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# Copper-Catalyzed Amide Radical-Directed Cyanation of Unactivated $C_{sp}^3$−H Bonds

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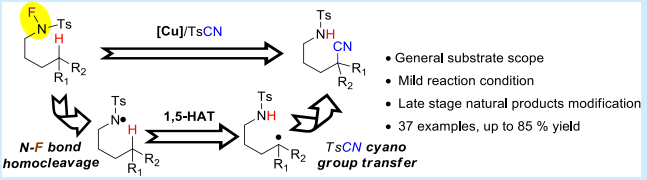
Supporting Information

**ABSTRACT:** A method for site-selective intermolecular $\delta/\varepsilon$-$C_{sp}^3$−H cyanation of aliphatic sulfonamides is developed using TsCN as the cyanating reagent, catalyzed by a Cu(I)/phenanthroline complex. The mild, expeditious, and modular protocol allows efficient remote $C_{sp}^3$−H cyanation with good functional group tolerance and high regioselectivity. Mechanistic studies indicate that the reaction might proceed through a Cu(I)-mediated N−F bond cleavage to generate an amidyl radical, 1,5-HAT, and cyano group transfer of the resulting carbon radical with TsCN.






Direct functionalization of alkyl $C_{sp}^3$−H bonds simplified the existing chemical synthesis and unlocks unique synthetic planning.[1] However, achieving site-selective functionalization of an inert $C_{sp}^3$−H bond remains a critical challenge due to their high bond strength and selectivity issues originating from their ubiquitous presence in organic compounds.[2] Over the past decade, Pd-catalyzed $\beta,\gamma$-$C_{sp}^3$−H functionalizations of aliphatic acids or aliphatic amides using directing groups have been extensively studied.[3] However, due to the predominant five-membered cyclometalation reactions, targeting more distal positions, such as the $\delta$-positions and $\varepsilon$-positions, are generally rare.[4] The Hofmann−Löffler−Freytag (HLF) reaction has constituted a key breakthrough in functionalization of unactivated $\delta$-positions on $C_{sp}^3$−H groups since it emerged in the early 1880s.[5] The reaction generally utilizes harsh condition to promote the homolysis of an *N*-halo amide to form the *N*-centered radical, followed by selective 1,5-hydrogen atom transfer (HAT), halogenation, and cyclization. However, the requirement of rather harsh conditions and intramolecular amination fashion limited its synthetic applications (Figure 1A). With the aim of searching for mild reaction condition to improve the HFL reactions, some elegant examples have been disclosed recently.[6] Nevertheless, harnessing the superior regioselectivity of an HFL-type reaction to activate the inert $C_{sp}^3$−H bond, and thus enable the intermolecular C−C bond formation under mild reaction conditions, is still highly desirable.

Recently, such a hypothesis has been achieved by the seminal contributions from the groups of Knowles[7a] and Rovis[7b] independently (Figure 1B). By leveraging the power of photoredox catalysis to split N−H bonds of amides, the key electrophilic amidyl radical can be formed under room temperature, enabling the efficient HFL-type distal $C_{sp}^3$−H alkylation in an intermolecular way. Following these, other elegant examples of intermolecular $C_{sp}^3$−H functionalization also appeared.[8] Of note, owing to its robust transformable properties to amines, amides, aldehydes, and carboxylic acids,

