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Enantioselective Synthesis of Quaternary Oxindoles: Desymmetrizing Staudinger–Aza-Wittig Reaction Enabled by a Bespoke HypPhos Oxide Catalyst

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c09421.

Full experimental procedures and analytical data (^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectral data; HPLC, HRMS, and X-ray crystallographic data) for new compounds (PDF)

Accession Codes

CCDC 2205082 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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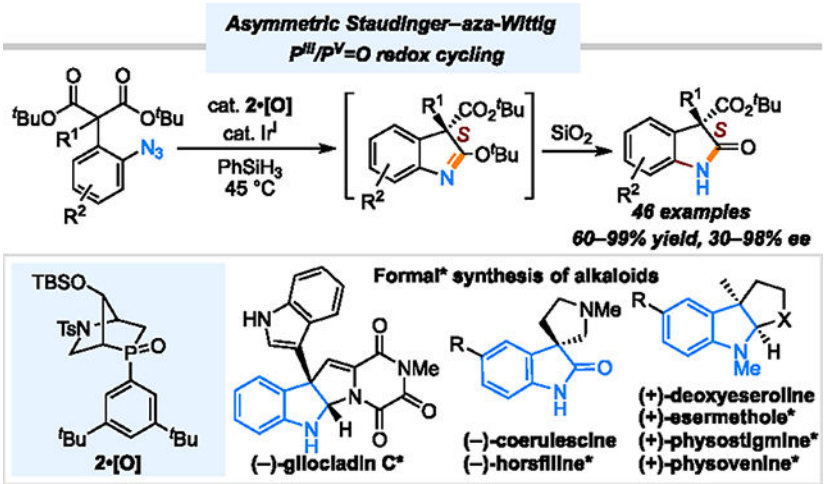
Abstract

This paper describes a catalytic asymmetric Staudinger–aza-Wittig reaction of (*o*-azidoaryl)malonates, allowing access to chiral quaternary oxindoles through phosphine oxide catalysis. We designed a novel HypPhos oxide catalyst to enable the desymmetrizing Staudinger–aza-Wittig reaction through the $P^{III}/P^{V}{=}O$ redox cycle in the presence of a silane reductant and an Ir^{I}-based Lewis acid. The reaction occurs under mild conditions, with good functional group tolerance, a wide substrate scope, and excellent enantioselectivity. Density functional theory revealed that the enantioselectivity in the desymmetrizing reaction arose from the cooperative effects of the Ir^{I} species and the HypPhos catalyst. The utility of this methodology is demonstrated by the (formal) syntheses of seven alkaloid targets: (−)-gliocladin C, (−)-coerulescine, (−)-horsfiline, (+)-deoxyeseroline, (+)-esermethole, (+)-physostigmine, and (+)-physovenine.

Graphical Abstract



INTRODUCTION

Organic phosphorus compounds are powerful reagents for the construction of C═C and C═N bonds through Wittig and aza-Wittig reactions.[1,2] Although many catalytic versions of these reactions have been reported to avoid the formation of phosphine oxide waste through $P^{III}/P^{V}{=}O$ redox cycling mediated by silanes,[3,4] catalytic enantioselective versions of Wittig and aza-Wittig reactions involving $P^{III}/P^{V}{=}O$ redox cycling are rare.[5] Werner et al. reported the first catalytic asymmetric Wittig reaction through desymmetrization of cyclopentane-1,3-dione with Me-DuPhos as the catalyst and phenylsilane as the terminal reductant.[6] The Christmann group reinvestigated Werner's asymmetric transformation and applied it in the total syntheses of *ent*-dichrocephone A and *ent*-dichrocephone B.[7] The Voituriez group developed an asymmetric α-umpolung addition–Wittig olefination cascade to access chiral (trifluoromethyl)cyclobutenes using e*xo*-anisyl-HypPhos oxide as the catalyst and phenylsilane as the reductant.[8] The Staudinger–aza-Wittig reaction figures

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prominently in the formation of nitrogen-containing compounds, especially heterocycles.[2] Despite the usefulness of the Staudinger–aza-Wittig reaction, asymmetric Staudinger processes are even rarer than asymmetric Wittig reactions.[5] In early examples, kinetic resolution of racemic azides (Figure 1A)[9] and desymmetrization of a 1,3-diketone (Figure 1B)[10] were realized by applying stoichiometric amounts of phosphines. Although Werner had achieved high enantioselectivity with $P^{III}/P^{V}{=}O$ redox cycling at high temperature (150 °C),[6,7] it would be preferable to have milder conditions for phosphine oxide recycling in asymmetric transformations. We and others have demonstrated that strained phosphines facilitate $P^{III}/P^{V}{=}O$ redox cycling mediated by hydrosilanes under mild conditions.[11,12] Accordingly, in a previous study, we developed a catalytic asymmetric Staudinger–aza-Wittig reaction of 1,3-diones, using our chiral phosphine HypPhos **1**, for the synthesis of heterocyclic amines (Figure 1C).[13] In recognition of the importance of the Staudinger–aza-Wittig reaction for synthesizing heterocycles, we wondered whether chiral lactams could be accessed through a Staudinger–aza-Wittig reaction and applied to the syntheses of complex alkaloids.

