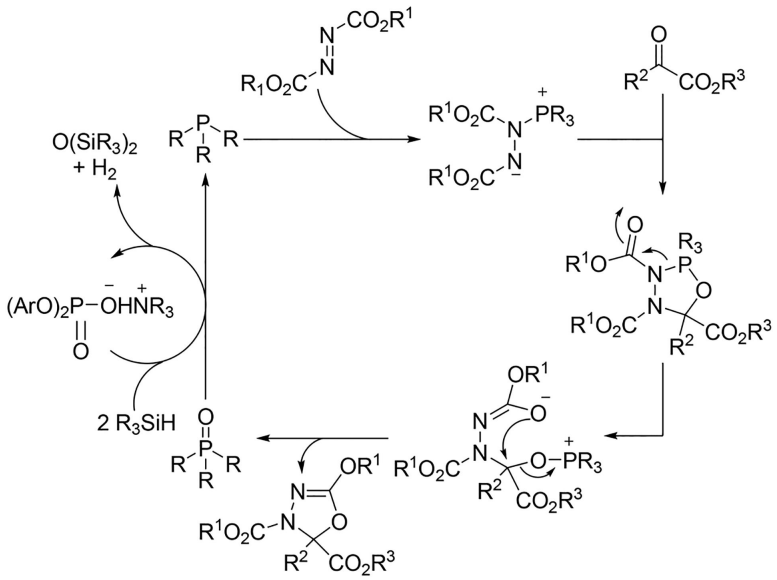
entry	R^1	R^2	R^3	yield (%)
1	Et	Br	allyl	65
2	*i*Pr	Br	Me	86
3	*i*Pr	H	Bn	61

Scheme 731.
Formation of Functionalized Spiro-1,3,4-oxadiazolineoxindoles



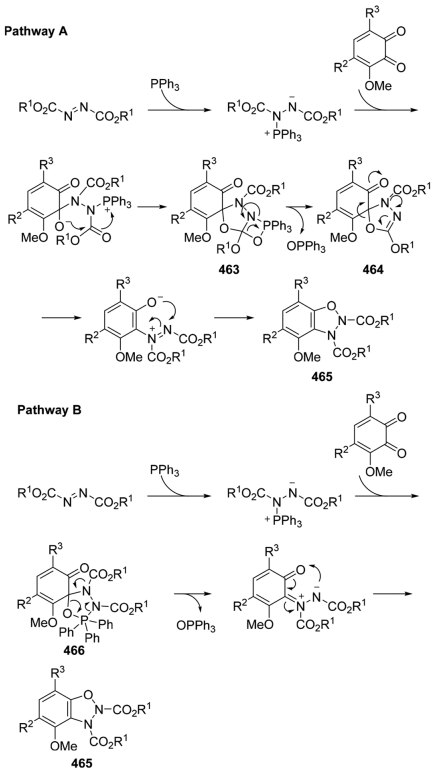
Scheme 732.

Phosphine-Catalyzed Hüisgen Reaction of Diazoesters and α-Ketoesters

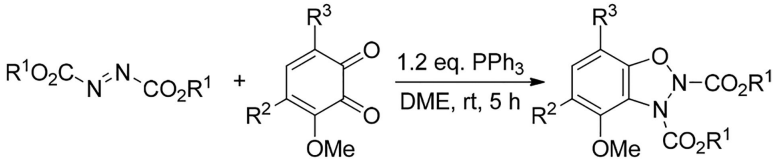


Scheme 733.

Proposed Mechanism for Phosphine-Catalyzed Hüisgen Reaction of Diazoesters and α-Ketoesters

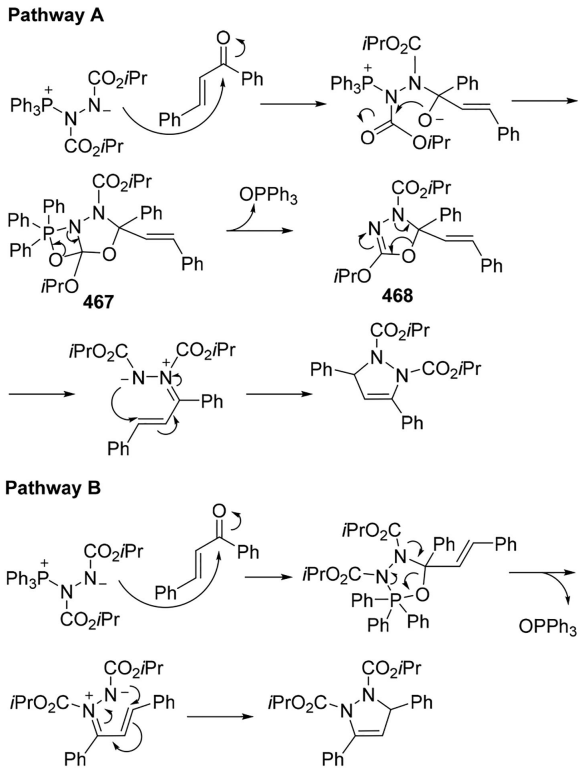


Scheme 734.
Formation of Dihydro-1,2,3-benzoxadiazoles



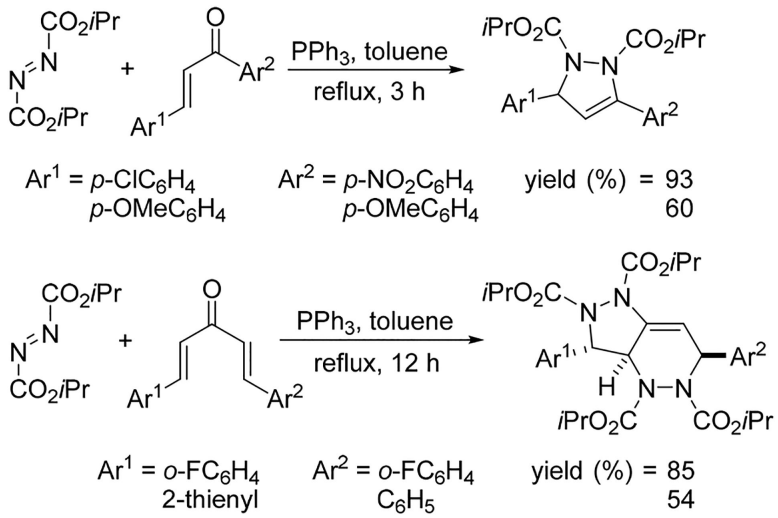
entry	R^1	R^2	R^3	yield (%)
1	Et	*t*Bu	H	91
2	*i*Pr	$CHPh_2$	$CHPh_2$	85

Scheme 735.
Formation of Derivatized Dihydro-1,2,3-benzoxadiazoles



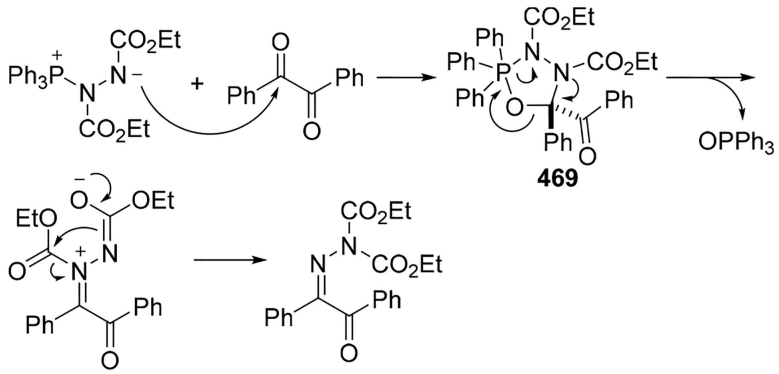
Scheme 736.

Mechanistic Routes for the Synthesis of a Pyrazoline from an Azodicarboxylate and a Conjugated Enone

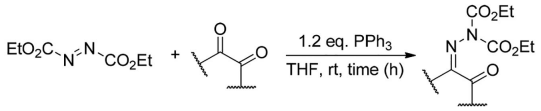


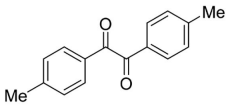
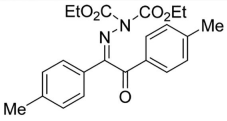
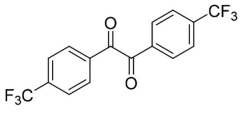
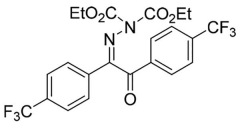
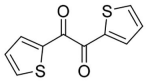
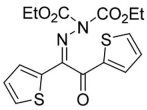
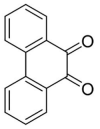
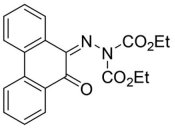
Scheme 737.

Formation of Functionalized Pyrazolines and Pyrazolopyridazines

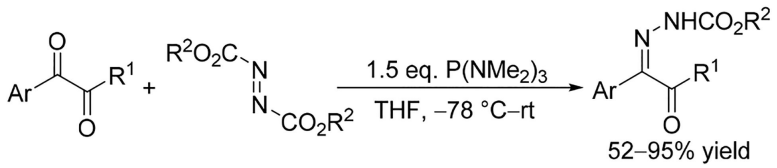


Scheme 738.
Proposed Pathway toward Hydrazone Derivatives



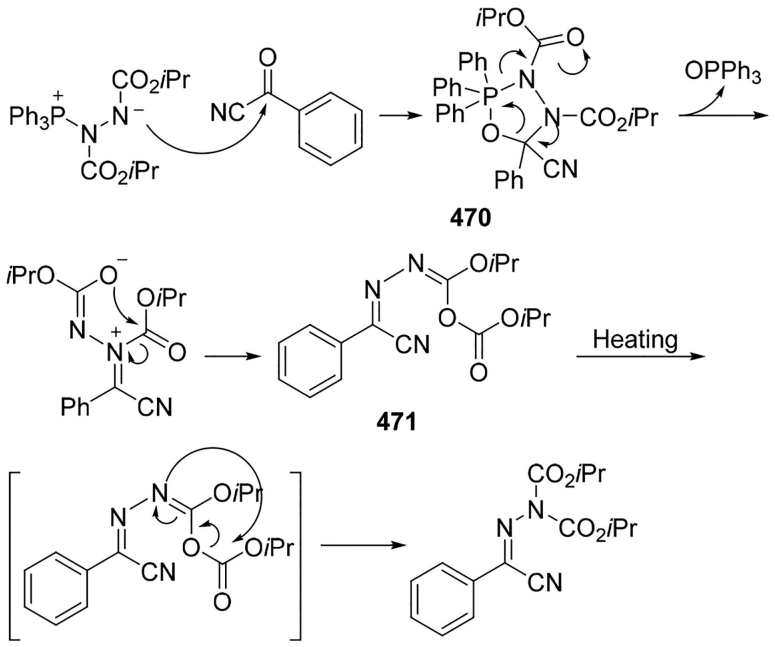
entry	1,2-diketone	product	time (h)	yield (%)
1			18	39
2			14	80
3			12	49
4			12	77

Scheme 739.
Formation of Derivatized Hydrazones



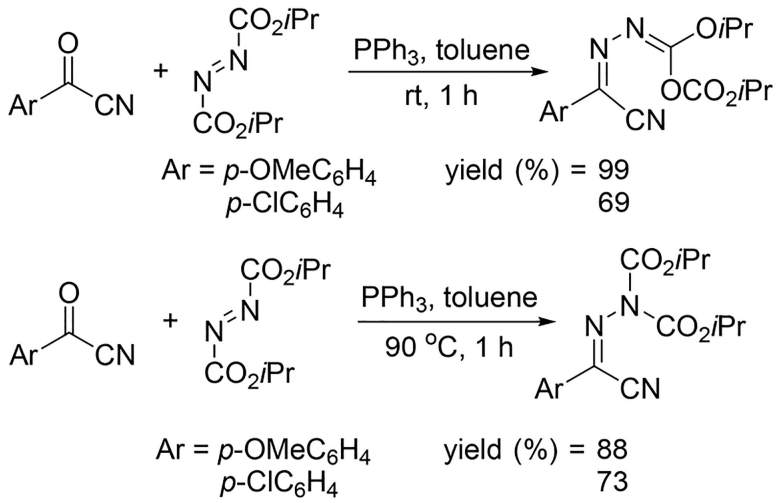
Scheme 740.

Phosphine-Mediated Addition of 1,2-Dicarbonyls to Diazenes

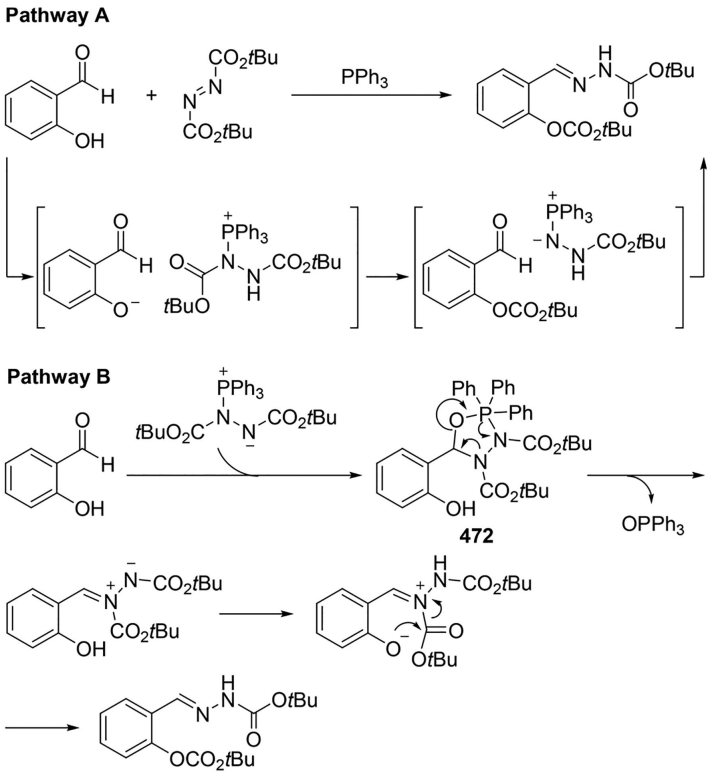


Scheme 741.

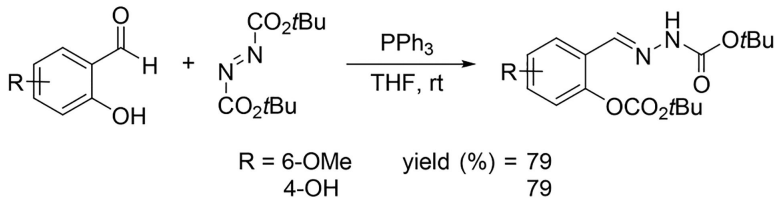
Synthesis of a Hydrozone from an Azodicarboxylate and a Cyano Ketone



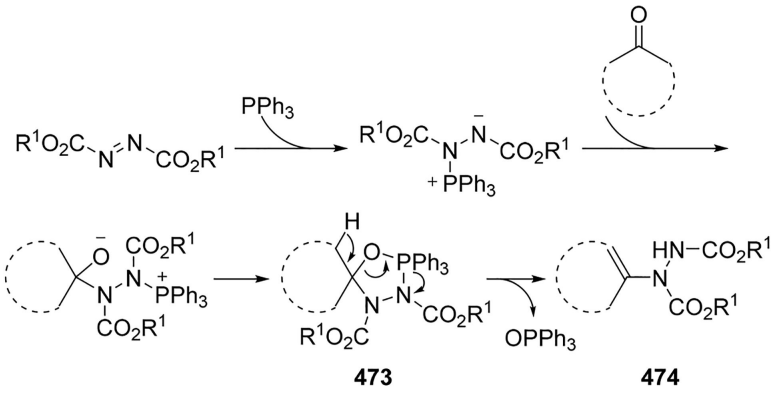
Scheme 742.
Formation of Azadienes and Hydrazones



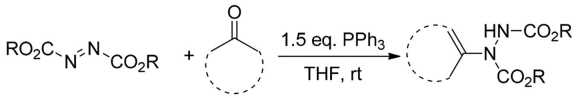
Scheme 743.
Proposed Mechanistic Pathways for the Hydrazone Formation

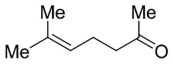
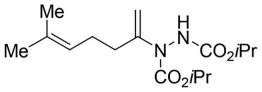
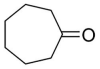
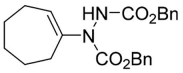
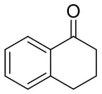
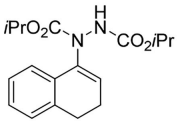


Scheme 744.
Formation of Boc-Protected Hydrazones

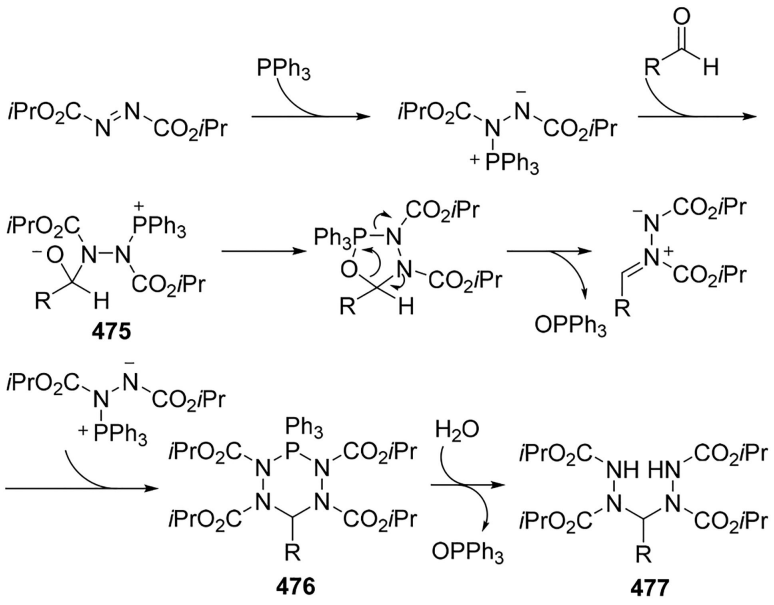


Scheme 745.
Proposed Mechanism for Enamine Formation



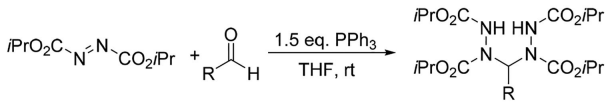
entry	R	ketone	product	yield (%)
1	*i*Pr			86
2	Bn			48
3	*i*Pr			81

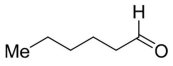
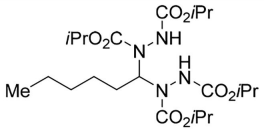
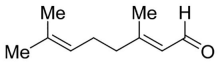
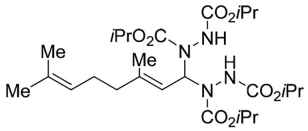
Scheme 746.
Formation of Functionalized Vinyl Hydrazines



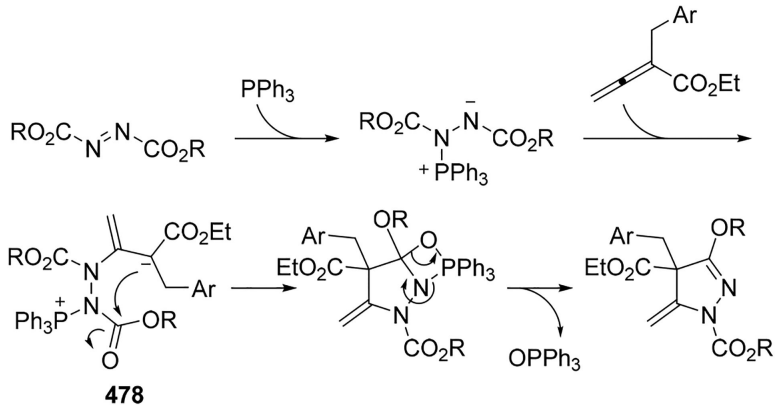
Scheme 747.

