ACCOUNTS of chemical research

Article

Cite This: Acc. Chem. Res. 2020, 53, 170−181

pubs.acs.org/accounts

Copper(I)-Catalyzed Asymmetric Reactions Involving Radicals

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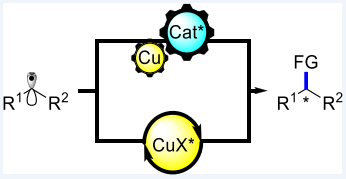
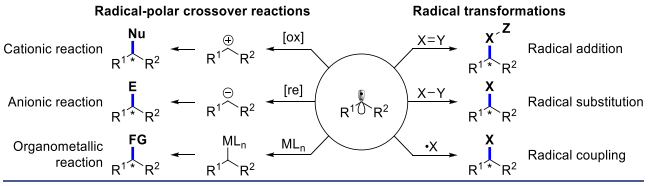
CONSPECTUS: Asymmetric functionalization of alkyl radicals represents a robust yet underdeveloped method for efficient construction and decoration of carbon skeletons in chiral organic molecules. In this field, we have been inspired by the excellent redox, alkyl radical trapping, and Lewis acidic properties of copper to develop several catalytic modes for asymmetric reactions involving alkyl radicals. At the beginning, we discovered tandem radical hydrotrifluoromethylation of unactivated alkenes and enantioselective alkoxylation of remote C(sp^3)−H bonds by copper/chiral phosphate relay catalysis. This success has stimulated us to develop an asymmetric three-component 1,2-dicarbofunctionalization of 1,1-diarylalkenes using a similar strategy via radical intermediates. Meanwhile, we also discovered a copper/chiral secondary amine cooperative catalyst for asymmetric radical intramolecular cyclopropanation of alkenes using α-aldehyde methylene groups as C1 sources. The trapping of alkyl radical intermediates by Cu^{II} species during the reaction was essential for the chemoselectivity toward cyclopropanation. Encouraged by the efficient enantiocontrol with chiral phosphate and the effective trapping of alkyl radicals with Cu^{II} species, we then sought to develop copper/chiral phosphate as a single-electron-transfer catalyst for asymmetric reactions involving alkyl radicals. Subsequently, we successfully achieved a series of highly enantioselective 1,2-aminofluoroalkylation, -aminoarylation, -diamination, -aminosilylation, and -oxytrifluoromethylation of unactivated alkenes. The key for high enantioinduction was believed to be the effective trapping of alkyl radicals by Cu^{II}/chiral phosphate complexes. Besides, an achiral pyridine ligand was found to be indispensable for achieving high enantioselectivity, presumably via stabilization of Cu^{III} species in the 1,2-alkoxytrifluoromethylation reaction. This discovery reminded us of tuning the redox properties and chemoreactivity of copper centers with an ancillary ligand. As a result, we subsequently identified cinchona alkaloid-derived sulfonamides as novel neutral-anionic hybrid ligands for simultaneous chemo- and enantiocontrol. We thus accomplished highly enantioselective 1,2-iminoxytrifluoromethylation of unactivated alkenes under the catalysis of copper/cinchona alkaloid-derived sulfonamide ligand, affording trifluoromethylated isoxazolines in high enantiomeric excess. Our copper-catalyzed asymmetric reactions with alkyl radicals provide expedient access to a diverse range of valuable chiral molecules with broad application potential in areas of organic synthesis, medicine, agrochemical, and material sciences.



1. INTRODUCTION

Transformations involving radical species have fascinated organic chemists for decades due to their ready accessibility, robust reactivity, excellent chemoselectivity, and wide functional group tolerance.[1] In particular, alkyl radical functionalization reactions have been well established as one of the most fundamental tools for the construction and decoration of carbon skeletons of a broad range of natural products, bioactive molecules, and functional materials. In this respect, versatile pathways have been developed, which can be roughly classified into two categories: (i) radical transformations that include radical addition, substitution, and coupling (Scheme 1, right) and (ii) radical-polar crossover reactions via radical oxidation to carbocation, reduction to carbanion, or trapping by transition metal to organometallics (Scheme 1, left). Despite these advances in functionalization of alkyl radicals, the development of corresponding enantioselective versions of these reactions has lagged far behind that of polar reactions. The major reason is their commonly low reaction barriers that readily lead to significant racemic background reactions. In addition, such low reaction barriers also prohibit a reasonable energy distribution

Scheme 1. Reaction Pathways for Alkyl Radical Functionalization



of different transition state stereoisomers, which is mandatory for high stereoselectivity. The situation for minimally functionalized alkyl radicals, e.g., simple benzylic or even pure alkyl-substituted ones, is even worse: the radicals lack vicinal polar substituents to form covalent bonds and/or noncovalent interactions with chiral catalysts for effective enantiodiscrimination. Nonetheless, over the past several decades, some efficient catalytic strategies using Lewis acid, transition metal, or organocatalyst have been elegantly established for highly enantioselective

Received: July 16, 2019
Published: October 28, 2019

DOI: 10.1021/acs.accounts.9b00381
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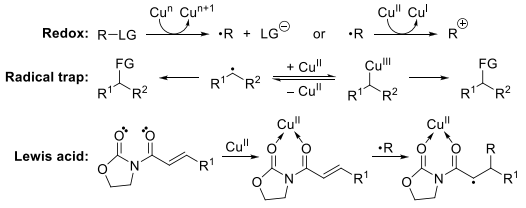
functionalization of alkyl radicals.[2−4] In particular, Fu and others have pioneered in using chiral nickel complexes to effectively trap those minimally functionalized alkyl radicals for highly enantioselective transformations.[5−9]

Copper is an appealing transition metal for catalysis[10] in mainly two aspects: (i) The abundance of copper is high and costs for copper catalysts are generally low. (ii) Copper is biologically less toxic than many other transition metals, which is of vital importance for applications in drug discovery.[11] Accordingly, researchers have made substantial efforts in developing copper-catalyzed asymmetric reactions with radical intermediates.[12−22] This field has been pioneered by the early landmark works on asymmetric Kharasch−Sosnovsky,[15] biaryl coupling,[12] and alkyl radical nucleophilic addition reactions.[16] Recent efforts have been directed toward alkene difunctionalization,[13,14,17,21,22] C−H functionalization,[13] and alkyl halide cross-coupling reactions.[18,20] Basically, copper is an excellent redox catalyst (Scheme 2, top): low-valent copper readily

Scheme 2. Different Roles of Copper in Transformations Involving Radicals



reduces oxidative precursors to radicals for reaction initiation and Cu^{II} is able to effectively oxidize alkyl radicals to carbocations.[23] More importantly, the metalloradical Cu^{II} is capable of reversibly trapping an alkyl radical[23−26] to form a high-valent Cu^{III} complex (Scheme 2, middle).[27,28] The benefits for this process are two-fold. First, the highly reactive alkyl radical can be effectively sequestered in the form of a relatively stable Cu^{III} complex. Thus, the concentration of the free alkyl radical decreases and the chemoselectivity for subsequent radical transformations might be enhanced thereafter. Second, the process entails radical-polar crossover that brings the alkyl radical to the realm of organometallic reactions, which, like that of nickel,[5,6] is invaluable for the challenging stereocontrol over minimally functionalized alkyl radicals. Besides, Cu^{II} is a good Lewis acid, which may enhance the electrophilicity of radical acceptors[16] or related reactants (Scheme 2, bottom).