Oxindoles and indolines bearing a C3-quaternary stereocenter are core structures of a diverse range of natural products and pharmaceuticals (Figure 1D).[14,15] As such, many enantioselective processes have been developed to access chiral quaternary oxindoles,[15] with most relying on stereoselective functionalization of pendant alkenes (e.g., through Heck-type reactions,[16a–f] cyanoamidation,[16g] or Ni-catalyzed dicarbofunctionalization[16h,i]) or existing oxindoles (e.g., through alkylation,[17a,b] Michael addition,[17c] Claisen rearrangement,[17d] Mannich,[17e] aldol,[17f] allylation,[17g] or acyl-migration[17h,i] approaches). Departing from those previous routes, we turned to a desymmetrization strategy (Figure 1D).[18,19] We envisioned that the chiral iminophosphorane intermediate formed from a prochiral 2-(*o*-azidoaryl)malonate **3** would differentiate its two ester units with enantioselective formation of an imidate through an aza-Wittig reaction. The resulting imidate would readily hydrolyze to give a lactam **4** with the quaternary stereogenic center unchanged. Previously reported Staudinger–aza-Wittig reactions of esters have been performed under harsh conditions (e.g., reflux in toluene).[2,20,21] In terms of the relatively low reactivity of esters and the challenges of asymmetric induction, we surmised that coordination of a Lewis acid and a chiral iminophosphorane might facilitate the aza-Wittig reaction of unactivated esters, considering that both 1,3-dicarbonyl groups and iminophosphoranes are good ligands for Lewis acids.[22,23] Moreover, Lewis acids can facilitate silane-mediated reductions of phosphine oxides, potentially assisting the $P^{III}/P^{V}{=}O$ redox cycling in this present case.[4,24] Accordingly, we applied a custom-made HypPhos oxide catalyst, **2**•[**O**], to the synthesis of valuable quaternary oxindoles, with the aid of cooperative Ir^{I}–$P^{III}/P^{V}{=}O$ redox cycling.

RESULTS AND DISCUSSION

Initially, we tested the commercially available [2.2.1] bicyclic chiral phosphines ("HypPhos" derivatives) **1** and **5**[25] for their suitability in the Staudinger–aza-Wittig reaction of the malonate **3a** (Table 1). A stoichiometric amount of *endo*-phenyl-HypPhos **1** provided efficiency and enantioselectivity (58% ee) better than those of *exo*-phenyl-HypPhos **5** (11% ee) (entries 1 vs 2). An attempt to lower the reaction temperature (from 70 to 40 °C) to increase the enantioselectivity produced only a trace amount of product (entry 3).

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Hypothesizing that a Lewis acid might enhance the electrophilicity of the malonate ester[22,23] and promote the silane-mediated reduction of the phosphine oxide,[4,24] we surveyed a variety of metal salts for the reactions involving the HypPhos oxide **1**•[**O**] (air-stable and, therefore, easier to handle than its tertiary phosphine counterpart) and phenylsilane.[26] Because both the phosphine ligand and metal ion were present in the reaction, we were cognizant that "self-quenching" might possibly preclude the Staudinger–aza-Wittig reaction.[27] To our delight, adding both CuF_2 and $PhSiH_3$ allowed the reaction to proceed at a lower temperature (35 °C) and produced **4a** with improved enantioselectivity (78% ee) (entry 4). In the absence of molecular sieves, the ee of the product varied, presumably because of racemization arising from hydrolysis of the imidate product. Switching the solvent from toluene to less polar cyclohexane slightly improved the enantioselectivity (82% ee), although the conversion was lower and the isolated yield was only 50% (entry 5). We reasoned that the low conversion might have resulted from self-quenching between the metal and phosphine. To alleviate that deleterious effect, we designed a series of "bulkier" phosphines that would presumably dissociate more readily from the transition metal ion. The most straightforward approach was the incorporation of a bulky aryl substituent on the phosphorus atom. Again to our delight, the use of *endo*-(3,5-di-*tert*-butylphenyl)-HypPhos oxide (**6**•[**O**]) under otherwise identical conditions produced the oxindole **4a** in a good isolated yield, albeit with slightly decreased stereoselectivity (92%, 77% ee) (entry 6).

In an attempt to increase the enantioselectivity, we modified the [2.2.1]-bicyclic skeleton of the catalyst, obtaining the *endo*-phenyl-7-trimethylsiloxy-HypPhos oxide **7**•[**O**] from commercially available L-proline.[26] Employing the HypPhos oxide **7**•[**O**] improved the enantioselectivity (89% ee) but decreased the reaction efficiency (30% isolated yield, entry 7). Thus, we combined a 3,5-di-*tert*-butylphenyl substituent on the phosphorus center and a trimethylsiloxy group at the apical carbon atom to assemble the phosphine oxide **8**•[**O**], which admirably catalyzed the conversion of the malonate **3a** to the oxindole **4a** in excellent yield and with good enantioselectivity (95%, 87% ee, entry 8). Changing the Lewis acid from CuF_2 to $[Ir(cod)Cl]_2$ further improved the enantioselectivity (95%, 92% ee, entry 9). Here, we added tetrabutylammonium tetrafluoroborate ($TBABF_4$), along with $[Ir(cod)Cl]_2$, to facilitate its chloride ion exchange.[28] In the absence of $TBABF_4$, the reaction was very slow (see Table S6 for details). When we performed the reaction at 45 °C, we could decrease the loadings of **8**•[**O**] and $[Ir(cod)Cl]_2$ to 10 and 5 mol %, respectively, while maintaining the yield and enantioselectivity (95%, 93% ee, entry 10). A survey of various silyl groups indicated that the TBS unit was optimal (entries 10–13). The yield and selectivity were comparable when employing 3 or 4 equiv of $PhSiH_3$ (cf. entries 14 and 12), but further decreasing it to 2 equiv diminished the yield (entry 15).

