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A Dual-Catalytic Strategy To Direct Asymmetric Radical Aminotrifluoromethylation of Alkenes

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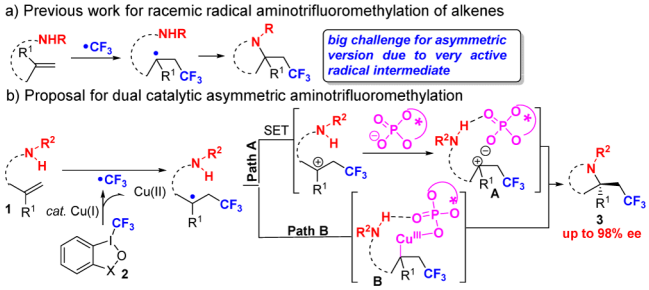
Supporting Information

ABSTRACT: A novel asymmetric radical aminotrifluoromethylation of alkenes has been developed for the first time, providing straightforward access to densely functionalized CF_3-containing azaheterocycles bearing an α-tertiary stereocenter with excellent enantioselectivity. The key to success is not only the introduction of a Cu(I)/chiral phosphoric acid dual-catalytic system but also the use of urea with two acidic N−H as both the nucleophile and directing group. The utility of this method is illustrated by facile transformations of the products into other important compounds useful in organic synthesis and medicinal chemistry.

The increasing importance of chiral CF_3-containing heterocycles in pharmaceuticals and agrochemicals as well as materials development has spurred vast efforts in the development of new catalytic asymmetric methods for their synthesis.[1] In particular, since the pioneering studies on Cu(I)-catalyzed deprotonative radical trifluoromethylation of olefins carried out by the research groups of Buchwald,[2a] Liu and Fu,[2b] and Wang,[2c] direct radical difunctionalization of alkenes and alkynes[3] has received increasing attention in recent years. Although great endeavors have been devoted to various racemic versions of radical trifluoromethylation of alkenes, the development of catalytic asymmetric methods has proven a formidable challenge, largely because of the intrinsic reactivity of the involved odd-electron species.[4] To address this challenge, Buchwald has more recently championed the copper-catalyzed enantioselective intramolecular oxytrifluoromethylation of alkenes with carboxylic acids in the presence of chiral bis(oxazoline) ligands, providing efficient access to CF_3-containing lactones with good enantioselectivities (74−83% ee).[5] *However, difunctionalization-type radical trifluoromethylation reactions with other types of nucleophiles, to the best of our knowledge, still remain unknown.* In the past several years, we and others have successfully developed the racemic Cu(I)-catalyzed radical aminotrifluoromethylation of alkenes, offering an efficient way to construct useful trifluoromethyl azaheterocycles (Scheme 1a).[6] Unfortunately, our initial attempts to the use of Cu(I)/bis(oxazoline) catalysis, as inspired by Buchwald's work, to achieve asymmetric aminotrifluoromethylation of *N*-alkenylurea **1a** with Togni's reagent **2a** or **2b** met with very low yield and enantioselectivity (Scheme S1). Clearly, a conceptually different approach is still very desirable to achieve highly efficient asymmetric radical aminotrifluoromethylation of alkenes.

Scheme 1. Asymmetric Radical Trifluoromethylation of Alkenes



After careful consideration of the reaction mechanism[3] and inspired by the recent great successes of asymmetric ion-pair catalysis with chiral phosphate counterions,[7] we envisioned that a dual-catalytic system consisting of a copper(I) source and an appropriate chiral phosphoric acid (CPA)[8,11b] might meet the challenge for the asymmetric radical aminotrifluoromethylation of alkenes. It has been assumed that the in situ-generated α-CF_3 alkyl radical might proceed via either a single-electron oxidation process to carbocation intermediate **A**[3] with a chiral ion pair through electrostatic interactions (Scheme 1b, path A)[9] or the formation of a chiral alkylcopper(III) phosphate species **B** (path B)[5,10] to provide the desired optically active difunctionalization product **3** with a superior level of enantiocontrol. If this approach is successful, it would not only be the first example of such an asymmetric radical reaction but also open up new avenues for the application of ion-pair catalysis for challenging radical reactions. However, the highly reactive nature of the radical species involved in this strategy makes it a formidable task to identify an appropriate dual-catalytic system as well as a suitable amine protecting group and hence to achieve a subtle balance among reactivity, stability, and stereocontrol. On the basis of our own experience in aminotrifluoromethylation[6] and asymmetric hydrogen-bonding and counteranion catalysis,[11] we report herein the successful development of *a dual-catalytic system of Cu(I) and CPA that enables the first catalytic asymmetric radical aminotrifluoromethylation of alkenes* with excellent efficiency and enantioselectivity, providing straightforward access to diversely functionalized CF_3-containing chiral pyrrolidines with the concomitant creation of an α-tertiary stereocenter (Scheme

