Communication

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Enantioselective Trifluoromethylalkynylation of Alkenes *via* Copper-Catalyzed Radical Relay

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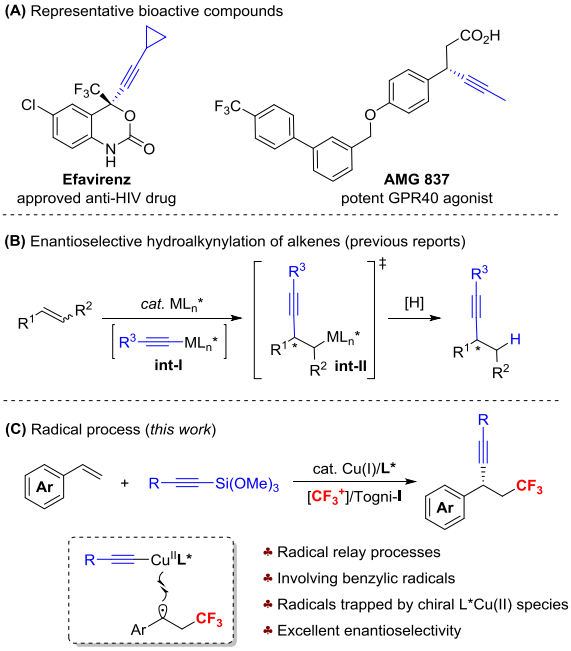
Supporting Information Placeholder

ABSTRACT: A novel enantioselective copper-catalyzed trifluoromethylalkynylation of styrenes, proceeding through a radical relay process, is described herein, which affords structurally diverse CF_3-containing propargylic compounds in good yield with excellent enantioselectivities under very mild conditions. In addition, the reaction features wide substrate scope and good functional group tolerance. Moreover, the trifluoromethylalkynylated products can be easily converted into synthetically useful chiral terminal alkynes, allenes, *Z*-alkenes, as well as CF_3-modified nonsteroidal *anti*-inflammatory drugs.

Molecules bearing a propargylic stereocenter are frequently found in a myriad of natural products and therapeutics, such as Efavirenz and AMG 837 (Scheme 1A).[1] Meanwhile, chiral alkynes have also been recognized as an important and useful synthon in organic synthesis.[1] Therefore, organic chemists made considerable effort to develop methodologies for their synthesis during the last several decades. Among them, catalytic asymmetric alkynylation of alkenes serves as one of the most efficient and prevalent tools.[1c,2] Nevertheless, the asymmetric alkynylation of alkenes has been less developed, only catalytic enantioselective hydroalkynylation of alkenes has been documented to date,[3,4] where *in situ* generated chiral organometallic acetylides **int-I** as a key intermediate underwent asymmetric addition across alkenes, leading to the formation of a propargylic stereocenter in the intermediate **int-II** (Scheme 1B). Herein, we communicate a novel enantioselective copper-catalyzed alkynylation of styrenes through a radical relay process, which involves a benzylic radical intermediate trapped by chiral L*Cu^{II}-alkynyl species (Scheme 1C).

Given that the incorporation of the trifluoromethyl group into pharmaceuticals and agricultural chemicals has a significant effect on their properties, the exploration of trifluoromethylation reactions has received much attention.[5] Very recently, the Li[6a] and Yu[6b] groups independently reported an intermolecular radical trifluoromethylalkynylation of alkenes by employing electrophilic alkynylating reagents (alkynyl-SO_2CF_3 or alkynyl-Ts) under metal-free conditions.[6] Meantime, the Zhu[7a-b] and Studer[7c] groups have demonstrated the intramolecular trifluoromethylalkynylation of alkenes, in which a Csp^3-Csp bond was forged through sequential carbon-centered radical addition to the C-C triple bond and β-elimination of the resultant vinyl radicals. Despite these advances, the involvement of highly reactive radical species



Scheme 1. Catalytic asymmetric alkynylation of alkenes.

