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Enantioselective Copper-Catalyzed Intermolecular Cyanotrifluoromethylation of Alkenes via Radical Process

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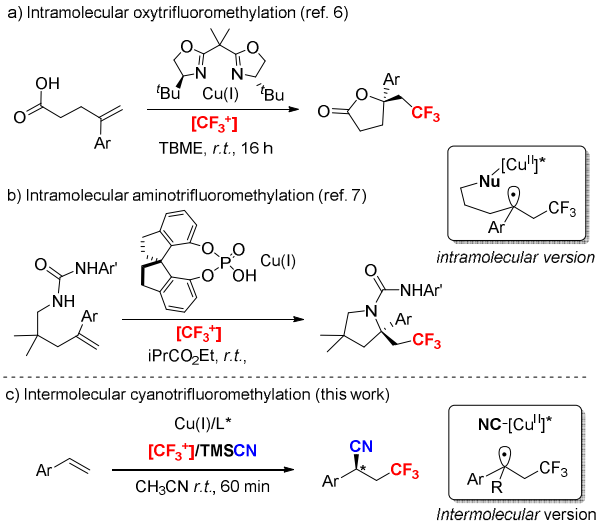
Supporting Information Placeholder

ABSTRACT: A novel enantioselective copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes has been developed, in which a variety of CF_3-containing alkylnitriles are furnished with excellent enantiomeric excess. Preliminary mechanistic studies reveals: 1) the reaction was initiated by a SET process between activated Togni's CF_3^+ reagent and Cu(I) catalyst; 2) the released CF_3 radical readily added to styrene to provide benzylic radical, which was then trapped by a chiral Cu(II) cyanide species to deliver the desired alkylnitirles; 3) low concentration of CN anion was crucial to obtain high enantioselectivity.

Difunctionalization of alkenes have proved to be powerful tools for constructing two vicinal carbon-carbon and carbon-heteroatom bonds in a single step from simple precursors, which significantly enhanced the molecular complexity with excellent step-economy.[1] Among the reported methods, atom transfer radical addition (ATRA) reaction is featured as one of most efficient strategy for the difunctionalization of alkenes, and has received much attention in the last several decades.[2] Apart from the pioneering work for introducing carbon-halide bonds, the concept of ATRA has been widely broadened with the unremitting endeavors of chemists. However, due to the extremely difficulty on the stereochemical control of highly reactive alkyl radical intermediate, the successful *enantioselective* ATRA-type reactions of alkenes are still quite limited.[3]

Recently, a number of CF_3 radical initiated ATRA-type reactions, catalyzed by copper complex, have been reported as an efficient protocol to build a variety of CF_3-containing molecules.[4,5] Given the prevalence of CF_3 group in pharmaceuticals, materials and agriculture chemicals, asymmetric trifluoromethylation of alkenes have attracted numerous attentions, meanwhile only two successful enantioselective examples limited on intramolecular version have been reported: 1) in 2013, Buchwald and co-workers reported a pioneering work on asymmetric oxytrifluoromethylation of alkenes in the presence of chiral bisoxazoline /Cu(I) catalyst, producing various of functionalized γ- or δ-lactones with good enantioselectivity (typically less than 85% ee, Scheme 1a);[6] 2) Liu and coworkers recently discovered an enantioselective aminotrifluoromethylation of alkenes with chiral phosphoric acid/Cu(I) catalyst, and the reactions provided excellent enantioselectivity (up to 97% ee), but generally with long reaction times (3-4 days, Scheme 1b).[7] In these reactions, the tethered carboxylic acid and amine units played an important role to promote enantioselective reaction between organic radical and chiral Cu(II) species. In contrast, the more challenging



Scheme 1. Asymmetric Cu-catalyzed CF_3 radical initiated ATRA reactions.

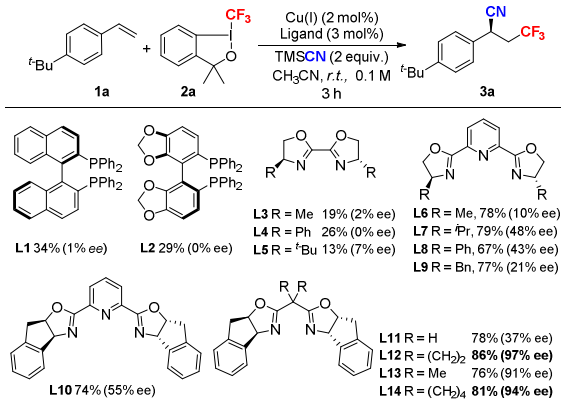
intermolecular reaction remains unexplored. Herein, we report our realization of highly enantioselective intermolecular cyanotrifluoromethylation of styrenes in the presence of chiral bisoxazoline/Cu(I) catalyst to provide a variety of enantiomeric enriched CF_3-substituted arylacetonitriles (up to 99% ee) with high efficiency (eg. 1 mol % catalyst, within 1 hour under room temperature, Scheme 1c).