Proposed Reaction Pathway for the Synthesis of Bis-Hydrazines



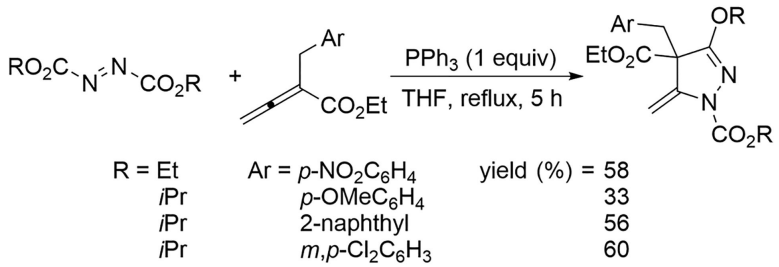
entry	aldehyde	Product	yield (%)
1			46
2			38

Scheme 748.
Formation of Functionalized Bis-Hydrazines



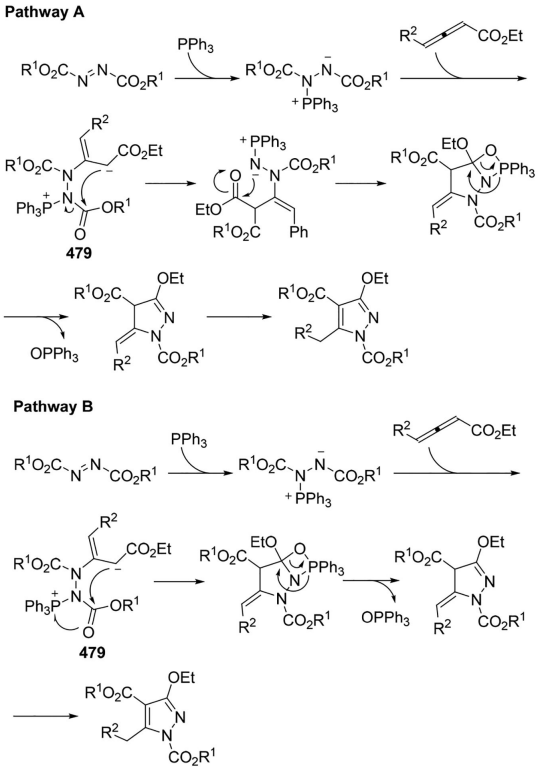
Scheme 749.

Synthesis of Pyrazolines from Azodicarboxylates and Allenoates

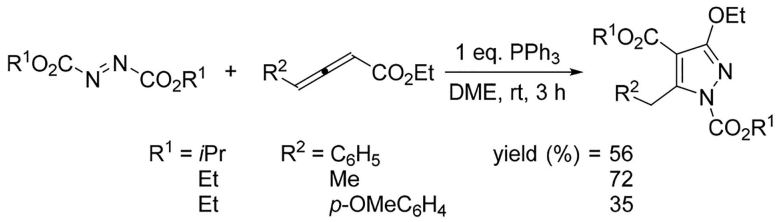


R = Et	Ar = *p*-$NO_2C_6H_4$	yield (%) = 58
*i*Pr	*p*-$OMeC_6H_4$	33
*i*Pr	2-naphthyl	56
*i*Pr	*m*,*p*-$Cl_2C_6H_3$	60

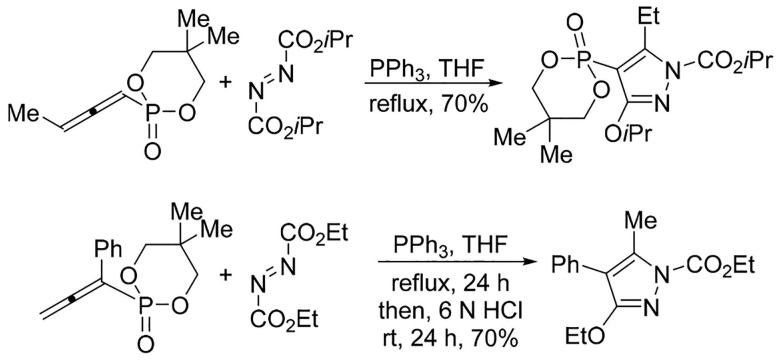
Scheme 750.
Formation of Functionalized Pyrazolines



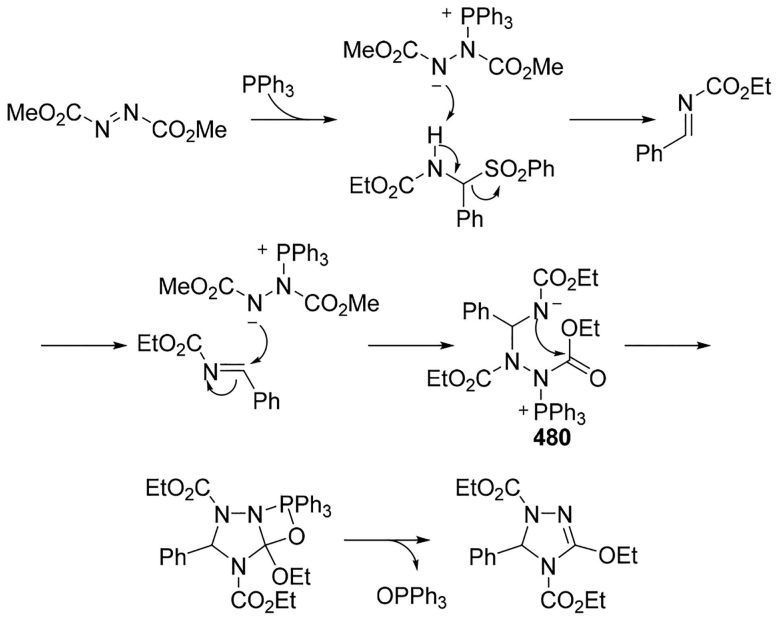
Scheme 751.
Synthesis of Pyrazoles from Azodicarboxylates and Allenoates



Scheme 752.
Formation of Functionalized Pyrazoles

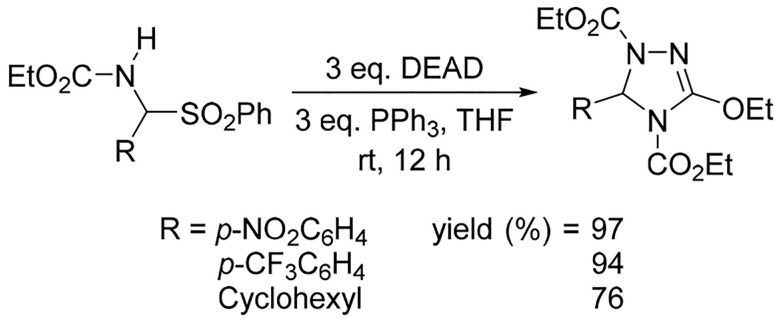


Scheme 753.
Formation of Functionalized Pyrazoles



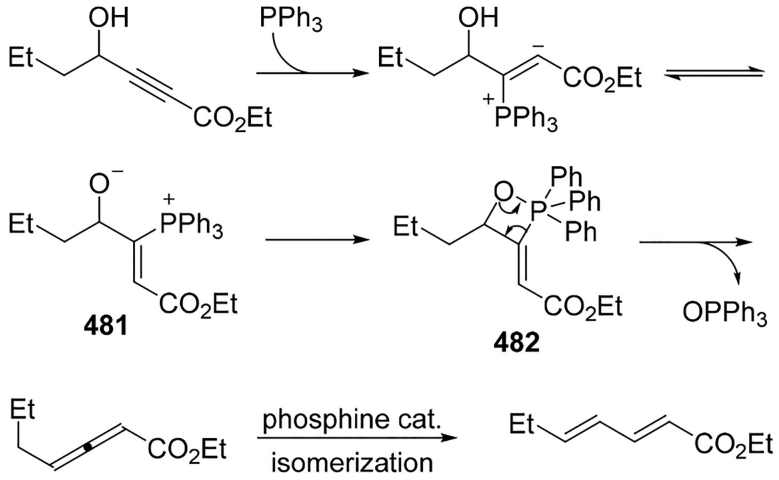
Scheme 754.

Synthesis of a 1,2,4-Triazoline from an Azodicarboxylate and an Imine

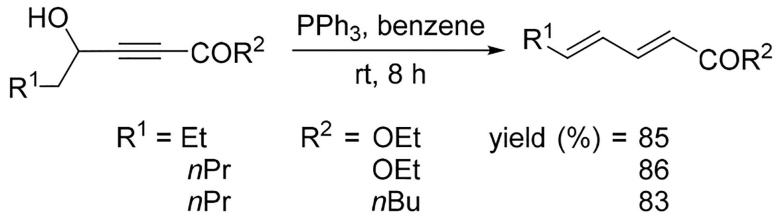


R = *p*-$NO_2C_6H_4$	yield (%) = 97
p-$CF_3C_6H_4$	94
Cyclohexyl	76

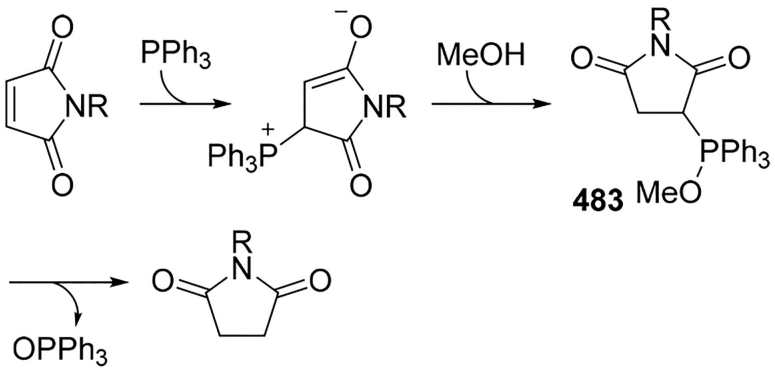
Scheme 755.
Preparation of Triazole Derivatives



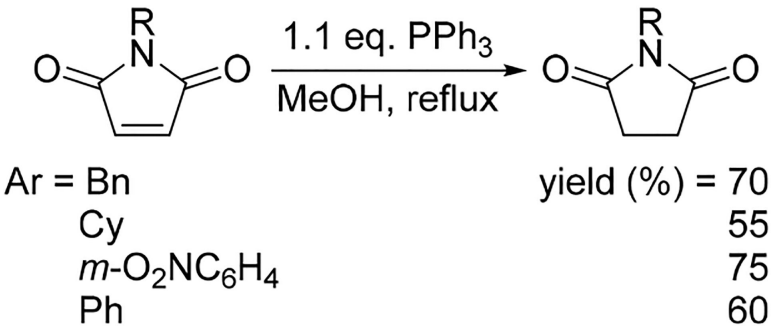
Scheme 756.
Proposed Pathway of Deoxygenation–Isomerization



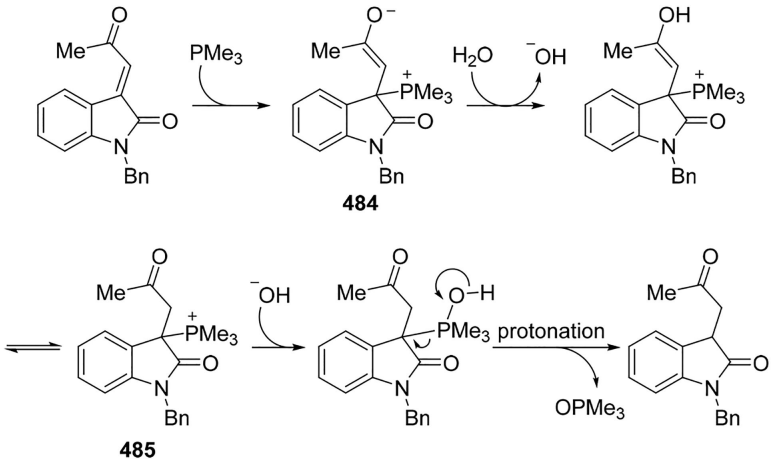
Scheme 757.
Deoxygenation–Isomerization of Alkynoates



Scheme 758.
Proposed Mechanism for Reduction of Maleimides

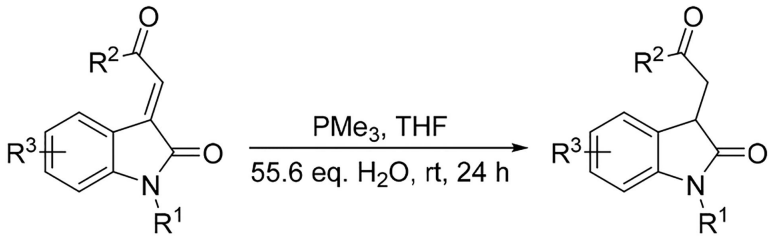


Scheme 759.
Synthesis of Functionalized Succinimides



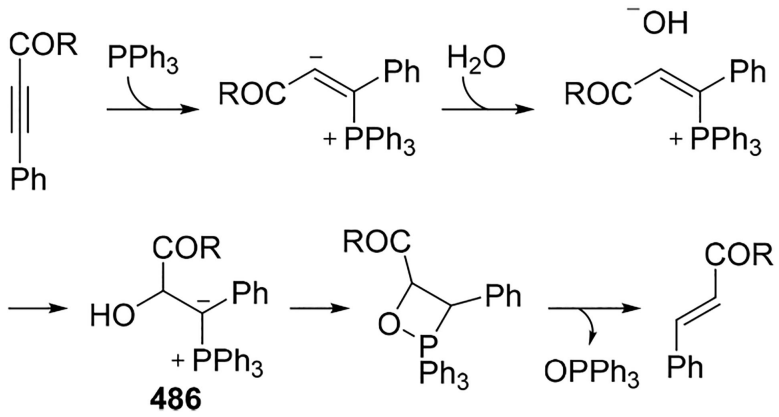
Scheme 760.

Proposed Pathway for Reduction of an Isatin-Derived Enone



entry	R^1	R^2	R^3	yield (%)
1	Bn	Et	H	99
2	Bn	OEt	H	99
3	Bn	OEt	5-Me	99
4	H	OEt	H	99
5	Bn	OEt	7-CF_3	16
6	Boc	OEt	H	53

Scheme 761.
Formation of Isatin Derivatives



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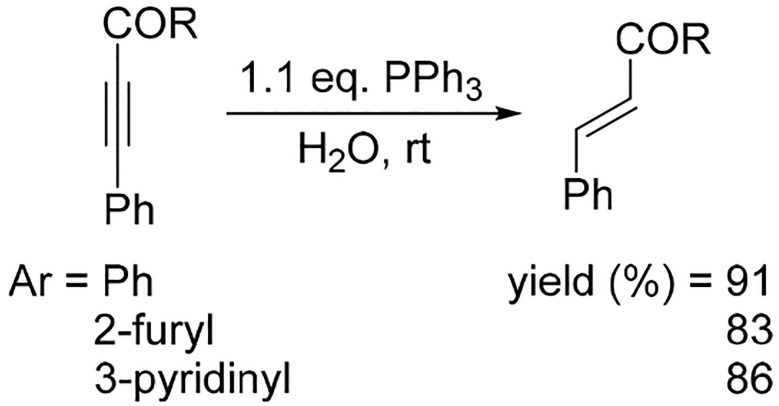
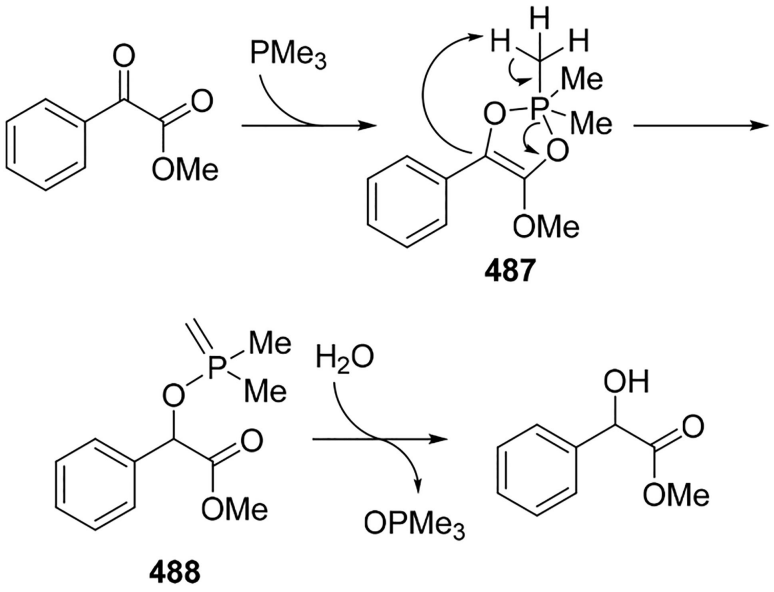
Scheme 762.
Proposed Mechanism of Alkynone Reduction

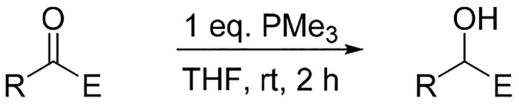


Scheme 763.
Reduction of Arylalkynones



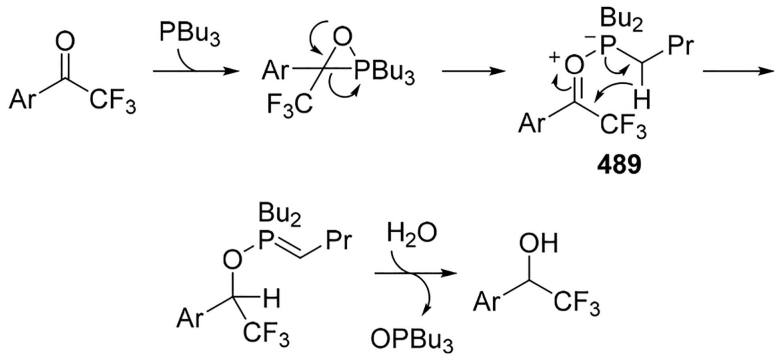
Scheme 764.