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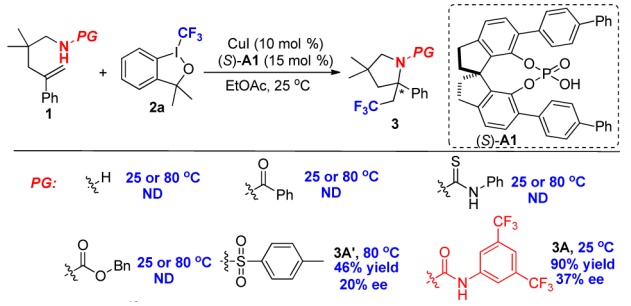
1b),[12] an important structural motif presented in a large number of pharmaceutical and agricultural chemicals.[12c]

Our study commenced with the examination of different N-protecting groups of alkenyl amines **1** with Togni's reagent **2a**[13] in the presence of CuI (10 mol %) and CPA (*S*)-**A1** (15 mol %) (Scheme 2). Various alkenyl substrates, including free amine and

Scheme 2. Evaluation of Different Protective Groups[a]



[a]Yields are based on ^{19}F NMR analysis of the crude products and ee values on HPLC. ND = not determined.

amide, carbamate, or thiourea-protected amines, hardly resulted in any formation of the desired products at room temperature or a higher temperature of 80 °C, presumably because of the susceptibility of free amines to oxidation and/or the poisoning of the transition-metal catalyst via strong ligation to the protected amine moieties. While a tosyl protecting group afforded the desired product **3A′** in 46% yield, albeit with low enantioselectivity (20% ee), at 80 °C in EtOAc, we were glad to find that the use of urea substrate **1a** resulted in a remarkable improvement in both the yield and enantioselectivity, even at room temperature. Its good performance compared with other protecting groups might be due to its suitable electron-withdrawing ability to ensure both necessary nucleophilicity of the nitrogen and to provide two acidic N−H for cooperative multiple hydrogen-bonding interactions with the CPA for effective activation and stereocontrol.

These results encouraged us to carry out further systematic optimizations of different reaction parameters (Scheme 3 and

Scheme 3. Screening of Reaction Conditions

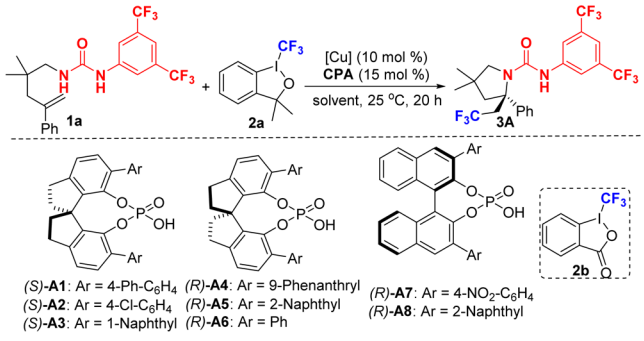
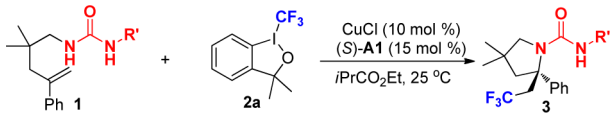


Table S1). Evaluation of various BINOL and SPINOL-based CPAs[14] indicated that the selectivity relies heavily on the substituents at the 3,3′-positions of the backbone. Among all of the catalysts screened, good results were obtained using (*S*)-**A1** with 4-Ph-phenyl groups at the 3,3′-positions (entries 1−8). We next screened different Cu salts and found that CuCl was the best in terms of enantioselectivity (81% ee; entry 9). Among the solvents screened, ethyl isobutyrate was found to be most efficient (85% yield and 91% ee; entry 15). Further investigation revealed that lowering the catalyst loading of acid to 10 mol % affected the chemical yield but did not lead to a decrease in enantioselectivity (entry 16). It is noteworthy that changing the CF_3 reagent from **2a** to **2b** resulted in a remarkable decrease in the enantioselectivity (75% ee; entry 17), which is largely due to the competitive nonasymmetric background processes catalyzed by 2-iodobenzoic acid that was generated in situ in the reaction system (for details, see Scheme S2). Only a trace amount of the desired product was obtained either in the presence of a cationic copper(II) salt or in the absence of copper(I) catalyst (entries 18 and 19), revealing that copper(I) is essential as a single-electron catalyst to activate Togni's reagent to generate CF_3 radical.