On examining the scope of the transformation, we found that malonates substituted with simple alkyl substituents (**3a–e**) gave their oxindoles (**4a–e**) in good yields (87–98%) and excellent enantioselectivities (92–94% ee), except in the case of the malonate with a methyl substituent (**3b**), where the selectivity was lower (68% ee) (Table 2A). A substrate having an acid-sensitive dimethyl acetal functional group (**3f**) was tolerated, with the corresponding oxindole **4f** isolated in 88% yield and 91% ee. Substrates with silyl ether substituents (**3g–i**) also reacted well to form their oxindoles (**4g–i**) in good yields (97–99%) and with moderate

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selectivity (85–87% ee). The malonate **3f** substituted with a (5-triisopropylsiloxy)pentyl group displayed improved enantioselectivity (91% ee) but lower yield (80%). Interestingly, the oxindole with a (3-ethoxycarbonyl)propyl substituent (**4k**) was obtained with lower selectivity (83% ee), presumably because of coordination of the ethyl ester unit to the Lewis acid, diminishing the effects of the latter in promoting the reactivity and enantioselectivity (vide infra). Malonates possessing sterically bulkier *tert*-butyl ester (**3l**) and more-electron-deficient phenyl ester (**3m**) units, which coordinate poorly when compared with ethyl ester units, behaved better, forming their oxindoles (**4l–m**) with improved yields (86–91%) and enantioselectivities (89–91% ee). Malonates substituted with α-benzyl groups were also suitable substrates (**3n–u**). For example, we isolated oxindoles with benzyl and fluoro- and pinacol boronic ester (Bpin)-substituted benzyl groups (**4n–p**) in good yields (68–99%) and excellent selectivity (90–93% ee). The specific rotation of our product (+)-**4n** was opposite to that of the known oxindole (*R*)-**4n**,[29] allowing us to assign the *S* configuration to our oxindole product. In other examples, we isolated oxindoles with protected indole units (**4q** and **4r**) and an aza-indole (**4t**) in high yields (88–98%) and good selectivity (88–91% ee). The substrate with an unprotected indole moiety (**3s**) produced its oxindole **4s** in good yield (96%), but the enantioselectivity was lower (86% ee). When we subjected the substrate **3u** (containing a pyridine heterocycle) to the reaction conditions, we observed the formation of the relatively stable imidate **11u**, which could be purified through NEt_3neutralized silica gel column chromatography in good yield (90%) and selectivity (91% ee). The isolation of this imidate indicated that the mechanism of our Staudinger–aza-Wittig reaction, between an azide and an ester, differed from those of Staudinger ligations used previously in chemical biology.[30] For the malonates with 3-phenylpropyl (**3v**) and 3-(naphth-2-yl)propyl (**3w**) substituents, we isolated their oxindoles in good yields (75–80%) and excellent enantioselectivities (92–93% ee). We obtained the heteroatom-substituted oxindole **4x** in excellent yield (99%) but with lower selectivity (30% ee).

Subsequently, we investigated malonates substituted with various *o*-azidoaryl groups (Table 2B). Oxindoles bearing electron-donating groups at the C6 position (**4y–aa**) were produced in good yields (97–99%) and excellent enantioselectivities (90–93% ee). An aromatic substituent at the C6 position could be tolerated, with the oxindole **4ab** obtained in 99% yield and 90% ee. Other electron-withdrawing groups at the C6 position were also compatible (**3ac–ae**), with the corresponding oxindoles **4ac–ae** isolated in good yields (83–97%) and enantioselectivities (89–94% ee). Substrates bearing halides at the C6 position (**3af–ah**) reacted well to give their oxindoles (**4af–ah**) in good yields (80–88%) and excellent enantioselectivities (91–95% ee). The enantioselectivity for the reaction of the 5-MeO oxindole was lower (**4ai**, 81% ee), but changing the MeO group to a less electron-donating tosyl group (**4aj**) increased the selectivity to 91% ee. Trifluoromethyl and fluoro groups at the C5 position (**4ak–am**) were tolerated, with the corresponding oxindoles isolated in good yields (91–95%) and enantioselectivities (87–93% ee). We prepared the C7-substituted oxindole **4an** in commendable yield (98%) and enantioselectivity (96% ee). When multiple halide atoms were present on the aromatic rings (**3ao** and **3ap**), the Staudinger–aza-Wittig reactions proceeded smoothly to give the desired products (**4ao** and **4ap**) in excellent yields (91–94%) and enantioselectivities (93% ee). Azido substrates featuring pyridine and quinoline units reacted to furnish the aza-oxindole **4aq**,

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the aza-imidate **11ar**, and the fused aza-oxindole **4as** in high yields (92–94%) and enantioselectivities (94–98% ee). Because the electron-deficiency of these heterocycles decreased the reactivity of the resulting iminophosphoranes, with the basic nitrogen atoms possibly coordinating to the Lewis acid, higher catalyst loadings {**2**•[**O**] (25 mol %), $[Ir(cod)Cl]_2$ (12.5 mol %)} and a longer reaction time (72 h) were required to ensure high conversions. Interestingly, the imidate **11ar** could also be purified, through column chromatography using NEt_3-neutralized silica gel, in 92% isolated yield. A bidirectional Staudinger–aza-Wittig reaction afforded the oxindole **4at** in 85% yield, with 5.3:1 dr and 90% ee. Notably, cyclization of the amine to the oxindole **4at** without the catalyst resulted in a 1:1.7 dr, favoring the formation of the meso-oxindole.