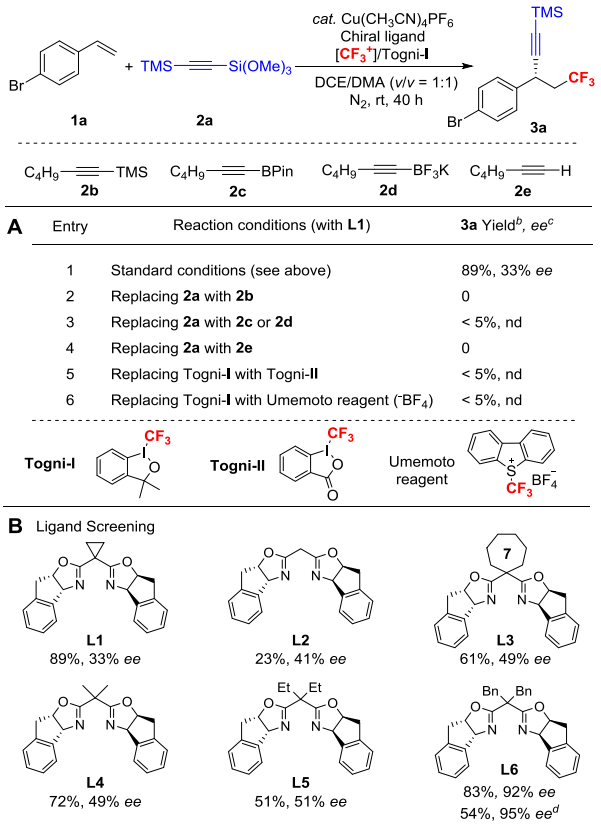
makes this asymmetric alkynylation of alkenes extremely difficult. To the best of our knowledge, no such asymmetric alkynylation reaction has been reported to date.

As our continuous research interest in asymmetric radical transformations (ARTs),[8] our group has developed a copper-catalyzed radical relay process for the enantioselective cyanation[9] and arylation[10] of styrenes or benzylic C-H bonds, using TMSCN and $ArB(OH)_2$ as nucleophiles.[11] Critical to the success of the copper-catalyzed radical relay process is that a benzylic radical intermediate is enantioselectively trapped by (L*)$Cu^{II}(CN)_2$ or (L*)Cu^{II}-Ar; in addition, a highly reactive (L*)Cu(III) intermediate was proposed for the formation of Csp^3-CN or Csp^3-Ar bonds through enantioselective reductive elimination.[9-12] Therefore, we reasoned that, if nucleophilic alkynylating reagents were suitable for the copper-catalyzed radical relay process, the enantioselective alkynylation of styrenes would be feasible (Scheme 1C).

Based on this hypothesis, several nucleophilic alkynylating reagents **2a-2e** were tested for the reaction of 4-bromostyrene **1a** with Tongi-**I** reagent in DCE/DMA (*v*/*v* = 1:1), using 10 mol%

$Cu(CH_3CN)_4PF_6$ and 12 mol% bisoxazoline (Box) ligand **L1**. As shown in Table 1A, disilyl-substituted acetylene **2a** proved to be a suitable reactant for the alkynylation reaction, giving the desired product **3a** in 89% yield, albeit with low enantioselectivity (33% *ee*, entry 1). Notably, the reaction exclusively occurred at the trimethoxysilyl position, with the trimethylsilyl group preserved, suggesting that an alkynyl-$Si(OMe)_3$ bond is more reactive than alkynyl-$SiMe_3$ bonds, with respect to transmetallation furnishing a key (L*)Cu(II)-alkynyl intermediate. In fact, the alkynylsilyl reagent **2b** was unsuitable for this reaction (entry 2). Additionally, alkynyl boron reagents **2c** and **2d** were also surveyed, but proved to be ineffective (entry 3). Terminal alkyne **2e**, a commonly-used alkynylating reagent, didn't deliver the desired product either (entry 4). Moreover, other elelctrophilic trifluoromethyl reagents, such as Togni-II and Umemoto reagent, were also examined, which couldn't promote the reaction (entries 5-6). Inspired by these results, a series of chiral Box ligands were then investigated (Table 1B). Compared to **L1**, the Box ligands **L2** without *gem*-substitutent and **L3** with *gem*-7-membered ring gave the product **3a** in worse yield, but with better enantioselectivities. The *gem*-disubstituted ligands **L4** and **L5** gave similar results as **L3**. To our delight, when the sterically bulkier ligand **L6** was employed, the reaction proceeded smoothly to give **3a** in 83% yield with 92% *ee*. The enantioselectivity of **3a** could be further improved to 95% ee using less amounts of DMA (DCE/DMA *v/v* from 1:1 to 7:1), however, but with a significantly diminished yield (54%).