Recently, we have discovered a copper-catalyzed enantioselective cyanation of benzylic C–H bonds via radical relay process,[8] in which a diffusible organic radical, generated from hydride radical abstraction, could rapidly react with a chiral copper cyanide species to form C-CN bond with excellent enantioselectivity. Meanwhile, the alkyl radical species, generated from addition of CF_3 radical to alkenes, was also proposed as key intermediate in our previously reported ATRA-type reactions.[9] We speculated that, if the trapping alkyl radical by chiral copper cyanide species could be compatible in these reactions, the asymmetric cyanotrifluoromethylation of alkenes might be expected to deliver optical CF_3-containing alkyl nitriles. Given the formidable challenge of enantioselective ATRA reactions, we believed that this investigation should be of great interest.

Based on our previous catalytic system,[9c] we commenced to investigate different types of chiral ligands in the presence of $Cu(CH_3CN)_4PF_6$ catalyst (Scheme 2). Phosphine ligands **L1**-**L2** and bisoxazoline ligands **L3**-**L5** only showed poor reactivity as well as low enantioselectivity. In contrast, Py-Box type ligands

L6-L10 performed better reactivities to provide **3a** in good yields, but with poor to moderate enantioselectivity. Further ligand screening was focused on the 1,3-bis-2-oxazoline ligands, **L11-L14** with indan group were proven privilege ligand, and ligand **L12** was able to catalyze the reaction in good yield (86%) and excellent ee (97%). While, ligand **L11** with methylene group provided poor enantioselectivity (37% ee). Further optimization of reaction conditions indicated that some reaction parameters, such as, solvent, copper catalyst, and temperature, have less impact on the enantioselectivity (see SI). Notably, trace amount (less than 5%) of side product, derived from homo-coupling of benzylic radical, was detected in the all of above reactions. Furthermore, when copper catalyst loading was lowered to 1 mol%, identical result could also be obtained after slightly prolonged reaction time. However, other inorganic cyanides, such as NaCN, KCN, failed to provide the desired product **3a**, indicated that the mutual activation of TMSCN and Togni's [CF_3^+] reagent was very important for the transformation.[9a-d]

Scheme 2. Ligand Screening.[a,b]

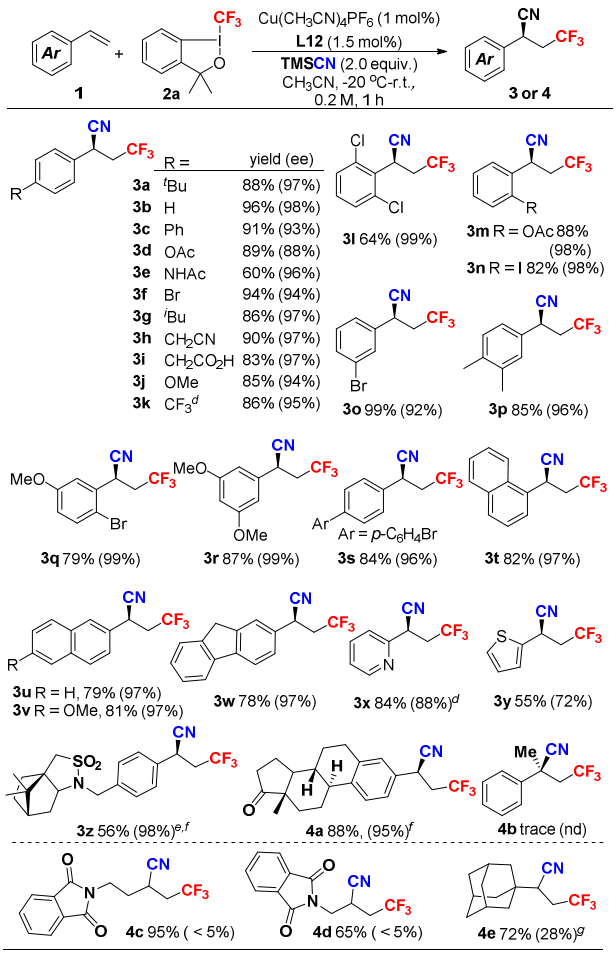


[a] All reactions were conducted in 0.1 mmol scale with $Cu(CH_3CN)_4PF_6$ as catalyst; [b] Yield was determined by ^{19}F-NMR with CF_3-DMAc as internal standard.