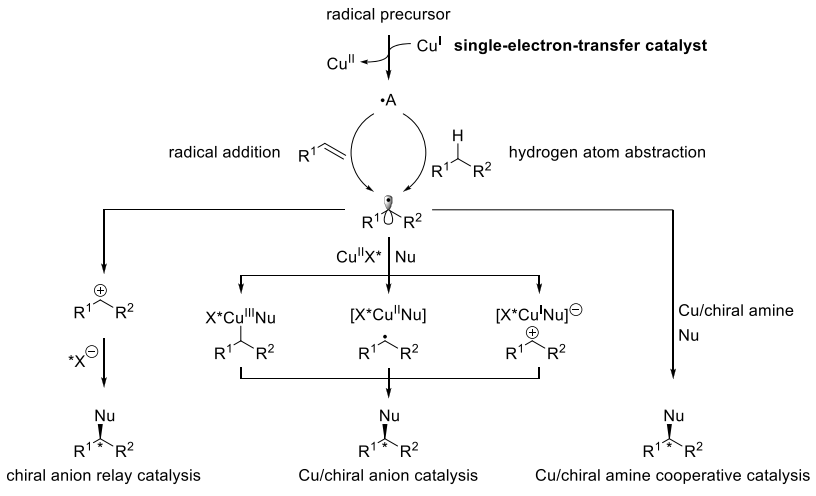
Bearing these in mind, we have initially developed copper/chiral anion relay catalysis[29] for tandem radical/carbocationic reactions (Scheme 3, left). Next, we capitalized on the feature of Cu^{II} for stabilizing alkyl radicals via radical trapping to develop copper/chiral amine cooperative catalysis[29] (Scheme 3, right). Recently, we have successfully devised copper/chiral anion single-electron-transfer (SET) catalysts that exhibited high levels of stereocontrol over the challenging minimally functionalized alkyl radicals via a Cu^{III} complex, or outer-sphere radical substitution, or a zwitterionic intermediate (Scheme 3, middle). It should be noted that neutral chiral Lewis bases, such as oxazolines,[13−16,19,21,22] phosphines,[17,18,20] and amines,[12] have long been recognized as superior ligands for copper-catalyzed asymmetric transformations involving radicals. In comparison, our works highlight the great potential of proper coordination of chiral counteranions or anionic ligands with copper for realizing highly enantioselective reactions via radical intermediates. Thus, our developed catalyst systems provide excellent complementary approaches to those based on copper/neutral ligand catalysts. We will discuss these works in detail in the following sections.

2. COPPER(I)-CATALYZED ALKENE FUNCTIONALIZATION INVOLVING ASYMMETRIC RELAY CATALYSIS WITH CHIRAL PHOSPHATE

We have long been interested in trifluoromethylation of unsaturated bonds[30,31] and asymmetric catalysis with chiral Brønsted acid, particularly chiral phosphoric acid (CPA).[32−37] During this process, we have initially discovered that Cu^{I}/**CPA1** efficiently catalyzed tandem 1,2-hydrotrifluoromethylation of unactivated alkenes and enantioselective remote C(sp^3)−H alkoxylation with the Togni's reagent **T1** as a trifluoromethyl source (Scheme 4).[38] The reaction exhibited excellent tolerance of various carboxylamide substrates **1** with either a benzo-fused or *gem*-dialkyl-substituted tether. Functionalized alcohols were also suitable for this transformation.

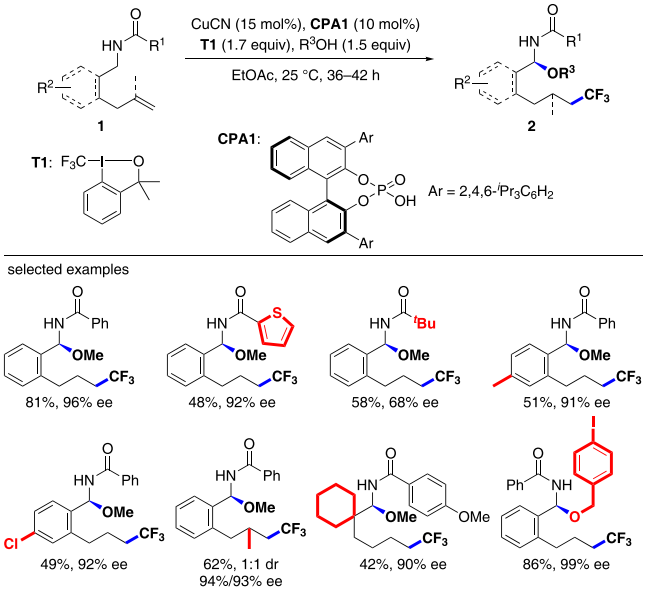
In addition, we have also realized a similar tandem 1,2-hydrotrifluoromethylation of unactivated alkenes and enantioselective remote C(sp^3)−H indolylation reaction (Scheme 5).[39] Thus, a range of electron-rich indoles were well accommodated in the presence of Cu^{I} and **CPA2**. In this case, the Togni's

Scheme 3. Different Strategies for Copper(I)-Catalyzed Asymmetric Reactions Involving Radicals

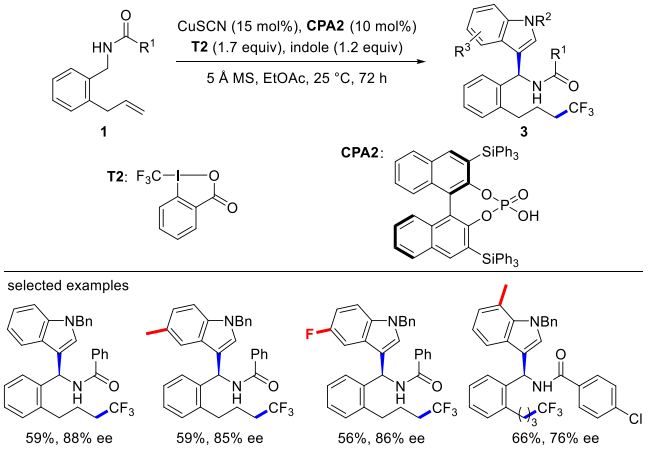


DOI: 10.1021/acs.accounts.9b00381
Acc. Chem. Res. 2020, 53, 170−181

Scheme 4. Enantioselective Remote C(sp^3)−H Alkoxylation Triggered by Radical Trifluoromethylation of Unactivated Alkenes



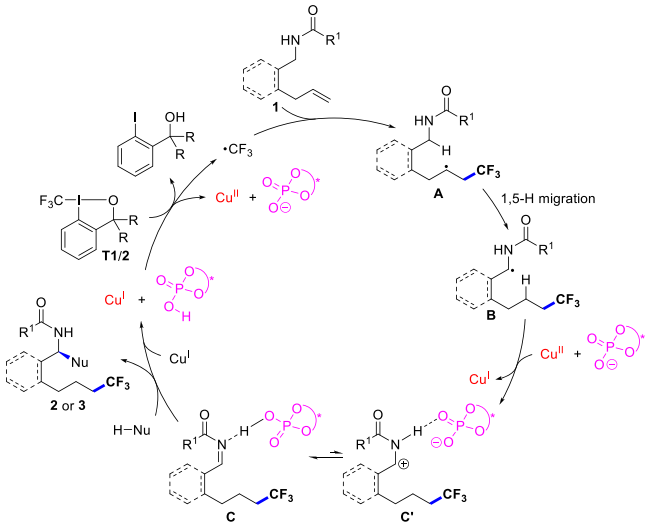
Scheme 5. Enantioselective Remote C(sp^3)−H Indolylation Triggered by Radical Trifluoromethylation of Unactivated Alkenes



reagent **T2** as the trifluoromethyl source afforded higher enantioselectivity compared with **T1**. This result is in stark contrast to that obtained in the aforementioned alkoxylation reaction,[38] where **T2** was inferior to **T1** in terms of product enantioselectivity. The difference might be accounted for by the lability of the N,O-aminal products toward the carboxylic acid side product from **T2**.

The subsequent mechanistic study revealed reaction inhibition by radical inhibitors, such as butylated hydroxytoluene (BHT) or (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). Also, TEMPO−CF_3 was isolated in the latter case, supporting a radical trifluoromethylation process. In addition, the deuterium-labeling experiment indicated an intramolecular H-migration process, on which an intramolecular kinetic isotopic effect (KIE) of 4.0 was observed. All these results suggested a radical hydrogen migration to afford an α-amino alkyl radical. In this sense, these reactions represent a rare example of enantioselective C(sp^3)−H functionalization via hydrogen atom transfer.[40] On the basis of these and other mechanistic experiments as well as literature precedents, an overall mechanism was proposed, shown in Scheme 6. The catalytic cycle starts with

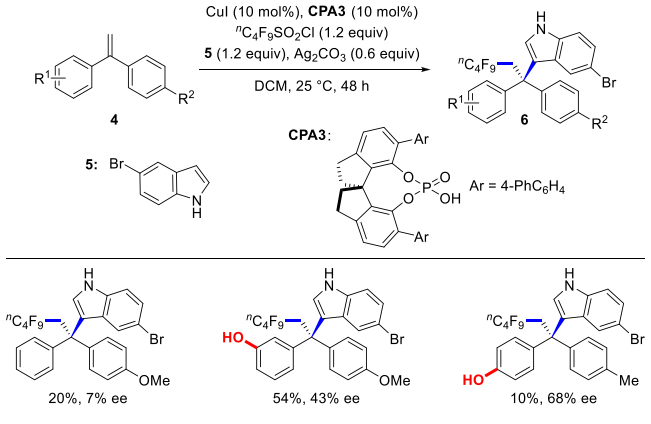
Scheme 6. Proposed Mechanism for Enantioselective Remote C(sp^3)−H Functionalization



single-electron reduction of Togni's reagents (**T1**/**T2**) by Cu^I together with CPA. Next, the thus generated trifluoromethyl radical adds to the alkene substrate **1** to afford alkyl radical **A**. Further intramolecular radical 1,5-hydrogen migration transforms **A** to more stable radical **B**. The Cu^{II} formed in the first redox step subsequently oxidizes this radical **B** to a N-stabilized carbocation and itself reverts back to Cu^I. Finally, the carbocation is quenched by a nucleophile under the stereocontrol of chiral phosphate via intermediates **C** or **C′**. Thus, products **2**/**3** are delivered and the CPA is regenerated.

