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Copper-Catalyzed Asymmetric Addition of Olefin-Derived Nucleophiles to Ketones

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Abstract

Enantioenriched alcohols found in an array of bioactive natural products and pharmaceutical agents are often synthesized by asymmetric nucleophilic addition to carbonyls. However, this approach generally shows limited functional group compatibility, requiring the use of preformed organometallic reagents in conjunction with a stoichiometric or sub-stoichiometric amount of chiral controller to deliver optically active alcohols. Herein we report a copper-catalyzed strategy for the stereoselective nucleophilic addition of propargylic and other alkyl groups to ketones using easily accessible (poly)unsaturated hydrocarbons as latent carbanion equivalents. Our method features the catalytic generation of highly enantioenriched organocopper intermediates and their subsequent diastereoselective addition to ketones, allowing for the effective construction of highly substituted stereochemical dyads with excellent stereocontrol. Moreover, this process is general, scalable, and occurs at ambient temperature.

One Sentence Summary

A mild and general method for the catalytic asymmetric addition of olefin-derived nucleophiles to ketones has been developed, providing an effective means to access highly enantioenriched alcohols bearing vicinal stereocenters with high levels of stereocontrol.

Stereochemically complex alcohols in optically pure form are commonly encountered structural elements in a diverse range of pharmaceutical drugs and biologically active natural products (Fig. 1(A)). Consequently, general methods allowing for the stereoselective assembly of highly substituted alcohols have long been sought after (1). The discovery of Grignard reagents and their subsequent addition to ketones and aldehydes have been widely considered as a milestone in synthetic chemistry, giving rise to a general synthesis of alcohols from preformed organomagnesium reagents and broadly available carbonyl compounds (2). Since then, extensive efforts have been devoted to the development of

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Supplementary Materials

Materials and Methods
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asymmetric variants of nucleophilic addition reactions to carbonyls using preformed organometallic reagents (1, 3–7). These synthetic endeavors proved to be exceptionally fruitful, culminating in a variety of useful protocols for enantioselective additions to carbonyls using either a chiral auxiliary-modified organometallic reagent or a sub-stoichiometric amount of chiral controller to achieve excellent levels of stereocontrol. Compared to aldehydes, however, the asymmetric nucleophilic addition to ketones has been studied to a lesser extent (5–7).

While numerous advances have been made in this area, considerable hurdles have impeded the further adaptation of these methods by the synthetic community. The requirement to prepare and use a stoichiometric quantity of an organometallic reagent complicates most of the existing methods. In addition, the highly nucleophilic and basic nature of organometallic reagents has posed substantial limitations with respect to the functional group compatibility of these processes. As a consequence, these methods are typically not amenable to the transformation of late-stage intermediates and other highly functionalized molecules. Furthermore, an additional synthetic operation is required to prepare these organometallic reagents from organic halide or unsaturated hydrocarbon precursors, imposing further constraints on the types of nucleophiles suitable for carbonyl addition.

In this context, a catalytic method for stereoselective additions to carbonyls using easily accessible olefins as latent carbanion equivalents in lieu of preformed organometallic reagents would circumvent these issues and greatly expand the scope of stereochemically well defined alcohols accessible from carbonyl addition processes. In elegant work using Ru-, Rh- and Ir-based noble metal catalysts, Krische has pioneered the development of a range of synthetically versatile stereoselective coupling reactions of olefins and carbonyls under hydrogenation and transfer hydrogenation conditions (8–10). To date, however, the synthesis of sterically demanding tertiary alcohols from simple ketones remains challenging with these processes, in part due to the increased steric hindrance and the attenuated electrophilicity of ketones relative to aldehydes. In a mechanistically distinct approach, Montgomery and Jamison have devised novel Ni-based methods for the enantioselective reductive coupling of alkynes and aldehydes (11–14). Additionally, Hoveyda has developed exceptional copper-catalyzed borylative processes for the addition of olefin-derived nucleophiles bearing a boryl moiety to carbonyls. This chemistry has been highly successful in the enantioselective preparation of secondary alcohols from aldehydes (15, 16), although ketones represent more challenging substrates for this enantioselective process (16). Alkenes and ketones constitute two of the most widely available building blocks for organic synthesis. Nevertheless, a broadly applicable and highly enantioselective catalyst system for the coupling of these orthogonal feedstocks remains elusive.

