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Asymmetric Catalysis

Copper-Catalyzed Enantioselective C(sp^3)–SCF_3 Coupling of Carbon-Centered Benzyl Radicals with $(Me_4N)SCF_3$

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Dedication to Prof. Vivian Wing-Wah Yam on the occasion of her 60th birthday.

Abstract: In contrast with the well-established C-(sp^2)–SCF_3 cross-coupling to forge the Ar–SCF_3 bond, the corresponding enantioselective coupling of readily available alkyl electrophiles to forge chiral C(sp^3)–SCF_3 bond has remained largely unexplored. We herein disclose a copper-catalyzed enantioselective radical C-(sp^3)–SCF_3 coupling of a range of secondary/tertiary benzyl radicals with the easily available $(Me_4N)SCF_3$ reagent. The key to the success lies in the utilization of chiral phosphino-oxazoline-derived anionic N,N,P-ligands through tuning electronic and steric effects for the simultaneous control of the reaction initiation and enantioselectivity. This strategy can successfully realize two types of asymmetric radical reactions, including enantioconvergent C(sp^3)–SCF_3 cross-coupling of racemic benzyl halides and three-component 1,2-carbotrifluoromethylthiolation of arylated alkenes under mild reaction conditions. It therefore provides a highly flexible platform for the rapid assembly of an array of enantioenriched SCF_3-containing molecules of interest in organic synthesis and medicinal chemistry.

Introduction

The trifluoromethylthio (SCF_3) functional group has privileged application in the field of agrochemicals and pharmaceuticals due to its strong electron-withdrawing nature, high lipophilicity ($\pi = 1.44$), and metabolic stability.[1] Consequently, considerable efforts have been devoted to the development of SCF_3-transfer reagents and new methods for the construction of C–SCF_3 bonds.[2] Among these endeavors, transition-metal-catalyzed cross-coupling reactions of aryl electrophiles/nucleophiles with nucleophilic SCF_3 reagents have emerged as an essential toolkit for the efficient formation of C(sp^2)–SCF_3 bond owing to good functional group compatibility (Scheme 1A).[3,4] Compared with the elegant C(sp^2)–SCF_3 coupling, the cross-coupling of alkyl electrophiles,[5] particularly the enantioconvergent coupling[6] of racemic electrophiles for expedited access to chiral C(sp^3)–SCF_3 bond has met with limited success (Scheme 1B). On one hand, the difficult oxidative addition and facile β-H elimination generally associated with alkyl electrophiles compared with their aryl counterparts should be overcome.[7] On the other hand, the easily-occurring racemic reactions via an S_N2 or S_N1 mechanism due to the inherent strong nucleophilicity of the SCF_3 anion have to be addressed.[8] Thus, the development of a stereoconvergence of racemic alkyl electrophiles amidst several competing processes is a formidable challenge (Scheme 1B).

It is well-known that chiral SCF_3-containing molecules might lead to further advances in drug discovery, but the enantioselective introduction of the SCF_3 group is still in its infancy.[9] In this context, the direct catalytic asymmetric trifluoromethylthiolation with electrophilic SCF_3 reagents[10] and the use of synthesized trifluoromethylthiolated building blocks[11] are two major approaches for the formation of the C(sp^3)–SCF_3 bond at the stereogenic center. In contrast, the catalytic asymmetric transformations utilizing easily available nucleophilic SCF_3 reagents have remained rare. Only until very recently have Zhang and co-workers elegantly achieved an enantioselective nucleophilic trifluoromethylthiolation of excessive secondary propargyl sulfonates with $AgSCF_3$ via a chiral copper-allenylidene intermediate (Scheme 1C).[12] Given the easy availability of racemic benzyl halides and nucleophilic $(Me_4N)SCF_3$ reagent,[3b,f–h,13] we envisioned that the aforementioned enantioconvergent C(sp^3)–SCF_3 cross-coupling of racemic benzyl electrophiles with nucleophilic $(Me_4N)SCF_3$ reagent would be appealing to access enantioenriched trifluoromethylthiolated molecules (Scheme 1B). As such, we expected that our recently developed copper catalysts with chiral multidentate anionic ligands for enantioconvergent radical cross-coupling reac-