Inspired by the aforementioned works, we have been intrigued to take advantage of this radical-carbocation crossover together with copper/chiral anion relay catalysis for developing asymmetric 1,2-difunctionalization of unactivated alkenes.[30,31,41] We started the investigation by exploring potentially suitable alkene substrates for such a reaction. Fortunately, we found that 1,1-diarylalkenes with a hydroxy group on either the *meta* or *para* positions of one of the two aryl rings were necessary for reasonable enantioinduction (Scheme 7). We speculated that the hydroxy group might have formed a directing hydrogen bond with chiral phosphate, thus assisting the presumed

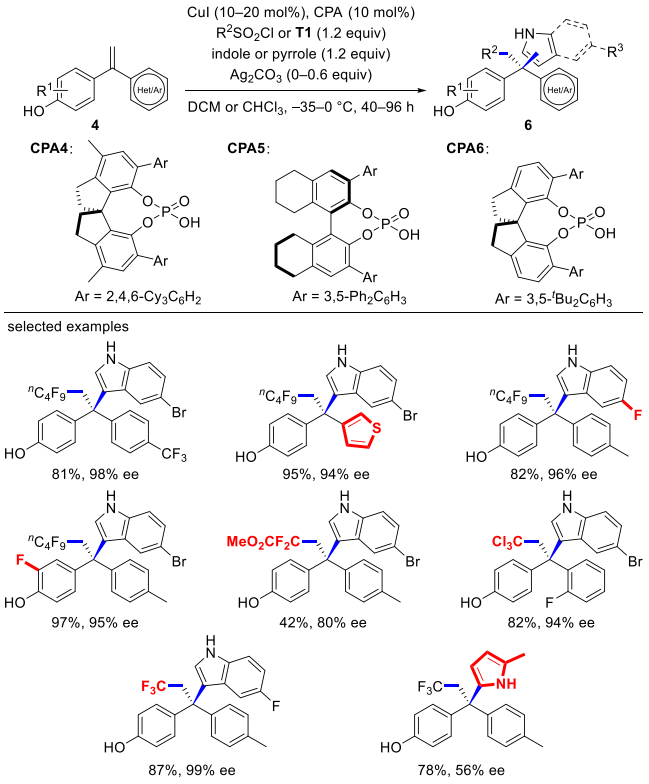
Scheme 7. Initial Exploration on Alkene Substrates



DOI: 10.1021/acs.accounts.9b00381
Acc. Chem. Res. 2020, 53, 170−181

ion-pairing interaction in inducing enantioselectivity.[42] After further systematic optimization of reaction conditions, we have been able to realize a highly efficient and enantioselective 1,2-dicarbofunctionalization of 1,1-diarylalkenes (Scheme 8).

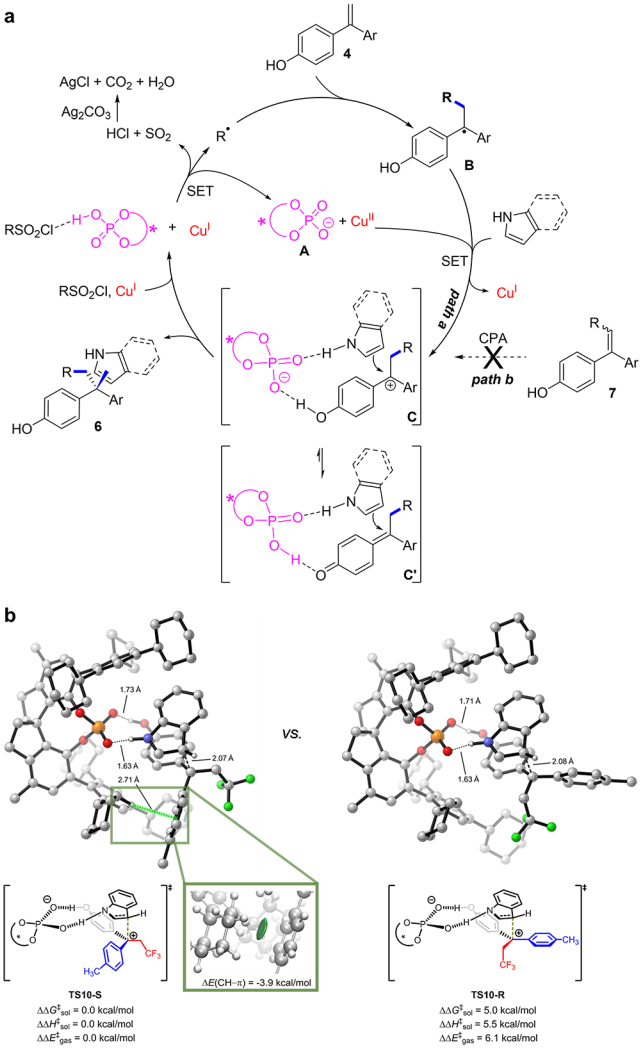
Scheme 8. Asymmetric Three-Component Radical-Initiated 1,2-Dicarbofunctionalization of Alkenes



The reaction was compatible with alkene substrates bearing a range of aryl or heteroaryl rings. In addition, both haloalkylsulfonyl chlorides and the Togni's reagent **T1** were viable alkyl radical precursors. Further, a series of 5-substituted indoles as well as a pyrrole were suitable nucleophiles for this reaction.

Subsequent mechanistic experiments suggested facile formation of $^{n}C_4F_9$ radicals promoted by CPA. In addition, they also indicated multiple hydrogen-bonding interactions between the indole nucleophile, the hydroxy-bearing alkene substrate, and the chiral phosphate for efficient enantiocontrol. Furthermore, experiments with scalemic CPA revealed a linear relationship between the ee values of the CPA and those of the product, thus suggesting only one CPA catalyst in the enantiodetermining step. Besides, control experiments also disproved a direct protonation pathway from internal alkene side products **7** to the desired products (Scheme 9a, path b). This result highlights the complementarity of the radical-carbocation pathway to the direct alkene protonation approach[43] for eliciting distinct carbocations. Accordingly, we have proposed a likely mechanism (Scheme 9a) similar to that for the enantioselective remote C(sp^3)–H functionalization (Scheme 6). The catalytic cycle involves sequential radical R$^\bullet$ generation, radical addition to alkene substrate **4**, oxidation of radical **B** to the carbocation, and enantioselective carbocation quenching by a nucleophile via intermediates **C** or **C′**. Our subsequent density functional theory (DFT) calculations on the enantiodetermining step supported the assumed hydrogen-bonding and ion-pairing interactions. More importantly, the calculations also revealed

Scheme 9. Mechanistic Proposal and DFT-Computed C–C Bond Formation Transition States



an important noncovalent CH–π interaction between the chiral phosphate and the substrate (Scheme 9b). These results showcased the significance of proper coordination of noncovalent interactions for high enantioinduction.