We have recently become interested in the development of copper(I) hydride (CuH) catalysis as a general means of accessing enantioenriched alkylcopper intermediates from readily available olefin precursors. By employing a class of electrophilic aminating reagents established by Johnson (17) to intercept these organometallic intermediates, our laboratory (18) and Miura and Hirano (19–21) have independently developed a CuH-catalyzed approach for the enantioselective hydroamination of olefins (22). Based on these studies and notable contributions from other groups in the area of copper-catalyzed enantioselective

reductive aldol reactions (6,7, 23–26), we envisioned the development of CuH chemistry as a general platform for the use of simple olefins as latent carbon nucleophiles in carbonyl addition (Fig. 1(B)). In particular, we were interested in investigating the coupling of (poly)unsaturated hydrocarbons and ketones via the diastereoselective addition of catalytically generated chiral organocopper intermediates to the carbonyl group. If successful, our proposed strategy would enable the use of an earth abundant first-row transition-metal catalyst for the diastereo- and enantioselective synthesis of alcohols, including those possessing vicinal tri- and tetrasubstituted stereogenic centers from olefins and carbonyls.

Our proposed catalytic cycle is described in Fig. 1(C). Enantioselective addition of a phosphine-bound copper hydride catalyst (**I**) across the C=C double bond of an olefin (**II**) would lead to the formation of an alkylcopper intermediate (**III**). Interception of this nascent alkylcopper intermediate with a ketone (**IV**) would provide the alkoxycopper species **V**. Ligand exchange of **V** with *tert*-butanol (**VI**) would furnish the asymmetric addition product (**VII**) and release copper *tert*-butoxide **VIII**. The latter upon undergoing a σ-bond metathesis with hydrosilane **IX** would then regenerate the copper hydride catalyst (**I**) and complete the catalytic cycle. The mechanistic proposal outlined herein does not require the use of any exogenous acidic or basic additives for substrate or catalyst activation, thereby potentially allowing for a range of sensitive functional groups to be tolerated. Mechanistically, in contrast to the majority of previously developed transition-metal-catalyzed reductive couplings (8–14), the strategy we envisioned does not involve redox processes at the copper(I) center while allowing for the polar and nonpolar building blocks to couple in a reductive fashion. Additionally, inexpensive and mild silane reagents are used as the reductant for the catalytic generation of organocopper intermediates.

At the outset, we recognized that the successful implementation of our proposed strategy would depend upon unprecedented chemo- and stereoselectivity with respect to the copper catalyst. The competitive hydrocupration of the carbonyl coupling partner is known to be a facile process and would lead to its unproductive reduction. Moreover, important work by Lipshutz and coworkers has demonstrated that the copper hydride species based on DTBM-SEGPHOS (**L1**), our optimal catalyst for olefin hydroamination (18), is highly robust and efficient for the asymmetric reduction of a variety of carbonyls, including ketones (27). On the other hand, the alkylcopper intermediate generated from olefin hydrometalation would need to be nucleophilic enough to facilitate the alkylation of a range of unactivated ketones, a process that has proven challenging with other transition metal catalysts. Nevertheless, we reasoned that judicious choice of the copper catalyst could suppress the undesired ketone reduction while still allowing for the effective olefin hydrocupration as well as ketone alkylation. Furthermore, we postulated that it would be feasible to access a catalyst capable of imposing effective stereochemical facial discrimination upon the prochiral olefin and the ketone to achieve high levels of enantio- and diastereoselectivity.

We focused our initial investigation on the transformation of enynes, a subset of olefins that could be conveniently prepared from terminal alkynes in a single operation. Previously work on the use of enynes for transition-metal catalyzed reductive and borylative transformations (28, 29, 30, 15) led us to postulate that these enyne substrates could serve as a suitable