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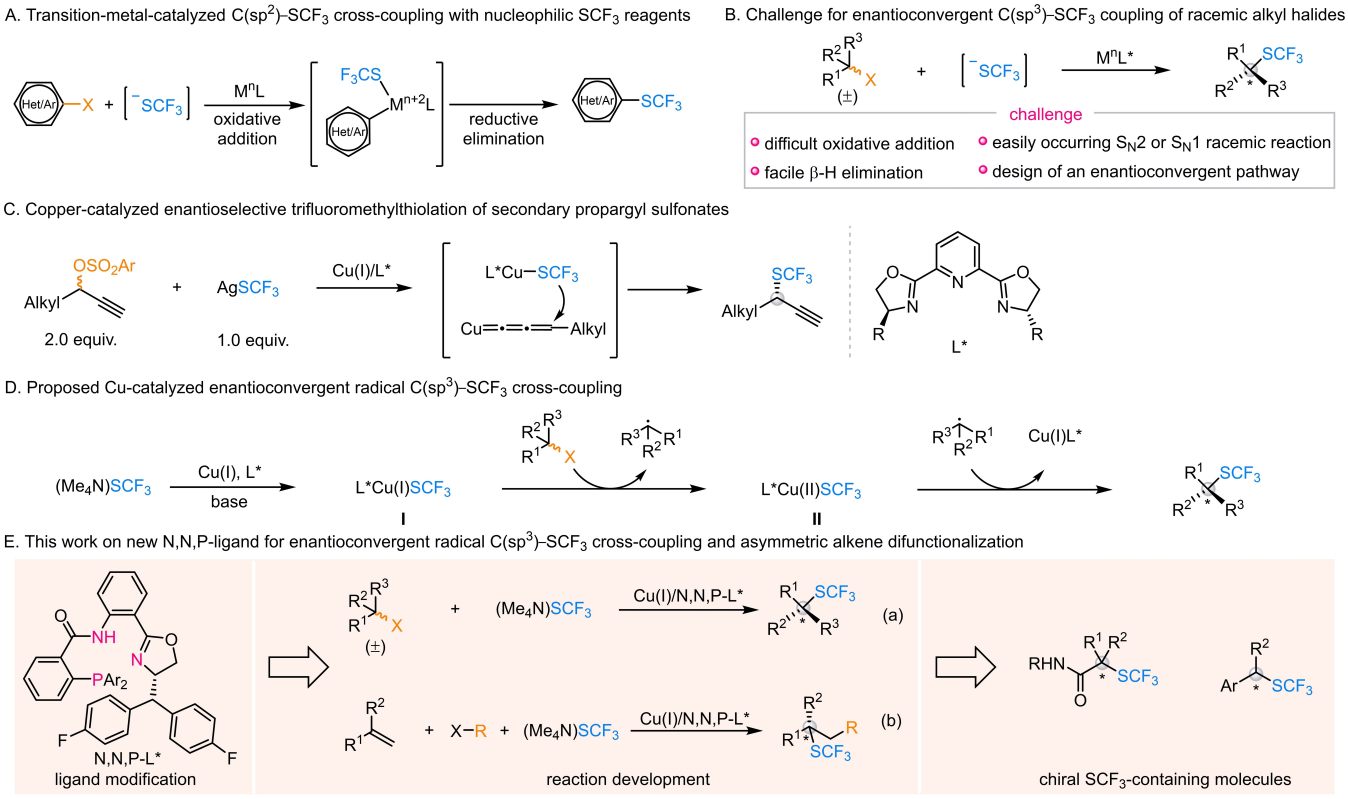


Scheme 1. Motivation and design of enantioconvergent radical C(sp^3)–SCF_3 cross-coupling and relative transformation.

tions could overcome the difficulties of the above-described approach.[7,14–16]