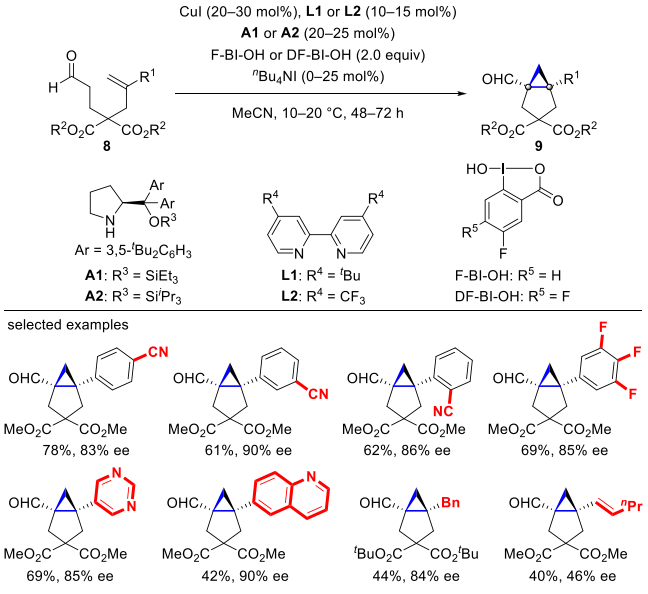
3. COPPER(I)/CHIRAL AMINE COOPERATIVE CATALYSIS FOR ASYMMETRIC CYCLOPROPANATION

Apart from the redox capability, another remarkable feature of Cu^{II} is its persistent metalloradical nature, which allows for efficient sequestration of transient alkyl radicals to enhance reaction selectivity.[26] On the basis of this notion, we have been able to develop a copper/chiral secondary amine cooperative catalyst system for asymmetric intramolecular radical cyclopropanation of 1,1-disubstituted alkenes (Scheme 10).[44] The reaction featured the use of α-aldehyde methylene groups as C1 sources. A panel of (hetero)aryl-, alkenyl-, and alkyl-substituted alkenes were compatible with the reaction. Thus, challenging chiral bicyclo[3.1.0]hexane compounds possessing two bridgehead quaternary all-carbon stereocenters were afforded with moderate to high enantioselectivity.

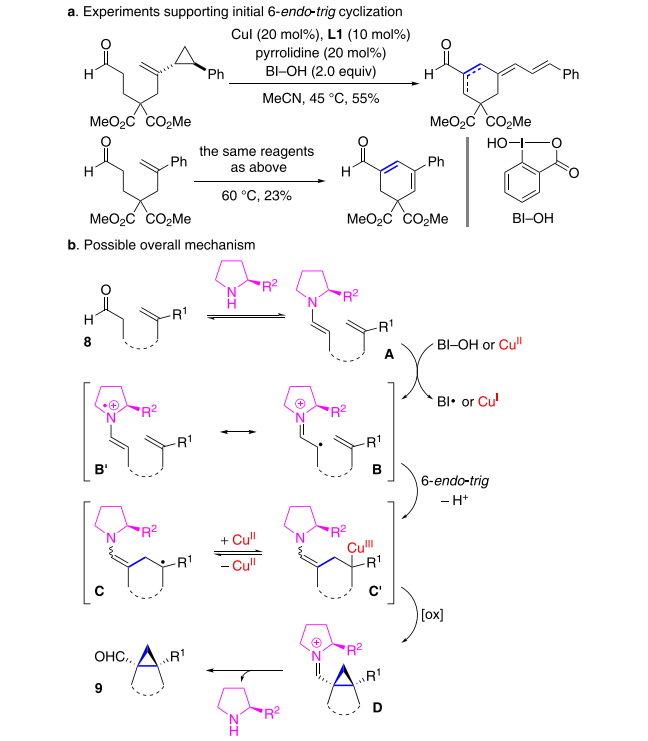
A series of radical inhibition, radical clock, and many other control experiments supported the formation of radicals **B**/**B′**

DOI: 10.1021/acs.accounts.9b00381
Acc. Chem. Res. 2020, 53, 170–181

Scheme 10. Asymmetric Intramolecular Radical Cyclopropanation of Alkenes



Scheme 11. Plausible Mechanism for Asymmetric Intramolecular Radical Cyclopropanation



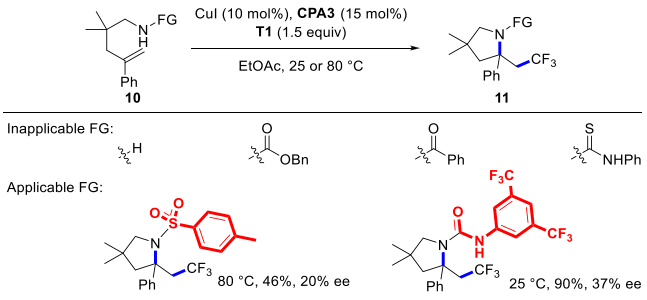
from the putative enamine intermediate **A** via oxidation by BI−OH (hydroxylbenziodoxole) or Cu^{II} (Scheme 11b). The subsequent radical 6-*endo*-*trig* cyclization to **C** was evidenced by the formation of six-membered ring products under similar racemic conditions (Scheme 11a). The trapping[23,24] of **C** by Cu^{II} to form **C′**[27,28] was believed to play an important role for maintaining high chemoselectivity toward cyclopropanation in the next step (Scheme 11b).[45] Otherwise, the reaction might suffer from side reactions such as tandem oxidation and deprotonation for alkene formation.[23] Thus, the alkyl radical **C** subsequently underwent 3-*exo*-*trig* cyclization under the control of the chiral secondary amine residue to provide the enantioenriched products upon further oxidation and hydrolysis (Scheme 11b).

4. COPPER(I)/CHIRAL ANION CATALYSIS FOR ASYMMETRIC 1,2-DIFUNCTIONALIZATION OF ALKENES INVOLVING RADICALS

4.1. Copper(I)/Chiral Phosphate Catalyst

As mentioned before, trapping of alkyl radicals by Cu^{II} could also lead to organometallic reactivity under appropriate conditions (Scheme 1).[23,24,27,28] In addition, the copper/chiral phosphate dual catalysts have provided excellent enantiocontrol in the tandem radical/carbocationic reactions discussed above.[38,39,41] Thus, we wondered whether such catalysts would exert direct enantiodiscrimination via trapping of an alkyl radical in the form of a Cu^{II}/chiral phosphate complex.[46] Given the importance of trifluoromethyl groups[47] and pyrrolidines in medicine, agrochemicals, and materials, we have become interested in developing trifluoromethyl radical-initiated asymmetric 1,2-aminotrifluoromethylation of unactivated alkenes.[48] At the beginning, we evaluated several different N-functional groups on alkenylamine substrates and observed marginal enantioselectivity with *p*-toluenesulfonyl and (3,5-ditrifluoromethylphenyl)-

Scheme 12. Initial Evaluation of Different Functional Groups on the Amine Nucleophile



aminocarbonyl groups (Scheme 12). These results have encouraged us to carried out further reaction optimizations, ending in the discovery of a highly enantioselective 1,2-aminotrifluoromethylation of unactivated alkenes (Scheme 13). Different substituents on the urea aryl rings, on the tethers, and on the alkenyl aryl rings were well tolerated. Particularly, a substrate without *gem*-disubstituents on the tether also underwent the desired reaction, albeit with low efficiency and moderate enantioselectivity.

Considering the significance of various fluoroalkyl groups in drug discovery,[47] we felt compelled to realize straightforward asymmetric 1,2-aminofluoroalkylation of unactivated alkenes using a similar approach as aforementioned.[49] The readily commercially available fluoroalkylsulfonyl chlorides seemed to be the best choice as precursors for a panel of diverse fluoroalkyl radicals. However, the stoichiometric hydrogen chloride side product would elicit not only strong racemic background reactions but also significant formation of hydroamination side products. To this end, we have managed to identify silver carbonate from various inorganic bases for efficient quenching of the hydrogen chloride. Thus, under the catalysis of CuBr and **CPA3**, a series of fluoroalkyl groups, such as $^nC_4F_9$, CF_2CO_2Me, CF_2H, and CF_3, were successfully introduced into enantioenriched pyrrolidines bearing distinct substituents (Scheme 14). The reaction was generally more robust than