starting point for our investigations, since hydrocupration of these substrates might be facilitated by the formation of an alkylcopper species stabilized by a neighboring alkynyl group. From the standpoint of utility, the enantioselective coupling of enynes to ketones would furnish synthetically versatile homopropargyl alcohol products (31–33). Prior to our experimental studies, we carried out density functional theory (DFT) calculations to gain some insight into the ligand effects on the ketone reduction and olefin hydrocupration processes (Fig. 1(D)). Our computational studies revealed that, while the hydrocupration of ketones is a kinetically facile and highly exergonic process, the choice of the ancillary phosphine ligand could dramatically influence the reactivity of the **L***CuH species. In particular, while the reduction of ketone **1** with a catalyst generated from DTBM-SEGPHOS indeed requires a low activation energy ($\Delta G^{\ddagger}$) of 9.9 kcal/mol, the same process is less facile when other commercially available ligands are employed. In particular, the use of a catalyst derived from Ph-BPE (**L2**), another ligand previously employed in CuH chemistry (20, 34), results in a higher activation energy ($\Delta G^{\ddagger}$ = 13.6 kcal/mol). Furthermore, calculations suggested that the activation barrier for the hydrocupration of enyne **3** is 1.3 kcal/mol lower than that of ketone **1** with this Ph-BPE-based catalyst, indicating the feasibility of chemoselective enyne hydrocupration in the presence of ketones. Indeed, these computational trends were corroborated by our experimental efforts to identify suitable conditions for the enantioselective addition of enyne-derived nucleophiles to ketones. The use of a catalyst based on DTBM-SEGPHOS gave the coupled product **4a** in only 48% yield with moderate stereoselectivity (2.3:1 dr, 85% ee) along with a significant amount of reduction product **4b** (52% yield). In contrast, under the optimized reaction conditions employing Ph-BPE as the ligand, the coupled product bearing adjacent tertiary and quaternary stereocenters (**4a**) formed in 97% yield with excellent diastereo- and enantiocontrol (>20:1 dr, 99.5% ee).

We next set out to examine the substrate scope of this enyne-ketone coupling process (Fig. 2). Electron-rich and electron-deficient acetophenones were successfully transformed into the corresponding tertiary alcohols (**5b** and **5c**) in good yield with excellent diastereo- and enantioselectivity. Ketones bearing aryl bromide (**5d**) and chloride (**5e**) functional groups were also compatible with our protocol, permitting further transformations of the alcohol product using cross-coupling technologies. Additionally, a variety of nitrogen heterocycles that are frequently found in medicinally active agents, including a pyrrole (**5h**), a thiazole (**5i**), a pyrazole (**5j**), a pyridine (**5k**), a thiophene (**5x**) and a carbazole (**6a**), could be applied with this stereoselective coupling. Appreciably less reactive aliphatic ketones could also be effectively converted into tertiary aliphatic alcohols with excellent enantioselectivity (**5l–5o**), further highlighting the excellent reactivity exhibited by this Ph-BPE-based alkylcopper intermediate. An α-ketoester (**5q**) and an enone (**5r**) also underwent the asymmetric carbonyl addition with outstanding enantiocontrol. Moreover, the current process displayed a broad scope with respect to the enyne fragment. In addition to enynes bearing aromatic substituents, aliphatic enynes were also readily accommodated under these reaction conditions (**5h, 5i, 5r–5v, 6a–6e**). Finally, substitution at the olefinic terminus of the enyne component (**5y**) was found to be compatible with our protocol.

The exceptional mildness of the reaction conditions required for the current asymmetric nucleophilic addition allowed for use of substrates possessing sensitive functional groups that are incompatible with preformed organometallic reagents. A variety of sensitive functional groups, such as a thioether (**5f**), a sulfonamide (**5t**), a methyl ester (**5q**), an alkyl tosylate (**5u**), an alkyl chloride (**5v**) and a tertiary amine (**5w**), were tolerated under these reaction conditions. Most usefully, various basic and acidic functional groups, including a secondary amine (**6a**), a secondary amide (**6b**), an alcohol (**6c**), a phenol (**6d**) and a carboxylic acid (**6e**), were compatible with our protocol, thereby eliminating the need for inefficient protection and deprotection sequences often required by traditional carbonyl alkylation methodologies that use stoichiometric organometallic reagents. The relative and absolute stereochemistry of the addition product were determined by X-ray crystallographic analysis of **5f**.

In addition, this copper-catalyzed enantioselective coupling process proved to be scalable and required a very low catalyst loading (Fig. 3(A)). We were able to perform a 50 mmol (13 gram) scale reaction to prepare **5c** using only 0.2 mol% $Cu(OAc)_2$ and 0.4 mol% (*S,S*)-Ph-BPE without lowering the yield or the stereoselectivity of the transformation (82% yield, 10:1 dr, 98% ee). The scalability and robustness of this copper-catalyzed asymmetric transformation illustrates its potential application in the manufacture of highly enantioenriched fine chemicals on an industrial scale. Furthermore, these synthetically versatile homopropargyl alcohols prepared by our method could be easily transformed into a variety of useful molecular architectures. For example, hydrogenation and CuH-catalyzed *cis*-selective semi-reduction of alkyne **5c** (35) furnished saturated alcohol **9a** and homoallylic alcohol **9b** as a single stereoisomer, respectively. These reactions allowed for the synthetic equivalent of asymmetric addition to ketones with nucleophiles derived from terminal aliphatic olefins and 1,3-dienes in a highly regio-, diastereo- and enantioselective fashion.