Table 1. Optimization of the reaction conditions.[a]



A

Entry	Reaction conditions (with **L1**)	**3a** Yield[b], *ee*[c]
1	Standard conditions (see above)	89%, 33% *ee*
2	Replacing **2a** with **2b**	0
3	Replacing **2a** with **2c** or **2d**	< 5%, nd
4	Replacing **2a** with **2e**	0
5	Replacing Togni-**I** with Togni-**II**	< 5%, nd
6	Replacing Togni-**I** with Umemoto reagent ($^-BF_4$)	< 5%, nd

Togni-I Togni-II Umemoto reagent

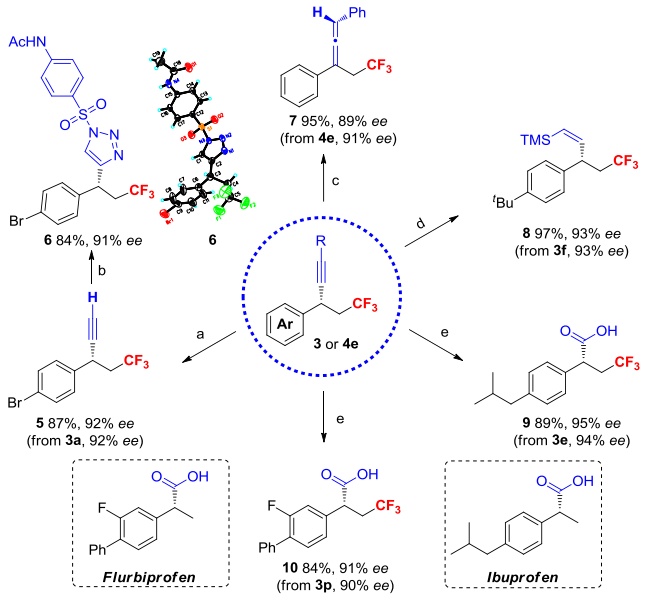
B Ligand Screening

[a] The reaction was performed on a 0.2 mmol scale, $Cu(CH_3CN)_4PF_6$ (10 mol %), ligand (12 mol %), **1a** (0.2 mmmol), **2a** (0.4 mmol), Togni-**I** (0.3 mmol) in DCE/DMA (4 mL) at room termperature. [b] ^{19}F-NMR yield with CF_3-DMA as a internal standard; [c] *ee* value was determined by HPLC on a chiral stationary phase. [d]DCE:DMA (4 mL, *v/v* = 7:1) was used.

After having established the optimal reaction conditions, we then investigated the substrate scope of this asymmetric reaction. As shown in Table 2, styrenes bearing both electron-donating and electron-withdrawing groups at the *para* position were suitable for the reaction, giving the corresponding products **3a-3l** in moderate to good yields (46-88%) with excellent enantioselectivities (91-97% *ee*). Notably, reactions of electron-rich styrenes **1d-1f** and **1i** in a mixed solvent (DCE:DMA, *v/v* = 40:1) generally yielded the desired products in slightly higher yields. In addition, reactions of *meta*-substituted styrenes also worked well to provide the desired products **3m-3o** in good yields (62-72%) with excellent enantioselectivities (88-95% *ee*). Furthermore, the substrate (**1p**) bearing two substituents on the aromatic ring reacted smoothly with **2a** to afford the desired product **3p** in 70% yield with 90% *ee*, and the aryl framework of styrenes can be extended to a naphthalene-derived system (**3q** 52%, 93% *ee*). Notably, various functional groups such as halogen, ether, ester and nitrile were well tolerated; in addition, benzyl chloride (**1g**) that is very prone to atom-transfer radical processes was also compatible with the radical relay process. The asymmetric trifluoromethylalkynylation reaction is also scalable, the reaction of **1a** could be performed on a 5-mmol scale to give 1.42g the desired product **3a** in 82% yield with 92% *ee*.

