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Authors: Xin-Yuan Liu, Xi-Tao Li, Qiang-Shuai Gu, Xiao-Yang Dong, and Xiang Meng

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Cinchona Alkaloid-Based Sulfonamide/Copper Catalyst for Asymmetric Radical Oxytrifluoromethylation of Alkenyl Oximes

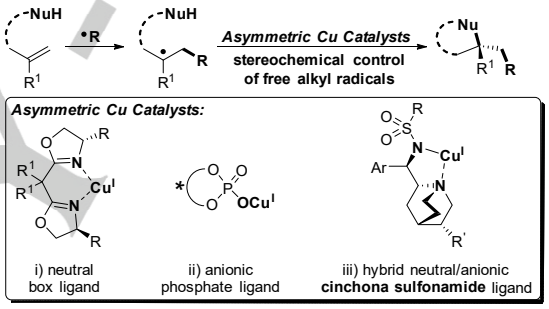
Xi-Tao Li, Qiang-Shuai Gu, Xiao-Yang Dong, Xiang Meng, and Xin-Yuan Liu*

Dedicated to Prof. Xiyan Lu on the occasion of his 90th birthday

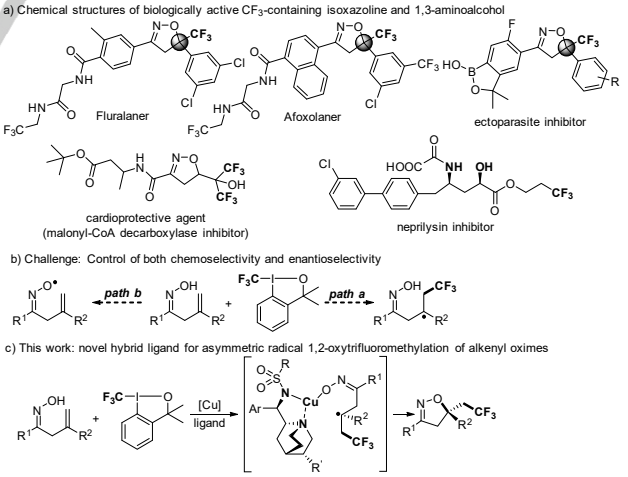
Abstract: A copper-catalyzed asymmetric radical oxytrifluoromethylation of alkenyl oxime and Togni's reagent has been successfully developed, providing straightforward access to CF_3-containing isoxazolines bearing α-tertiary stereocenters with excellent yield and enantioselectivity. The key to success is the rational design of cinchona alkaloid-based sulfonamide as neutral/anionic hybrid ligand to effectively control the stereochemistry in copper-catalyzed reaction involving free alkyl radical species. The utility of this method is illustrated by efficient transformation of the products into useful chiral CF_3-containing 1,3-aminoalcohols.

The development of radical asymmetric catalysis has been a formidable challenge in organic synthesis, largely because of the difficulty related to the stereochemical control of the involved highly reactive radical species.[1] In this aspect, transition-metal catalyzed intermolecular addition of radical species to alkenes to realize 1,2-difunctionalization has emerged as one of the most attractive strategies for the construction of two vicinal chemical bonds.[2] However, there has been limited catalytic systems for the enantioselective control of free alkyl radical species.[3-5] In particular, Buchwald and Liu pioneered the use of a neutral chiral Cu/bis(oxazoline) system to elegantly realize enantioselective alkene difunctionalizations, respectively (Scheme 1(i)).[4] At the same time, our group has also developed the copper/chiral anionic phosphate system to realize asymmetric transformations (Scheme 1(ii)).[1f,5] Despite the above impressive achievements, given the widespread applications of radical alkene difunctionalization,[2] the design and invention of new catalytic systems for radical-initiated asymmetric alkene difunctionalizations have been still highly demanded.

The cinchona alkaloids have been a privileged platform for chiral catalyst and ligand development in asymmetric organocatalysis and transition-metal catalysis, respectively.[6] In particular, cinchona alkaloid-derived sulfonamides have proved to be powerful bifunctional organocatalysts.[7] Driven by our keen interest in developing new catalytic system for radical-initiated asymmetric reactions,[5] we envisaged whether cinchona alkaloid-derived sulfonamides could be used as novel neutral/anionic hybrid ligands with copper through a single-electron-transfer (SET) catalytic cycle to realize enantioselective radical 1,2-difunctionalization of alkenes (Scheme 1(iii)). *It has been assumed that such sulfonamide might act as a hybrid N,N-bidentate ligand, encompassing both a neutral tertiary amine N and an anionic deprotonated sulfonamide N atoms, to form five-membered bis-chelating copper complex, enabling facile tuning of the electronic property of the copper center for new reactivity while benefiting from the well-established N,N-bidentate ligand-controlled chirality induction strategy.*[4] If this approach is successful, a new neutral/anionic hybrid ligand-based SET catalytic system derived from cinchona alkaloid derivatives could be readily established for effective control of stereochemistry involving free alkyl radical species.