The late-stage modification of medicinally relevant molecules allows for the rapid generation of analogous bioactive compounds and facilitates structure-activity relationship studies. To further demonstrate the synthetic utility of our method in this context, we selected two widely prescribed pharmaceutical agents, terbinafine (Lamisil, **10a**) and fenofibrate (Tricor, **10b**), and subjected them to our coupling protocol (Fig. 3(B)). Both substrates were effectively converted into the tertiary alcohol adduct with excellent levels of enantioselectivity (99% ee and 99% ee, respectively), further highlighting the utility of our method in a more complex setting.

Energies were calculated at the M06/SDD–6-311+G(d,p)/SMD(cyclohexane) level of theory with geometries optimized at the B3LYP/SDD–6-31G(d) level.

We also performed DFT calculations to investigate the mechanism and the origin of stereoselectivity of this copper-catalyzed enyne-ketone coupling. The computed free energy profile of the overall catalytic cycle is shown in Fig. 4(A) (See Supplementary Materials for a detailed discussion). Our computational studies suggest that the initial enyne hydrocupration is irreversible and thus constitutes the enantiodetermining step for this reaction. The hydrocupration involves a four-membered transition state in which the delivery

of the hydride and the formation of the Cu–C bond take place simultaneously. To better understand the enantioinduction that occurs during the hydrocupration event, we divided the coordination space of this C_2 symmetric copper catalyst into four quadrants (Fig. 4(B)). The phenyl substituents on the ligand's phospholane moieties in quadrants II and IV point out of the plane of the paper, rendering these two quadrants sterically inaccessible for a substrate coming toward this plane. In contrast, quadrants I and III are relatively unencumbered with the two phenyl groups pointing away from the plane of the paper. In **TS2a**, the unfavorable repulsion between the olefin's alkynyl substituent and the catalyst's sterically crowded quadrant IV is avoided, thereby leading to the preferential formation of the (*S*)-propargylcopper intermediate **13a** with an activation free energy that is 5.5 kcal/mol lower than the disfavored transition state **TS2b**.

Subsequent 1,3-isomerization of the highly enantioenriched propargylcopper **13a** proceeds in a stereospecific fashion, affording an axially chiral allenylcopper intermediate **14** as a single diastereomer. Furthermore, this 1,3-shift is found to be facile and exergonic (ΔG = −2.6 kcal/mol), thus setting the stage for the ketone addition involving a six-membered cyclic transition state (Fig. 4(C)). In the lowest-energy transition states of this diastereoselectivity-determining step (**TS4a** and **TS4b**), the phenyl group of the ketone is *anti* to the allenylcopper (*i.e.*, *gauche* to the Me and H substituents on distal terminus of the allenyl moiety) to avoid close contact with the Ph-PBE ligand (see Supplementary Materials for details). In the preferred diastereomeric transition state **TS4a**, the chiral allenyl moiety (highlighted in green) attacks the (*Re*)-face of the ketone, placing the hydrogen atom of the allene *gauche* to the methyl and the phenyl groups flanking the carbonyl group. In the disfavored (*Si*)-face attack transition state **TS4b**, the bulkier Me group of the allene is *gauche* to the two carbonyl substituents. In addition, **TS4b** is also destabilized by the proximity of the allenyl moiety with the Ph-BPE ligand as evidenced by a relatively short H···H distance of 2.32 Å. Taken together, the substrate-substrate and ligand-substrate interactions combine to confer high levels of diastereocontrol in the C–C bond forming event leading to the homopropargyl copper alkoxide (**15a**) and eventually the homopropargyl alcohol product (**16**).

In preliminary studies we have demonstrated that a range of other structurally diversified olefins could also be utilized in this mode of catalysis in a highly enantioselective fashion (Fig. 3(C)). By applying slightly modified reaction conditions, a related process with a cyclic diene (**17**) and acetophenone (**1**) afforded tertiary alcohols possessing contiguous tertiary and quaternary stereocenters in > 10:1 dr and 94% ee. Styrenes (**19**), a class of abundant feedstock chemicals possessing moderate levels of reactivity towards hydrometalation, were also effectively converted into the tertiary alcohol adduct with excellent enantiocontrol (95% ee). Furthermore, thione **22**, which could easily be synthesized from the parent ketone, was also suitable for this coupling process. The highly enantioselective preparation of tertiary thiol **23** (> 10:1 d.r., 96% ee) using our strategy represents a synthetically valuable advance, given that enantioenriched thiols are prevalent structural motifs in a variety of small molecule therapeutics and only a handful of enantioselective methods are available for their preparation (36).