With the optimal conditions established, the generality of the current dual-catalytic system for the asymmetric radical trifluoromethylation was next investigated. First, a wide range of substrates with *N*-aryl urea groups were surveyed (Table 1). It

Table 1. Substrate Scope of Different Urea Groups[a]



entry	R'	3	t (h)	y (%)[b]	ee (%)[c]
1	3,5-$(CF_3)_2C_6H_3$	**3A**	72	80	91
2	4-$CF_3C_6H_4$	**3B**	70	71	91
3	3-$CF_3C_6H_4$	**3C**	64	70	97
4	4-FC_6H_4	**3D**	64	72	96
5	3-ClC_6H_4	**3E**	64	78	97
6	4-BrC_6H_4	**3F**	64	83	92
7	3-BrC_6H_4	**3G**	64	73	95
8	3-MeC_6H_4	**3H**	64	69	98
9	3-$MeOC_6H_4$	**3I**	64	88	91
10	2-BrC_6H_4	**3J**	64	50	90
11	2-$CF_3C_6H_4$	**3K**	96	51	92

[a]All of the reactions were conducted on a 0.2 mmol scale. [b]Isolated yields based on **1**. [c]Determined by chiral HPLC analysis.

was found that both the position and electronic nature of the substituents on the aromatic ring (R′) have a negligible effect on the reaction efficiency and stereoselectivity of the process. For example, substrates **1** bearing electron-withdrawing (CF_3, F, Cl, Br) or electron-donating (Me, OMe) groups at different positions (para or meta) of the aryl ring reacted efficiently to afford the corresponding products **3A**−**I** in 69−88% yield with 91−98% ee (entries 1−9). Moreover, the sterically hindered ortho-substituted substrates **1j** and **1k** (including CF_3 and Br) gave the corresponding products **3J** and **3K** in 50−51% yield, respectively, with excellent enantioselectivity (entries 10 and 11). Particularly noteworthy is that halo substituents such as F, Cl, and Br at different positions were well-tolerated, which is significant since aryl halides are usually incompatible with other copper-catalyzed trifluoromethylation reaction systems[15] and could offer opportunities for further useful modifications. The absolute configuration of **3F** was determined to be *R* by X-ray crystallographic analysis (Figure S1), and those of other trifluoromethyl-containing products were determined in reference to **3F**.

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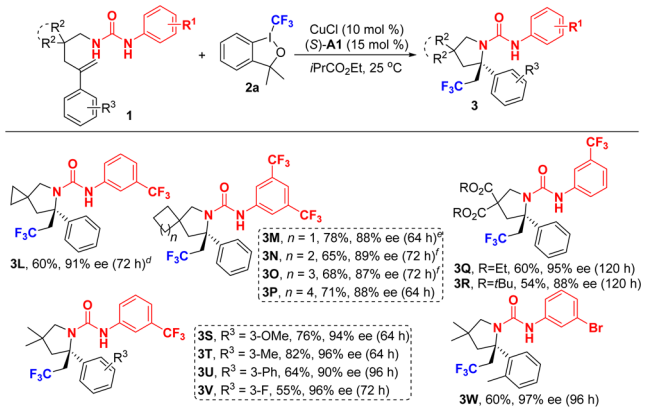
We next explored the substrate scope with a variety of *gem*-disubstituted alkenes bearing different tethering groups (Table 2). A variety of cyclic *N*-alkenyl ureas containing three- to seven-membered rings were well-tolerated and provided a diverse set of enantioenriched trifluoromethylated spiro products **3L**–**P** in moderate to good yields with 87–91% ee. Interestingly, changing the alkyl groups to ester groups in the tether, such as an ethyl (**1q**) or *tert*-butyl (**1r**) ester group, had no significant influence on the reaction, and **3Q** and **3R** were obtained in 60 and 54% yield with 95 and 88% ee, respectively. To further investigate the reaction scope, we tested the use of other *gem*-disubstituted alkenes as substrates. A range of diversely functionalized *N*-alkenyl ureas with electron-rich or electron-poor substituents on the aromatic ring were viable in this transformation, giving the corresponding products **3S**–**W** in 55–82% yield with 90–97% ee. However, nonbranched *N*-urea-4-pentenylamine substrate **1x** gave the desired product **3X** in low yield and ee (Scheme S3).