Scheme 1 Copper catalysis for asymmetric radical 1,2-difunctionalization of alkenes



Scheme 2 Asymmetric 1,2-oxytrifluoromethylation of alkenyl oximes

Given the increasing interest for the CF_3 group in the development of pharmaceuticals and agricultural chemicals,[2,8] methods enabling facile access to CF_3-containing compounds are desirable. Particularly, chiral CF_3-containing isoxazolines with an *α*-tertiary stereocenter are important structural motifs in numerous biologically active compounds,[9] and also serve as important building blocks for the construction of valuable 1,3-aminoalcohols

[a] Dr. X.-T. Li, X.-Y. Dong, X. Meng, Prof. Dr. X.-Y. Liu*
Department of Chemistry, South University of Science and Technology of China, and Shenzhen Grubbs Institute, Shenzhen, 518055, China.
E-mail: liuxy3@sustc.edu.cn
Website: http://liuxy.chem.sustc.edu.cn/
Dr. Q.-S. Gu
Academy for Advanced Interdisciplinary Studies, South University of Science and Technology of China, Shenzhen, 518055, China.
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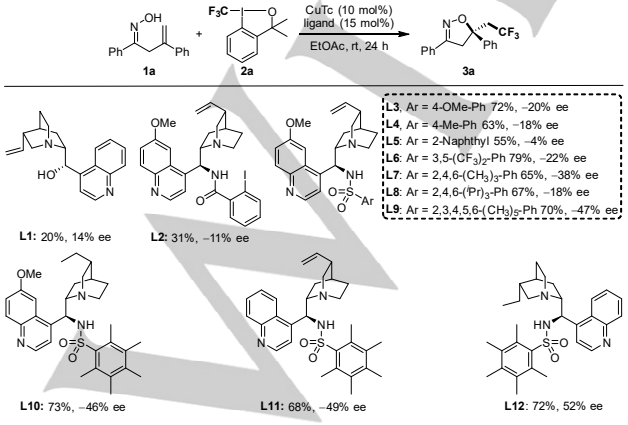
(Scheme 2a).[10] Recently, radical oxytrifluoromethylation of alkenyl oximes provides an efficient way to such backbones in the presence of different catalytic systems.[11] In contrast, the development of an enantioselective version remains inherently more challenging, due to the possibility for the concurrent occurrence of two radical pathways involving either iminoxyl radicals[12] or α-CF_3 alkyl radicals[11] in the oxidative conditions, therefore rendering it extremely difficult to efficiently control both chemoselectivity and enantioselectivity (Scheme 2b). Herein, we report the successful development of a cinchona alkaloid-based sulfonamide/copper catalyst that enables asymmetric radical oxytrifluoromethylation of alkenyl oximes, leading to highly enantioselective construction of CF_3-containing isoxazolines with the creation of an α-tertiary stereocenter (Scheme 2c).