Proposed Pathway for PMe_3-Mediated Reduction of an α-Ketoester



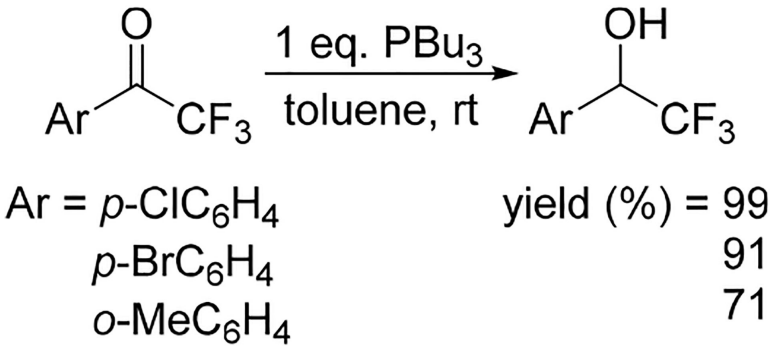
R =	E =	yield (%) =
p-ClC_6H_4	CO_2Et	81
p-$OMeC_6H_4$	CO_2Et	85
Cyclohexyl	CO_2Et	96
C_6H_5	$P(O)(OEt)_2$	86

Scheme 765.
Reduction of Glyoxylates

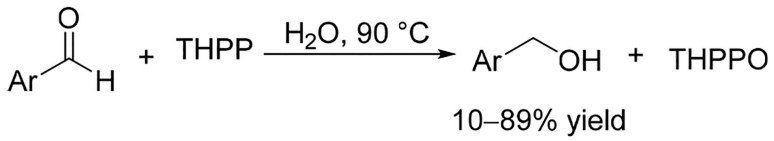


Scheme 766.

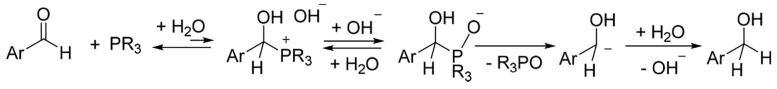
Proposed Mechanism for PMe_3-Mediated Reduction of Trifluoromethylketones



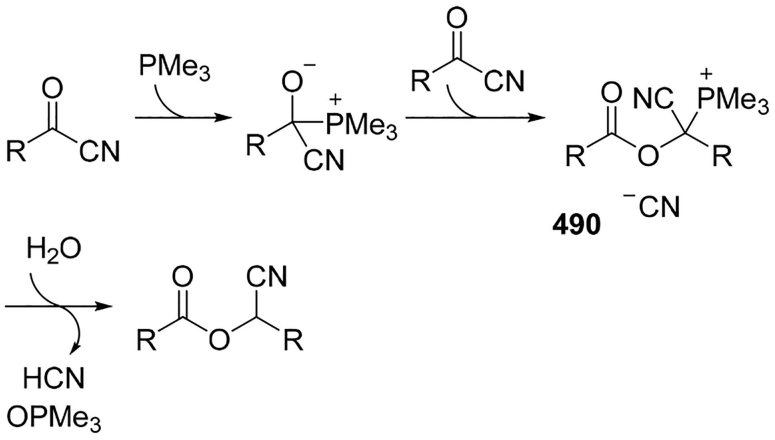
Scheme 767.
Synthesis of Functionalized Trifluoromethylalcohols



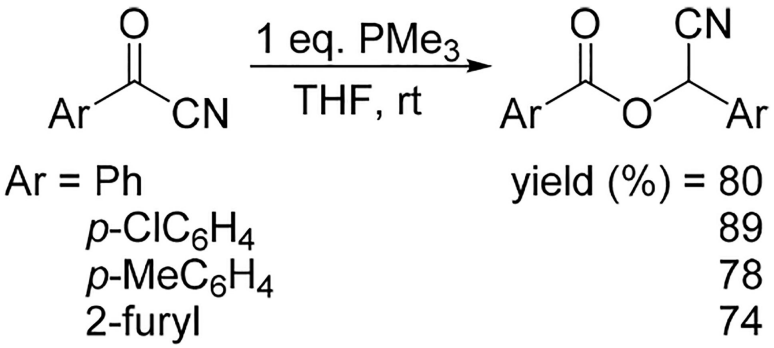
Scheme 768.
Reactions of Aromatic Aldehydes with THPP



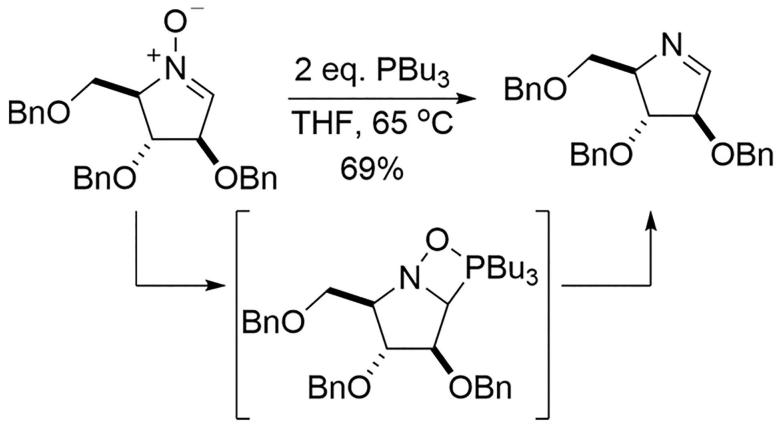
Scheme 769.
Plausible Mechanism for the Reduction of Aldehydes



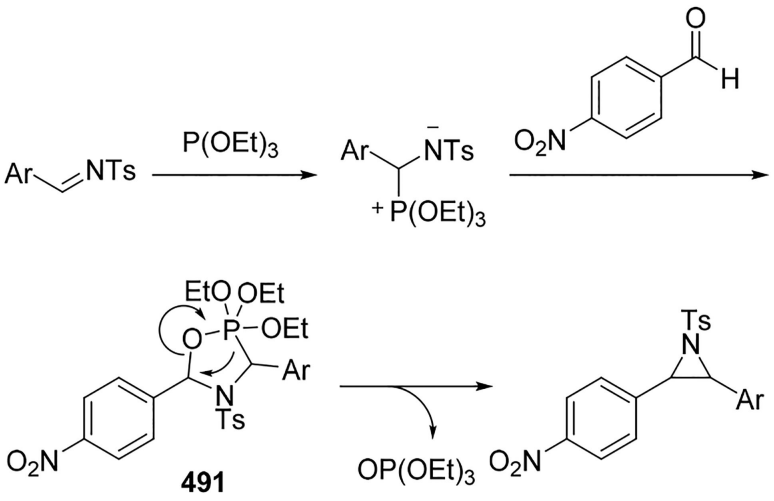
Scheme 770.
Proposed Mechanism of Reductive Coupling



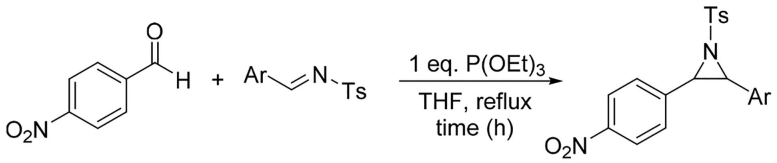
Scheme 771.
Synthesis of Functionalized Cyanohydrins



Scheme 772.
Reduction of a Cyclic Nitrone

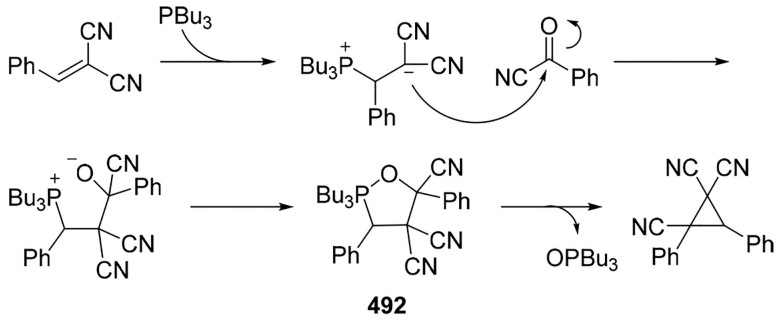


Scheme 773.
Proposed Mechanism for Aziridine Formation



entry	Ar	time (h)	yield (%)	*cis*/*trans*
1	*p*-BrC_6H_4	3	75	42:58
2	Ph	5	39	41:59
3	*p*-MeC_6H_4	24	28	37:63

Scheme 774.
Formation of Functionalized Aziridines



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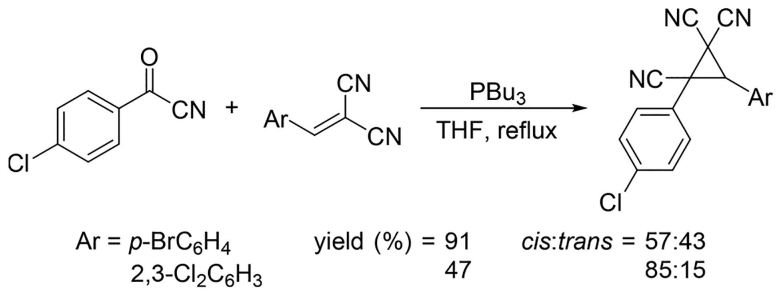
Scheme 775.

Proposed Mechanism for Reductive Cyclopropanation

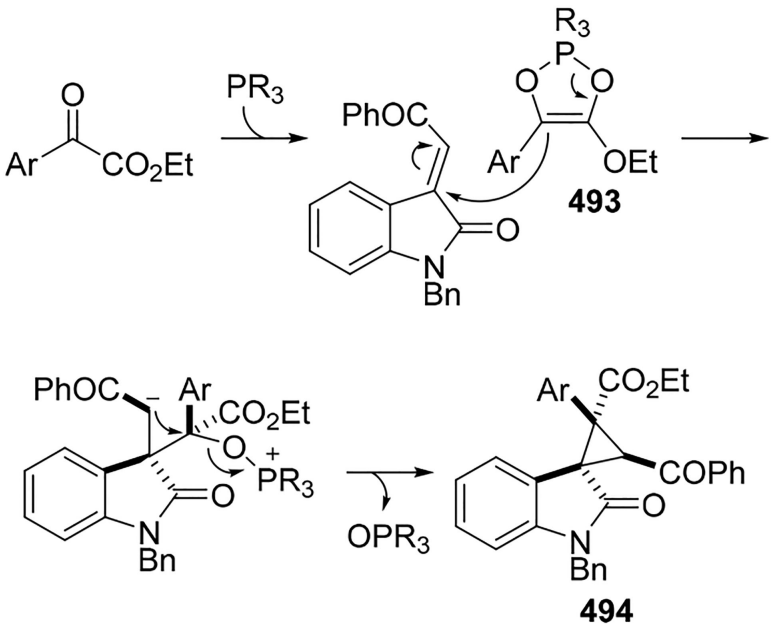


Ar = *p*-BrC_6H_4 yield (%) = 91 *cis*:*trans* = 57:43

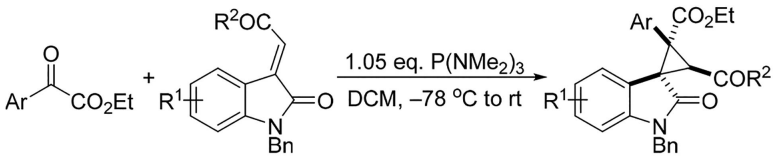
2,3-$Cl_2C_6H_3$ 47 85:15

Scheme 776.

Formation of Cyclopropanes and Aziridines

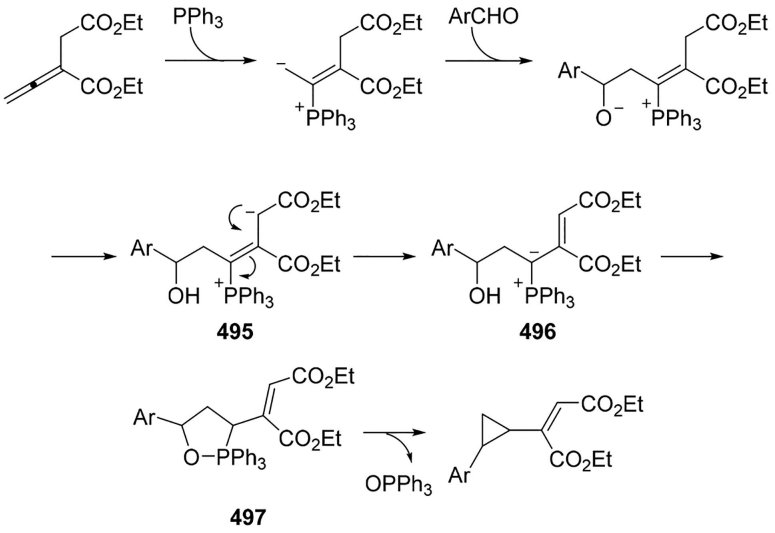


Scheme 777.
Proposed Mechanism of Reductive Cyclopropanation



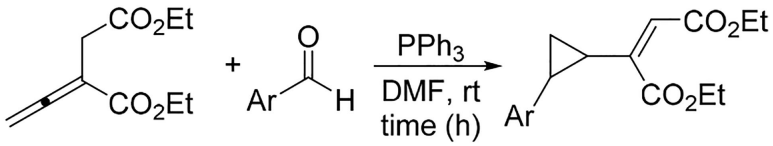
entry	Ar	R^1	R^2	yield (%)	dr
1	Ph	H	Ph	95	11:1
2	Ph	H	*p*-$F_3CC_6H_4$	75	20:1
3	Ph	6-Br	Ph	99	5:1
4	*p*-MeC_6H_4	H	Ph	92	20:1
5	2-thienyl	H	Ph	85	5:1

Scheme 778.
Synthesis of Functionalized Spirocyclopropaneoxindoles



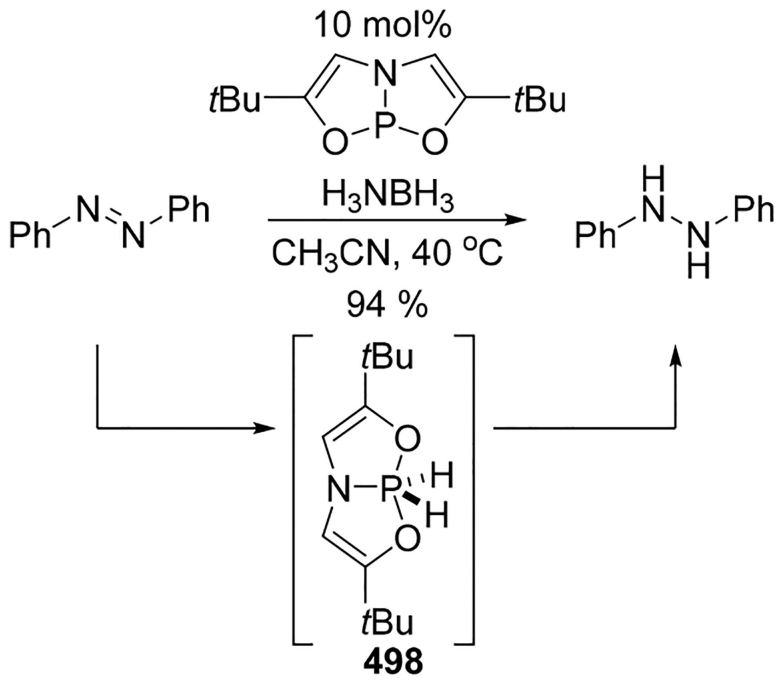
Scheme 779.