Our strategy represents a departure from the use of preformed organometallic reagents in classic carbonyl addition chemistry. Furthermore, this C–C bond forming process readily accommodates a wide range of olefin and ketone coupling partners, allowing for the highly stereoselective preparation of alcohols bearing adjacent tri- and tetrasubstituted stereogenic centers. We anticipate that the design of optimal ligand scaffolds will enable the transformation of a broader range of unactivated olefins, ultimately delivering a powerful tool for the asymmetric addition of olefin-derived nucleophiles to carbonyls that will be of broad synthetic utility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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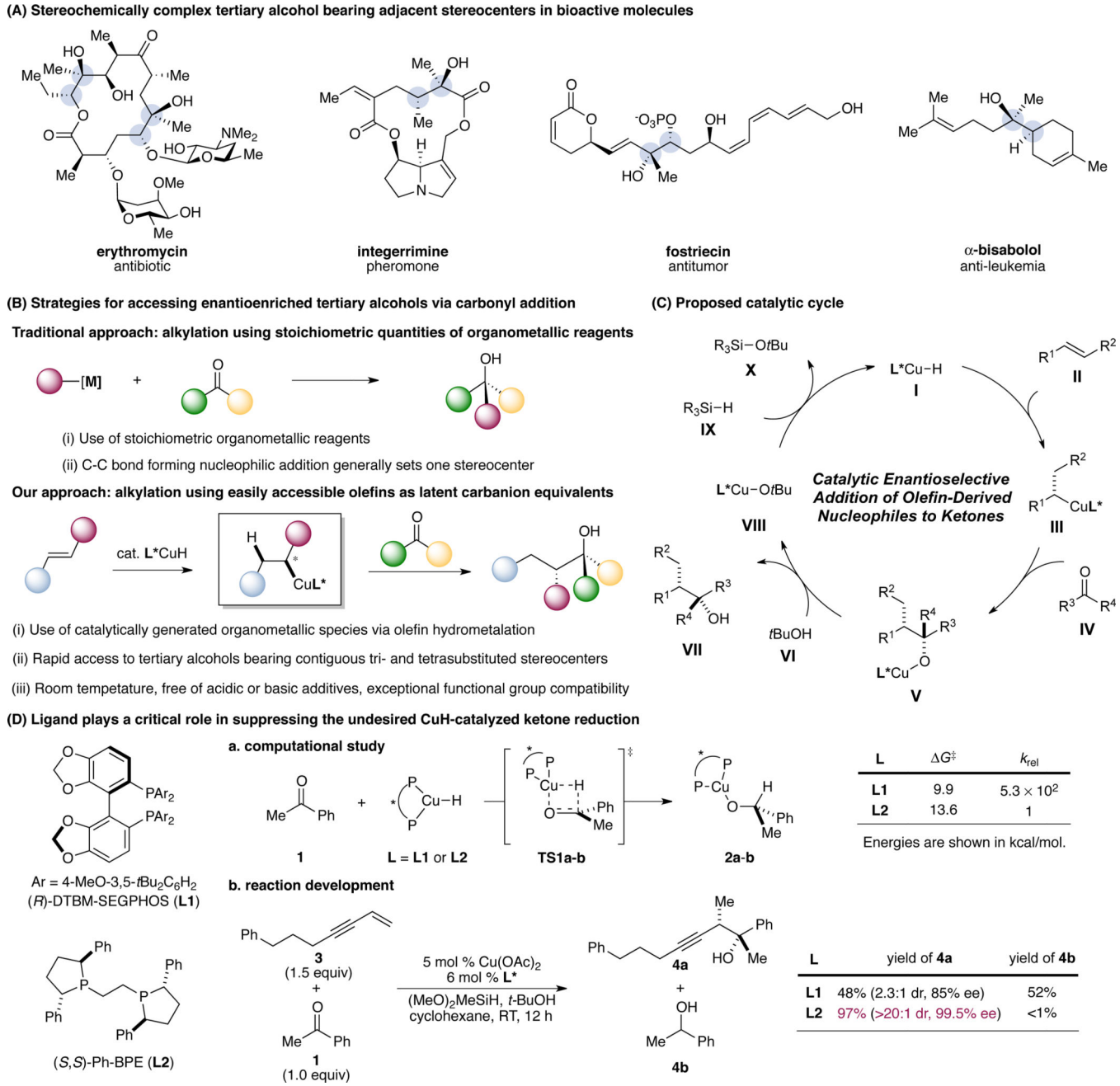