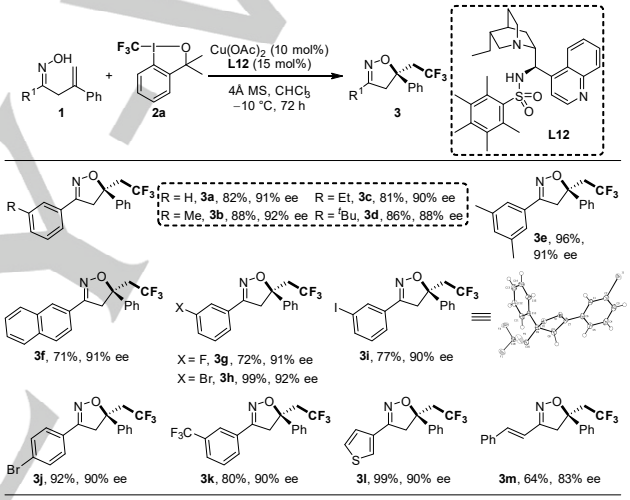
At the outset, we began our investigation by reacting β,γ-unsaturated ketoxime **1a** with Togni's reagent **2a**[13] in the presence of the previously reported asymmetric catalytic systems. Unfortunately, our attempts with the use of Cu(I)/chiral bis(oxazoline)[4] or our developed Cu(I)/chiral phosphate catalysis[5] under various reaction conditions met with very low enantioselectivity (Scheme S1 in SI). Based on our above-mentioned proposal for a cinchona alkaloid-derived hybrid ligand/copper catalytic system, we chose a series of cinchona alkaloid-derived tertiary amines featuring acidic functional groups as the ligand (Scheme 3). The reactions using cinchonine **L1** and quinine amide **L2,** respectively, gave the product **3a** in poor yield and enantioselectivity, presumably due to the weak acidity of the corresponding hydroxy or amide groups. To address this problem, we proposed that increasing the acidity by incorporating a sulfonamide group would favor the reaction efficiency and enantioselective control. Indeed, we were encouraged to observe significantly increased yield (72%) and enantioselectivity (52% ee) in the presence of CuTc (Tc = thiophene-2-carboxylate) and cinchonine-derived sulfonamide **L12** after a thorough evaluation of various quinine-, cinchonidine-, and cinchonine-derived sulfonamides. We next screened different Cu salts and found that $Cu(OAc)_2$ was the best in terms of reaction efficiency and enantioselectivity (Table S1 in SI). Among the solvents screened, chloroform gave rise to the best enantioselectivity (60%). Further investigation revealed that the addition of 4 Å molecular sieves could improve enantioselectivity to 71% ee. The enantioselectivity was further increased up to 91% by lowering the reaction temperature to −10 °C.



Scheme 3 Representative catalyst screening

With the optimal conditions being established, we next explored the substrate scope for different functional groups of the oxime moiety (Table 1). The results revealed that both the position and the electronic property of the substituents on the aromatic ring of oxime have a negligible effect on the reaction efficiency and stereoselectivity. All the substrates with electron-neutral (H), electron-rich (Me, Et, ^{t}Bu), and electron-deficient (F, Br, I, CF_3) functional groups at the *para*- or *meta*-position of the arene and a dimethyl-substituted phenyl ring as well as a polyarene naphthalene ring, were well tolerated, giving **3a–3k** in 71–99% yields with 88–92% ee. The absolute configuration of **3i** has been determined to be *S* by X-ray structural analysis (Figure S1 in SI).[14] Of particular note is that substrate bearing a strongly coordinating thiophene ring also delivered **3l** in 99% yield with 90% ee. In addition, substrate containing an additional internal alkene afforded the product **3m** in 64% yield and 83% ee with the internal alkene being intact.

Table 1 Substrate scope for different oxime moieties[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $Cu(OAc)_2$ (0.02 mmol), **L12** (0.03 mmol), 4Å MS (200 mg), and $CHCl_3$ (4 mL) were used. [b] Isolated yield, and ee was determined by chiral HPLC analysis.

We next examined various *gem*-disubstituted alkenes (Table 2). A range of substrates **1n**–**1t**, including those having phenyl rings with electron-donating or -withdrawing groups at different positions (*meta* or *para*) as well as a polyarene naphthalene ring afforded **3n**–**3t** in 80–99% yields with 82–91% ee. Furthermore, many common functional groups, such as ester (**1u**), nitro (**1v**) and potentially reactive free aldehyde (**1w**) as well as acetal (**1x**) groups, were all compatible with these conditions. Next, we tested the use of heteroarene-substituted alkenes as the substrate to give **3y** and **3z** in 75% and 85% ee, respectively. Noteworthy is that alkenyl-substituted alkene (diene) could also be employed in the reaction to give **3aa** in 79% yield with moderate enantioselectivity, which is currently under further optimization in our laboratory.

The enantioenriched isoxazolines can be transformed into valuable chiral CF_3-containing 1,3-aminoalcohols (Scheme 4). For example, simple reduction of **3a** smoothly generated the corresponding chiral 1,3-aminoalcohols **4a** and **4b** as a nearly 1:1 mixture of diastereomers in 96% overall yield without diminishing