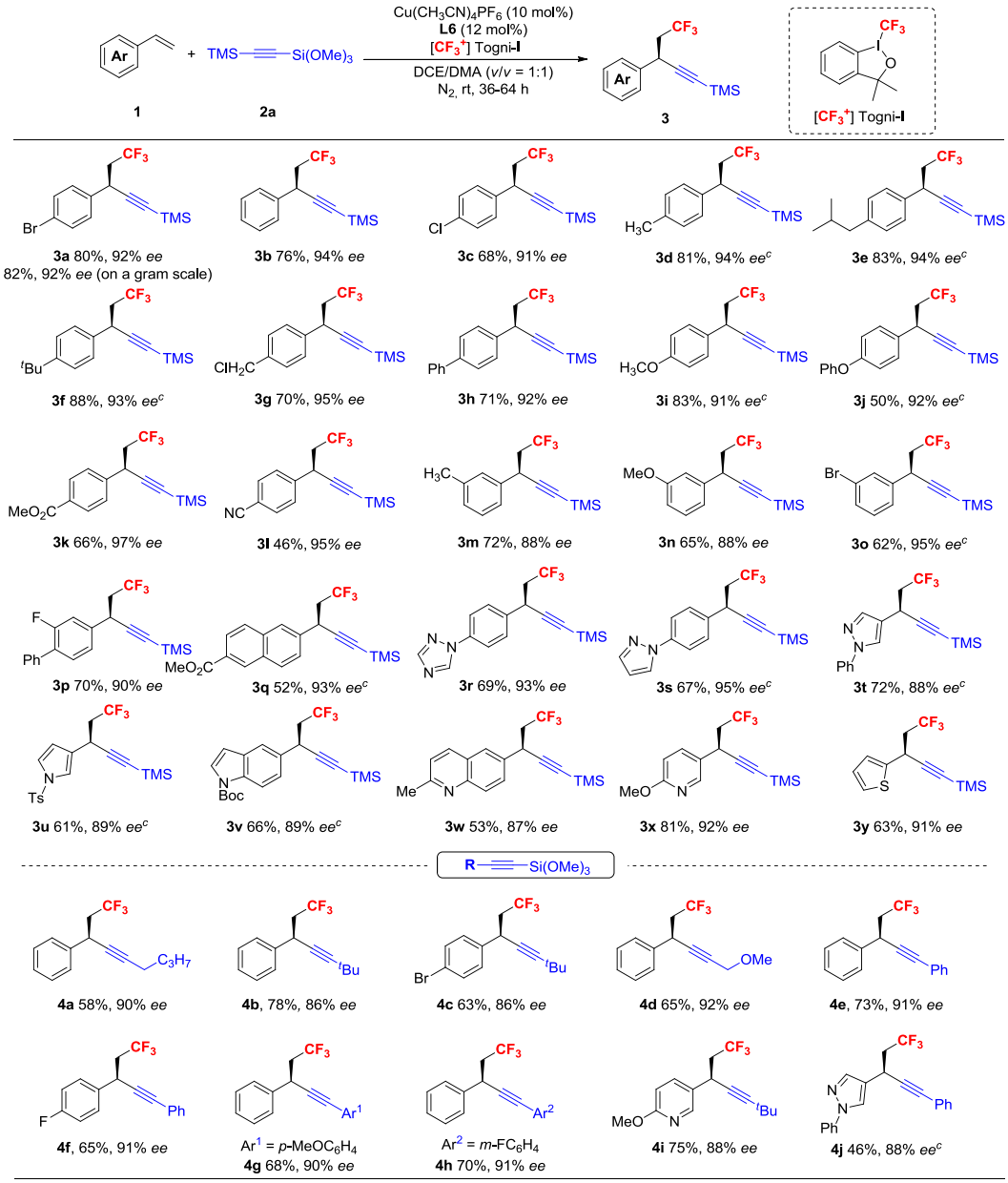
Importantly, reactions of vinylheteroarenes worked nicely to afford the desired enantiomerically enriched propargylic products **3r-3y** in good yields (53-81%) with excellent enantioselectivities (88-95% ee); notably, heterocycles commonly existing in therapeutics, such as 1,2,4-triazoles, pyrazoles, indole, quinoline, pyrrole, pyridine and thiophene, were well tolerated under the current conditions, which once again showcased the robustness of our method. More importantly, structural variations in the alkynylating reagents **2** were also realized. As revealed in Table 2, substituents on the C-C triple bond can be various alkyl (e.g., ^{n}Bu, ^{t}Bu, methoxymethyl) and aryl groups, and all these alkynylating reagents **2** exhibited good reactivity to afford the desired products **4a-4j** in good yields (46-78%) with excellent enantioselectivities (86-92% *ee*).

Scheme 2. Synthetic applications.



Reaction conditions: (a) NH_4F (8.0 equiv.) in MeOH, room temperature, 24 h. (b) CuTc (10 mol%) in toluene, room temperature, 4 h. (c) TBD (20 mol%) in THF, room temperature, 48 h. (d) DIBAL-H (5.0 equiv.) in Et_2O, 40 ^oC, 24 h. (e) $RuCl_3$ (5 mol%), $NaIO_4$ (4.0 equiv.) in a mixed solvent of $CCl_4/CH_3CN/H_2O$ (*v/v/v* = 2:2:3), room temperature, 2 h.