Proposed Pathway for Cyclopropanation of an Allenoate

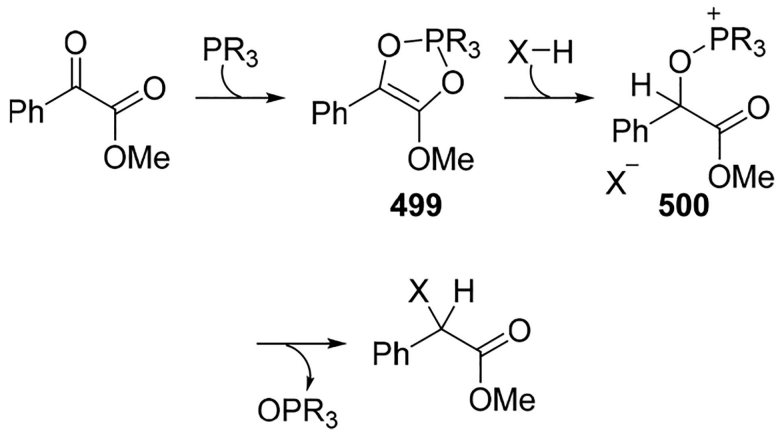


entry	Ar	time (h)	yield (%)	dr
1	*o*-$F_3CC_6H_4$	19	93	>20:1
2	4-pyridinyl	3	86	>20:1
3	*p*-$O_2NC_6H_4$	5	82	4:1
4	*p*-MeC_6H_4	60	35	>20:1

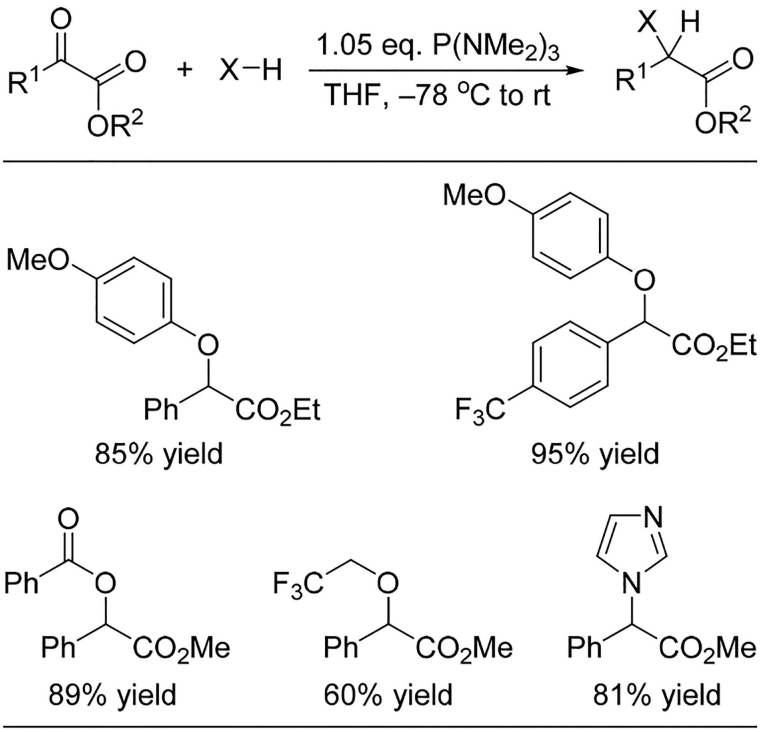
Scheme 780.
Formation of Vinyl Cyclopropanes



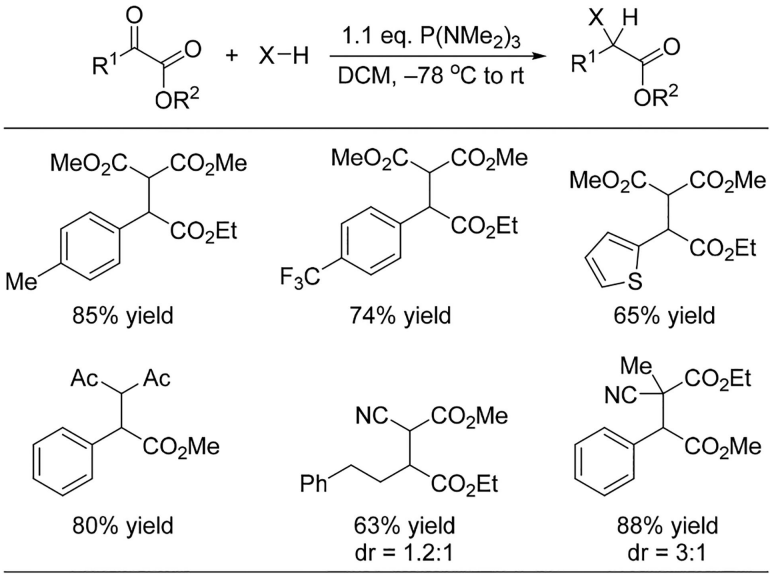
Scheme 781.
Phosphine-Catalyzed Transfer Hydrogenation of Azobenzene



Scheme 782.
Proposed Mechanism of Reductive Coupling

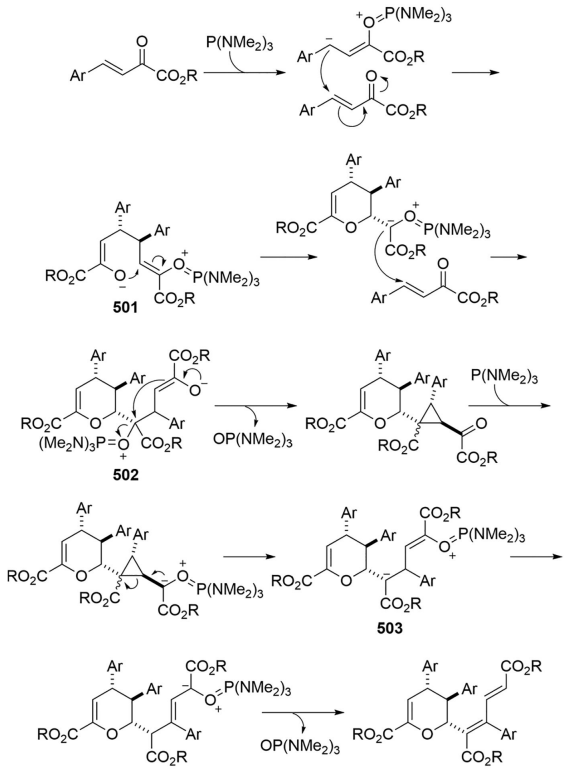


Scheme 783.
Synthesis of Functionalized Esters

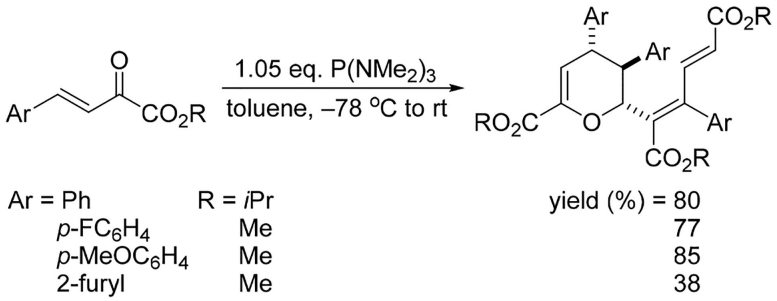


Scheme 784.

Synthesis of Functionalized 1,4-Dicarbonyl Compounds

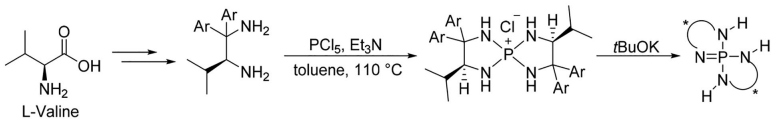


Scheme 785.
Proposed Reaction Mechanism

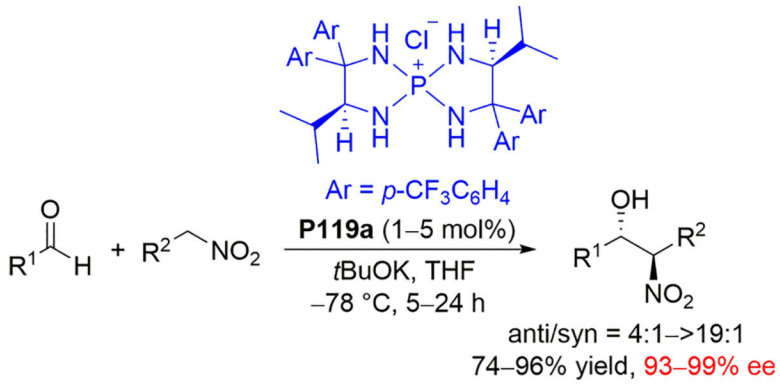


Ar = Ph	R = *i*Pr	yield (%) = 80
p-FC_6H_4	Me	77
p-$MeOC_6H_4$	Me	85
2-furyl	Me	38

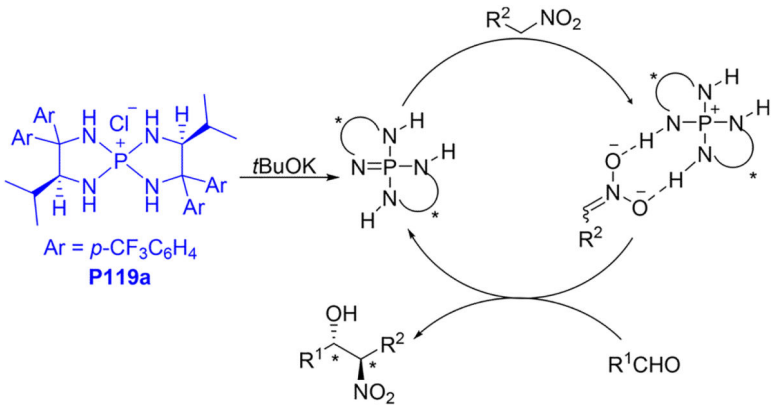
Scheme 786.
Synthesis of Functionalized Dihydropyrans



Scheme 787.
Synthesis of Chiral Tetraaminophosphonium Salts

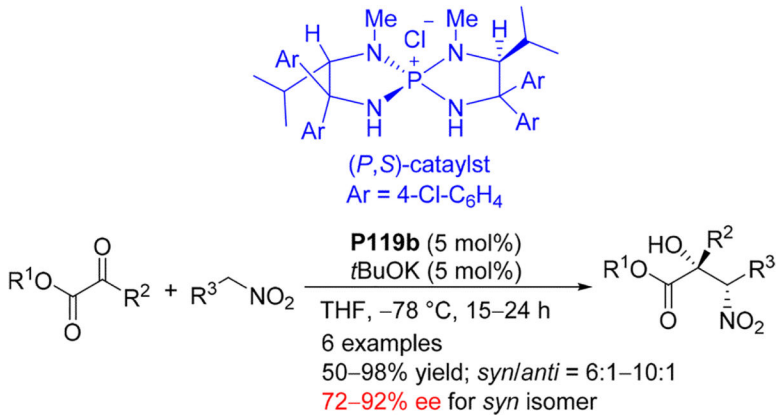


Scheme 788.
Chiral Tetraaminophosphonium Salt-Catalyzed Asymmetric Direct Henry Reaction



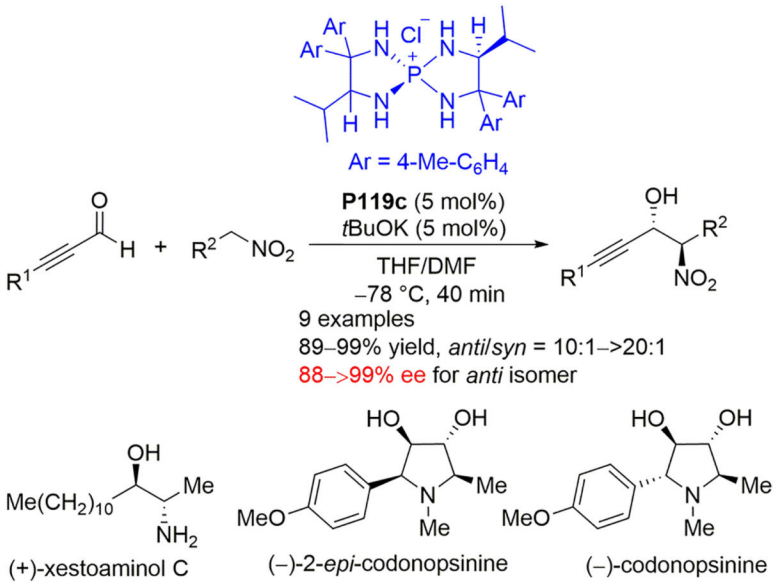
Scheme 789.

Proposed Mechanism for Phosphonium Salt P119a-Mediated Asymmetric Direct Henry Reaction



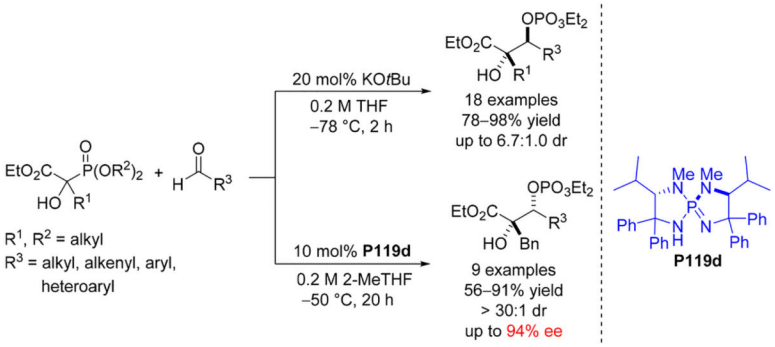
Scheme 790.

Chiral Iminophosphoranes Precatalyst in the Henry Reaction



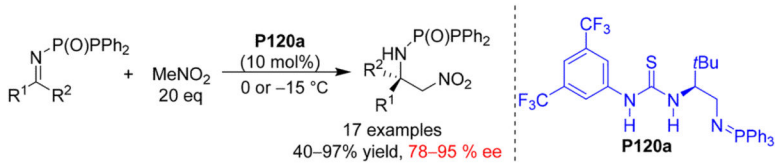
Scheme 791.

Chiral Tetraaminophosphonium Salt-Catalyzed Asymmetric Direct Henry Reaction



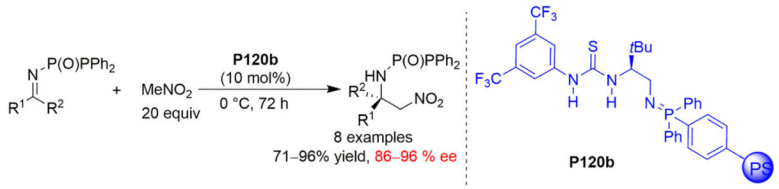
Scheme 792.

Direct Aldolization of α-Benzyl-α-hydroxyphosphonoacetate Through Iminophosphorane Catalysis



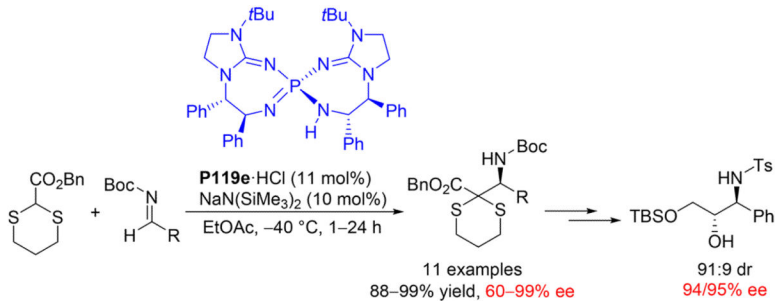
Scheme 793.

BIMP for Enantioselective Mannich Reactions



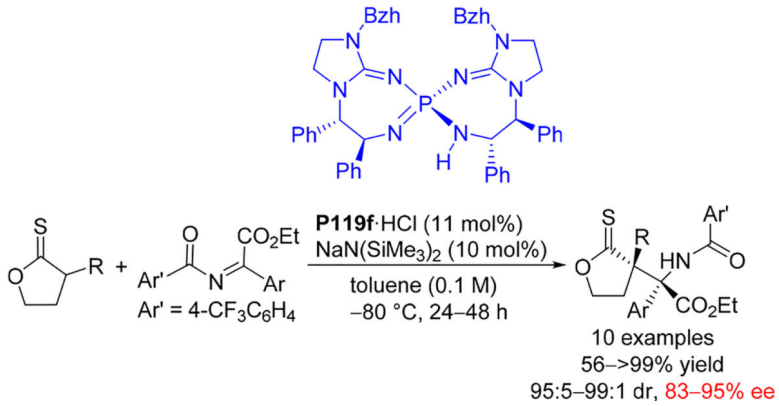
Scheme 794.

An Immobilized BIMP for Enantioselective Mannich Reactions



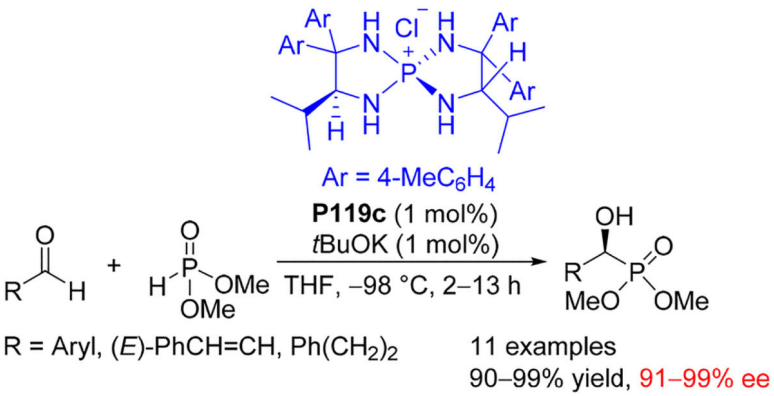
Scheme 795.

Chiral Bis(Guanidino) Iminophosphorane-Catalyzed Enantioselective Addition of 2-Alkoxycarbonyl-1,3-dithiane to Imines

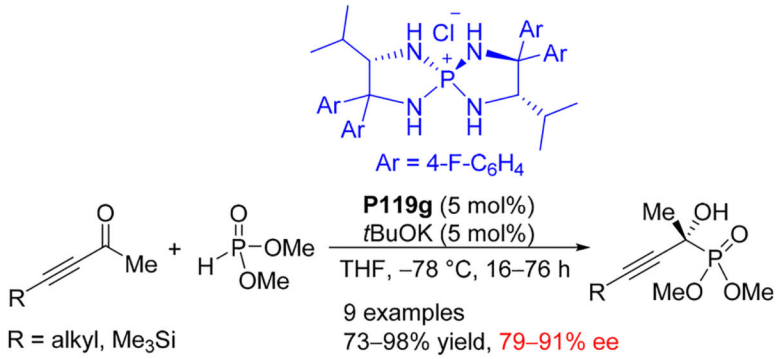


Scheme 796.

Chiral Bis(guanidino) Iminophosphorane-Catalyzed Asymmetric Direct Mannich-Type Reaction of α-Iminophenylacetate Esters with Thionolactones

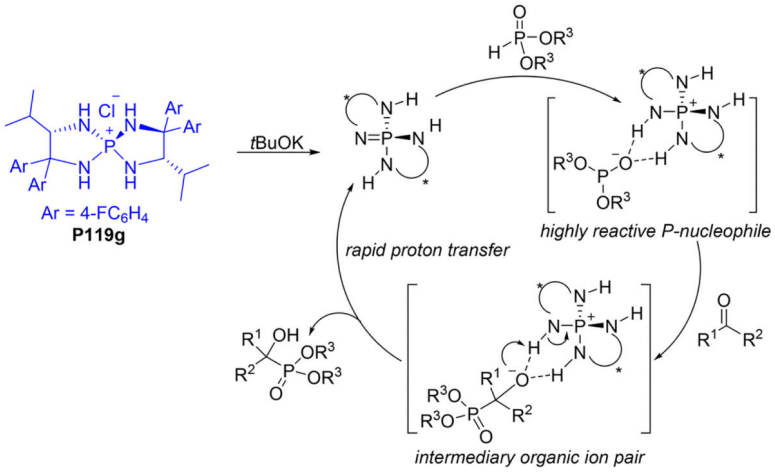


Scheme 797.
Chiral Iminophosphoranes Precatalyst in the Pudovik Reaction



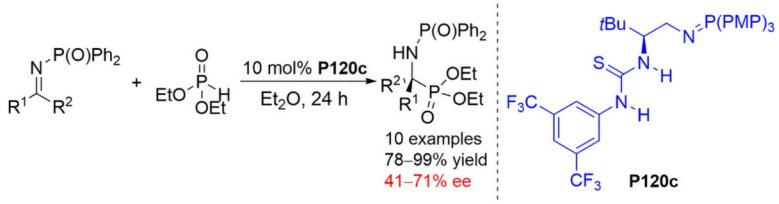
Scheme 798.

