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Enantioselective Copper-Catalyzed 1,5-Cyanotrifluoromethylation of Vinylcyclopropanes

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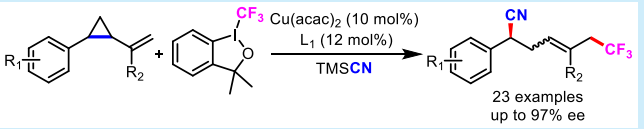
Supporting Information

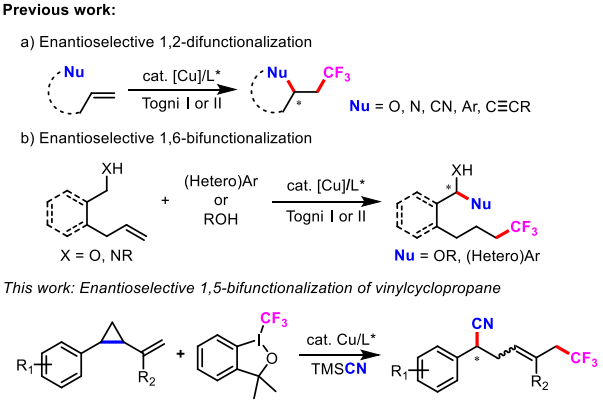
ABSTRACT: A copper-catalyzed enantioselective 1,5-cyanotrifluoromethylation of vinylcyclopropanes has been developed using a radical relay strategy. This asymmetric reaction has demonstrated high enantioselective control, broad substrate scope, and mild conditions. Initiated by the *in situ* generated CF_3 radical from Togni's reagent, this method offers a new solution for remote enantioselective bifunctionalization of alkenes and thus provides a straightforward way for the synthesis of chiral CF_3-containing internal alkenylnitriles.



Trifluoromethylated compounds have been widely used as pharmaceuticals, agrochemicals, and special materials, for the incorporation of a trifluoromethyl group (CF_3) into organic molecules could obviously enhance the lipophilicity, metabolic stability, and bioavailability compared with the parent molecules.[1] As a result, the selective introduction of the trifluoromethyl group into the biologically active molecules has long been used as a powerful strategy for drug design and screen.[2] Accordingly, considerable efforts have been devoted to the development of novel trifluoromethylation methods in an efficient and straightforward manner.[3] In view of the fact that the active CF_3 radical could be triggered easily via different pathways, direct capture of CF_3 radical by alkenes has been well established to construct a variety of trifluoromethylated compounds by following various radical functionalizations.[4]

Difunctionalization of alkenes has long been widely known as an efficient synthetic method for incorporation of two functional groups into the C═C bond-involving molecules in single step.[5] Accordingly, a number of highly step- and atom-economic transformations have been developed in alkene difunctionalizations using the radical relay strategy.[6] While Togni's reagent used to generate trifluoromethyl radical *in situ*, which was then trapped by alkenes to afford bifunctional products after the following radical functionalization,[7−11] diverse transformations including the asymmetric ones have recently been developed for efficient construction of CF_3-containing molecules.[12,13] Not surprisingly, most research works on this area focused on the enantioselective 1,2-difunctionalization reactions, including cyanotrifluoromethylation,[12a] trifluoromethylarylation,[12b] trifluoromethylalkynylation,[12c] and heterotrifluoromethylation,[12d−h] either in inter- or intramolecular fashion (Scheme 1a). Meanwhile, several asymmetric 1,6-bifunctionalization reactions triggered by $CF_3^•$ have also been reported using a radical 1,5-hydrogen atom transfer as the key step (Scheme 1b).[13] However, despite these advances, enantioselective 1,5-bifunctionalizations are far from being solved and remain still as a challenge.[12c]

Scheme 1. Togni's Reagent-Initiated Enantioselective Radical Difunctionalization of Olefins