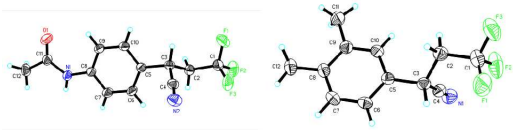
With the optimized reaction condition in hand, substrate scope of styrenes was explored in the presence of 1 mol% of copper catalyst, and results were summarized in Table 1. A series of styrenes, with various substituents on the aromatic ring, were found suitable candidate to provide the corresponding products **3a-3s** in good to excellent yields and excellent ee. And an array of functional groups, such as halogen, ester, ether, carboxylic acid, and amide, were compatible with the reaction condition. Importantly, compared to *para*- and *meso*-substituted styrenes, *ortho*-substituted substrates exhibited a higher enantioselectivity (**3l-3n** and **3q**). In addition, α- and β-vinyl naphthylenes and vinylfluorene were also tolerated under the reaction condition to give products **3t-3w** with excellent results. In contrast, slightly lower enantioselectivities were observed in the cases of vinyl heteroarenes (88% ee for **3x** and 72% ee for **3y**). Finally, for the complex styrene substrates, excellent stereoselectivities were also observed to generate products **3z** (98% de) and **4a** (95% de). The absolute configuration of (*S*)-**3e** and (*S*)-**3p** were determined by X-Ray.[10] However, the present protocol suffered from some limitations: a) 1,1-disubstituted alkene exhibited poor reactivity (**4b**); b) terminal alkenes with alkyl substituent provided good reactivity but poor enantioselectivities (**4c-4e**).

It was worth noting that, without further purification after the standard trifluoromethylation, the related amine derivatives **5** could be obtained directly in 72 yield and 95% ee with sequential hydrogenation over a Raney nickel catalyst (eq 1, for details, see SI). Interestingly, when internal alkenes, *β*-methylstyrene Z-**6** and E-**6**, were treated under standard reaction condition, both reactions gave

Table 1. Substrate Scope.[a,b,c]

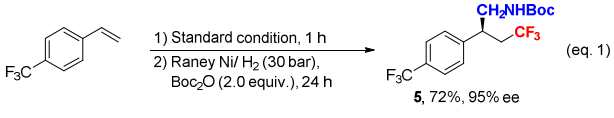


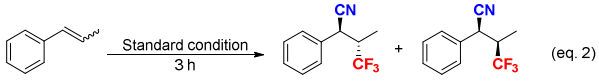
[a]Reaction condition: substrate (0.4 mmol), **2a** (0.6 mmol), TMSCN (0.8 mmol), $Cu(CH_3CN)_4PF_6$ (0.004 mmol, 1 mol %), **L12** (0.006 mmol, 1.5 mol %), CH_3CN (2.0 mL) at -20 °C - *r.t.*, [b]Isolated yield. [c]Enantiomertic excess (*e.e.*) determined by HPLC on a chiral stationary phase. [d]ee of the crude product. [e]0.2 mmol scale. [f] Diastereoselective excess (*d.e.*). [g]Enantiomertic excess was determined by GC on a chiral stationary phase.



(S)-**3e** (S)-**3p**

identical results to yield isomers *anti*-**7** and *syn*-**7** with excellent enantioselectivity, but in moderate yield (eq 2). In addition, the minor isomer, *syn*-(1S,2R)-**7**, presented a higher enantioselectivity than that of major product, *anti*-(1S,2S)-**7**. The differences in enantiomeric ratio and yield of two diastereomer *anti*-**7** and *syn*-**7** probably reflect a matched-mismatched effect between the ligand and organic radical intermediates.





substrate	*anti*-**7**	*syn*-**7**
Z-**6**	34% (94% ee)	11% (99% ee)
E-**6**	35% (94% ee)	12% (99% ee)

To gain insight into the mechanism, a set of control experiments were conducted. For the possibility of radical pathway, the standard reaction was dramatically inhibited by adding radical scavengers, such as Tempo or $PhN(O)CO_2Me$ (NO), and the corresponding benzyl NO-C and NO-CF_3 bond formation products were obtained (see SI). Combined with the results in eq 2, these observations were consistent with the involvement of CF_3 and benzyl radicals in the catalytic system.