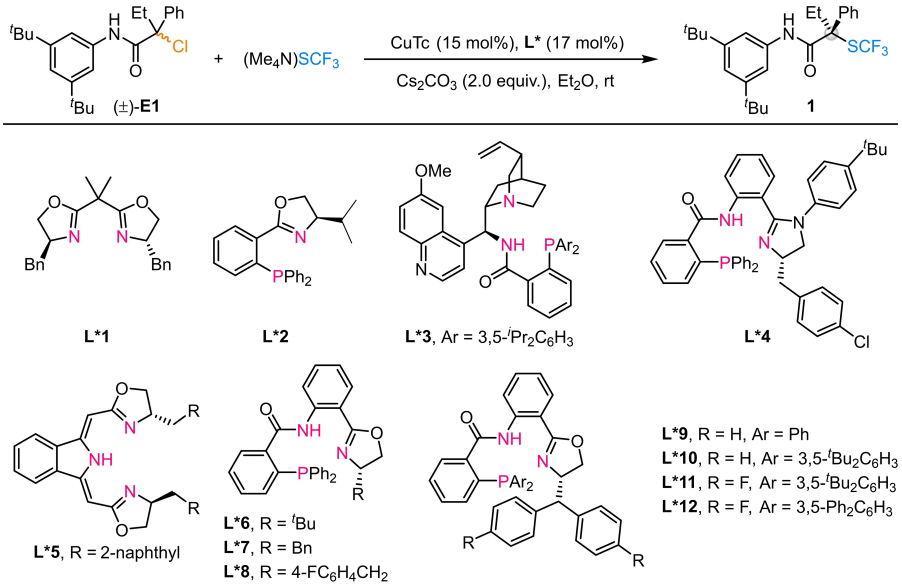
Our proposal is based on the assumption that the in situ-generated chiral ligand-chelated L*Cu(I)SCF_3 complex would reduce racemic benzyl halides via a single-electron-transfer process to generate prochiral benzyl radicals for the initiation of the radical process. The interaction of benzyl radicals with the thus-oxidized L*Cu(II)SCF_3 complex would give rise to the chiral C(sp^3)–SCF_3 bond and regenerate the L*Cu(I) species for the next catalytic cycle (Scheme 1D). Notably, the trap of alkyl radicals by a Cu(II)SCF_3 complex could successfully achieve several racemic alkene/alkyne difunctionalization and C–H functionalization.[17] As such, we envisaged that the selection of a chiral ligand scaffold would be crucial to success-not only enhancing the reducing capability of copper catalyst to initiate a single-electron-transfer process but also providing an ideal chiral environment to achieve the challenging enantiocontrol over the highly reactive radical species. Herein, we disclose a copper-catalyzed enantioconvergent radical C(sp^3)–SCF_3 cross-coupling of racemic benzyl halides with $(Me_4N)SCF_3$ reagent under mild reaction conditions (Scheme 1E). The key to the success is the utilization of a class of chiral phosphino-oxazoline-derived anionic N,N,P-ligands[18] through tuning electronic and steric effects for the simultaneous control of the reaction initiation and enantioselectivity. The reaction covers both secondary and tertiary benzyl halides. Given the ready generation of prochiral carbon-centered radical species derived from the radical alkene addition process,[19] this catalytic system could be further extended to the asymmetric radical 1,2-carbotrifluoromethylthiolation of alkenes (Scheme 1E).

Results and Discussion

Reaction Development

The construction of enantioenriched acyclic quaternary stereocenters bearing an SCF_3 group is difficult due to the steric hindrance in the formation of fully-substituted carbon centers.[11c] As such, we first investigated the enantioconvergent C(sp^3)–SCF_3 cross-coupling reaction of α-aminocarbonyl-α-phenyl alkyl chloride (±)-**E1** with $(Me_4N)SCF_3$ based on our previous report that the NH motif played a key role in the enantiocontrol[14a] (Table 1 and Tables S1–S4 for more details in the Supporting Information). Not surprisingly, the racemic product **1** was easily obtained in the presence of copper and Cs_2CO_3 in many polar organic solvents presumably through a substitution pathway (Table 1, entry 1, and Table S1 in the Supporting Information). To avoid the background reaction, Et_2O was chosen to screen the reaction since no obvious background reaction was observed in low polar solvents (Table 1, entry 2, and Table S1 in the Supporting Information). To verify the feasibility of ligand effect to induce the proposed enantioconvergent radical process (Scheme 1D), different types of ligands were screened. Although neutral bidentate ligands, such as N,N-