Vinylcyclopropane framework is widely used as a famous radical clock and a key building-block for efficient synthesis of complex molecules or intermediates in organic synthesis.[14,15] Liu and co-workers reported the only example of 1,5-cyanotrifluoromethylation of vinylcyclopropane for radical mechanistic study,[16] while the enantioselective version of such transformation is still to be developed. We envisioned that the trap of CF_3 radical by vinylcyclopropane followed by a radical cycle-opening process could afford the carbon radical, which could be recaptured by a chiral copper catalyst to realize an asymmetric 1,5-bifunctionalization after a copper-catalyzed enantioselective 1,5-cyanotrifluoromethylation of vinylcyclopropanes through a bond-forming reductive elimination. Herein, we report a radical relay strategy. This asymmetric reaction has demonstrated high enantioselective control, broad substrate scope, and mild conditions. With Togni's reagent

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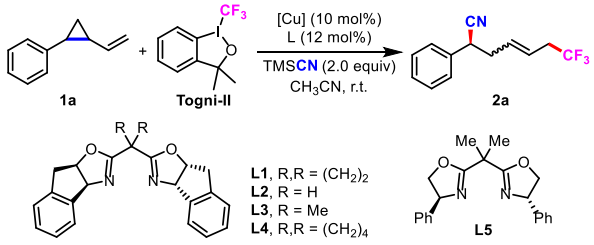
used as the trifluoromethyl radical initiator, this method offers a new solution for remote enantioselective bifunctionalization of alkenes and thus paves a path for facile synthesis of chiral CF_3-containing internal alkenyl organonitriles.

We commenced our initial investigation with (2-vinylcyclopropyl)benzene (**1a**) used as the pilot substrate, Togni-II reagent as the trifluoromethylating reagent, and trimethylsilyl cyanide (TMSCN) as the cyano source in the presence of a catalytic amount of $Cu(CH_3CN)_4PF_6$ (10 mol %) in CH_3CN at room temperature. To our delight, the desired bifunctionalized product **2a** was afforded in 58% yield with 10/1 *E*/*Z* ratio and 83% ee when bisoxazoline L_1 was used as the ligand (Table 1, entry 1). Encouraged by this result, a careful screening of various copper salts using L_1 as the ligand was next performed (Table 1, entries 1−5; for details, see the SI), which showed that different copper salts could furnish **2a** with similar *E*/Z ratio and ee, and $Cu(acac)_2$ afforded the desired product **2a** in higher yield (72%) (Table 1, entry 3). Furthermore, solvents were then investigated and indicated that acetonitrile was the best choice (for details, see the SI, Table S2). To improve the enantioselectivity of this transformation, the reaction temperature was lowered to −20 °C, but afforded **2a** with the same ee while the yield decreased to 50% (Table 1, entry 6). To our interest, slowly warming the reaction system from −20 °C to room temperature within 3 h could improve the ee of **2a** to 88% in 67% yield (Table 1, entry 7). To further improve the yield, the amounts of Togni-II reagent and TMSCN were then investigated (for details, see the SI, Table S4 and S5), which indicated the yield could be increased to 77% with 89% ee when 1.5 equiv of Togni-II reagent and 1.6 equiv of TMSCN were used (Table 1, entry 8). While decreasing or increasing the loading of $Cu(acac)_2$ catalyst and ligand L_1 could not improve the yield or ee (Table 1, entry 9−10), normally used nitrogen-containing ligands were next screened, and bisoxazoline ligand L_1 was still the optimal choice for this reaction with the best yield and ee (Table 1, entries 11−14; for details, see the SI, Table S7). To our pleasure, rescreening the reaction time and temperature indicated that slowly warming the reaction from 0 to 10 °C within 3 h could furnish the desired product **2a** in even higher yield and ee (88% isolated yield, 90% ee, Table 1, entry 15).