To demonstrate the synthetic utility of this methodology, we first performed the reaction of **3f** on a 2.1 g scale (Scheme 1A). Using a lower catalyst loading {**2**•[**O**] (5 mol %), $[Ir(cod)Cl]_2$ (3 mol %)} and longer reaction time (6 d), we isolated the desired oxindole (+)-**4f** in 81% yield and 92% ee, along with recovery of the HypPhos **2** in 82% yield. Crystallization of (+)-**4f** from cyclohexane and EtOAc yielded higher enantiopurity (97% ee), with X-ray crystallography confirming the absolute configuration to be *S*.[26,29,31] The potential utility of this method was further illustrated through the syntheses of several alkaloid targets (Schemes 1B–D). Reduction of (+)-**4f** with DIBAL-H afforded (+)-**12** in 83% yield (Scheme 1B). After TBS protection, the Fischer indole reaction catalyzed by $ZnCl_2$ yielded (+)-**13**, a key intermediate in the synthesis of gliocladin C,[32,33] in 90% yield, completing the formal synthesis of (−)-gliocladin C. Gliocladin C is a known precursor of gliocladine C.[32b] Notably, the activity of (−)-gliocladine C (IC_{50}: 0.35 μM) against melanoma (A2508) cell lines is better than that of natural (+)-gliocladine C (IC_{50}: 0.68 μM).[32c] Treatment of (+)-**12** with MsCl and NEt_3 gave (+)-**14** in 91% yield (Scheme 1C). Deprotection of the dimethoxy acetal group, using $In(OTf)_3$ in acetone, followed by reductive amination and spontaneous cyclization furnished (−)-coerulescine in 64% yield.[34] A two-step protocol has been reported previously for the preparation of horsfiline from coerulescine,[34d] allowing us to claim a formal synthesis of (−)-horsfiline. Methylation of (+)-**14**, reduction of the mesylate with $NaBH_4$, followed by deprotection of the dimethoxy acetal group afforded (−)-**15** in 54% overall yield (Scheme 1D). Formation of the imine with $MeNH_2$ and $MgSO_4$ followed by in situ reduction with $LiAlH_4$ and cyclization furnished (+)-deoxyeseroline in 81% yield. Following the reported procedure,[16c,35] (+)-deoxyeseroline could be used to prepare (+)-esermethole and (+)-physostigmine. Interestingly, (−)-physostigmine is clinically useful as an anticholinergic drug for Alzheimer's disease, whereas its enantiomer (+)-physostigmine is not, but it has been used experimentally to protect animals from organophosphate poisoning.[36] Treatment of (−)-**15** with $LiAlH_4$ gave the aminal (+)-**16**, a known precursor of (+)-physovenine.[37]

We used density functional theory (DFT) calculations to elucidate the reaction mechanism and origin of enantioselectivity of the asymmetric Staudinger–aza-Wittig reaction (see the SI for computational details). We investigated the reaction of the Lewis acid–bound iminophosphorane **17** derived from the chiral phosphine **2** and the malonate **3a** in the presence of phenylsilane as the reductant and $[Ir(cod)Cl]_2$ as the Lewis acid (Figure 2A).[38] From **17**, the concerted [2 + 2] cycloaddition (**TS1**) gives the oxazaphosphetane

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intermediate **18** followed by stepwise retro-[2 + 2] cycloaddition[39] to cleave the P–N and C–O bonds sequentially, via transition states **TS2** and **TS3**, respectively. Because both of the enantiotopic malonate ester groups might have reacted with the two different π-faces of the PN bonds in the *cis* and *trans* isomers of the iminophosphorane, we considered all eight of these possible stereoisomeric pathways (pathways **A–H**). Figure 2A presents the reaction energy profiles of the two most favorable pathways (**A** and **B**) leading to the (*S*)- and (*R*)-enantiomers of the product (**11** and **ent-11**, respectively; see Figures S2–S5 for the less favorable pathways). In the rate- and enantioselectivity-determining P–N bond cleavage step (**TS2**), pathway **A** leading to the major enantiomeric product **11** has an activation barrier 2.5 kcal/mol lower than that of pathway **B** leading to ent-**11**, consistent with the high ee we observed experimentally (93% ee). In pathway **A**, the ratedetermining transition state for retro-[2 + 2] cycloaddition (**TS2-A**) is stabilized by [C–H$\cdots\pi$] interactions between the 7-OTBS group on HypPhos and the benzene ring on the substrate (Figure 2B). The computed geometry of **TS2-A** features a Me group on the OTBS unit positioned optimally from the benzene ring on the substrate (3.10 Å) to form a stabilizing [C–H$\cdots\pi$] interaction, rather than a repulsive one.[40] On the other hand, in **TS2-B**, the bulky *tert*-butoxy unit, rather than the benzene ring, is positioned toward the bicyclic framework of the HypPhos scaffold, leading to unfavorable steric interactions between the *tert*-butoxy and HypPhos units.