Table 1: Effect of ligands in the model reaction.[a]



entry	L*	solvent	yield [%]	ee [%]
1	–	MeCN	99	–[b]
2	–	Et_2O	14	–[b]
3	**L*1**	Et_2O	57	5
4	**L*2**	Et_2O	99	−5
5	**L*3**	Et_2O	28	6
6	**L*4**	Et_2O	85	46
7	**L*5**	Et_2O	<5	–[b]
8	**L*6**	Et_2O	99	31
9	**L*7**	Et_2O	99	57
10	**L*8**	Et_2O	93	62
11	**L*9**	Et_2O	99	52
12	**L*10**	Et_2O	89	81
13	**L*11**	Et_2O	99	83
14	**L*12**	Et_2O	99	89
15[c]	**L*12**	**Et_2O**	**99**	**90**

[a] Reaction conditions: (±)-**E1** (0.05 mmol), $(Me_4N)SCF_3$ (0.075 mmol), CuTc (15 mol%), **L*** (17 mol%), and Cs_2CO_3 (2.0 equiv.) in solvent (1.0 mL) at rt for 36 h under argon. Yield is based on ^{19}F NMR analysis of the crude product using CF_3CH_2OH or CF_3OPh as an internal standard. Ee value of **1** is based on chiral HPLC analysis. [b] Not determined.[c] Conducted at 0 °C with 1.0 equiv. Cs_2CO_3 for 120 h. ^{t}Bu, *tert*-butyl; Tc, thiophene-2-carboxylate.

ligand **L*1**, and N,P-ligand **L*2** could efficiently initiate the reaction, poor enantioselectivity was observed (Table 1, entries 3 and 4). We then investigated ligands **L*3**–**L*5** that performed well in our recently reported enantioselective C(sp^3)–S coupling.[15] Interestingly, cinchona alkaloid-derived N,N,P-ligand **L*3** afforded **1** with poor ee, but dihydroimidazole-derived N,N,P-ligand **L*4** gave a moderate ee (Table 1, entries 5 and 6). Unfortunately, the N,N,N-ligand **L*5** afforded almost no coupling product (Table 1, entry 7). The promising result of **L*4** encouraged us to screen the oxazoline-derived N,N,P-ligands. To our delight, Ph_2P-derived N,N,P-ligand **L*6**[18] could initiate this reaction in excellent yield with 31 % ee (Table 1, entry 8). Changing the bulky ^{t}Bu to less-crowded benzyl/dibenzyl-type substituents (**L*7**–**L*9**) further enhanced the ee (Table 1, entries 9–11). During the process, we found that the installation of a fluorine atom at the *para* position of the aryl ring (**L*8**) delivered **1** with a higher ee than that of the aryl ring (**L*7**) (Table 1, entries 9 and 10). Considering the substantial role that the phosphine motif might play in affecting the reaction efficiency and enantioselectivity, we found that the installation of a bulky ^{t}Bu group at the *meta* positions of the *P*-aryl ring (**L*10**) led to a great enhancement of ee, albeit with a slightly decreased yield (Table 1, entry 12). The ee was further enhanced by installing a fluorine atom at the oxazoline ring (**L*11**), following the same trend as that of **L*8** (Table 1, entry 13). We finally found that ligand **L*12** with the phenyl substituent at *meta* positions of the *P*-aryl ring with 99 % yield and 89 % ee (Table 1, entry 14). Collectively, the modified N,N,P-ligand bearing both bulky *P*-substituent and di(4-fluoro)phenylmethyl shielding substituent at 4-position of the oxazoline ring were beneficial to the enantioselectivity. After further optimization of reaction parameters including the copper catalysts, reaction temperature, organic solvents as well as inorganic bases (Tables S2–S4), we identified the optimal conditions as follows:

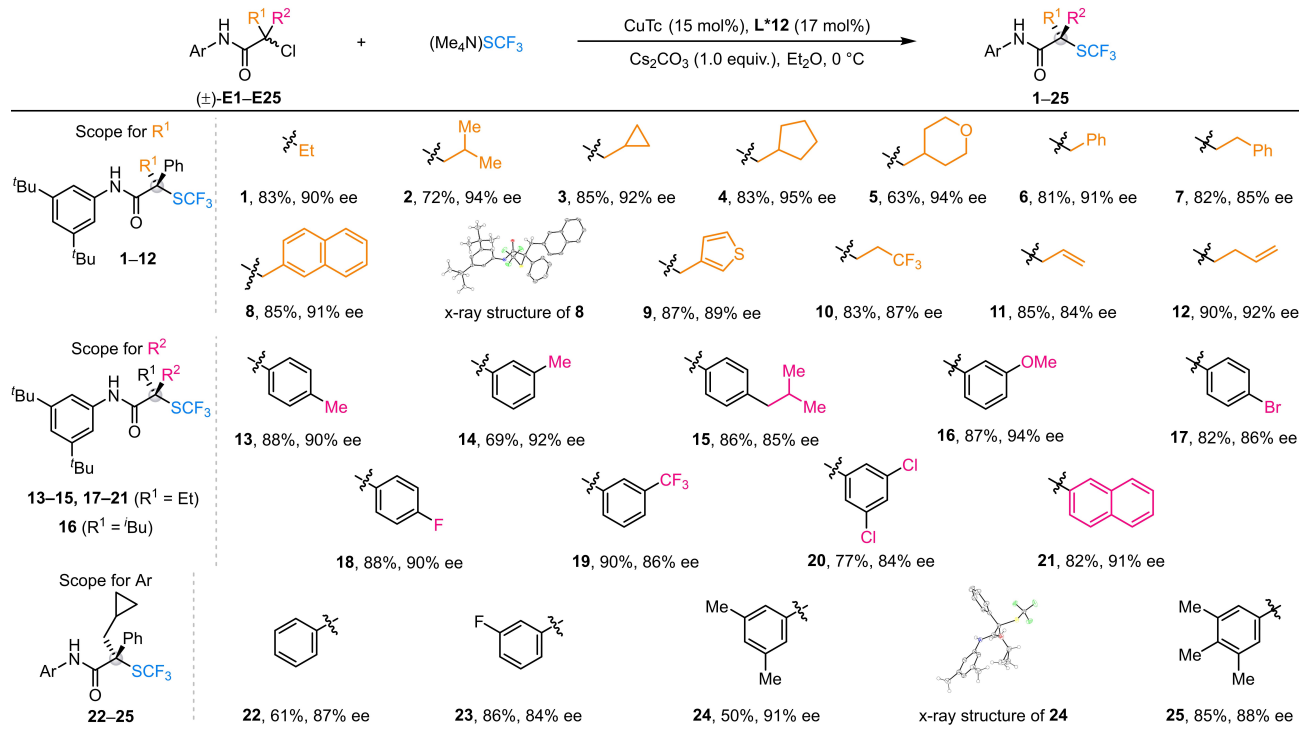
1.0 equiv. (±)-**E1**, 1.5 equiv. $(Me_4N)SCF_3$, 15 mol % CuTc, 17 mol % **L*12**, and 1.0 equiv. Cs_2CO_3 in Et_2O at 0 °C. Under the optimal conditions, the desired product **1** was obtained in 99 % NMR yield with 90 % ee (Table 1, entry 15).

Substrate Scope

With the optimal reaction conditions established, we examined the generality of α-aminocarbonyl-α-aryl alkyl chlorides for the reaction (Table 2). Regarding the α-alkyl substituent (R^1 group in the substrate), a wide range of substrates bearing linear or branched unfunctionalized aliphatic side chains as well as those functionalized with tetrahydro-2*H*-pyranyl, phenyl, naphthyl, thienyl, trifluoromethyl, and alkenyl groups were all well accommodated in this process to deliver **1**–**12** in 63–90 % yields with 84–95 % ee. Moreover, a series of α-phenyl rings with electron-donating or -withdrawing groups at different positions as well as an α-naphthyl ring were compatible with the reaction conditions, delivering **13**–**21** with satisfactory yields and ee. Besides, a variety of secondary amides derived from aniline and its analogues also worked well to afford **22**–**25** in 50–86 % yields with 84–91 % ee. As for alkyl amine or secondary aryl amine-derived substrates, no corresponding products were observed (Scheme S1 in the Supporting Information). These results showed that the N–H bond in the substrates is crucial to the reaction and the weakly acidic N–H bond cannot be deprotonated to afford the desired product. The absolute configurations of **8** and **24** (Table 2 and Figures S2 and S3 in the Supporting Information) were determined to be *R* by X-ray crystallographic analysis, and other products were assigned by analogy accordingly.[20]