Table 1. Optimization of Conditions[a]



entry	[Cu]	L	yield (%)[b]	*E*/*Z*[b]	ee (%)[c]
1	$Cu(CH_3CN)_4PF_6$	L_1	58	10:1	83
2	CuCl	L_1	44	10:1	83
3	$Cu(acac)_2$	L_1	72(68)	10:1	85
4	$CuCl_2$	L_1	45	10:1	83
5	$Cu(OAc)_2$	L_1	44	10:1	84
6[d]	$Cu(acac)_2$	L_1	50	10:1	84
7[e]	$Cu(acac)_2$	L_1	67(63)	10:1	88
8[e,f]	$Cu(acac)_2$	L_1	82(77)	10:1	89
9[e,f,g]	$Cu(acac)_2$	L_1	86(80)	10:1	87
10[e,f,h]	$Cu(acac)_2$	L_1	71(67)	10:1	85
11[e,f]	$Cu(acac)_2$	L_2	65	10:1	79
12[e,f]	$Cu(acac)_2$	L_3	87	10:1	60
13[e,f]	$Cu(acac)_2$	L_4	85	10:1	84
14[e,f]	$Cu(acac)_2$	L_5	90	10:1	73
15[f,i]	$Cu(acac)_2$	L_1	93(88)	10:1	90

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), Togni-II (1.0 equiv), [Cu] (10 mol %), L (12 mol %), TMSCN (2.0 equiv), CH_3CN (3.0 mL), r.t., 3 h, under N_2. [b]Yield and ratio of *E*/*Z* were determined by ^{19}F-NMR using $PhOCF_3$ as the internal standard, isolated yield in parentheses. [c]ee was determined by HPLC analysis. [d]−20 °C, 3 h. [e]−20 °C to r.t., 3 h. [f]Togni-II (1.5 equiv) and TMSCN (1.6 equiv) were used. [g]$Cu(acac)_2$ (5 mol %) snd L_1 (6 mol %) were used. [h]$Cu(acac)_2$ (20 mol %) and L_1 (24 mol %) were used. [i]0−10 °C, 3 h.

With the optimized reaction conditions in hand, we next explored the scope of vinylcyclopropanes bearing various substituted (hetero)arenes. As shown in Scheme 2, a number of vinylcyclopropanes installed with electron-donating groups (R_1) including Me (**1b**), MeO (**1f**), BnO (**1j**), and MeS (**1k**), and electron-withdrawing groups (R_1) including F (**1e**), Cl (**1c**−**1d**, **1u**−**1v**), and CO_2Me (**1p**) on the aromatic rings were well tolerated, giving the desired bifunctionalized products **2** in good to excellent yields and ees. Electron-donating groups delivered products in a slightly lower enantioselectivity under the general method but can be further increased to moderate ees by lowering the reaction temperature to −20 °C and prolonging the reaction time to 4 h (**2j**−**2k**), while an electron-withdrawing functional group such as fluorine and ester can be transformed into the corresponding products in excellent yield (93%) and ees (90% and 94%) (**2e** and **2p**). It must be pointed out that the *E*/*Z* selectivity of these reactions was highly relevant to the steric hindrance of substituents linked to the C═C double bonds (R_2). While vinylcyclopropanes bearing no substituents on the alkenyl 2-carbon delivered products with 10:1 *E*/*Z* ratio (**2a**−**2c**), not surprisingly, methyl-substituted substrates furnished the desired alkenes with a relatively lower *E*/*Z* ratio due to the decreased distinction of steric hindrance between the formed trifluoroethyl group and methyl group (3:1, **2d**−**2g**). As expected, further increasing the steric hindrance of R_2, such as tertiary butyl and aryl group, could furnish *E*-alkenes as the major products in excellent selectivity (**2h**−**2w**). Meanwhile, *ortho*-substituents on the aryl rings could afford even higher ee (94%−97%) in good yields (71%−77%) (**2c**, **2u**−**2w**) compared with the *meta*- and *para*-substituted substrates, and the absolute configuration of **2w** was confirmed by X-ray diffraction.[17] Additionally, fused aryl and heteroaryl rings were also well compatible with these reaction conditions and afforded the corresponding products in moderate to excellent yields and good ees (**2g**, **2l**, **2m**, and **2n**). To our satisfaction, the investigation of the substituent effect on aryl rings located at R_2 showed the electronic nature of the substituents had little impact on the reaction, affording the desired products in similarly excellent yields (88−92%) and moderate ees (85−89%, **2o**, **2q**−**2t**). Unfortunately, the subjection of unactivated vinylcyclopropane **1x** into this catalytic system afforded an inseparable mixture with only trace amount of desired product.