Chiral Iminophosphoranes Precatalyst in the Pudovik Reaction—Synthesis of Propargylic Alcohols

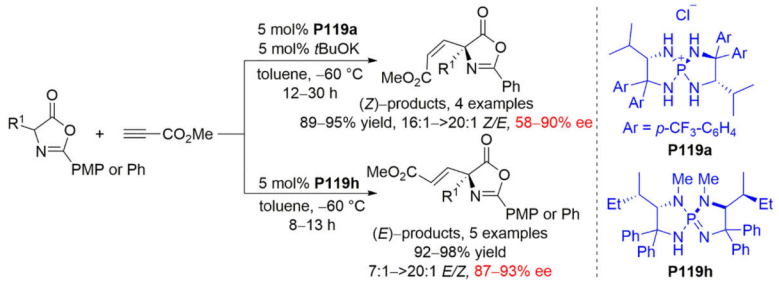


Scheme 799.

Hypothesized Mechanism for the Asymmetric Pudovik Reaction

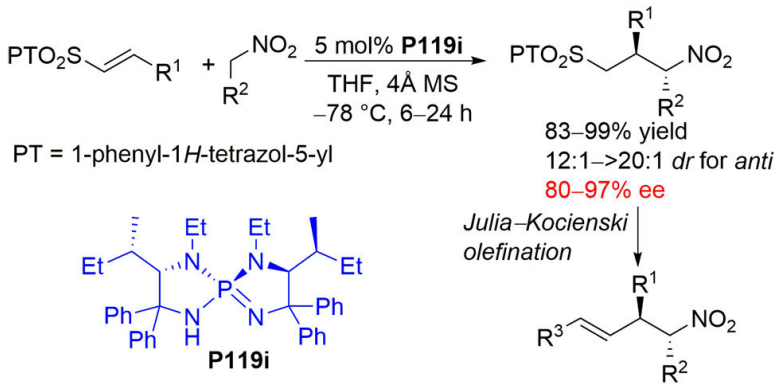


Scheme 800.
BIMP-Catalyzed Phospha-Mannich Reactions



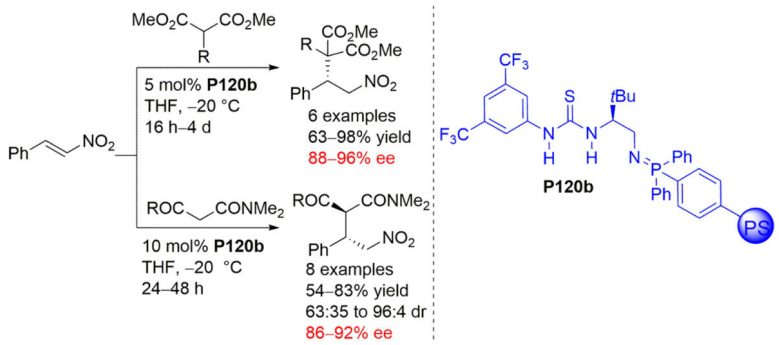
Scheme 801.

Highly Stereoselective Michael Additions of Azlactones to Electron-Deficient Triple Bonds Under P-Spiro Chiral Iminophosphorane Catalysis



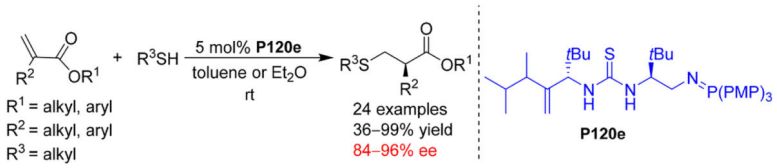
Scheme 802.

Iminophosphoranes in the Michael Reactions of Nitroalkanes with Alkenes

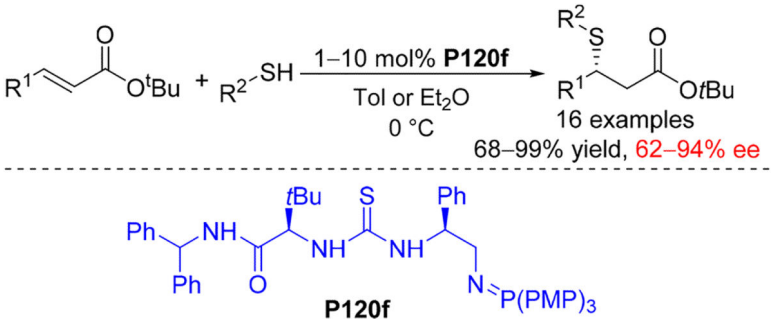


Scheme 803.

An Immobilized Chiral BIMP in Michael Reactions

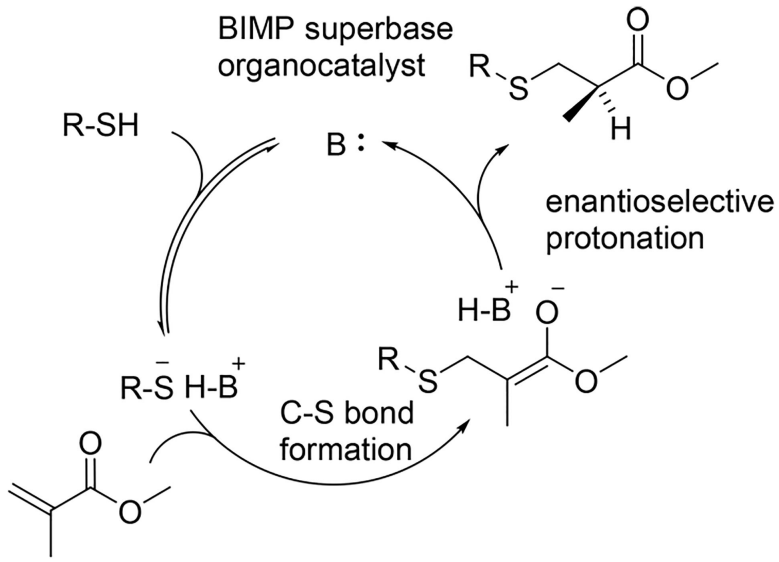


Scheme 804.
BIMP-Catalyzed Enantioselective SMAs

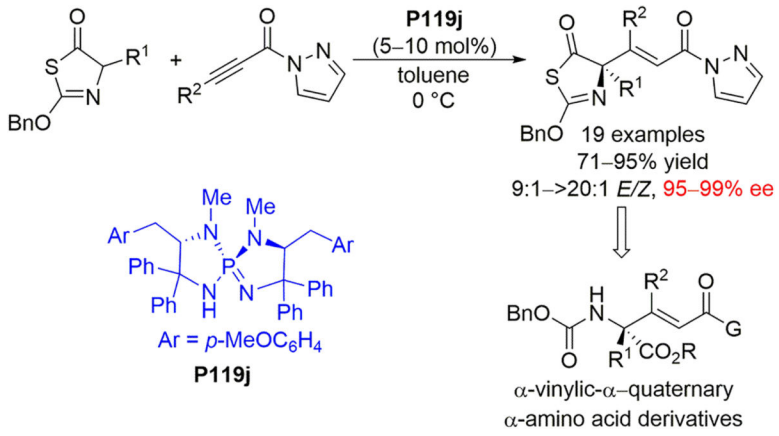


Scheme 805.

BIMP-Catalyzed SMAs of Alkyl Thiols to Unactivated β-Substituted-α,β-unsaturated Esters

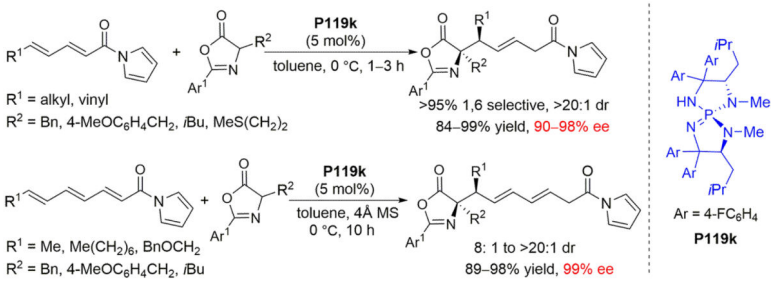


Scheme 806.
Mechanism of BIMP-Catalyzed SMA to Methyl Methacrylate



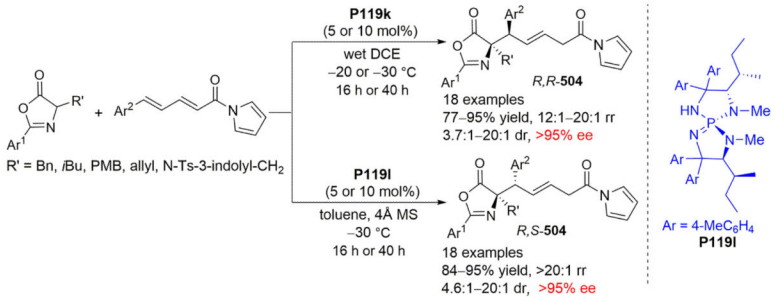
Scheme 807.

Chiral Iminophosphorane-Catalyzed Highly *E*-Selective and Enantioselective Michael Additions



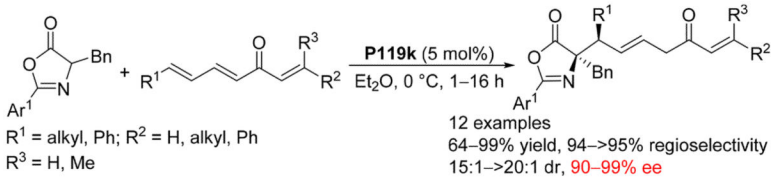
Scheme 808.

1,6 and 1,8-Additions of Azlactones to *N*-Acylpyrroles



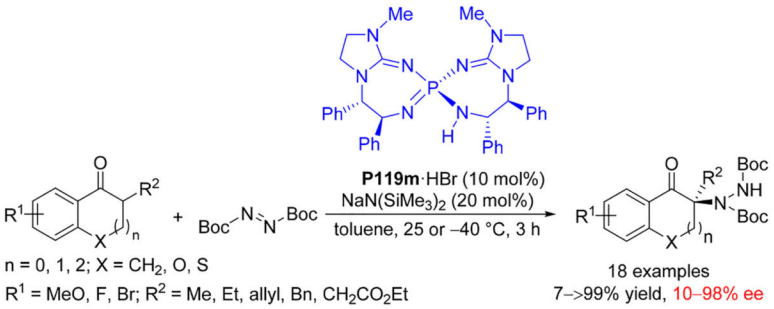
Scheme 809.

Diastereodivergent 1,6-Additions of Azlactones to *δ*-Aryl Dienyl Carbonyl Compounds



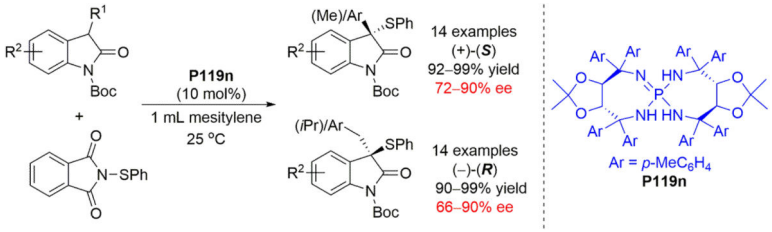
Scheme 810.

1,6-Additions of Azlactones to Dienyl Ketones Catalyzed by a Chiral Iminophosphorane



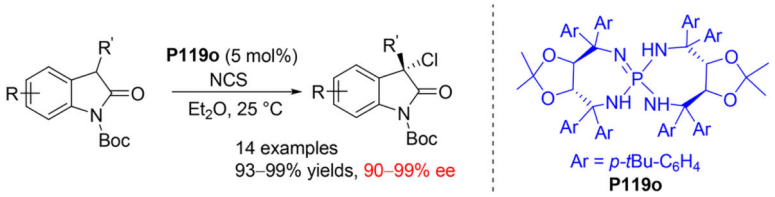
Scheme 811.

Chiral Bis(guanidino) Iminophosphorane-Catalyzed Enantioselective Amination of Ketones



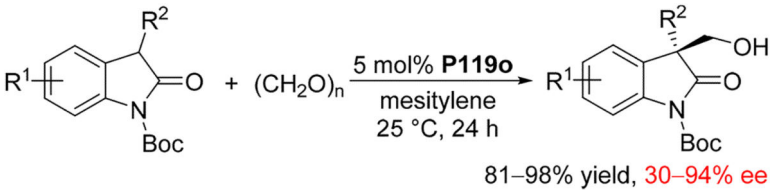
Scheme 812.

Using an Iminophosphorane in Sulfenylations of 3-Substituted Oxindoles



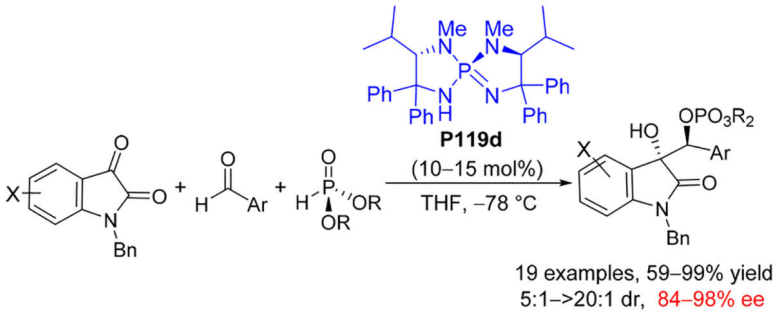
Scheme 813.

Asymmetric NCS-Mediated Chlorinations of 3-Substituted Oxindoles Catalyzed by a Tartrate-Derived Iminophosphorane



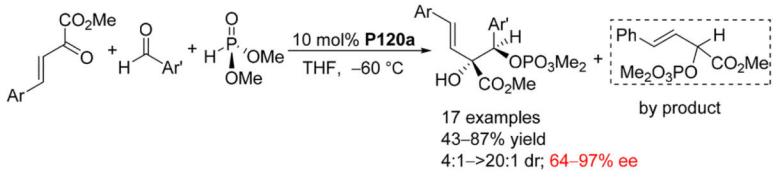
Scheme 814.

Asymmetric Paraformaldehyde-Mediated Hydroxymethylations of 3-Substituted Oxindoles Catalyzed by a Tartrate-Derived Iminophosphorane



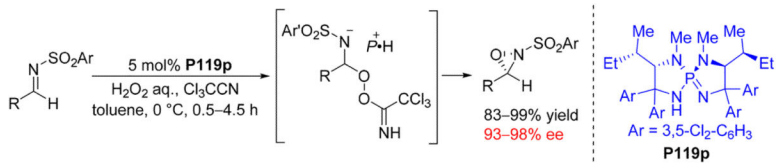
Scheme 815.

Asymmetric Reductive Multicomponent Coupling Reactions



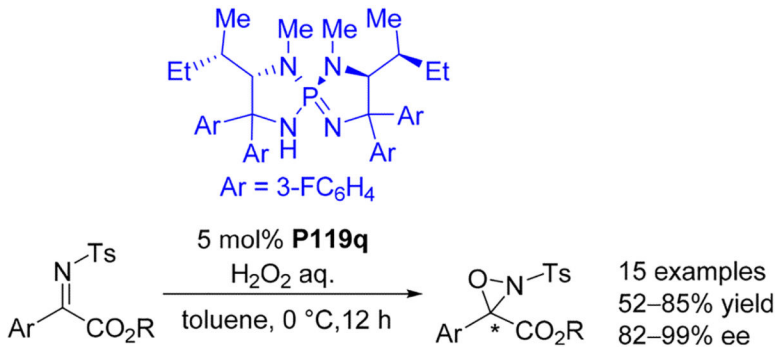
Scheme 816.

Using a BIMP Catalyst in Three-Component Reductive Coupling Reactions



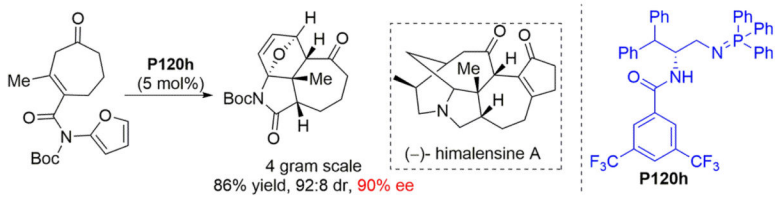
Scheme 817.

Iminophosphoranes in the Asymmetric Oxidations of *N*-Sulfonyl Imines



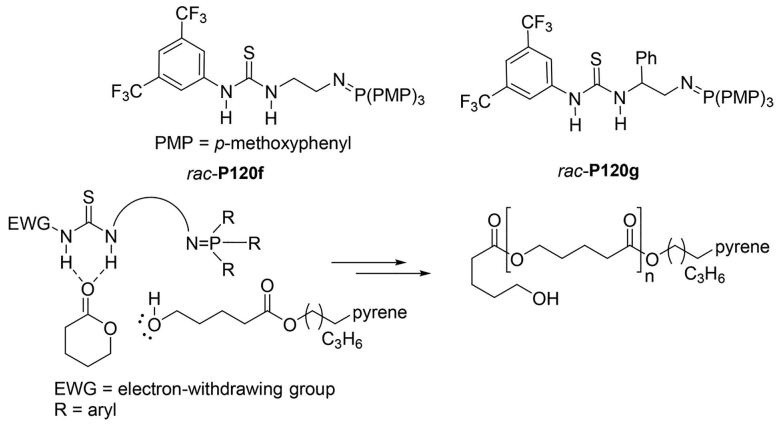
Scheme 818.