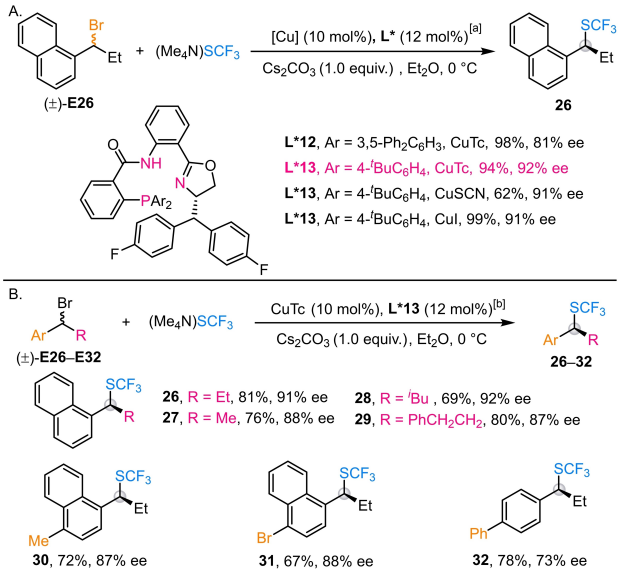
To further strengthen the synthetic utility of this methodology, we switched our attention to extending the coupling of secondary benzyl electrophiles. To our delight, the corresponding coupling of racemic 1-(1-bromopropyl)naphthalene (±)-**E26** with $(Me_4N)SCF_3$ afforded the product **26** in 98 % yield with 81 % ee in the presence of the originally superior ligand **L*12** for tertiary benzyl halides (Table 3a). Further improvement of the stereoselectivity indicated that ligand **L*13** bearing a bulky ^{t}Bu group at the *para* position of the *P*-aryl ring was the best one for such a process, giving **26** in 94 % yield with 92 % ee. We speculated that the lack of amide group in the substrate (±)-**E26** might lead to a different catalyst-substrate interaction in the enantiocontrol step and thus the optimal ligands are different for **E1** and **E26**. As for the scope, a range of secondary benzyl bromides possessing both linear and branched alkyl chains as well as differently substituted naphthyl rings were suitable for the reaction to provide **26**–**31** in 67–81 % yields with 87–92 % ee (Table 3b). More importantly, the benzyl bromide substrate was also suitable for the reaction to afford **32** in good ee. The absolute configuration of **27** was determined to be *S* by chiroptical methods (See Figure S4 in Supporting Information for

Table 2: Substrate scope of tertiary benzyl halides.[a]



[a] Standard reaction conditions: (±)-**E** (0.1 mmol), $(Me_4N)SCF_3$ (0.15 mmol), CuTc (15 mol %), **L*12** (17 mol %), and Cs_2CO_3 (1.0 equiv.) in Et_2O (2.0 mL) at 0 °C for 120 h under argon. Isolated yields are shown. Ee values are based on chiral HPLC analysis. ^{i}Bu, *iso*-butyl. ^{t}Bu, *tert*-butyl. Tc, thiophene-2-carboxylate.

Table 3: Reaction development and substrate scope of secondary benzyl halides.