Fig. 1. Asymmetric addition of olefin-derived nucleophiles to ketones using a copper-hydride catalyst

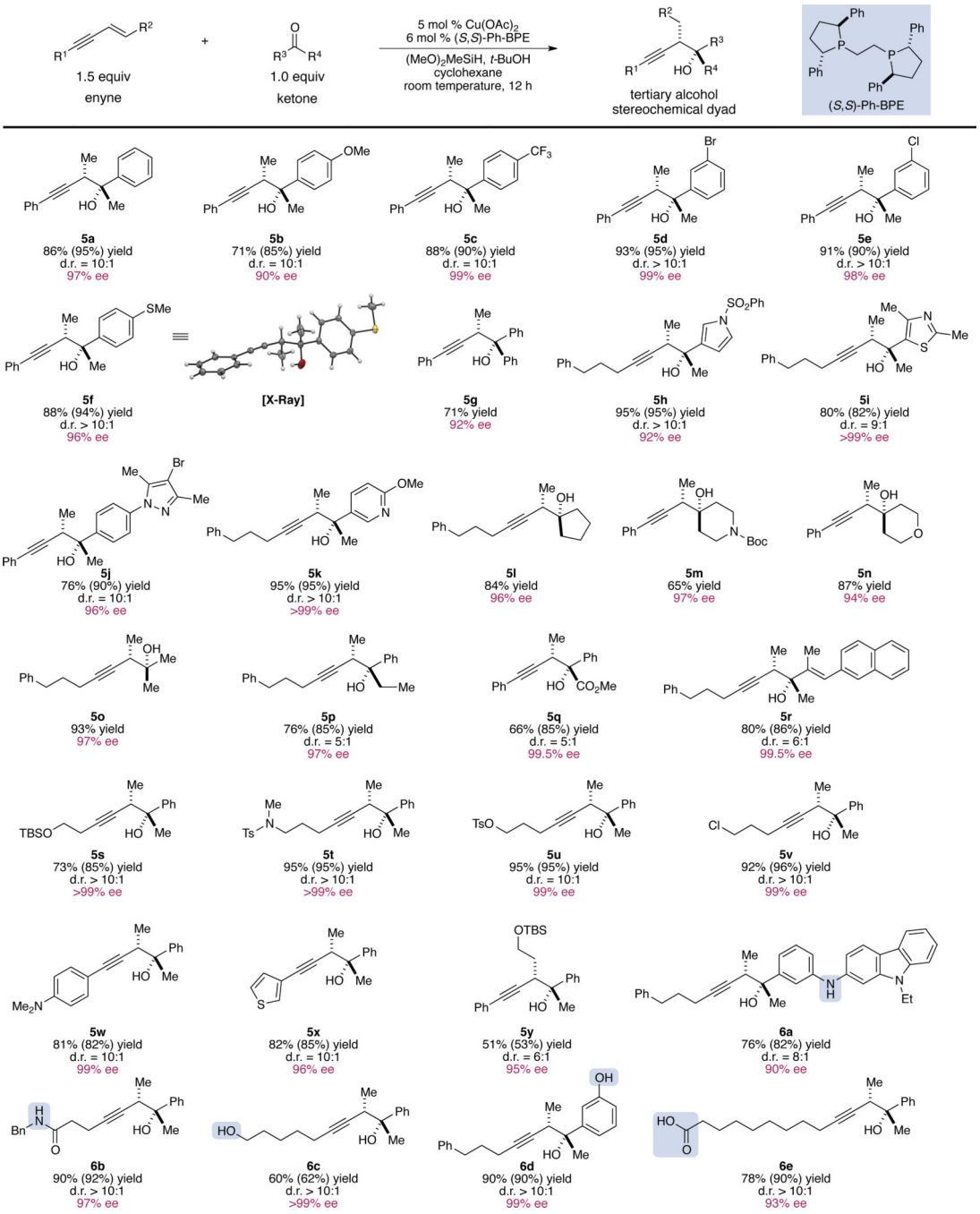

Fig. 2. Substrate scope of the copper-catalyzed diastereo- and enantioselective addition of enyne-derived nucleophiles to ketones