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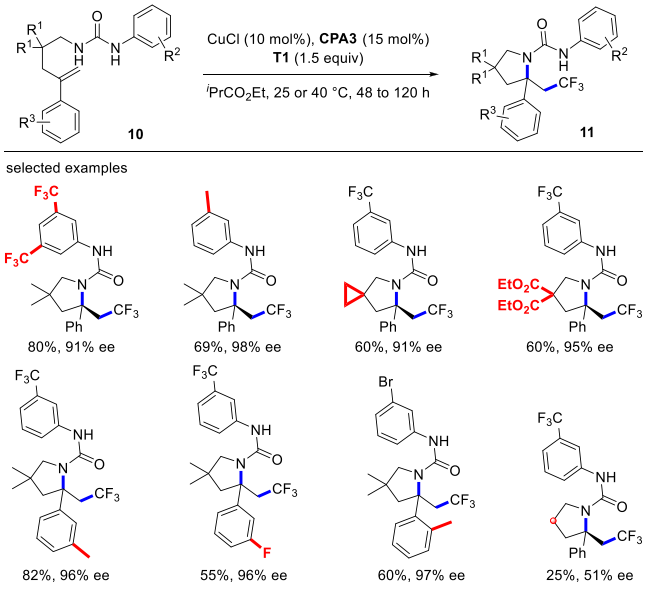
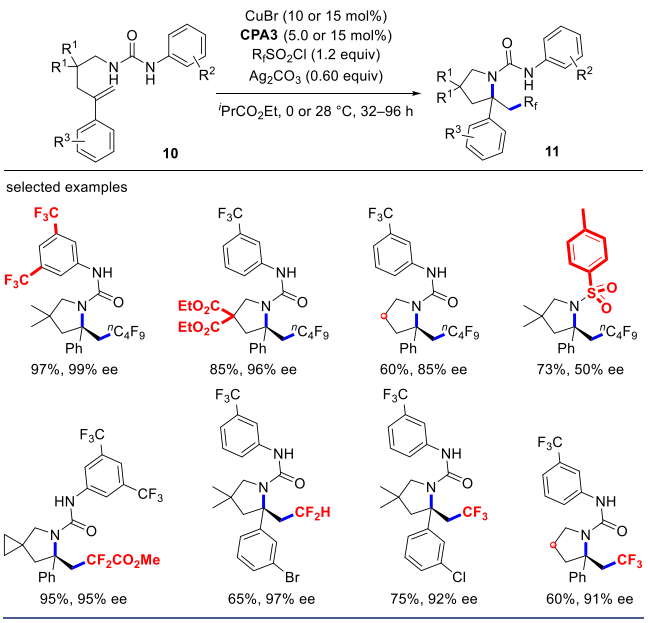
Scheme 13. Asymmetric 1,2-Aminotrifluoromethylation of Alkenes Involving Radicals



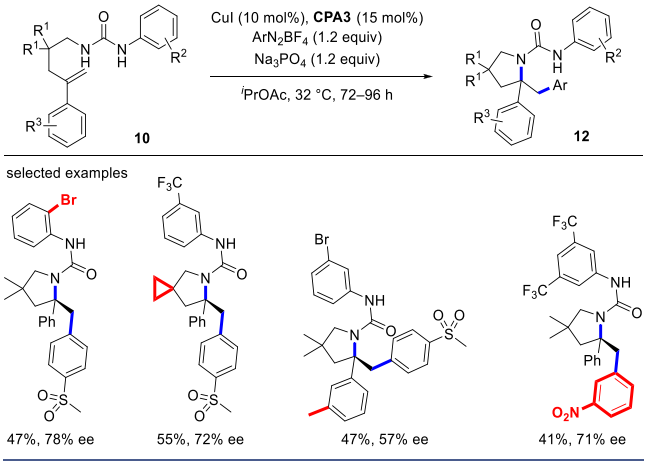
Scheme 14. Asymmetric 1,2-Aminofluoroalkylation of Alkenes Involving Radicals



that using the Togni's reagent **T1** as the fluoroalkyl source.[48] Thus, alkenylamine substrates without *gem*-disubstituents on the tethers also smoothly underwent the desired reaction in high enantioselectivity. More strikingly, *meta*-bromo and *meta*-chloro substituents on the alkenyl aryl rings were well tolerated under the current conditions while incompatible with the previous conditions.[48] In addition, a *p*-toluenesulfonyl protected alkenylamine substrate also afforded the corresponding 1,2-aminoperfluoroalkylated product in high yield with moderate ee. We tentatively ascribe the enhanced reactivity and stereoselectivity to the sequestration of halide ions from both the copper catalyst and the sulfonyl chloride by formation of insoluble silver salts. This might have resulted in more electron-deficient copper centers, which more readily bind to N nucleophiles in urea/sulfonamide substrates for subsequent C–N bond formation. In addition, the elevated electron deficiency of copper centers might have also promoted the final reductive elimination from a putative Cu^{III} species (e.g., structure **C** in Scheme 19b). As for the stereoselectivity, the more electron-deficient copper might have bound to or associated with both the substrates and the phosphate more tightly, resulting in closer and more effective substrate–phosphate interactions. We are currently carrying out further experimental and theoretical studies on this issue, and the results will be disclosed in due course.

Besides fluoroalkyl radicals, we have also found aryl radicals to be viable reactants under our copper/chiral phosphate catalysis with aryldiazonium salts as precursors (Scheme 15).[50]

Scheme 15. Asymmetric 1,2-Aminoarylation of Alkenes Involving Radicals



Thus, the asymmetric 1,2-aminoarylation of unactivated alkenes was successfully achieved. Also, a set of differently substituted alkenylamine substrates reacted well with *p*-sulfonylphenyl or *m*-nitrophenyl diazonium salts in moderate to good enantioselectivity.

The initial radicals are not limited to carbon radicals. In this respect, we have been tantalized by the challenge and significance of catalytic asymmetric diamination of unactivated alkenes for valuable enantioenriched vicinal diamine products. Other efforts in this field have been focused on transition-metal[51] or aryliodine(I) catalysts[52] for installation of amino groups masked with electron-withdrawing groups. These protecting groups are indispensable for tuning down the coordination capability and oxidation susceptibility of free amines, which would otherwise result in poisoning of transition-metal catalysts and/or undesired oxidation side reactions. In comparison, we have successfully employed *O*-acylhydroxylamines as suitable N-alkyl aminyl radical[53] precursors to accomplish direct incorporation of N-alkyl amino groups in asymmetric diamination of unactivated alkenes (Scheme 16).[54] Alkenylamine substrates with a *gem*-disubstituted or unsubstituted linear tether were well accommodated. Also, many oxidation-labile functional groups, such as formyl and alkyne groups, survived the oxidative reaction conditions. Aryl, heteroaryl-, and alkenyl-substituted alkene substrates were all applicable in the reaction. A number of aminyl radicals derived from six- and seven-membered N-heterocycles were compatible with the reaction conditions. In addition, azido radicals from reagent **T3** were also workable in the presence of **CPA7** instead of **CPA3**. In this case, a mild base $NaHCO_3$ was required to quench the carboxylic acid side product.

DOI: 10.1021/acs.accounts.9b00381
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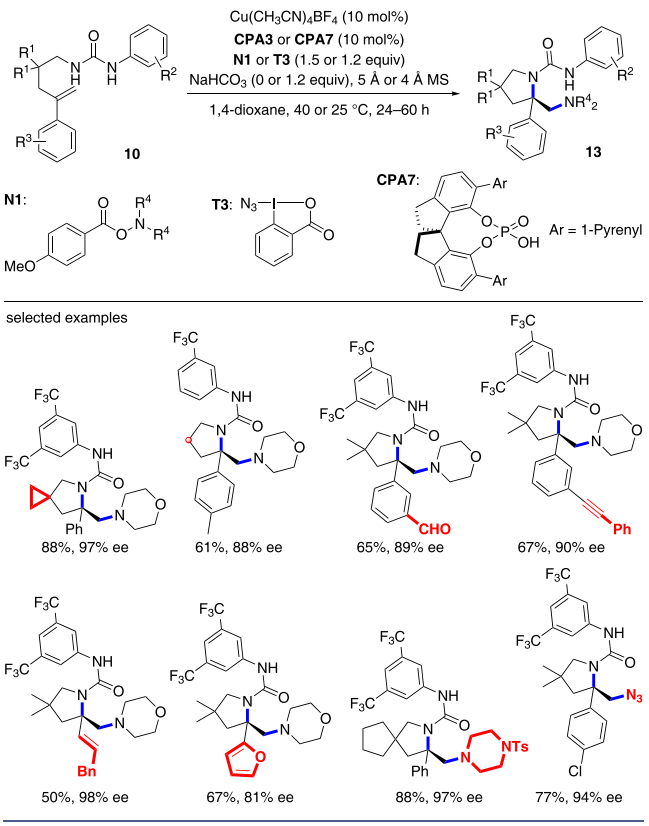
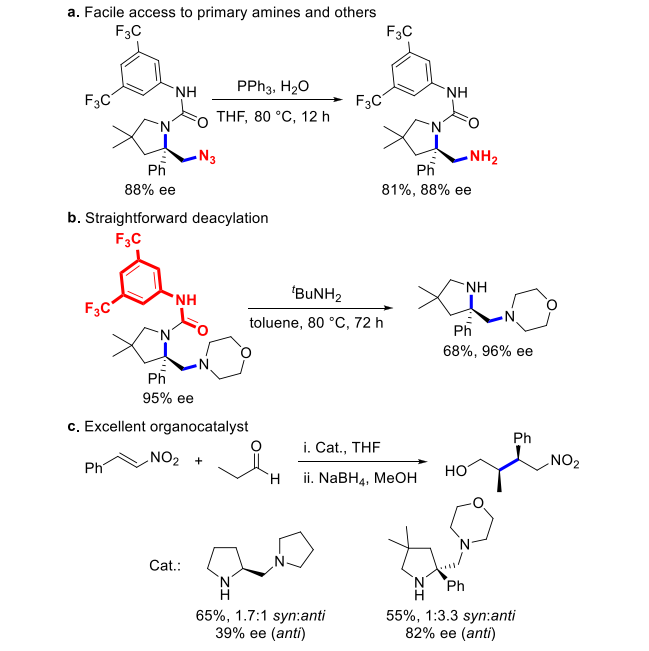
Scheme 16. Asymmetric 1,2-Diamination and 1,2-Azidoamination of Alkenes Involving Radicals