It should be mentioned that gram scale reactions of **1h** and **1o** proceeded smoothly with slightly lower yield and ees (75% yield and 83% ee for **2h**; 85% yield and 82% ee for **2o**), when the catalyst loading could be decreased to 1 mol% (Scheme 3). The chiral alkenes produced via this cyanotrifluoromethylation

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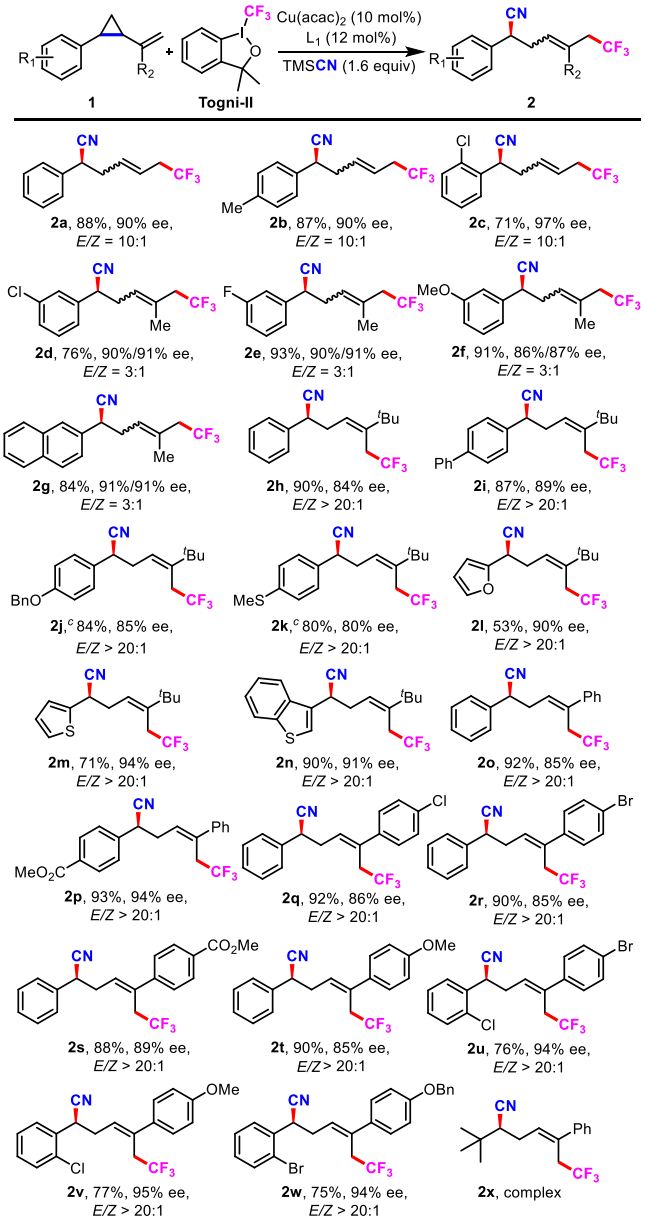
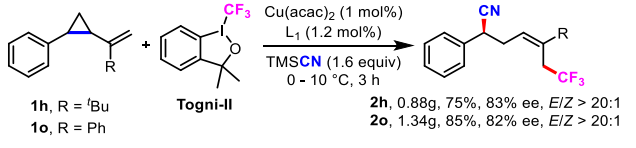
Scheme 2. Substrate Scope[a,b]



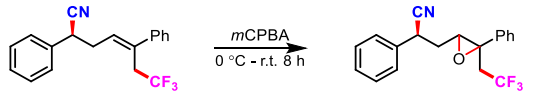
[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), Togni-II (1.5 equiv), $Cu(acac)_2$ (10 mol %), L_1 (12 mol %), TMSCN (1.6 equiv), CH_3CN (3.0 mL), 0−10 °C, 3 h, under N_2. [b]Isolated yield, ratio of *E*/*Z* was determined by ^{19}F-NMR. [c]−20 °C, 4 h.