Table 2. Substrate Scope of Tethers and Alkenyl Moieties[a,b,c]

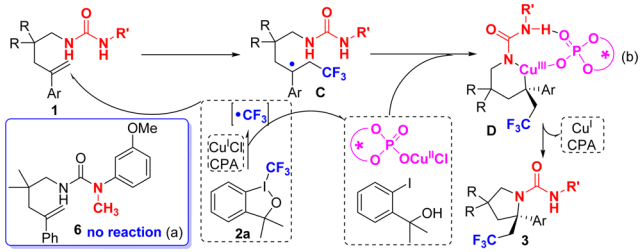


[a]All of the reactions were conducted on a 0.2 mmol scale. [b]Isolated yields based on **1** are shown. [c]The ee values were determined by HPLC analysis. [d]4 mol % CuCl. [e]7.5 mol % CuCl. [f]5 mol % CuCl.

To further evaluate the practicality of this process, the selective reduction of **3A** by $BH_3{\cdot}SMe_2$ successfully generated the desired α-tertiary amine **4** in 80% yield (Scheme S4). Furthermore, in the presence of [bis(trifluoroacetoxy)iodo]benzene (PIFA), **3A** was smoothly cyclized to give tricyclic amine **5** bearing an α-tetrasubstituted carbon stereocenter in 46% yield without decreasing the ee value (Scheme S4). The tricyclic structure of **5** is the core structure of many biologically active natural alkaloids such as hinckdentine A.[16]

To obtain some insights into the reaction mechanism, radical trapping experiments were conducted with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and 1,4-benzoquinone (BQ) (Scheme S5, eq 1). The reaction was found to be remarkably inhibited by these reagents, and together with the previous studies of radical trifluoromethylation of alkenes with Togni's reagent by Cu(I) catalysts,[2,3] this suggests that the CF_3 radical is likely involved as the reactive species under the current reaction conditions.[17] To further understand the role of the phosphoric acid, treatment of **1a** with **2a** under otherwise identical conditions in the presence of either CuCl alone or (*S*)-**A1** alone (see Scheme S5, eq 2 and Table S1, entry 19) gave the corresponding product **3A** in only low yield (the detailed kinetic behavior is shown in Figure S2), thus revealing that both the Cu(I) salt and the phosphoric acid are necessary for the reaction and that the activation of Togni's reagent could be facilitated by the phosphoric acid in this dual-catalytic system.[11b,18] Furthermore, no desired product was observed under the standard conditions with methyl-protected urea derivative **6** as the substrate (Scheme 4a and Scheme S5, eq 3), clearly indicating that the urea with two acidic N–H at the appropriate positions plays a crucial role in asymmetric induction.

Scheme 4. Mechanistic Proposal



On the basis of the above observations and previous studies,[2,3,5,17] two possible reaction pathways for the asymmetric radical aminotrifluoromethylation are proposed, although further studies are needed to clarify the details. Initially, the CF_3 radical and chiral Cu(II) phosphate are generated from the reaction of **2a** with Cu(I) and the phosphoric acid, and this is followed by the addition of CF_3 radical to the alkene to afford α-CF_3 alkyl radical **C**. The alkyl radical intermediate and urea could be trapped by Cu(II) to generate Cu(III) species **D**,[5,10] wherein the chiral phosphate anion could be coordinated as an anionic ligand (Scheme 4b).[7] During this course, the chiral phosphate could control the facial selectivity of the reaction via both hydrogen-bonding interactions with the N–H bond adjacent to the aryl group and ion-pairing interactions in a concerted transition state. Finally, reductive elimination of **D** would take place to furnish **3** and regenerate copper(I) and the phosphoric acid. Another pathway via single-electron oxidation of **C** to the corresponding carbocation **A** by Cu(II) through ion pairing (Scheme 1b, path A),[9] cannot be ruled out at the present stage.[19]

In summary, we have developed the first catalytic asymmetric radical aminotrifluoromethylation of alkenes. The overall process serves as a novel, efficient, and simple approach for straightforward access to diversely substituted CF_3-containing pyrrolidines bearing an α-tertiary stereocenter with excellent efficiency, remarkable enantioselectivity, and excellent functional group tolerance. Critical to the success of this process is not only the introduction of a Cu(I)/phosphoric acid dual-catalytic system but also the use of urea with two acidic N–H as both the nucleophile and directing group. The highly enantioenriched and diversely functionalized products can be easily transformed into other useful chiral CF_3-containing building blocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04077.

Experimental procedures, characterization data, Table S1, Schemes S1–S5, and Figures S1 and S2 (PDF)
Crystallographic data for **3F** (CIF)

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Notes

The authors declare no competing financial interest.

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