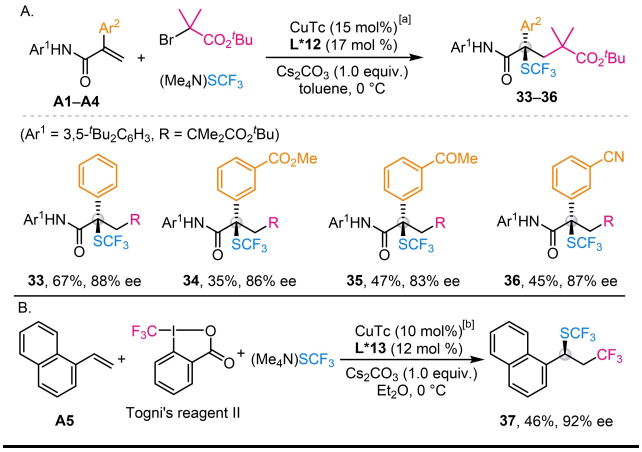


[a] Standard reaction conditions: (±)-**E26** (0.05 mmol), $(Me_4N)SCF_3$ (0.075 mmol), Cu (10 mol%), **L*** (12 mol%), and Cs_2CO_3 (1.0 equiv.) in Et_2O (1.0 mL) at 0 °C for 72 h under argon. Yield is based on ^{19}F NMR analysis of the crude product using CF_3OPh as an internal standard. [b] Reaction conditions: (±)-**E26**–**E32** (0.1 mmol), $(Me_4N)SCF_3$ (0.15 mmol), CuTc (10 mol%), **L*13** (12 mol%), and Cs_2CO_3 (1.0 equiv.) in Et_2O (2.0 mL) at 0 °C for 120 h under argon. Isolated yields are shown. Ee values are based on chiral HPLC analysis. ^{i}Bu, *iso*-butyl. ^{t}Bu, *tert*-butyl. Tc, thiophene-2-carboxylate.

details) and other products were assigned by analogy accordingly.

Inspired by the enantioconvergent radical cross-coupling and easy availability of alkenes,[19] we wondered whether an asymmetric radical 1,2-carbotrifluoromethylthiolation of alkenes could be achieved with the current catalytic system. After simple screening of reaction conditions, we found that the reaction of phenyl-substituted acrylamide **A1**, *tert*-butyl α-bromoisobutyrate, and $(Me_4N)SCF_3$ in the presence of CuTc/**L*12** provided **33** in 67 % yield and 88 % ee in toluene (Table 4). Several functional groups on the phenyl ring were readily tolerated to deliver **34**–**36** with good results. Noteworthy is that the scope of alkene is not limited to the disubstituted alkenes. For example, 1-vinylnaphthalene reacted well to afford the expected 1,2-trifluoromethyltrifluoromethylthiolation product **37** in 46 % yield with 92 % ee using Togni's reagent **II** as the radical precursor in the presence of chiral ligand **L*13**. Collectively, this strategy not only achieved the asymmetric radical 1,2-carbotrifluoromethylthiolation of *mono*- and *di*-substituted alkenes but also provided strong evidence in support of the generation of carbon-centered benzyl radical species in the cross-coupling process.

Table 4: Substrate scope of alkenes.[a]

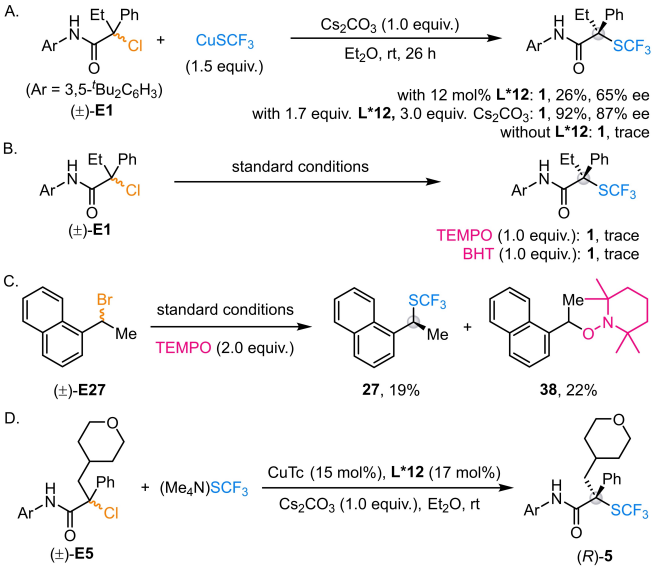


[a] Reaction conditions: **A1**–**4** (0.1 mmol), $BrMe_2CCO_2{}^tBu$ (0.3 mmol), $(Me_4N)SCF_3$ (0.3 mmol), CuTc (15 mol%), **L*12** (17 mol%), and Cs_2CO_3 (1.0 equiv.) in toluene (2.0 mL) at 0 °C for 120 h under argon. [b] Reaction conditions: **A5** (0.1 mmol), Togni's reagent **II** (0.2 mmol), $(Me_4N)SCF_3$ (0.2 mmol), CuTc (10 mol%), **L*13** (12 mol%), and Cs_2CO_3 (1.0 equiv.) in Et_2O (2.0 mL) at 0 °C for 120 h under argon. Isolated yields are shown. Ee values are based on chiral HPLC analysis. ^{t}Bu, *tert*-butyl. Tc, thiophene-2-carboxylate.