Iminophosphoranes in Asymmetric Oxidation of *N*-Sulfonyl α-Imino Esters



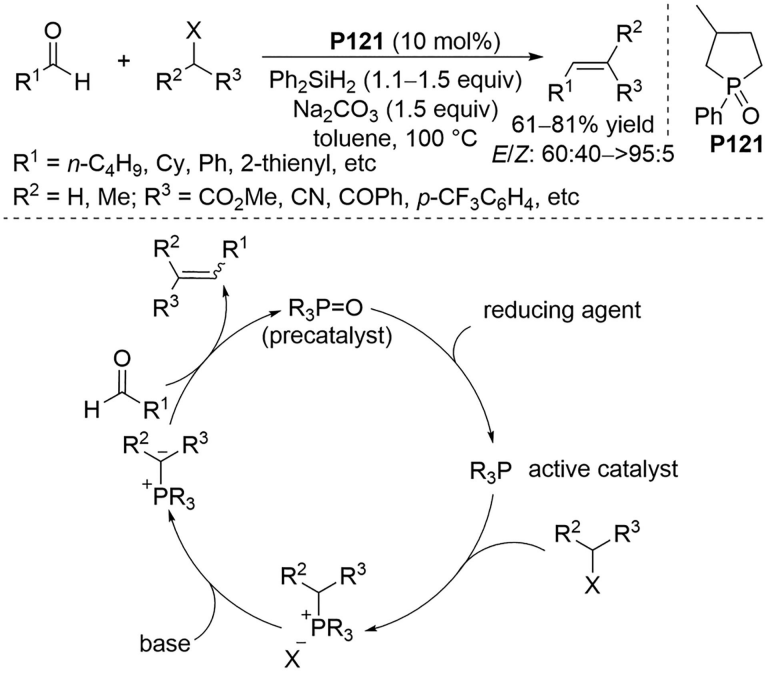
Scheme 819.

A Key Enantioselective IMDAF Reaction Catalyzed by a BIMP

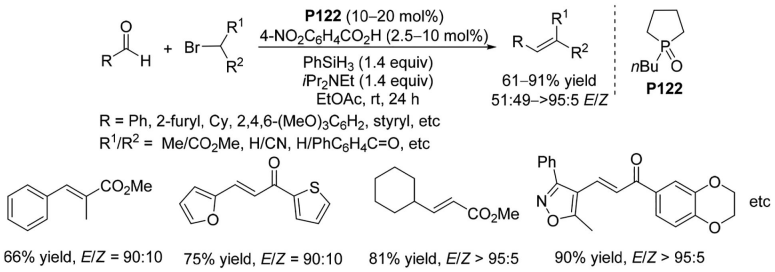


Scheme 820.

Organocatalytic ROP of Cyclic Esters Mediated by BIMP Catalysts

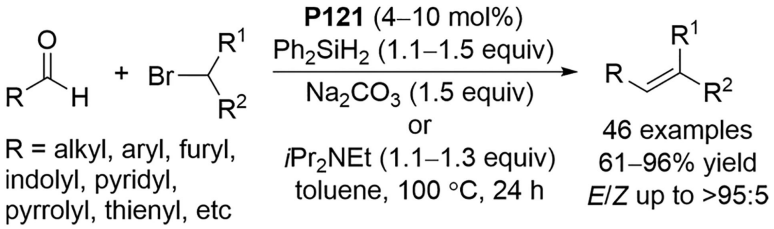


Scheme 821.
Catalytic Wittig Reactions and a Proposed Mechanism

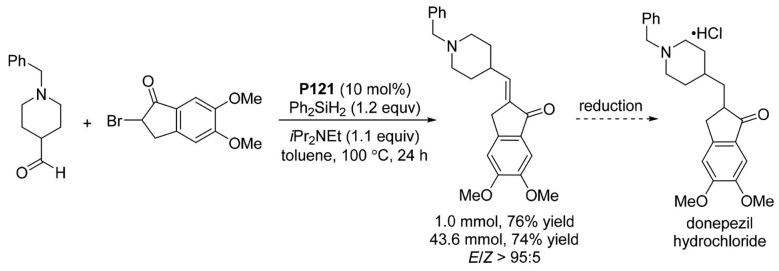


Scheme 822.

Phosphine-Catalyzed Wittig Reactions Performed at Room Temperature

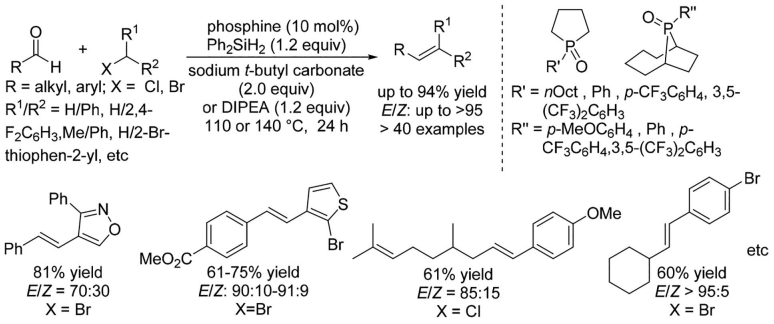


Scheme 823.
Phosphine-Catalyzed Wittig Reactions



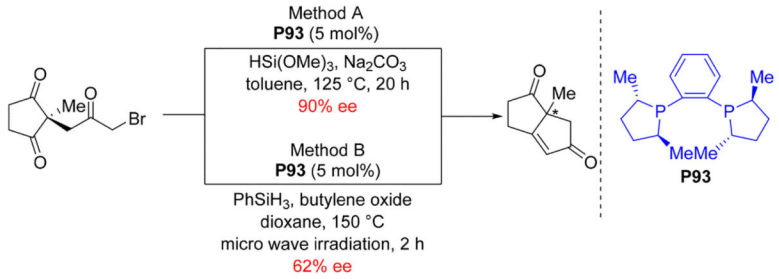
Scheme 824.

Multigram Synthesis of a Precursor of the Anti-Alzheimer Drug Donepezil Hydrochloride

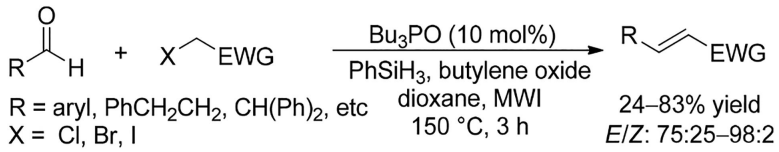


Scheme 825.

Phosphine-Catalyzed Wittig Reactions of Aldehydes with Alkyl Halides

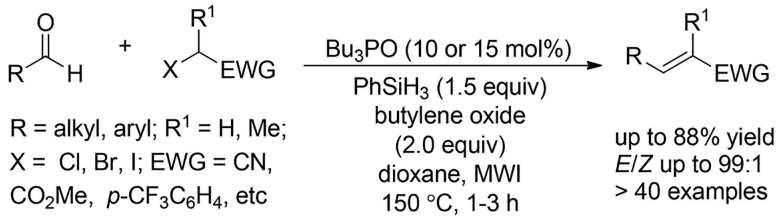


Scheme 826.
Asymmetric Phosphine-Catalyzed Wittig Reactions



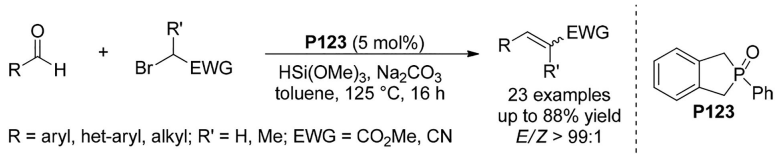
Scheme 827.

Microwave-Assisted Phosphine-Catalyzed Wittig Reactions of Aldehydes with Alkyl Halides



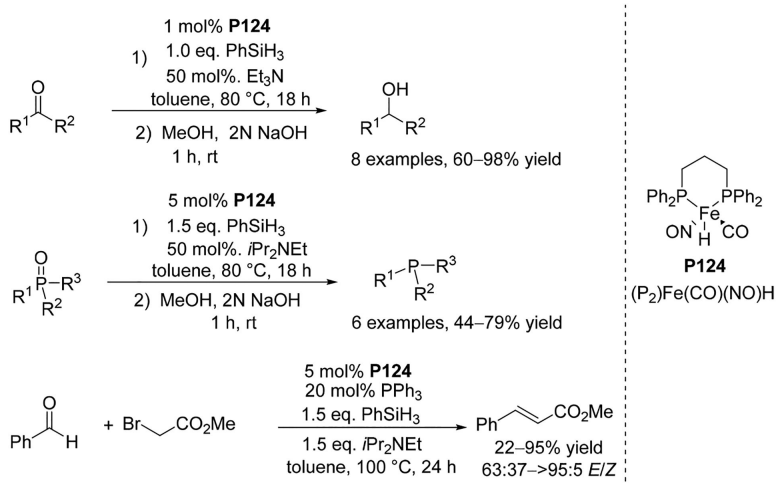
Scheme 828.

Phosphine-Catalyzed Wittig Reactions of Aldehydes with Alkyl Halides



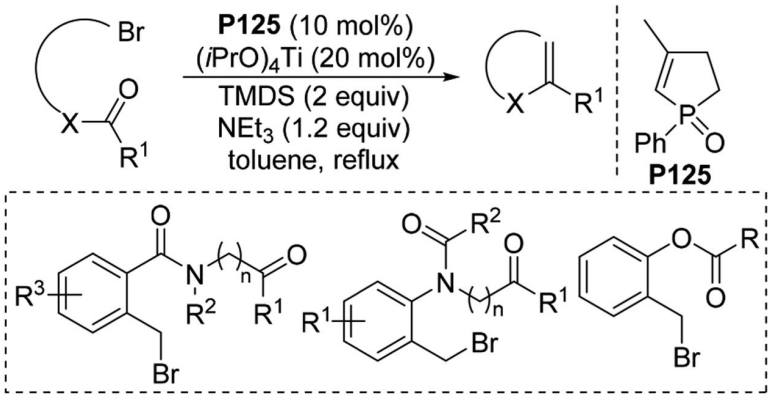
Scheme 829.

Phosphine-Catalyzed Wittig Reactions of Aldehydes with Alkyl Halides



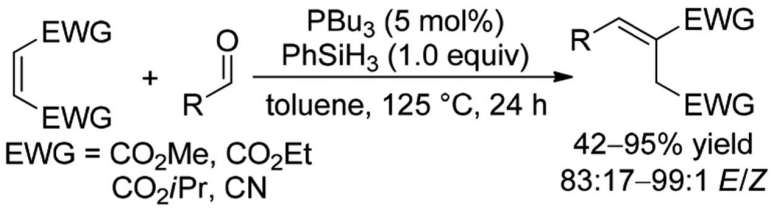
Scheme 830.

Dual Fe/Phosphine Catalysis in Catalytic Wittig Olefinations



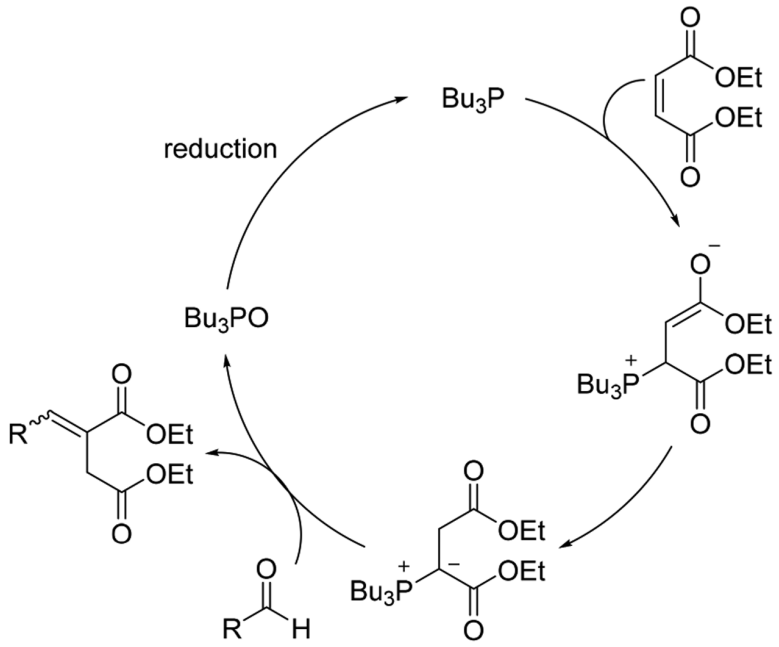
Scheme 831.

Catalytic Intramolecular Wittig Reactions of Carbonyl-Containing Bromides Based on a Phosphine/Phosphine Oxide Catalytic Cycle



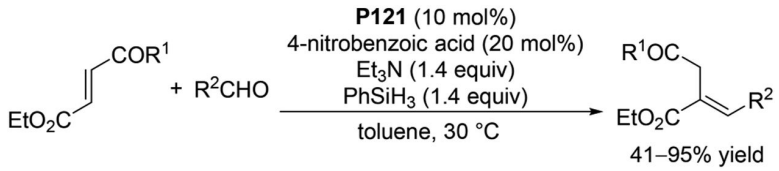
Scheme 832.

Base-Free Catalytic Wittig Reactions of Aldehydes with Acceptor-Substituted Alkenes



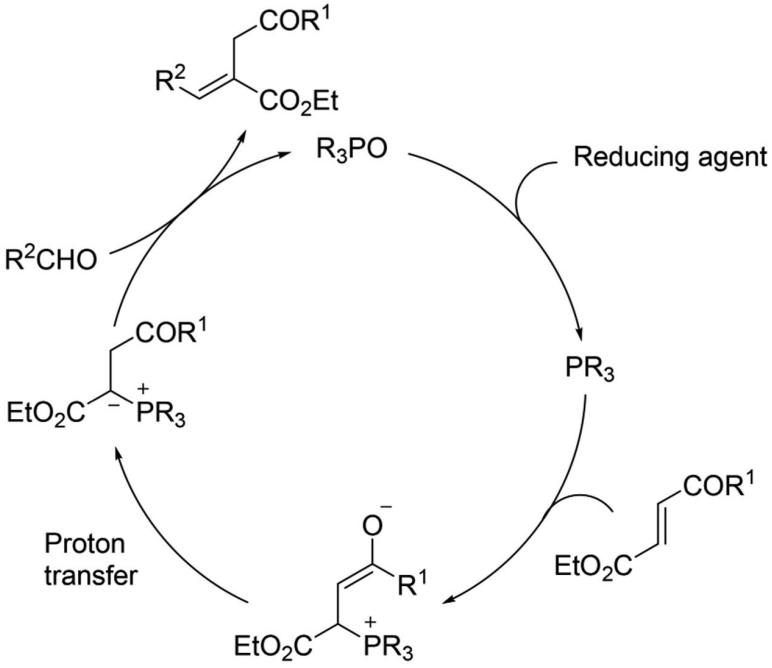
Scheme 833.

Proposed Reaction Sequence for the Base-Free Catalytic Wittig Reactions of Aldehydes with Acceptor-Substituted Alkenes



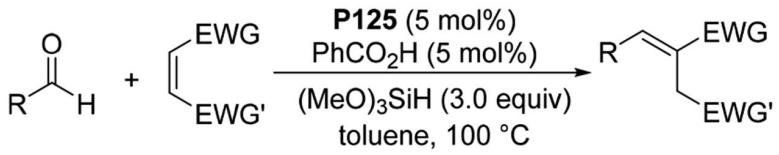
Scheme 834.

Phosphine-Catalyzed Wittig Reactions of Aldehydes and Substituted Acrylates



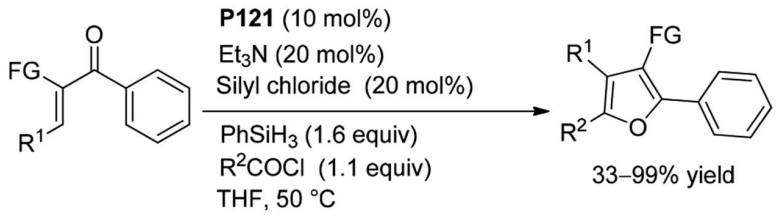
Scheme 835.

Proposed Reaction Sequence for the Phosphine-Catalyzed Wittig Reactions of Aldehydes and Substituted Acrylates



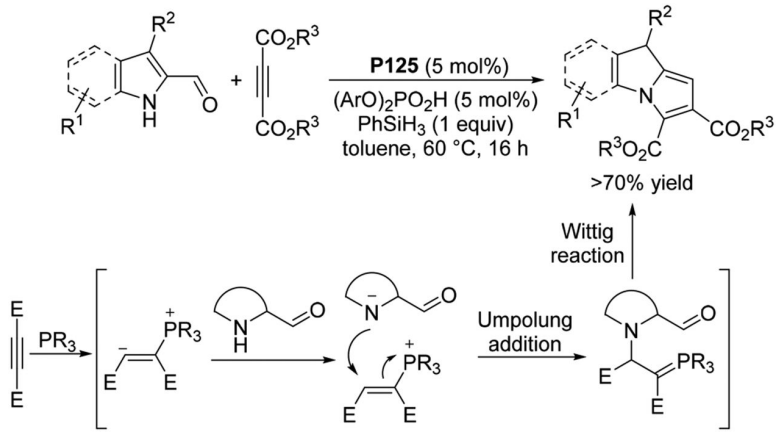
Scheme 836.

Base-Free Catalytic Wittig Reactions of Aldehydes and Alkenes with Benzoic Acid as an Additive



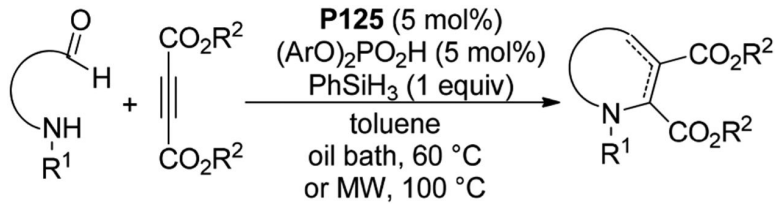
Scheme 837.

Triethylamine-and-Phosphine-Catalyzed Chemoselective Reduction/Wittig Reactions



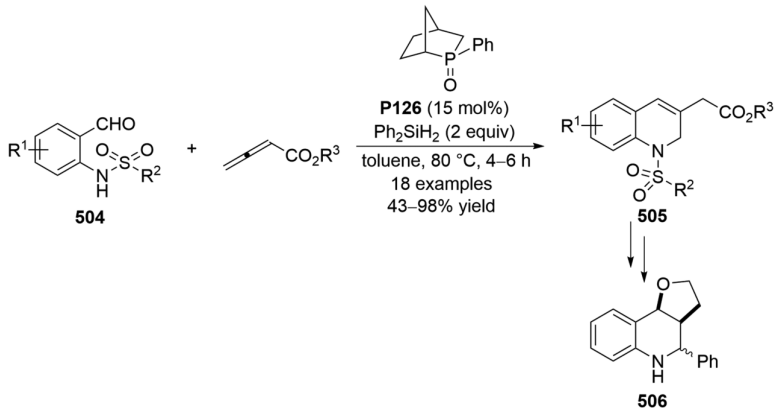
Scheme 838.