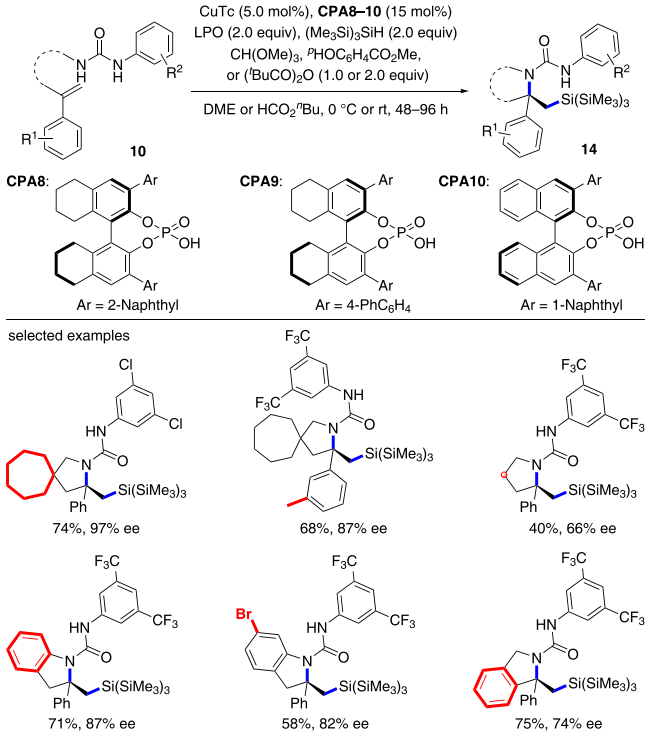
Scheme 17. Transformation and Application of the Asymmetric Diamination/Azidoamination Reactions



The incorporation of an azido group has allowed for facile access to primary amines (Scheme 17a) as well as other more substituted amines, which significantly strengthens the synthetic power of this methodology. In addition, we have also shown that a free secondary amine could be readily obtained after straightforward deacylation (Scheme 17b). More importantly, this amine proved to be an excellent organocatalyst for an enantioselective Michael addition reaction (Scheme 17c). Both the resulting diastereo- and enantioselectivity outcompeted those obtained with a reported amine catalyst.[55] These results highlight the great application potential of this asymmetric diamination reaction.

In addition to the aminyl radicals discussed above, we have also found that a silyl radical readily participated in copper/chiral phosphate-catalyzed asymmetric 1,2-aminosilylation of unactivated alkenes (Scheme 18).[56] In this reaction, we employed

Scheme 18. Asymmetric 1,2-Aminosilylation of Alkenes Involving Radicals



a combination of two readily commercially available reagents, i.e., lauroyl peroxide (LPO) and tris(trimethylsilyl)silane (TTMSS), for the facile generation of silyl radicals under copper catalysis. Thus, the reaction of an array of alkenylamine substrates bearing linear, branched, spiro, and benzo-fused tethers proceeded uneventfully. Also, corresponding silylated chiral pyrrolidines were afforded in moderate to excellent enantioselectivity.

In these asymmetric alkene 1,2-aminofunctionalization reactions, mechanistic investigations, such as radical inhibition and radical clock experiments, have been carried out to indicate the involvement of radical species. Thus, a general mechanism can be drawn, as shown in Scheme 19a. The generation of the initial radical is commonly via a SET process between Cu^{I} and an appropriate radical precursor, and CPA may promote this step by hydrogen bonding with the precursor. Subsequent radical addition to an alkenylamine substrate generates the highly reactive alkyl radical **A**, which is then trapped by a Cu^{II}/chiral phosphate complex to afford **B**. Finally, the product is formed and Cu^{I} as well as CPA is regenerated, closing the catalytic cycle. As for the exact pathway for the final step (**B** to the product) in most of these reactions, we prefer the formation of a Cu^{III} complex (**C**, Scheme 19b, left) and its subsequent reductive elimination: high enantioselectivity would be readily

DOI: 10.1021/acs.accounts.9b00381
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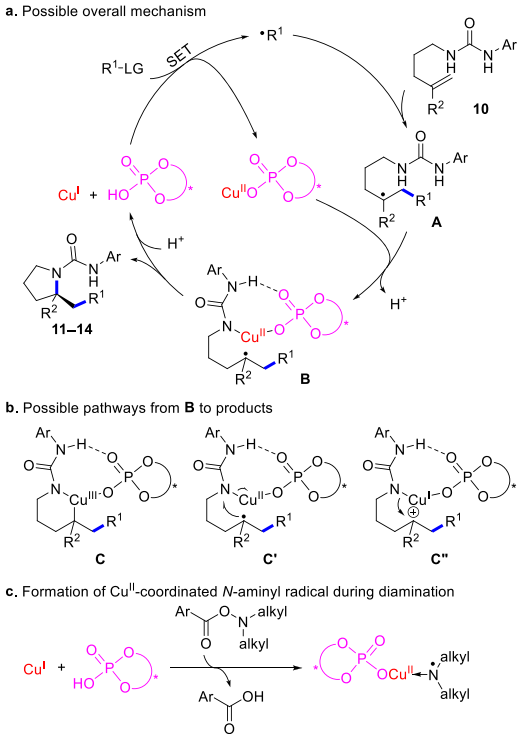
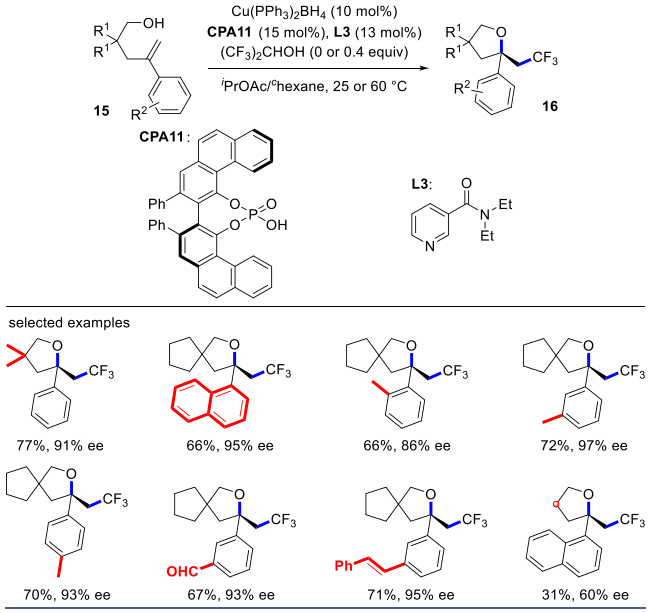
Scheme 19. Mechanism for Asymmetric Alkene 1,2-Aminofunctionalization Involving Radicals



achievable via the compact transition state along this pathway. This rationale is in accordance with that put forward by Liu et al. in their recent account.[13] Nonetheless, we currently have no solid evidence to exclude the other two possible pathways involving outer-sphere radical substitution (**C′**, Scheme 19b, middle)[57] and intramolecular redox/electrophilic amination (**C″**, Scheme 19b, right),[23] respectively. Especially for the last step in the asymmetric 1,2-aminosilylation reaction, the third pathway invoking carbocation formation (**C″**, Scheme 19b, right) might be favored due to the well-known β-silicon effect.[58] An exception that slightly deviates from this general mechanistic proposal is the asymmetric diamination reaction. During reaction, the N-alkyl aminyl radical is supposed to coordinate to Cu^{II} after the initial SET process (Scheme 19c) for activation toward radical addition.[59]