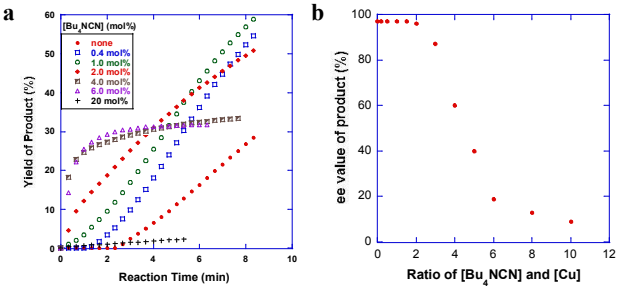


Figure 1. Extra cyanide effect on the reaction rates (a) and ee values (b). Extraneous Bu_4NCN (0 ~ 20 mol%) was added to the standard reaction using 2 mol% copper catalyst loading (**L12**:Cu = 1.5:1) at -10 °C.

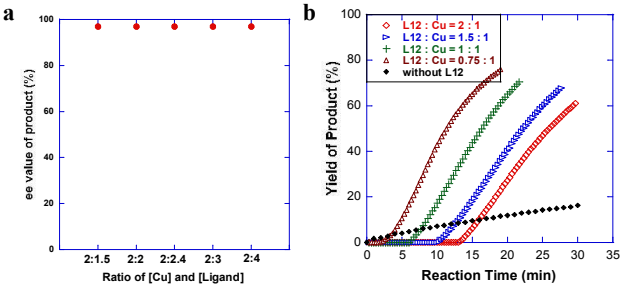
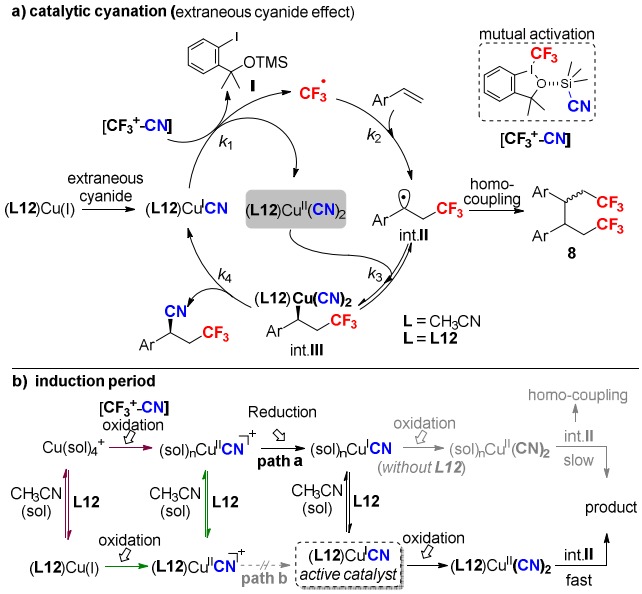


Figure 2. Ligand effect on the ee values of the product (a) and reaction rates (b).

Additional studies were conducted to provide further mechanistic insights. We were surprised to observe an obvious induction period in the time course studies, which was monitored by ^{19}F-NMR. During this period, only side-product, derived from the homo-coupling of benzyl radical species, was detected. Interestingly, when different amount of extraneous cyanide (Bu_4NCN, 0.4 - 2 mol %) was added to the catalytic system, the induction period is significantly shortened, and finally disappeared (Figure 1a). Within this Bu_4NCN loading range, same ee (97%) of the product was obtained, while the enantioselectivity was decreased dramatically with further increase of Bu_4NCN (Figure 1b). Importantly, when Bu_4NCN was increased to 20 mol % (10 times of Cu catalyst), the reaction proceeded with much lower reaction rate to furnish the desired product with low ee (< 15%) value (Figure 1). We reasoned that, relatively high concentration of cyanide performed negative effect on the coordination between catalyst and chiral ligand, resulting in the dissociation of **L12** from copper center, which was supported by individual ^{1}H-NMR experiments (see SI). These observations indicated that the low concentration of cyanide in the reaction system was vital for excellent enantioselective control and the mutual activation between [CF_3^+] and TMSCN presents a good reaction mode to release cyanide slowly. Furthermore, the enantio-selectivity of the product was proportional to the enantiomeric excess of the chiral ligand. The absence of non-linear effects supported the active catalyst species for the chiral induction was consistent with a 1:1 ratio of copper catalyst and ligand (See SI).