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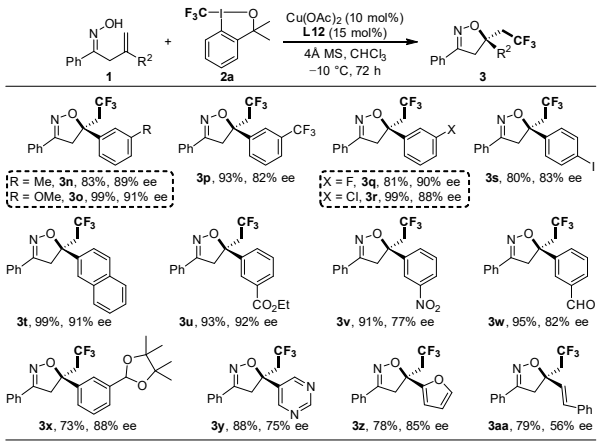
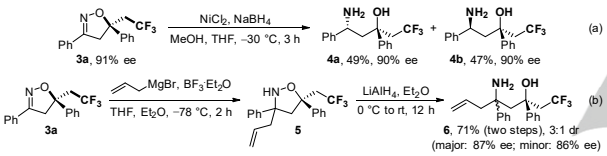
the enantioselectivity. Besides, treatment of **3a** with allylmagnesium bromide[10] followed by reduction with $LiAlH_4$ delivered 1,3-aminoalcohol **6** bearing two tertiary stereocenters as a 3:1 mixture of diastereomers.

Table 2 Substrate scope for different alkene moieties[a,b]



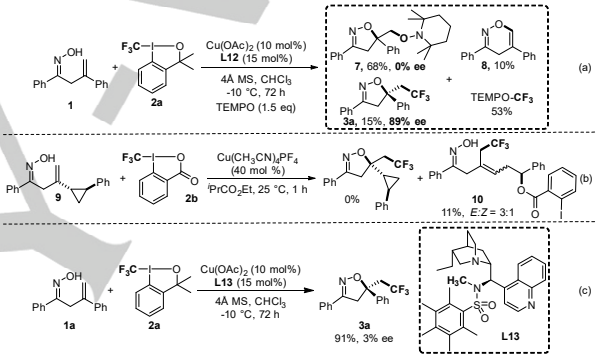
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $Cu(OAc)_2$ (0.02 mmol), **L12** (0.03 mmol), 4Å MS (200 mg), and $CHCl_3$ (4 mL) were used. [b] Isolated yield, and ee was determined by chiral HPLC analysis.



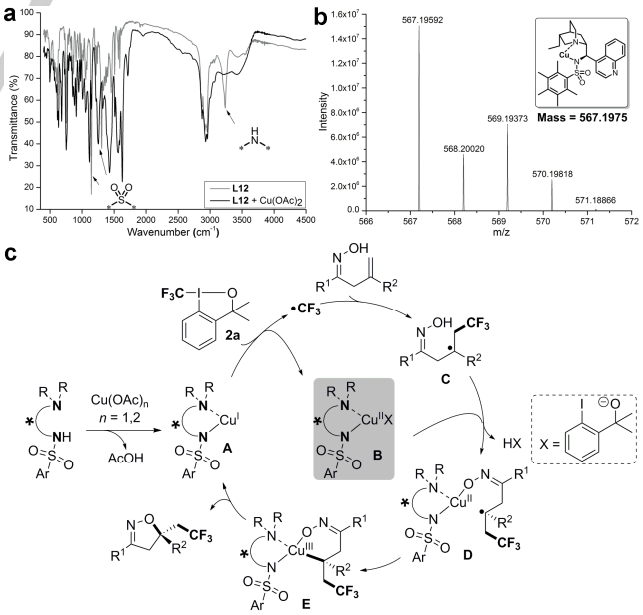
Scheme 4 Versatile transformations

Prior mechanistic study reveals that there exist two possible pathways involving either iminoxyl radicals[12] or *α*-CF_3 alkyl radicals[11] in the reaction (Scheme 2b). The radical-trapping experiment (Scheme 5a) using 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO) as a radical scavenger provided TEMPO-trapped isooxazoline **7** and 4*H*-1,2-oxazine **8** in 68% and 10% yields, respectively. The latter was formed presumably via a radical *6-endo-trig* cyclization. This observation, together with previous studies on such reactions,[12] suggests the presence of an iminoxyl radical intermediate and its subsequent intramolecular cyclization onto the pendant double bond in the presence of stoichiometric TEMPO. Note that **7** was racemic, while **3a** obtained at the same time had the essentially identical ee (89% ee). These results clearly indicate that a mechanism involving an iminoxyl radical intermediate to give the trifluoromethylation product is unlikely. On the other hand, TEMPO-CF_3 was also formed in 53% yield. Furthermore, the radical clock experiment on substrate **9** under the typical conditions yielded **10** in 11% yield as an inseparable mixture, presumably via a radical addition/cyclopropane ring opening/acid trapping cascade process (Scheme 5b). These observations suggest that CF_3 radical is likely generated *in situ*, which upon further addition to alkene gives rise to α-CF_3 alkyl radical (Scheme 2b, path a).