Reaction conditions: $Cu(OAc)_2$ (0.5 mol%), (*S,S*)-Ph-BPE (6 mol %), ketone (0.5 mmol, 1.0 equiv), enyne (0.75 mmol, 1.5 equiv), *t*-BuOH (0.5 mmol, 1 equiv), $(MeO)_2MeSiH$ (2.5 mmol, 5 equiv), room temperature, 12 h. Yields refer to isolated yields of the major diastereomer (>10:1 dr). Yields in parentheses refer to the combined yields of two diastereomers determined by ^1H NMR spectroscopy calibrated using an internal standard. The diastereomeric ratios (dr) were determined by ^1H NMR spectroscopic analysis of the

crude reaction mixture and the enantiomeric excess (ee) values were determined by chiral HPLC analysis.

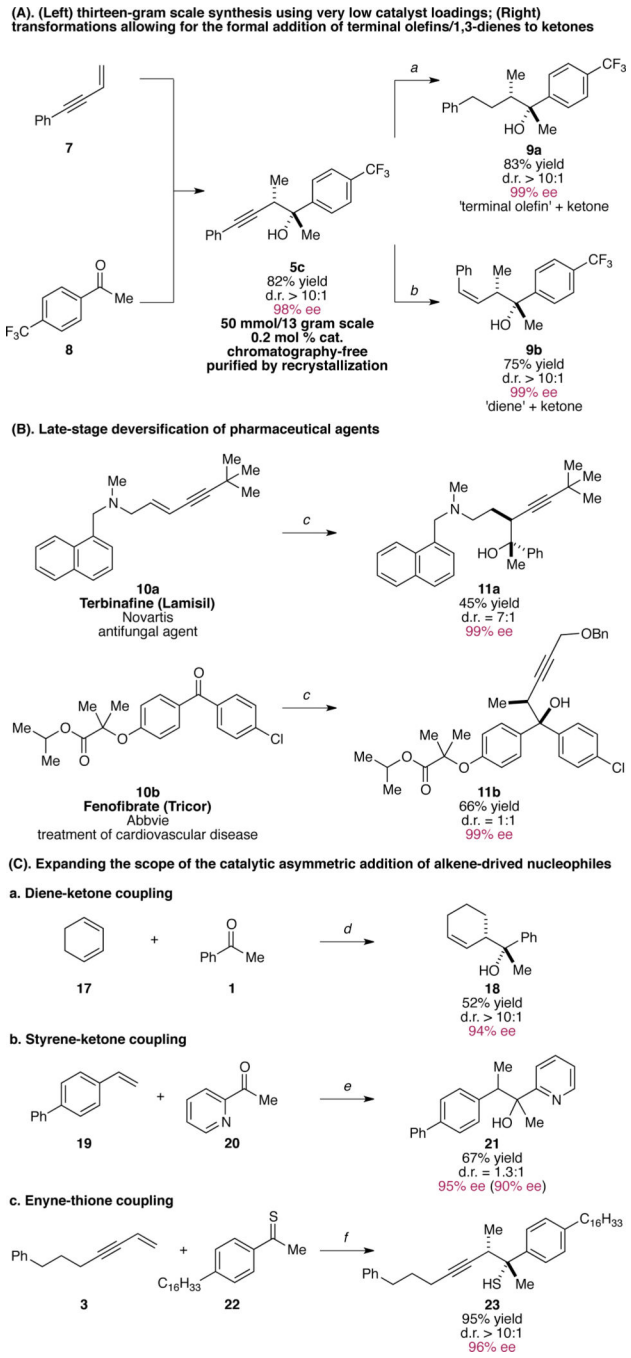

Fig. 3. Application and further extension of the copper-catalyzed asymmetric addition of olefin-derived nucleophiles

a. $Pd(OH)_2/C$, H_2 (balloon pressure), MeOH, RT, 12 h. *b*. 5 mol % IPrCuCl, 6 mol % LiO*t*Bu, $(MeO)_2MeSiH$, *t*-BuOH, toluene, RT, 48 h. *c*. 5 mol % $Cu(OAc)_2$, 6 mol % (*S,S*)-Ph-BPE, $(MeO)_2MeSiH$, *t*-BuOH, cyclohexane, room temperature, 12 h. *d*. 5 mol % $Cu(OAc)_2$, 6 mol % (*S,S*)-Ph-BPE, **17** (2.0 equiv), **1** (1.0 equiv), $(MeO)_2MeSiH$, THF, RT, 12 h. *e*. 5 mol % $Cu(OAc)_2$, 6 mol % (*S,S*)-Ph-BPE, **19** (2.0 equiv), **20** (1.0 equiv), $(MeO)_2MeSiH$, MTBE, room temperature, 12 h. *f*. 5 mol % $Cu(OAc)_2$, 6 mol % (*S,S*)-Ph-

BPE, **3** (1.5 equiv), **22** (1.0 equiv), $(MeO)_2MeSiH$, *t*-BuOH, cyclohexane, room temperature, 12 h.