As our research on asymmetric alkene 1,2-difunctionalization continued, we targeted chiral trifluoromethylated tetrahydrofurans considering their great potential in drug discovery.[60] However, our initial extensive reaction optimization only resulted in poor enantioselectivity. Such results were not unexpected since the only successful catalyst for asymmetric 1,2-carboxytrifluoromethylation of alkene via radical intermediates was inapplicable for 1,2-alkoxytrifluoromethylation either.[21,22] In addition, the hydroxy group is a much weaker hydrogen-bond donor compared with the urea group, which has robustly anchored copper/chiral phosphate for high levels of enantiocontrol, as mentioned above.[48−50,54,56] To this end, we have resorted to an ancillary achiral ligand for stabilizing the presumed Cu^{III} intermediate. We speculated that this stabilization might render the conjectured more enantioselective Cu^{III} pathway more favorable than other potentially competing pathways, such as radical substitution or tandem intramolecular redox/electrophilic substitution. Thus, further screening efforts have culminated in identifying pyridine **L3** as the optimal ancillary ligand to afford the desired trifluoromethylated tetrahydrofurans in the presence of Cu^{I} and **CPA11** (Scheme 20).[61] High enantioselectivity was generally obtained on substrates bearing different *gem*-disubstituents on tethers and distinct aryl rings on the alkene groups, respectively. Particularly noteworthy was the tolerance of reactive formyl and alkene functional groups. Besides, a substrate without any *gem*-disubstituents on the tether also underwent the desired reaction to provide the corresponding product in low yield and with moderate ee.

Scheme 20. Asymmetric 1,2-Alkoxytrifluoromethylation of Alkenes Involving Radicals



As for the exact role of pyridine **L3**, we have observed slight reaction retardation by the addition of pyridine (Scheme 21a), possibly due to the presumed stabilization of Cu^{III} species via coordination. In addition, we have identified **L3**-coordinated Cu^{I} species $[Cu(PPh_3)\mathbf{L3}]^+$ from a reaction mixture using high-resolution mass spectroscopy analysis (Scheme 21b). Furthermore, we have extensively evaluated a large set of pyridine derivatives with different pK_a values and found no correlation between their basicity and ee values of products (Scheme 21c). The results disproved a proton shuttle mechanism.[62] Instead, appropriate coordination capability was apparently necessary for the pyridine additive to provide high enantioselectivity (pK_a 3−5 in the absence of obvious steric hindrance around the N atom). All these results strongly supported a role for **L3** as a ligand in coordinating and stabilizing the speculative Cu^{III} species[61] such as **A** (Scheme 22, left), through which the chiral phosphate could have exerted efficient enantiodiscrimination. The possibility for the other two pathways via radical substitution (**A′**, Scheme 22, middle)[57] or intramolecular redox/electrophilic alkoxylation (**A″**, Scheme 22, right),[23] respectively, cannot be excluded for now.

4.2. Copper(I)/Chiral Sulfonamide Catalyst

In the aforementioned reactions, we have utilized chiral phosphate for enantiocontrol, primarily via steric and other noncovalent interactions.[48−50,54,56,60] In one particular case, we have also used an additional achiral neutral ligand mainly for chemocontrol, i.e., stabilizing Cu^{III} species to favor the presumed highly enantioselective pathway via coordination (Scheme 23, top).[60] The latter success has prompted us to become aware of one salient drawback of copper/chiral anion

DOI: 10.1021/acs.accounts.9b00381
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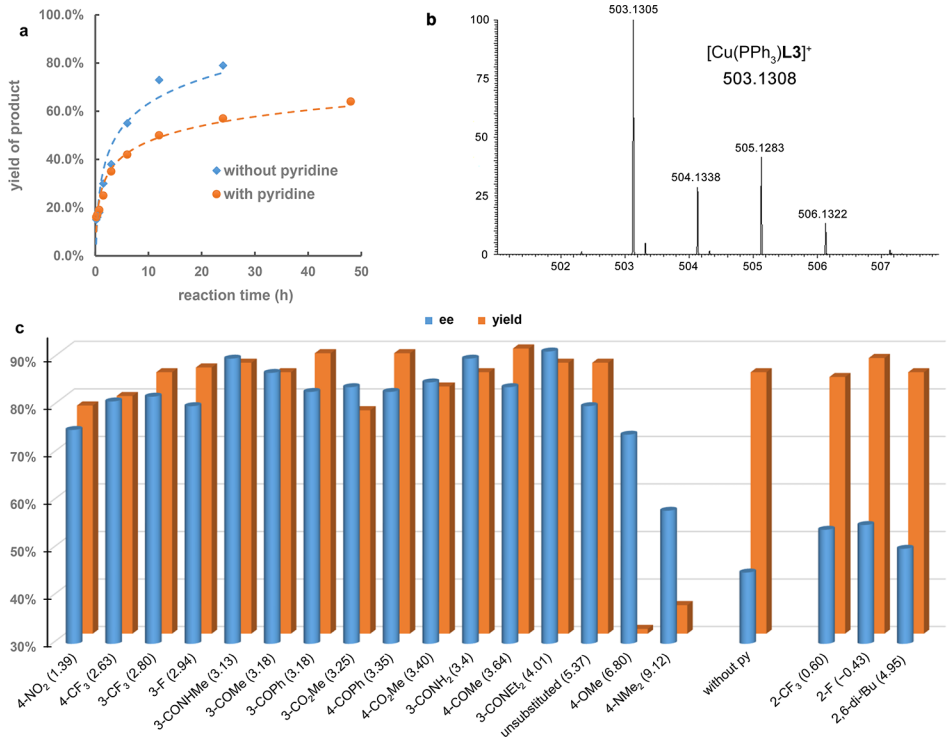
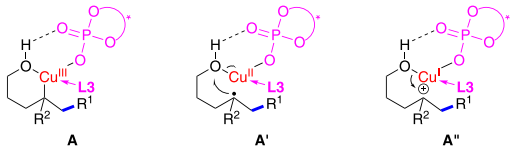
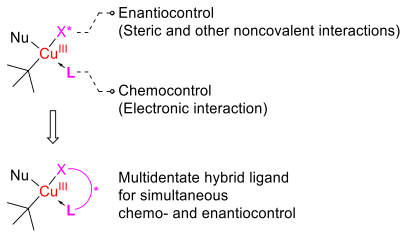
Scheme 21. Experimental Results Supporting Coordination of Pyridine Ligands to Copper



Scheme 22. Proposed Pathways for the Enantiodetermining C−O Bond Formation Assisted by the Achiral Pyridine Ligand



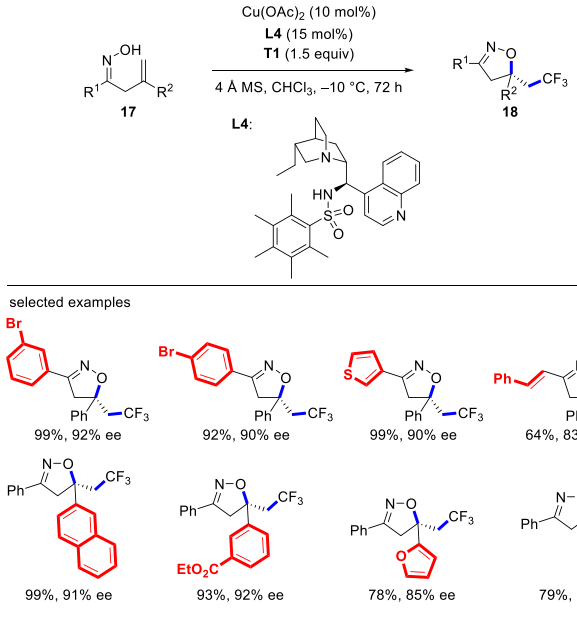
Scheme 23. Exploitation of Novel Chiral Neutral-Anionic Hybrid Ligands



catalysts: the anions lack sufficient electronic interactions with the copper centers for tuning their chemoselectivity. Therefore, we envisioned that a multidentate neutral-anionic hybrid ligand would not only allow for simultaneous chemo- and enantiocontrol but also provide a more rigid chiral environment for better enantioinduction (Scheme 23, bottom). This thought has enabled us to discover cinchona alkaloid-derived sulfonamides as novel hybrid ligands for asymmetric 1,2-iminoxytrifluoromethylation of unactivated alkenes via copper catalysis.[63]