Phosphine-Catalyzed Annulations of 1*H*-Indole-2-carbaldehydes with Acetylenedicarboxylates



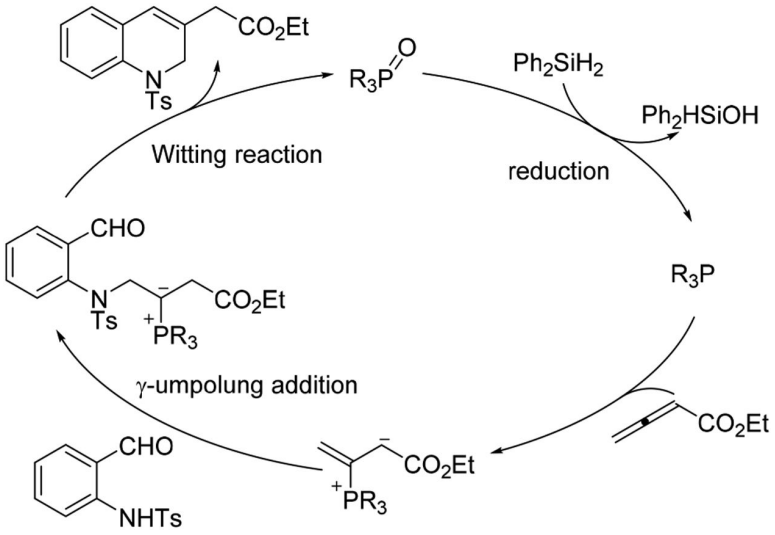
Scheme 839.

Phosphine-Catalyzed Michael Addition/Intramolecular Wittig Reactions

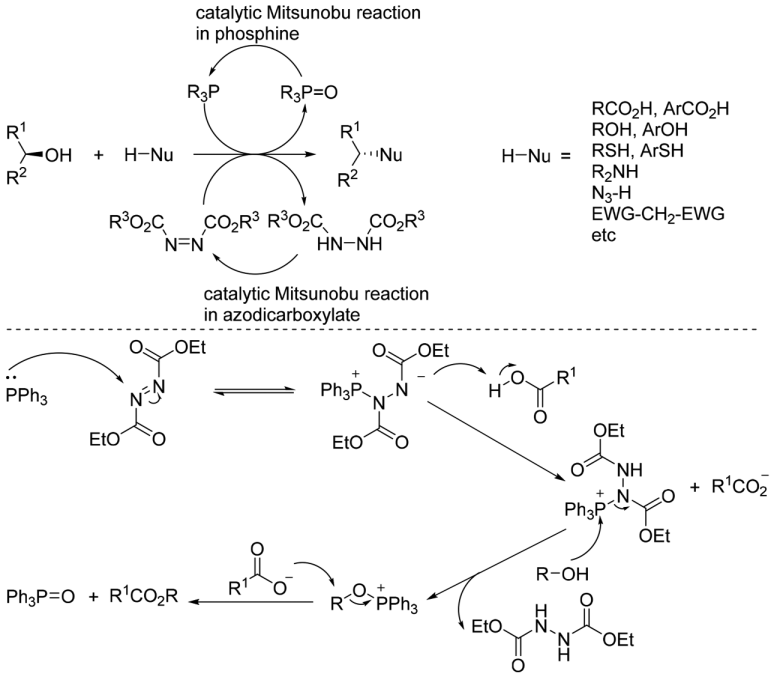


Scheme 840.

Bridged [2.2.1] Bicyclic Phosphine Oxide-Catalyzed γ-Umpolung/Wittig Reaction

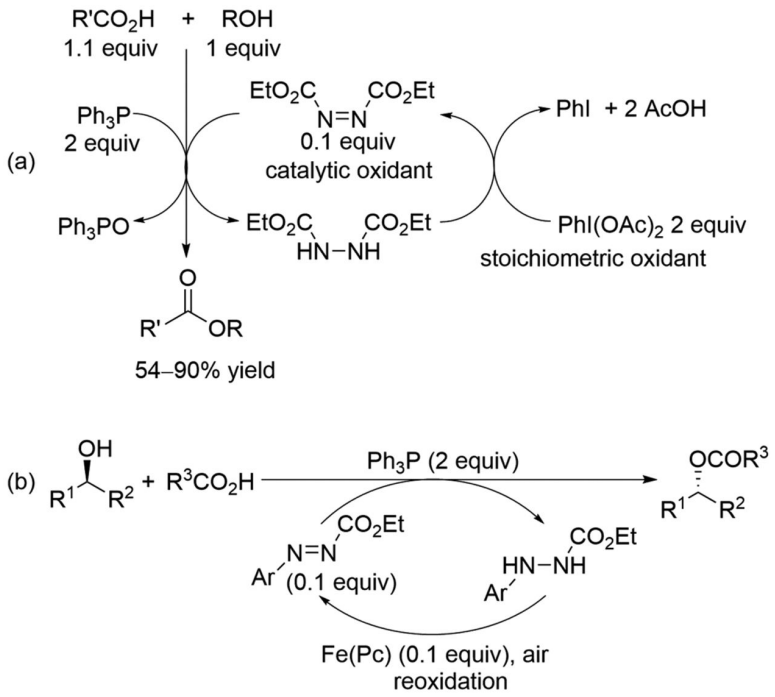


Scheme 841.
Proposed γ-Umpolung/Wittig Reaction Pathway

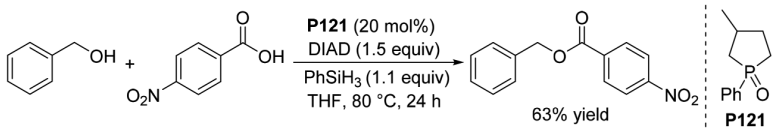


Scheme 842.

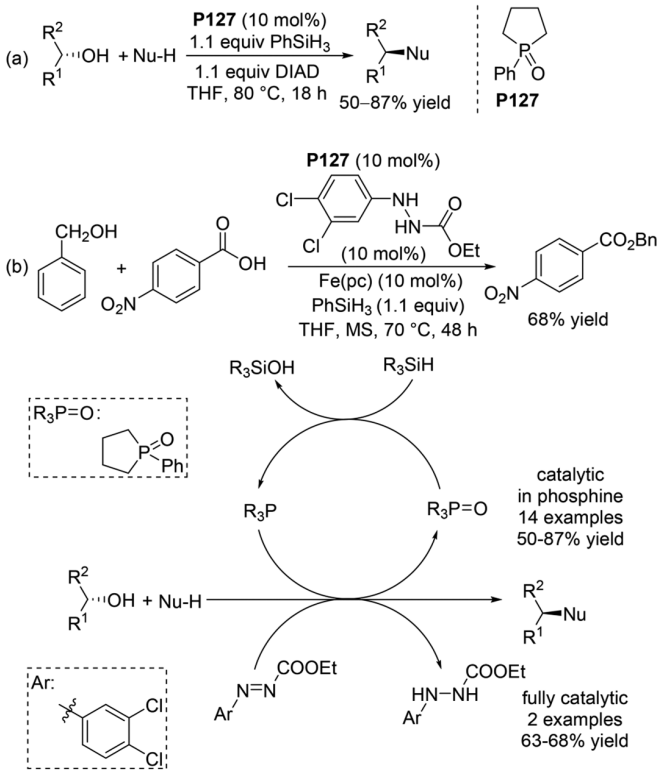
Mitsunobu Reactions and Plausible Mechanisms



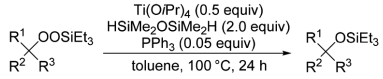
Scheme 843.
Mitsunobu Reaction Catalytic in the Azo Reagent

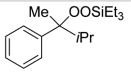
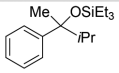
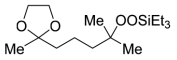
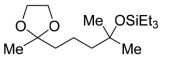
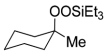
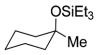
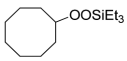
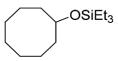
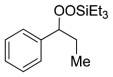
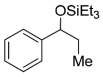
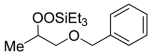
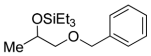
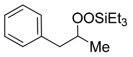
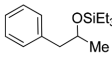
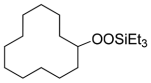
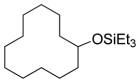


Scheme 844.
Mitsunobu Reaction Catalytic in a Phosphine

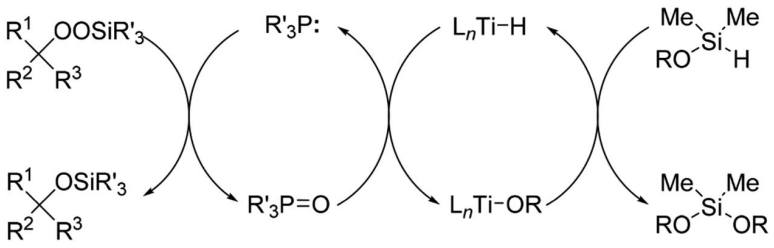


Scheme 845.
Phosphine-Catalyzed Mitsunobu Reactions

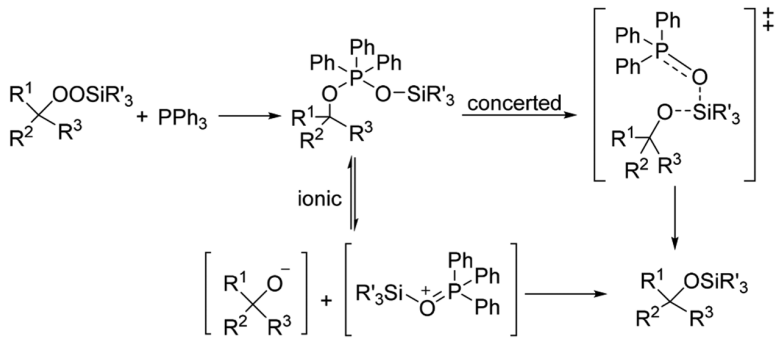


Entry	Substrate	Product	Yield(%)
1			73
2			77 (+9% alcohol)
3			46
4			66
5			73
6			79
7			69
8			79

Scheme 846.
Phosphine-Assisted Reduction of the O–O Bonds of Silyl Peroxides

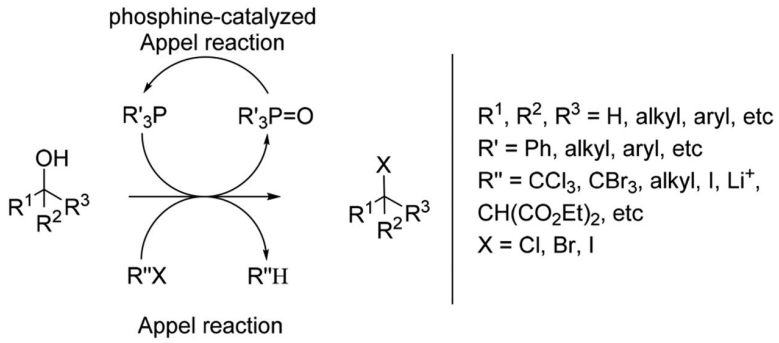


Scheme 847.
Generation of Phosphine Catalysts



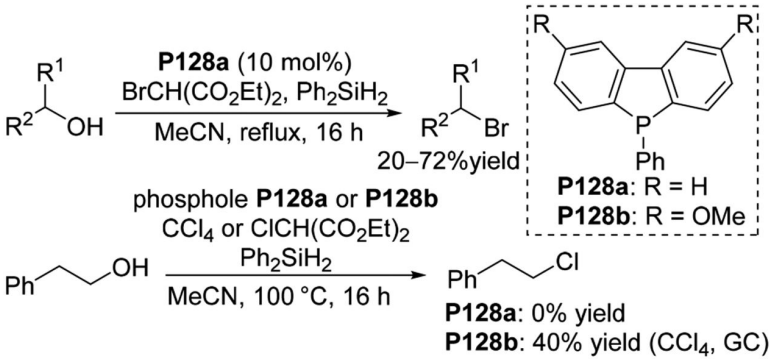
Scheme 848.

Plausible Mechanism for Reduction of the O–O Bonds of Silyl Peroxides



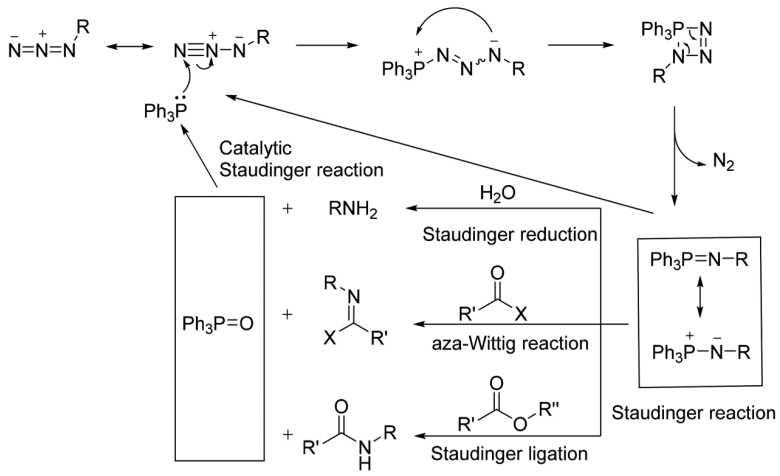
Scheme 849.

Appel Reactions and the Phosphine-Catalyzed Appel Reaction

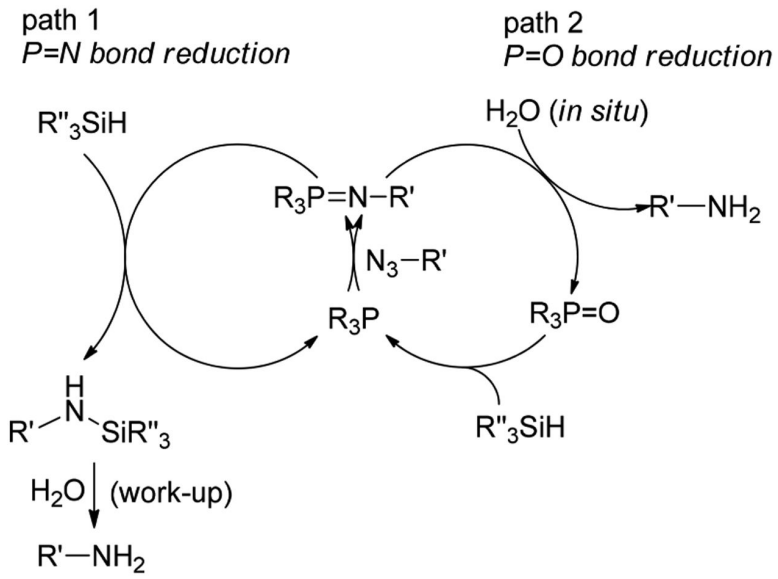


Scheme 850.

Phosphine-Catalyzed Appel Reactions of Alcohols

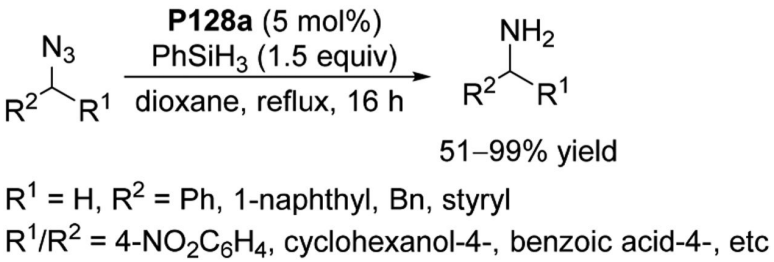


Scheme 851.
Staudinger Reactions



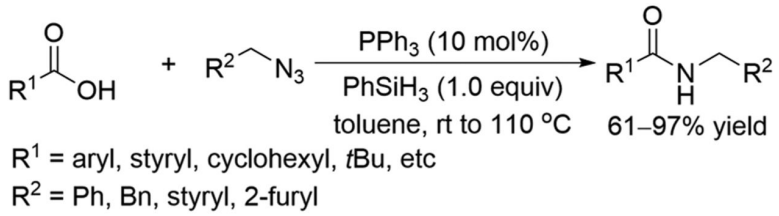
Scheme 852.

Two Paths for Catalytic Staudinger Reductions: P=N and P=O Bond Reductions



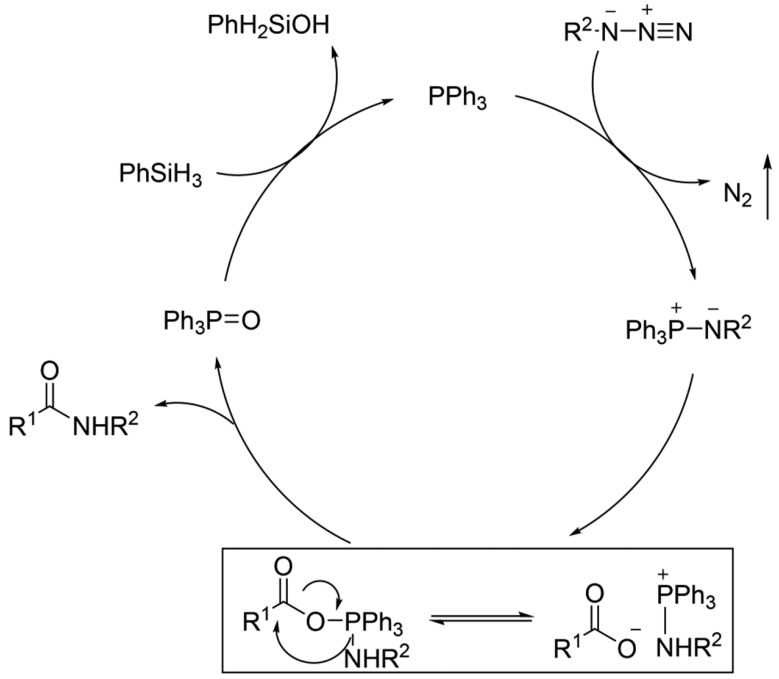
Scheme 853.