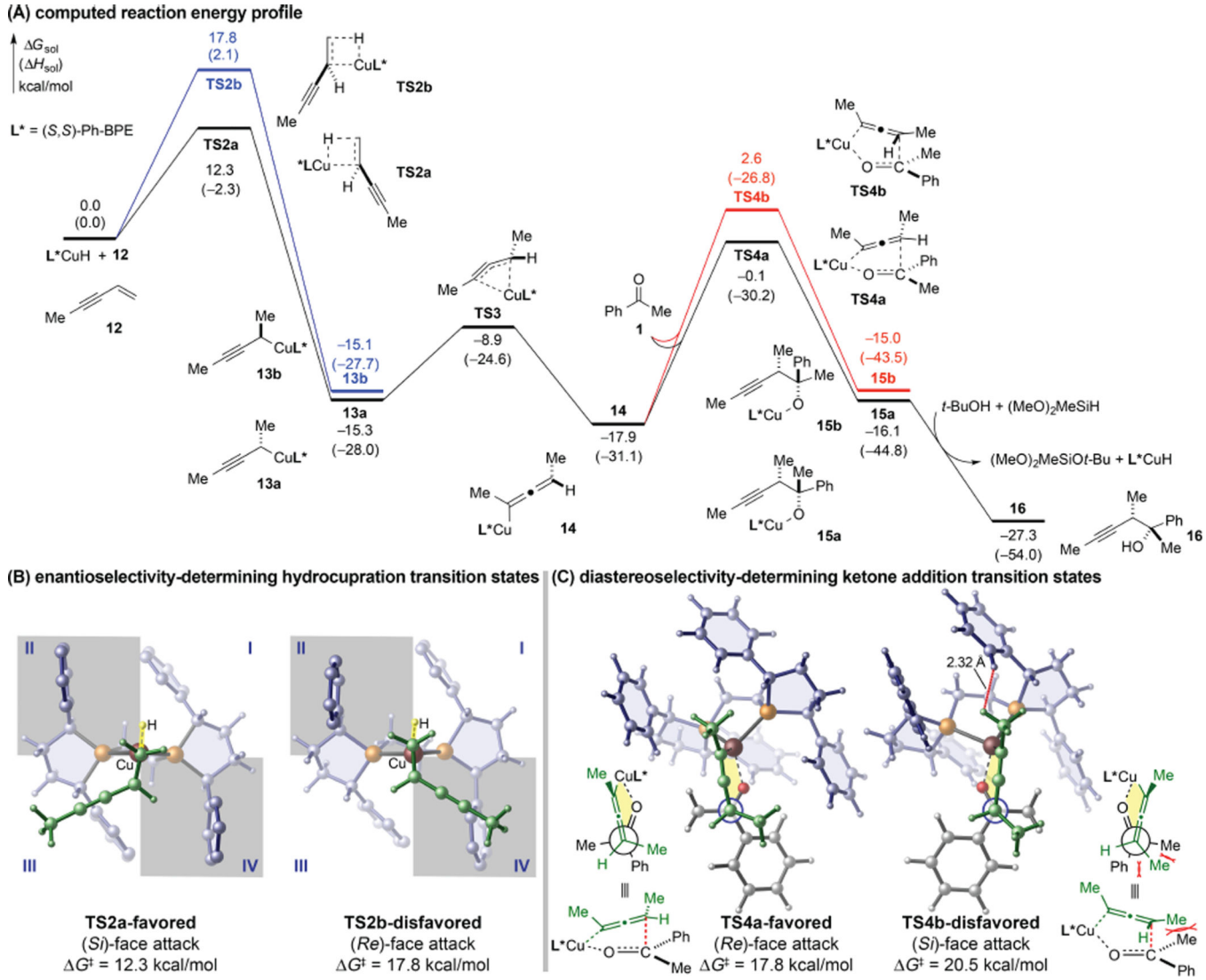

Fig. 4. DFT-calculated enantio- and diastereochemical determining transition states for the copper-catalyzed addition of an enyne (12)-derived nucleophile to ketone 1