Furthermore, ligand effect on the enantiomeric excess of product was also evaluated (Figure 2a). We were surprised to find that the ee of **3a** retained with various ratio of **L12** and Cu catalyst, even in the case of **L12** slightly less than catalyst. Meanwhile, the ligand effect was also observed on induction period, which was prolonged with increased amount of **L12** (Figure 2b). However, there is no induction period in the absence of ligand **L12**, but the reaction proceeded with much slower rate to give product in low yield (19%), companied a significant amount side benzylic radical self-coupling product **8** (15% yield).



Scheme 3. Proposed Mechanism.

Based on above observations, the proposed mechanism was given in Scheme 3. Owing to the shortened induction period with addition of extraneous cyanide (Figure 1a), we believed that the newly formed (**L12**)Cu^ICN could act as active catalyst that underwent the initial single electron transfer (SET) with mutual activated [**CF_3^+-CN**] complex to generate (**L12**)$Cu^{II}(CN)_2$ and CF_3 radical. The latter rapidly added to styrene to yield benzylic radical int.**II**, which combined with (**L12**)$Cu^{II}(CN)_2$ to yield Cu(III) species int.**III**.[11] The final reductive elimination of int.**III** provided desired C-CN bond-forming product **3** in excellent enantiomeric excess (Scheme 3a).[8,12]

The relationship of induction period and ligand loading shown in Figure 2b suggested that the dissociation of **L12** from Cu center to give (sol)Cu^I (brown arrow) or (sol)$Cu^{II}CN$ (green arrow) species could be the key step for the generation of active (**L12**)Cu^ICN catalyst species. The generated (sol)$Cu^{II}CN$ was sequentially reduced and recoordinated with **L12** to give (**L12**)Cu^ICN (path a).[13] In contrast, the direct transformation from (**L12**)$Cu^{II}CN$ to (**L12**)Cu^ICN (path b) is unlikely. One rational reason is that free Cu^{II} can be readily reduced to Cu^I in the presence of cyanide anion, but the related bidentate nitrogen ligated Cu^{II} cyanide is quite stable.[14] Thus, in the absence of **L12,** (sol)Cu^ICN can be readily obtained via path a, and then was oxidized to (sol)$Cu^{II}(CN)_2$ species, which further reacts with benzylic radical to deliver product without reduction period. However, in comparison with the (**L12**)$Cu^{II}(CN)_2$ species, (sol)$Cu^{II}(CN)_2$ showed much lower reactivity, thus resulted in low yield of cyanation product, and significant amount of homo-coupling side product **8** simultaneously. Finally, we have to mention that, the detailed mechanism, especially for the generation of active Cu(I)CN species, is unclear at the moment.

In summary, we have developed a novel copper-catalyzed enantioselective trifluoromethylcyanation of alkenes, which exhibited good substrate scope and functional group compatibility. A variety of CF_3-containing organonitriles were obtained with excellent enantiomeric excess under mild reaction condition- with low catalyst loading. Preliminary mechanistic studies demonstrated that the enantioselective C-CN bond formation is possibly resulted from reaction of the active (**L12**)$Cu^{II}(CN)_2$ species with benzyl radical. Further detailed mechanistic studies and applications based on this chemistry are in progress in our laboratory.

ASSOCIATED CONTENT

Synthetic procedures, characterization, mechanistic study data and additional data. The supporting information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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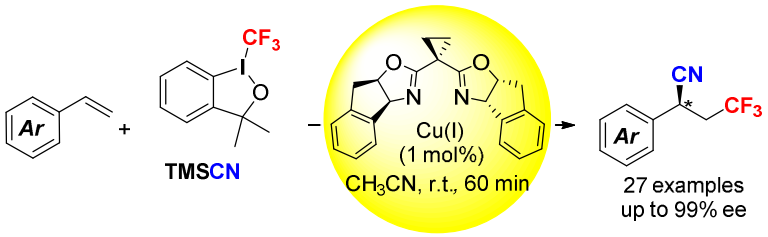

Highly enantioselective intermolecular copper-catalyzed cyano-trifluoromethylation of alkenes