Next, we investigated how the Lewis acid affected the reactivity and enantioselectivity. For the reaction of the iminophosphorane **21** in the absence of a Lewis acid, our calculations indicate that the [2 + 2] and retro-[2 + 2] cycloaddition steps both occur with higher activation barriers and that the computed enantioselectivity ($\Delta\Delta G^{\ddagger}$ = 0.4 kcal/mol) is diminished (Figure 2C). These findings are consistent with the lower reactivity and enantioselectivity we observed experimentally in the absence of a Lewis acid (Table 1). The Lewis acid not only promotes the [2 + 2] cycloaddition by enhancing the nucleophilicity of the carbonyl group but also facilitates the retro-[2 + 2] cycloaddition step kinetically. In the absence of a Lewis acid, the retro-[2 + 2]-cycloaddition occurs in a concerted manner[13] with an activation barrier of 27.2 kcal/mol. When [Ir(*cod*)Cl]$_2$ was present, the retro-[2 + 2] cycloaddition occurs through a kinetically more favorable stepwise process in which the Lewis acid stabilizes the negative charge in the zwitterionic intermediate **19-A**.

CONCLUSIONS

In conclusion, we have developed a phosphine oxide-catalyzed asymmetric Staudinger–aza-Wittig reaction of (*o*-azidoaryl)malonates, allowing access to a range of valuable chiral quaternary oxindoles. The reaction occurs under mild conditions, with good functional group tolerance, a wide substrate scope, and excellent enantioselectivity. The success of this reaction relies on the rationally designed HypPhos oxide **2**•[**O**] featuring a strained [2.2.1]-bicyclic core structure (facilitating $P^{III}/P^{V}{=}O$ redox cycling) and steric bulk (avoiding "self-quenching" in the presence of Lewis acids {e.g., [Ir(*cod*)Cl]$_2$}). The Ir^{I} center acts as a Lewis acid in this process, promoting the aza-Wittig reaction of relatively inert malonates and assisting the $P^{III}/P^{V}{=}O$ redox cycling in the presence of phenylsilane as the reductant. Through DFT-based calculations, we elucidated the origin of the enantioselectivity and highlighted the cooperative effects of the Ir^{I} center and our

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designed HypPhos in facilitating the desymmetrization. Moreover, we highlight the utility of this methodology through (formal) syntheses of seven alkaloid targets: (−)-gliocladin C, (−)-coerulescine, (−)-horsfiline, (+)-deoxyeseroline, (+)-esermethole, (+)-physostigmine, and (+)-physovenine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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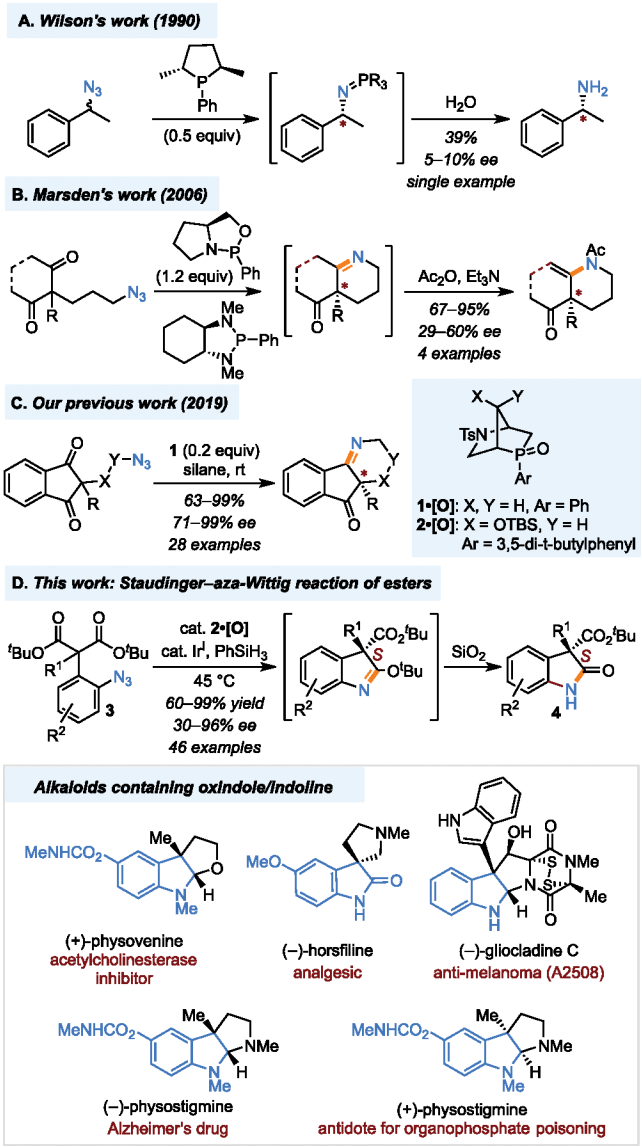

Figure 1.
Asymmetric Staudinger processes.