Mechanistic Investigation

Concerning the reaction mechanism, the stoichiometric reaction of synthesized $CuSCF_3$[21] with racemic (±)-**E1** afforded **1** in 26 % yield and 65 % ee with a catalytic amount of **L*12** and in 92 % yield and 87 % ee with a stoichiometric amount of **L*12**. However, a trace of product **1** was observed without ligand (Scheme 2A). This result suggested that the ligand-coordinated **L***$CuSCF_3$ might serve as the key species for the initiation of the reaction. The subsequent radical inhibition experiments with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-*tert*-butyl-4-methylphenol) for substrates **E1** and **E27** revealed substantial reaction inhibition and the TEMPO-trapped product **38** was isolated for **E27**, respectively (Scheme 2B and 2C). These results together with the above-mentioned radical 1,2-carbotrifluoromethylthiolation in Table 4 consistently indicated the generation of carbon-centered radical species in the reaction.

Interestingly, the reactions of enantiopure substrates **E5** revealed that the consumption rate of enantiopure **E5** is higher than that of its enantiomer **E5′**. Further experiments for racemic **E5** at different time intervals indicated the enantioenrichment of **E5′** from the recovered substrate (Scheme 2D). These experiments suggested that the reduction of benzyl halides with L*Cu(I)SCF_3 involved a partial kinetic resolution of racemic **E5**.[22] The observed ee values of the product remained nearly constant with the two enantiomers **E5**/**E5′** and racemic substrates (±)-**E5** at different time intervals (Scheme 2D), respectively. This result favored that the enantioselective radical $C(sp^3)$–SCF_3 bond formation step should involve a likely uniform enantiodetermining transition state along with the same reaction pathway. Overall, all these preliminary experimental results



entry	substrate	time	recovered **E5**	(*R*)-**5**
1	**E5** (> 99% ee)	2.75 h	32% of **E5**	52%, 92% ee
2	**E5'** (> –99% ee)	2.75 h	55% of **E5'**	34%, 92% ee
3	(±)-**E5** (0% ee)	4 h	70%, –21% ee for **E5'**	24%, 92% ee
4	(±)-**E5** (0% ee)	6 h	33%, –61% ee for **E5'**	44%, 92% ee

Scheme 2. Mechanistic investigations.

together with previous mechanistic studies are in support of our initial proposal, as shown in Scheme 1D.

Conclusion

In summary, we have described a copper-catalyzed enantioconvergent radical C(sp^3)–SCF_3 cross-coupling of racemic secondary and tertiary benzyl halides with easily available $(Me_4N)SCF_3$ reagent under mild conditions. The key to the success is the utilization of a class of chiral phosphinooxazoline-derived anionic N,N,P-ligands with high electronic and steric demanding for good reaction efficiency and enantioselectivity. Furthermore, an asymmetric three-component radical 1,2-carbotrifluoromethylthiolation of alkenes has been realized through a similar stereocontrol process. The asymmetric radical C(sp^3)–SCF_3 coupling reactions from easily available substrates provide a flexible platform for the synthesis of an array of enantioenriched SCF_3-containing molecules. We anticipate that this strategy would open up new avenues for more asymmetric radical C-(sp^3)–SCF_3 coupling with more readily available feedstocks.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Cambridge Crystallographic Data Centre at https://www.ccdc.cam.ac.uk/structures/, reference numbers 2220219 (compound **8**), 2220238 (compound **24**), and 2220220 (intermediate **E** in the Supporting Information).

Keywords: copper catalysis · radical reaction · cross-coupling · benzyl halides · alkenes

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