In accord with our reasoning just mentioned, traditional copper/bisoxazoline (Box)[13−16,19,21,22] and our recent copper/chiral phosphate catalysts[48−50,54,56,60] both failed to provide good enantioselectivity for this reaction. However, the desired 1,2-iminoxytrifluoromethylation reaction proceeded smoothly

Scheme 24. Asymmetric 1,2-Iminoxytrifluoromethylation of Alkenes Involving Radicals



to afford highly enantioenriched trifluoromethylated isoxazolines **18** under the copper/**L4** catalysis (Scheme 24). Various aryl, heteroaryl, and alkenyl substituents on either the oxime or alkene moieties were tolerated. The substrate with a conjugated diene moiety also provided a promising moderate ee under the standard conditions.

The involvement of radical species in this reaction has been supported by radical inhibition/trap and radical clock experiments. As for the real role of **L4**, we have conducted a control experiment with N-methylated ligand **L5** and observed no enantioinduction under the otherwise optimized conditions

DOI: 10.1021/acs.accounts.9b00381
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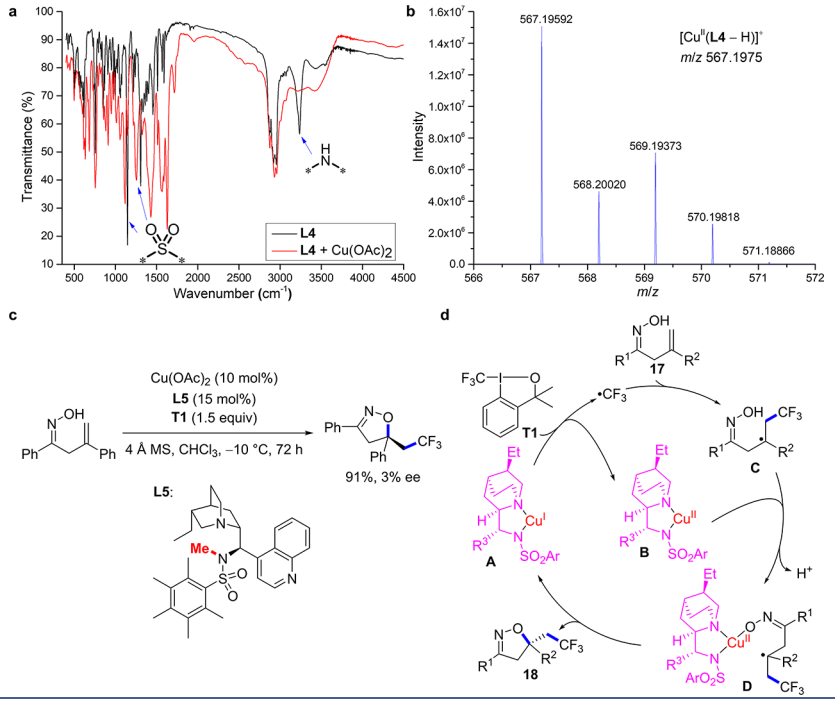
Scheme 25. Mechanistic Experiments and Proposal for Asymmetric 1,2-Iminoxytrifluoromethylation



(Scheme 25c). In addition, we have observed the disappearance of the peak that belongs to the N−H bond of **L4** in the subsequent infrared spectroscopy analysis upon mixing it with $Cu(OAc)_2$ (Scheme 25a). Further high-resolution mass spectroscopy analysis of a mixture of **L4** and $Cu(OAc)_2$ indicated formation of $[Cu^{II}(\mathbf{L4} - H)]^+$ (Scheme 25b). All these results supported the coordination of **L4** to copper after deprotonation. Thus, the catalytic cycle shown in Scheme 25d has been proposed to begin with Cu^I complex **A** bearing bidentate chiral ligand **L4**. Consecutive trifluoromethyl radical generation via SET, radical addition to **17**, trapping of radical **C** by chiral Cu^{II} complex **B**, and C−O bond formation lead to the formation of product **18**, which is similar to that of other reactions in this series.

5. SUMMARY AND PERSPECTIVES

Radical reactions are excellent but underdeveloped platforms for devising asymmetric transformations due to the robust reactivity, outstanding chemoselectivity, and high functional group compatibility. The utmost challenge to be overcome in this field has always been the delicate stereocontrol under the shallow energy barriers for radicals to proceed. This is particularly true for highly reactive minimally functionalized alkyl radicals, which lack covalent and/or noncovalent interactions with most chiral catalysts. In this respect, we have been focusing on copper catalysts for establishing relay catalysis with chiral phosphate in the tandem radical/carbocationic reactions, cooperative catalysis with chiral secondary amine in the radical transformation, and ultimately asymmetric copper catalysis in radical-organometallic crossover reactions. In these reactions, a diverse types of $C(sp^3)$−H functionalization and unactivated alkene difunctionalization have been achieved, providing expedient access to valuable enantioenriched products in high enantioselectivity. These results emphasize the versatility and adaptability of copper catalysis for developing asymmetric transformations involving radicals.

Nonetheless, several limitations of our current portfolio of copper catalysts still remain: (i) The redox potential window of most of our copper catalysts is narrow due to the lack of sufficient electronic interactions with chiral anions, which in turn results in a limited number of applicable oxidative radical precursors. (ii) The alkyl radicals amenable to our enantioselective functionalization are mostly confined to tertiary benzylic radicals with few exceptions. (iii) In most of the examples, nucleophiles for functionalization of alkyl radicals are N- and O-based ones to a large extent and C-based ones in only a few cases. We tentatively ascribe these limitations to the lack of manipulation on the ligand sphere for tuning the redox properties and chemoreactivity of copper catalysts. Therefore, we will make efforts in this direction for expanding the scope of copper-catalyzed asymmetric reactions involving radicals in the future.

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Funding

Financial support from the National Natural Science Foundation of China (Grants 21722203, 21831002, and 21801116) and Shenzhen Nobel Prize Scientists Laboratory Project (Grant C17783101) is greatly appreciated.

Notes

The authors declare no competing financial interest.

Biographies

Qiang-Shuai Gu got his B.Sc. in 2008 from University of Science and Technology of China and Ph.D. in 2013 from The University of Hong Kong under the guidance of Professor Dan Yang. He did postdoctoral research in the same research group afterwards. In 2016, he joined

DOI: 10.1021/acs.accounts.9b00381
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Zhong-Liang Li obtained his B.Sc. from University of Science and Technology of China in 2009 and completed his Ph.D. in Professor Dan Yang's group at The University of Hong Kong in 2014. In 2015, he moved to Southern University of Science and Technology (SUSTech) for postdoctoral research. He has been a research assistant professor in SUSTech Academy for Advanced Interdisciplinary Studies ever since September 2017. His research focuses on radical-initiated remote C−C bond cleavage and asymmetric reactions involving radicals.

Xin-Yuan Liu received his B.Sc. in 2001 from Anhui Normal University and M.Sc. in 2004 from Anhui Normal University in conjunction with Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China, under the guidance of Professor Shaowu Wang and Professor Shi-Zheng Zhu, respectively. In 2010, he obtained his Ph.D. from The University of Hong Kong under the supervision of Professor Chi-Ming Che. Then he did postdoctoral research initially in the same research group and later in the group of Professor Carlos F. Barbas III at The Scripps Research Institute. In September 2012, he joined Southern University of Science and Technology (SUSTech) as an associate professor and was promoted to full professor in 2018. His research interests include transition metal catalysis, asymmetric catalysis, radical chemistry, and fluorine chemistry.

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DOI: 10.1021/acs.accounts.9b00381
Acc. Chem. Res. 2020, 53, 170−181