Scheme 3. Gram Scale Experiments



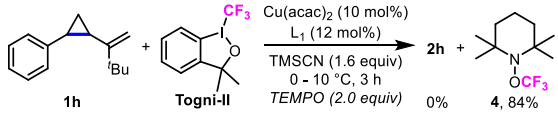
reactions are versatile synthetic intermediates for further transformation to various CF_3-containing compounds. For instance, with 3-chloroperoxybenzoic acid (*m*-CPBA) used as the oxidant in dichloromethane (DCM) at 0 °C to room temperature for 8 h, the epoxidation of **2o** furnished CF_3-containing epoxide **3o** as a mixture of diastereoisomers (dr = 1.3:1) in 87% yield without any loss of enantioselectivity (Scheme 4).

Scheme 4. Further Transformation



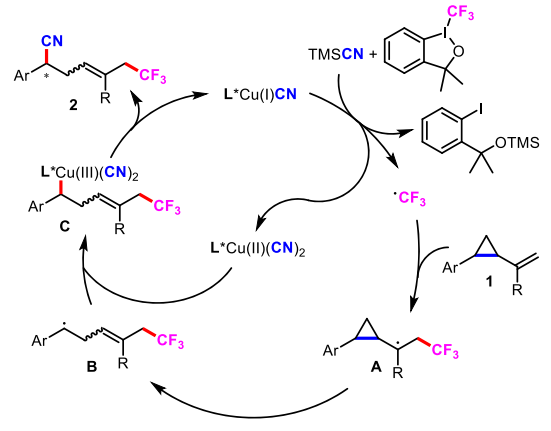
To gain further insight into the mechanism of this transformation, some control experiments were conducted. Indeed, the subjection of 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a widely used radical scavenger, into the standard reaction could completely quench the reaction, and the corresponding coupling product **4** was afforded in 84% NMR yield (Scheme 5). This observation clearly indicated that this transformation initiated from the attack of the trifluoromethyl radical to the C═C bond of vinyl cyclopropane.

Scheme 5. Mechanistic Study



On the basis of all above observations and previous reports,[7−13] a Cu(I)/Cu(III)-catalyzed catalytic cycle involving a radical-mediated ring-opening C−C bond cleavage is proposed in Scheme 6. Starting from the L*Cu(I)CN

Scheme 6. Proposed Mechanism



catalyst,[12a] which may generate by reduction of the Cu(II) species,[18] a single electron transfer (SET) process from the Cu(I) species to Togni-II reagent affords L*Cu(II)$(CN)_2$ and CF_3 radical. The CF_3 radical is rapidly trapped by the C═C bond to furnish radical species **A**, followed by a selective *β*-fragmentation of cyclopropane to result in benzylic radical **B**. The subsequent enantioselective recapture of **B** by L*Cu(II)-$(CN)_2$ gives the chiral Cu(III) species **C**, which furnishes the chiral cyanotrifluoromethylation alkene **2** after the following reductive elimination and regenerates L*Cu(I)CN to enter the next catalytic cycle.

In conclusion, we have developed a copper-catalyzed enantioselective 1,5-cyanotrifluoromethylation of vinylcyclo-

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propanes with Togni's reagent used as the trifluoromethyl source. This method has demonstrated high enantioselective control, broad substrate scope, and mild conditions. This radical relay strategy offers a new solution for remote enantioselective bifunctionaliziation of alkenes and thus paves a path for facile synthesis of chiral CF_3-containing internal alkenyl organonitriles. Further investigation on novel radial-involved asymmetric remote bifunctionalization of alkenes is still under way in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03012.

Experimental procedure and characterization of all new compounds (PDF)

Accession Codes

CCDC 1886397 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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