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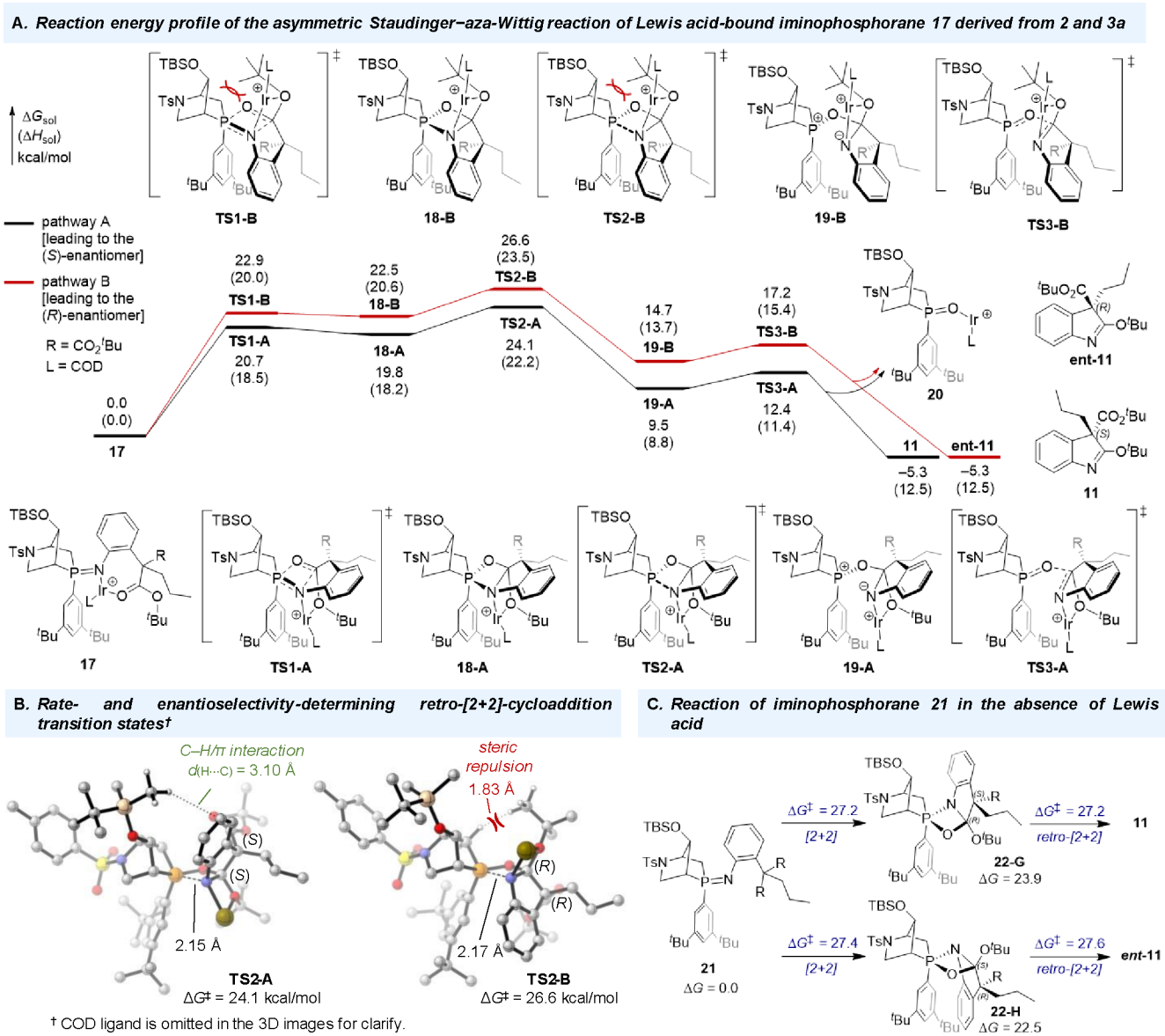

Figure 2.

Computational study of the mechanism, origin of enantioselectivity, and effect of the Lewis acid of the asymmetric Staudinger–aza-Wittig reaction. All Gibbs free energies and enthalpies (in kcal/mol) were computed at the ωB97X-D/6-311 + G(d,p)–SDD(Ir)/SMD(cyclohexane)//B3LYP-D3/6-31G(d)-SDD(Ir) level of theory.