Catalytic Staudinger Reductions of Organoazide Compounds via Silane-Mediated In Situ P=N Bond Reduction

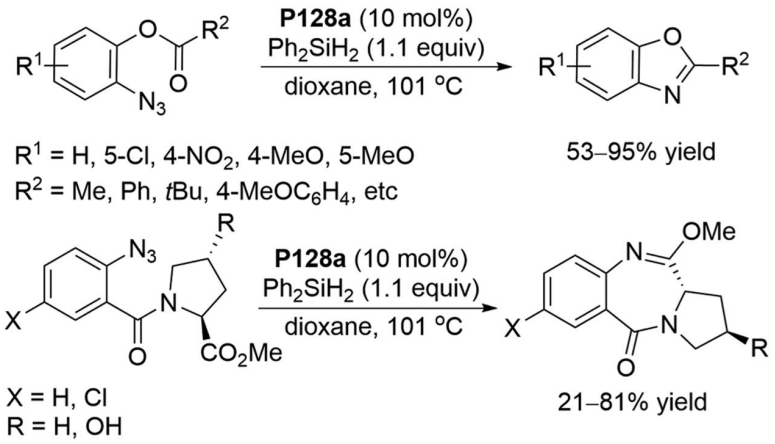


Scheme 854.

Catalytic Staudinger Ligations of Carboxylic Acids and Organoazides Via Silane-Mediated In Situ Reduction of P=O Bonds

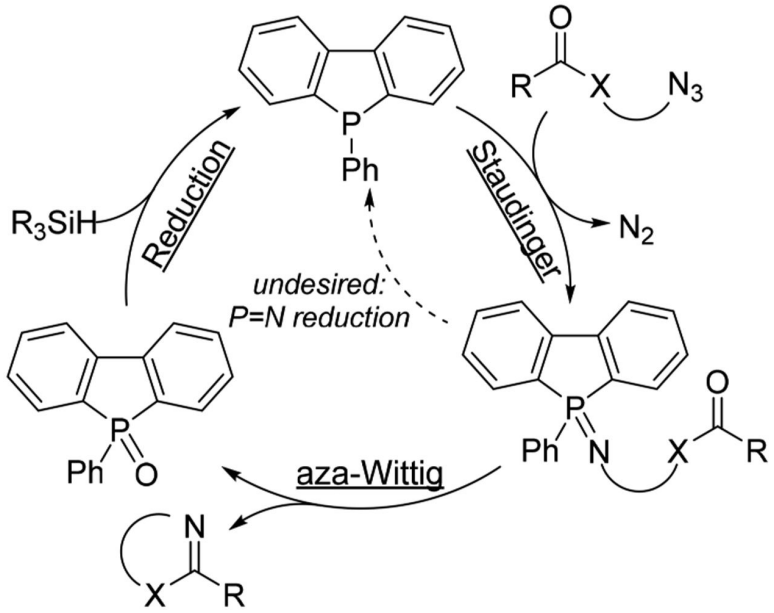


Scheme 855.
Proposed Reaction Mechanism for the Catalytic Staudinger Ligation

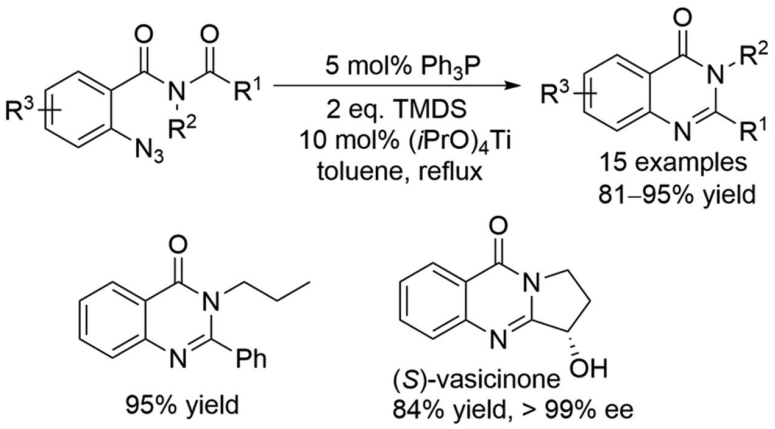


Scheme 856.

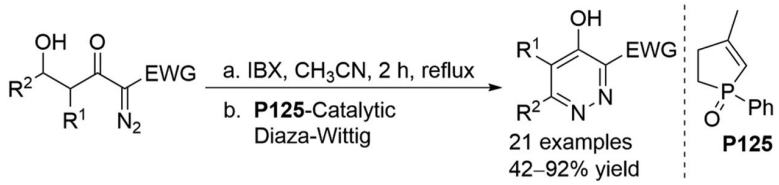
Phosphine-Catalyzed Staudinger/Intramolecular Aza-Wittig Sequence for the Preparation of N-Containing Heterocycles



Scheme 857.
Plausible Mechanism for the Staudinger/Intramolecular Aza-Wittig Sequence

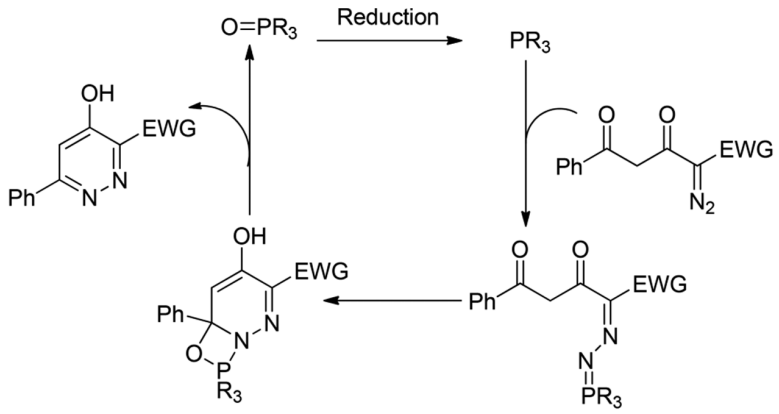


Scheme 858.
Reversible P(III)/P(V) Redox: Catalytic Aza-Wittig Reaction

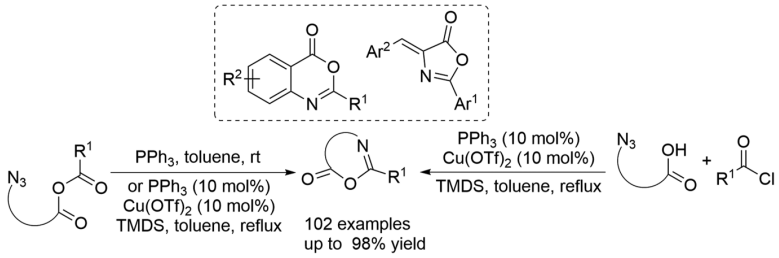


Scheme 859.

Organophosphorus-Catalyzed Diaza-Wittig Reactions

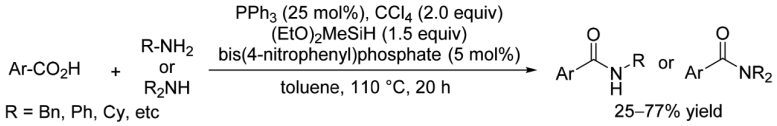


Scheme 860.
Mechanism of the Diaza-Wittig Reaction

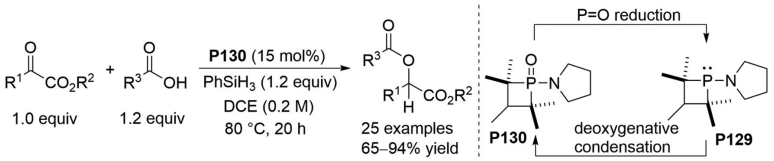


Scheme 861.

Aza-Wittig and Catalytic Aza-Wittig Reactions of Anhydrides

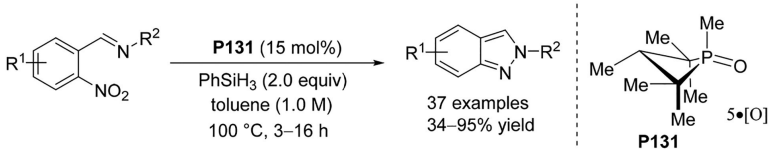


Scheme 862.
Phosphine-Catalyzed Amidation Reactions



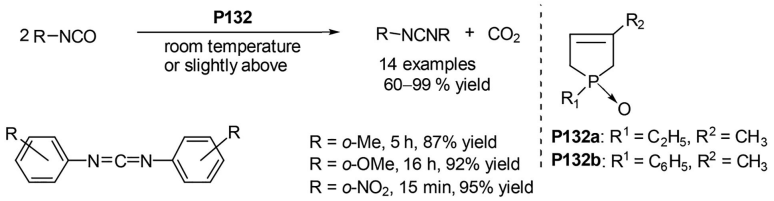
Scheme 863.

Phosphetane-Catalyzed Deoxygenative Condensation of α-Keto Esters



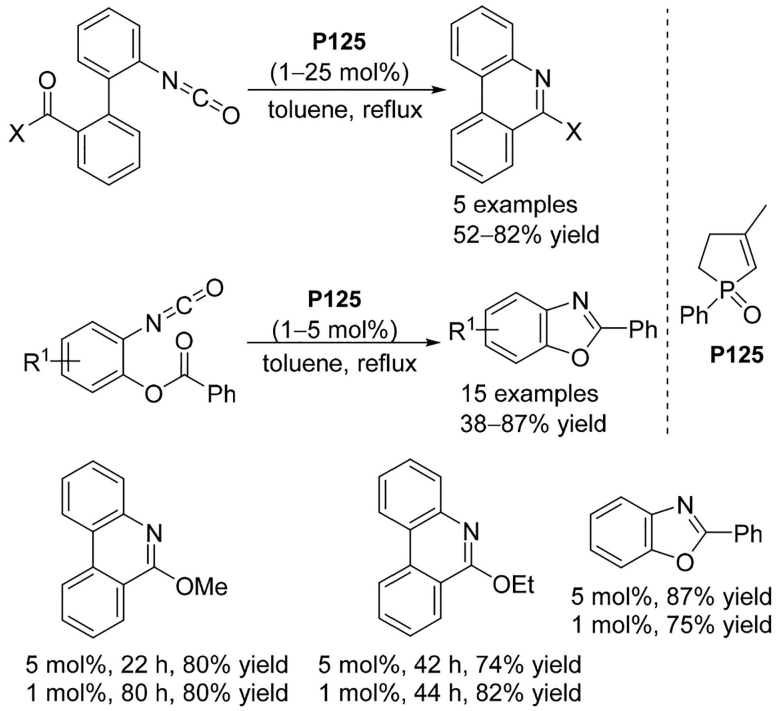
Scheme 864.

A Biphilic Phosphetane Catalyzes N–N Bond-Forming Cadogan Heterocyclization Via P^{III}/P^{V}=O Redox Cycling

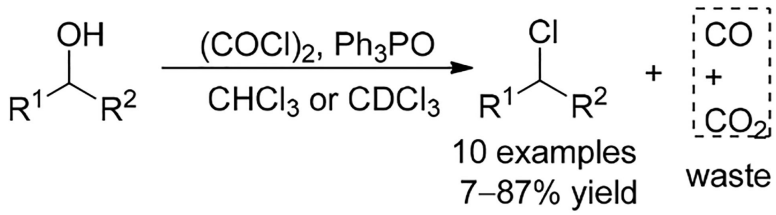


Scheme 865.

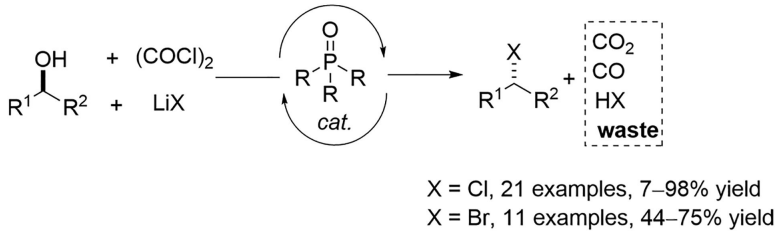
Conversion of Isocyanates to Carbodiimides Using Phospholine Oxide Catalysts



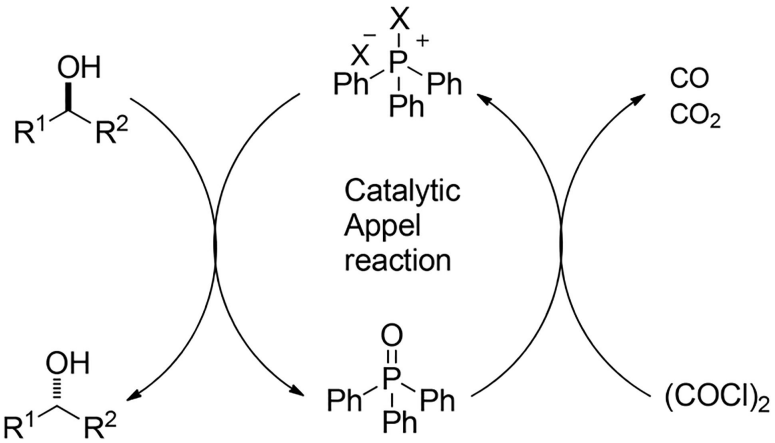
Scheme 866.
Organophosphorus-Catalyzed Aza-Wittig Cyclizations



Scheme 867.
Phosphine Oxide-Catalyzed Chlorination of Alcohols Under Appel Conditions

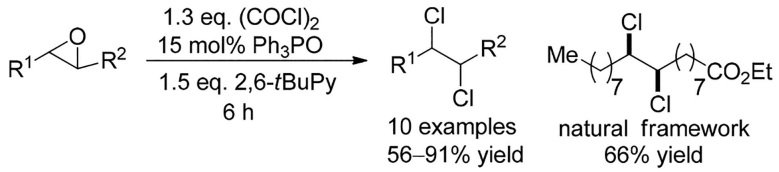


Scheme 868.
Phosphorus(V)-Mediated Appel Reaction



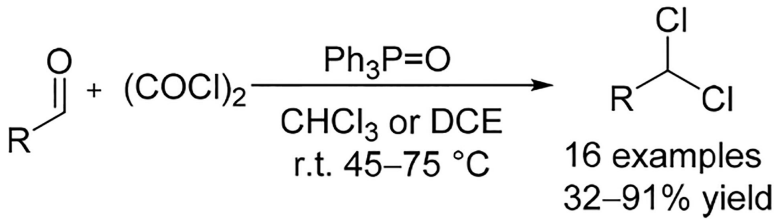
Scheme 869.

Proposed Mechanism for P(V)-Mediated Nucleophilic Substitution Using Consumable Oxalate Reagents

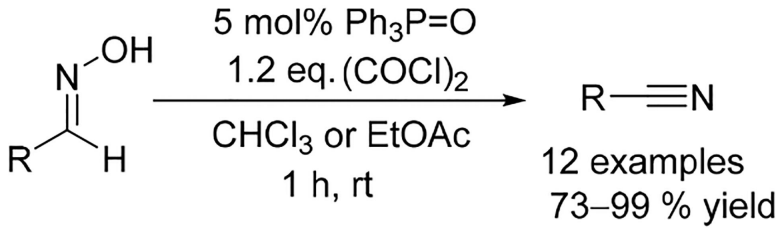


Scheme 870.

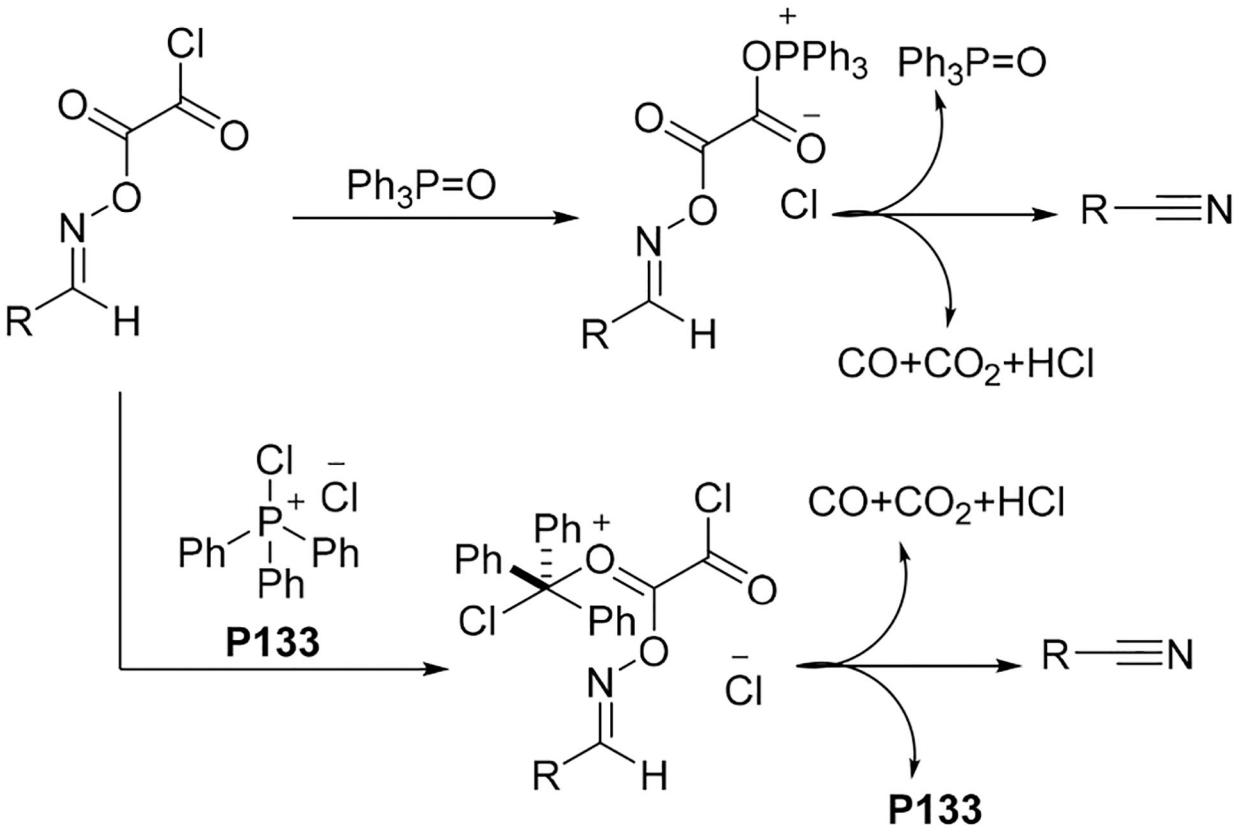
Phosphorus(V)-Mediated Dichlorination of Epoxides Under Appel Conditions



Scheme 871.
Phosphorus(V)-Catalyzed Deoxydichlorination of Aldehydes



Scheme 872.
Phosphonium Salt-Catalyzed Synthesis of Nitriles From In Situ-Activated Oximes



Scheme 873.
Proposed Mechanism