Further experiments were conducted to ascertain the roles of cinchona alkaloid-based sulfonamide ligand and copper metal in the current reaction. First, the control reaction with methyl-protected sulfonamide **L13** derived from **L12** as the ligand under the standard conditions furnished **3a** in 91% yield with poor enantioselectivity (Scheme 5c), clearly indicating that the sulfonamide N–H bond is critical to control asymmetric induction. In addition, FTIR spectroscopy of **L12** showed one peak at ca. 3237 cm^{-1} corresponding to the sulfonamide N–H bond. This peak completely disappeared after mixing **L12** with $Cu(OAc)_2$ (Scheme 6a), indicating that deprotonation of this sulfonamide and subsequent coordination to $Cu(OAc)_2$ might have occurred to afford complex Cu-**L12**.[15] Although attempts to obtain single crystals of a ligand−Cu complex according to Thompson's method[16] failed, our high-resolution mass spectrometry (HRMS) analysis of a reaction mixture of $Cu(OAc)_2$ and **L12** in a 1:1 ratio in $CHCl_3$ revealed a peak at *m/z* 567.1975 attributable to a Cu-**L12** complex formed by ligand exchange (Scheme 6b). These observations possibly suggest that **L12** acts as a *N,N*-bidentate ligand, binding copper through both the tertiary amine and the sulfonamide anionic N atom to form a five-membered bis-chelating complex. Nonetheless, solid evidence on the real catalyst is still missing for now and needs further studies in future.



Scheme 5 Mechanistic study



Scheme 6 Mechanistic proposal. **a,** FTIR spectroscopy investigation. **b,** High-resolution mass spectrometry (HRMS) analysis. **c,** A proposed working mechanism.

On the basis of the above mechanistic investigations and previous studies,[4,5] a working mechanism for the current catalytic system is tentatively proposed in Scheme 6c: The *in situ* formed bis-chelating Cu^{I} complex **A** through ligand exchange could act as an active catalyst to undergo the initial single electron transfer with **2a** to generate Cu^{II} complex **B** and the CF_3 radical. The latter rapidly added to the alkene to yield radical intermediate **C**, which could be trapped by Cu^{II} complex **B** to form a Cu^{II} species **D** through ligand exchange. Subsequent intramolecular redox reaction generated a Cu^{III} species **E**, followed by reductive elimination to give the final product.[17] However, an alternative scenario where the anionic sulfonamide monodentately coordinates to copper and the quinuclidine tertiary amine works cooperatively as a base to activate the hydroxy group cannot be ruled out at the present stage (Scheme S2 in SI). Further studies are required to fully elucidate the mechanistic details of the reaction.

In summary, we have successfully developed a class of cinchona alkaloid-based sulfonamides performing as effective hybrid ligand in combination with copper metal, which enables the catalytic asymmetric radical oxytrifluoromethylation of alkenyl oximes for straightforward access to CF_3-containing isoxazolines bearing an α-tertiary stereocenter with excellent yield and enantioselectivity. The obtained products can be readily transformed into useful chiral CF_3-containing 1,3-aminoalcohols. Further studies including the investigation of the origin of stereocontrol and the development of other radical-initiated asymmetric chemistry with such a catalytic system are ongoing in our laboratory.

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Keywords: alkene oxytrifluoromethylation • alkenyl oxime • asymmetric radical reactions • copper catalysis • CF_3-containing isoxazolines

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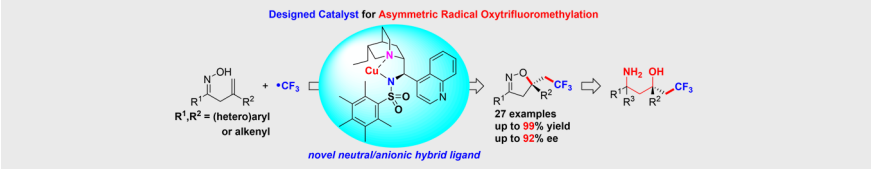

Powerful hybrid ligand: Cinchona alkaloid-based sulfonamide has been designed as effective hybrid ligand with copper, which enables catalytic asymmetric radical oxytrifluoromethylation of alkenyl oximes to give CF_3-containing isoxazolines bearing α-tertiary stereocenters with excellent yield and enantioselectivity.

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