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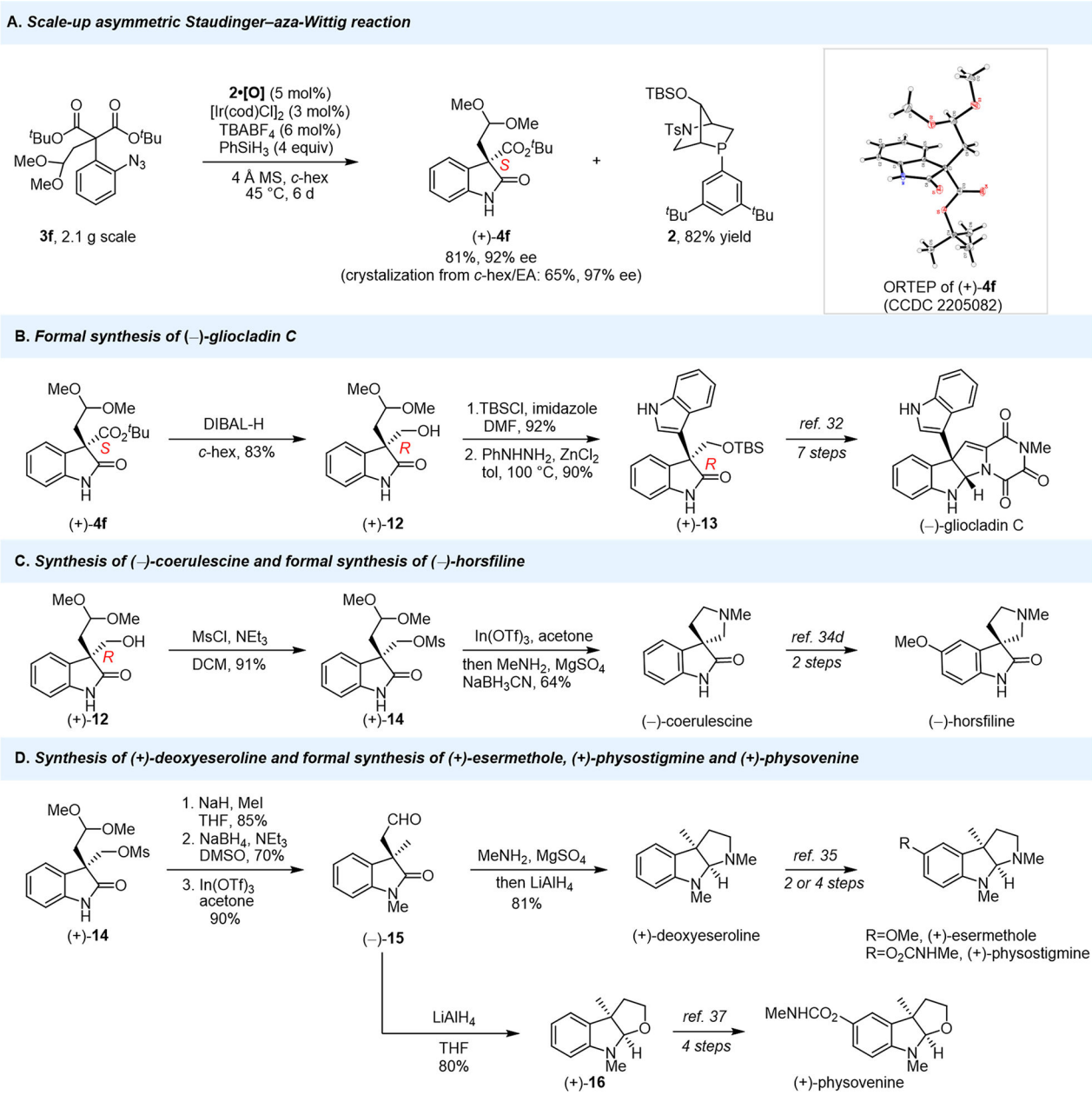

Scheme 1.

Scaled-up Staudinger–aza-Wittig Reaction and Synthetic Applications

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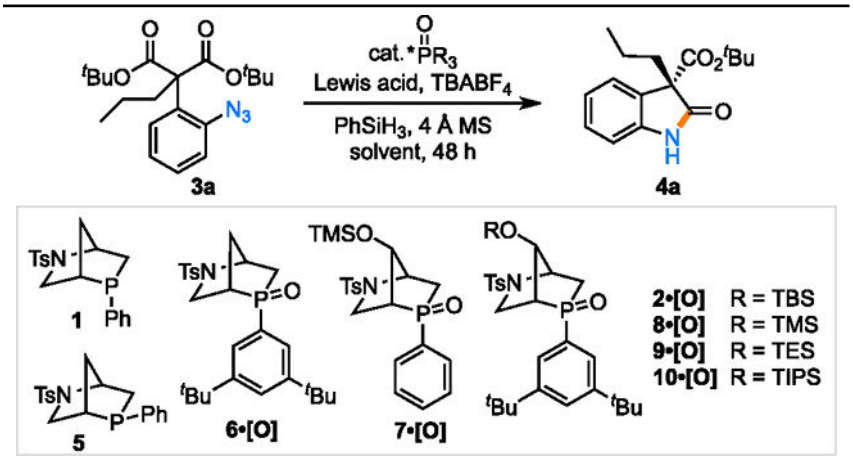
Table 1.

Optimization of Reaction Conditions[a,i]



entry	*PR$_3$ (mol %)	Lewis acid (mol%)	solvent	*T* (°C)	yield[b] (%)	ee[c] (%)
1[d,e,f]	1 (100)		tol	70	95	58
2[d,e,f]	5 (100)		tol	70	85	11
3[d,e,f]	1 (100)		tol	40	trace	n.d.
4[f]	1•[O] (20)	CuF_2 (20)	tol	35	81	78
5[f]	1•[O] (20)	CuF_2 (20)	*c*-hex	35	50	82
6[f]	6•[O] (20)	CuF_2 (20)	*c*-hex	35	92	77
7[f]	7•[O] (20)	CuF_2 (20)	*c*-hex	35	30	89
8[f]	8•[O] (20)	CuF_2 (20)	*c*-hex	35	95	87
9	8•[O] (20)	[Ir(*cod*)Cl]$_2$ (10)	*c*-hex/tol (1:1)	35	95	92
10	8•[O] (10)	[Ir(*cod*)Cl]$_2$ (5)	*c*-hex	45	95	93
11	9•[O] (10)	[Ir(*cod*)Cl]$_2$ (5)	*c*-hex	45	98	92
12	2•[O] (10)	[Ir(*cod*)Cl]$_2$ (5)	*c*-hex	45	96	93
13	10•[O] (10)	[Ir(*cod*)Cl]$_2$ (5)	*c*-hex	45	88	88
14[g]	2•[O] (10)	[Ir(*cod*)Cl]$_2$ (5)	*c*-hex	45	98	93
15[h]	2•[O] (10)	[Ir(*cod*)Cl]$_2$ (5)	*c*-hex	45	92	92