Table 2. Substrate scope.[a,b]

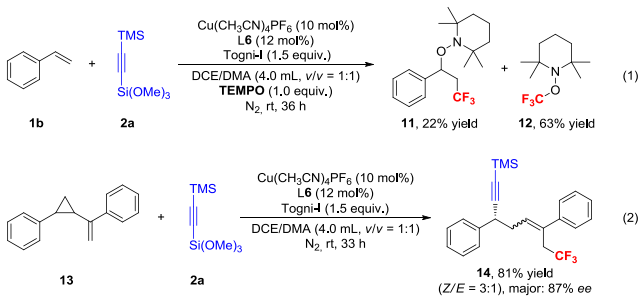


[a] Reaction conditions: $Cu(CH_3CN)_4PF_6$ (10 mol%), **L6** (12 mol %), **1** (0.2 mmol), Togni-**I** (0.3 mmol) and alkyne **2** (0.4 mmol) in a mixed solvent of DCE/DMA (4.0 mL, *v*/*v* = 1:1) under N_2. [b] Isolated yield and enantiomeric excess (*ee*) was determined by HPLC on a chiral stationary phase. [c] Mixed solvent of DCE/DMA (4.0 mL, *v*/*v* = 40:1) was used.

To demonstrate the synthetic utility of our method, further transformations of the trifluoromethylalkynylation products were surveyed (Scheme 2). Upon treatment of **3a** with ammonium fluoride, the TMS group in **3a** was successfully removed to afford the terminal alkyne **5** in 87% yield without loss of enantioselectivity, and the compound **5** could be further converted to 1-sulfonyl-1,2,3-triazole **6** in 84% yield with 91% *ee* by click reaction,[13] by which the absolute configuration of the products (*R*)-**3** and (*R*)-**4** was unambiguously determined. Notably, the product **4e** (91% *ee*) was isomerized to allene **7** in 95% yield with 89% *ee* by employing triazabicyclodecene (TBD) as catalyst.[14] Moreover, the C-C triple bond in **3f** was selectively reduced by diisobutylaluminium hydride (DIBAL-H) to deliver *Z*-alkene **8** in 97% yield with 93% *ee*. More importantly, for nonsteroidal *anti*-inflammatory drugs, e.g. high-profile Ibuprofen and Flurbiprofen, the oxidation of the C-C triple bond in the products **3e** and **3p** gave the enantiomerically enriched CF_3-modified Ibuprofen **9** and Flurbiprofen **10** in good yield (89% and 84%) without loss of enantioselectivity (95% *ee* and 91% *ee*).[15]

To provide some insight into the plausible radical mechanism for this novel trifluoromethylalkynylation reaction, TEMPO as a radical scavenger was subjected to our standard conditions. As we expected, the reaction was significantly inhibited; in addition, both CF_3 radical and benzylic radicals were trapped by TEMPO to give the products **11** and **12** (eq 1). Moreover, the ring-opening product **14** was obtained in the reaction of radical clock substrate **13** (eq 2).

In conclusion, we have developed the first enantioselective copper-catalyzed trifluoromethylalkynylation of styrenes *via* a radical relay process, which provides an easy access to the



structurally diverse and enantiomerically enriched CF_3-containing propargylic products. In addition, the reaction features wide substrate scope and high functional group tolerance. Moreover, the trifluoromethylalkynylation products can be easily converted into very useful chiral terminal alkynes, allenes, *Z*-alkenes and carboxylic acids. Enantioselective trapping of a benzylic radical with chiral (Box)Cu^{II}-alkynyl species is a key step for the construction of a propargylic stereocenter. Further expansion of this strategy is still in progress in our laboratory.

ASSOCIATED CONTENT

Experimental procedures and characterization data. This material 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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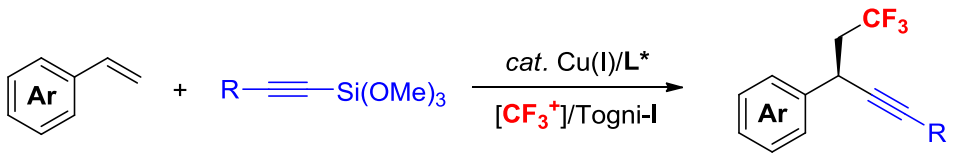

Enantioselective radical relay process

35 examples, up to 88% yield and 97% ee