[a]Reactions performed on a 0.05 mmol scale with 4.0 equiv of $PhSiH_3$, unless otherwise noted.

[b]Isolated yield.

[c]Enantiomeric excess (ee) determined using chiral-phase HPLC.

[d]No $PhSiH_3$.

[e]No 4 Å molecular sieves.

[f]No $TBABF_4$.

[g] $PhSiH_3$: 3 equiv.

[h] $PhSiH_3$: 2 equiv.

[i] $TBABF_4$: tetrabutylammonium tetrafluoroborate; tol: toluene; n.d.: not detected; *c*-hex: cyclohexane; cod: 1,5-cyclooctadiene.

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Table 2.

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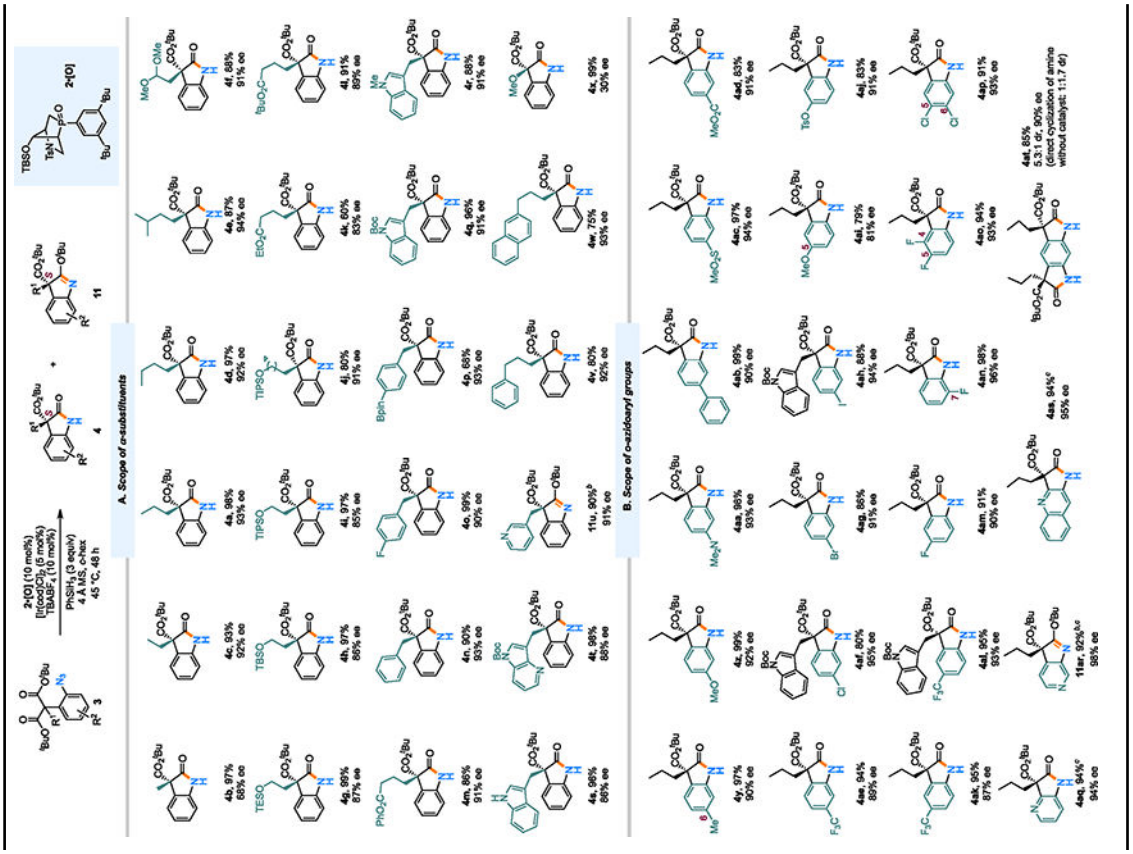
Scope of Malonate Substrates[a]



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[a]Conditions: Substrate **3** (0.05 mmol), **2**•[O] (10 mol %), [Ir(*cod*)Cl]$_2$ (5 mol %), TBABF$_4$ (10 mol %), PhSiH$_3$ (3 equiv), 0.05 M in *c*-hex at 45 °C. Isolated yields are given; enantiomeric excess (ee) determined using chiral-phase HPLC.

[b]Column chromatography through NEt$_3$-neutralized silica gel was used for purification.

[c]**2**•[O] (25 mol %), [Ir(*cod*)Cl]$_2$ (12.5 mol %), TBABF$_4$ (25 mol %), PhSiH$_3$ (4 equiv), 72 h.