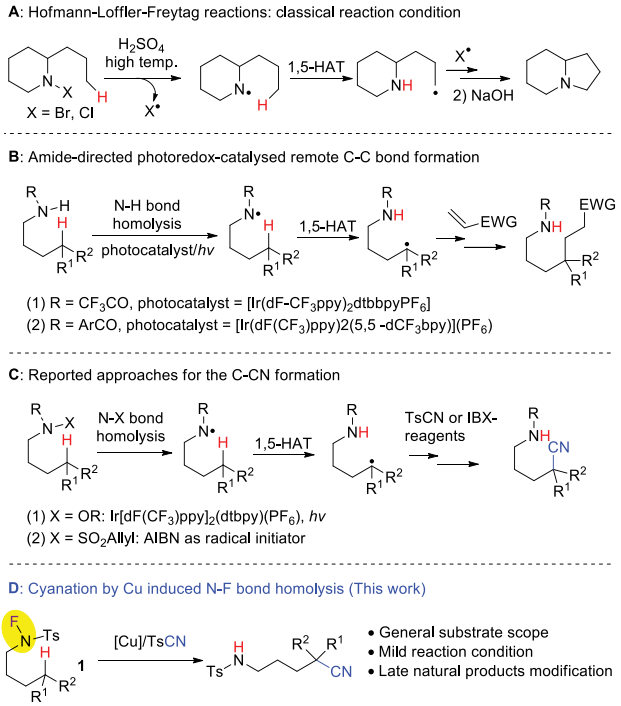



**Figure 1.** HFL-type reaction for site-selective $C_{sp}^3$−H cyanation.

etc.,[9] nitrile compounds are of great importance in both academia and industry.[10] However, direct utilization of an HFL-type strategy to construct $C_{sp}^3$−CN is still rare, and limited examples are disclosed. Concurrent with this work, the groups of Leonori and Studer achieved such cyanation by splitting N−O[11a] and N−S[11b] bonds with the help of Ir photoredox catalysts and AIBN radical initiator, respectively

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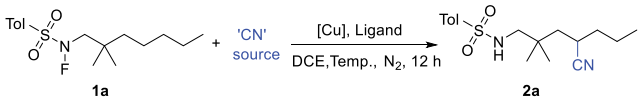
(Figure 1C). Obviously, exploring other readily available precursors for this purpose would be also very useful.

Inspired by the works of Zhang[12] and others[13] that N−F bond of *N*-fluorobenzenesulfonimide (NFSI) can be effectively reduced by Cu(I) to produce the corresponding nitrogen-centered radical, we wondered whether the structurally similar[14] yet easily accessible *N*-fluoro-*N*-alkyltosylamide **1** can be used for the formation of amidyl radical under copper catalysis and if the following 1,5-HAT will promote the site-specific $C_{sp}^3$−H abstraction to generate the key aliphatic radical. If so, trapping of the carbon radical with a suitable cyano source will provide a new approach to realize the intermolecular $C_{sp}^3$−H cyanation. However, as disclosed by Cook[15] and others,[16] one key scientific issue in this scenario is to inhibit undesired C−F bond formation. Herein, with our interest in $C_{sp}^3$−H functionalization, we wish to report our preliminary result on executing such a strategy to realize the very useful cyano group transfer using the commercially available TsCN[17] as the radical CN source (Figure 1D). Different from previous reports by the groups of Leonori and Studer, the current approach starts from readily available *N*-fluoro substrates **1**[18] and relies on using a simple catalytical amount of Cu(I) to reduce N−F bond under mild conditions, leading to the formation of the key amidyl radical.

We commenced the optimal condition screen by using 10 mol % of CuBr, *N*-fluorotosylamide (**1a**, 0.2 mmol), and TsCN (1.5 equiv) with absolute 1,2-dichloroethane (DCE) as solvent, and the reaction was run at 25 °C for 12 h under $N_2$ atmosphere. A trace amount of desired cyanation product **2a** was observed by the crude NMR (Table 1, entry 1), while no cyanation product was observed in the absence of the copper catalyst (entry 2). Inspired by the previous reports that phenanthroline ligands played important roles in Cu(I)-promoted reduction of N−F to form nitrogen radical,[12,13] the simplest 10 mol % of 1,10-phenanthroline was added at first, and to our delight, the yield of **2a** could be isolated with 52% yield (entry 3), indicating the essential role of ligand for improving the yield. Encouraged by this, other substituted phenanthroline ligands were also screened, and it turned out that bathocuproine (**BC**) is the best choice in our case, affording **2a** in 66% yield (entry 4). Only inferior yields were obtained for ligands such as neocuproine (**NC**) and 1,10-phenanthroline-5,6-dione (**L1**) (entries 5 and 6) (for full details, see the Supporting Information). The systematic screen of copper salts bearing different anions showed that CuCN was the best choice (entries 7−11). While increasing the loading of TsCN had minimal effect on the yield, elevating the temperature from 25 to 60 °C could further increase the yield of **2a** to 76% (entry 9 vs 12). The yield slightly increased to 78% when the catalyst loading was reduced to 5 mol % of copper and 5 mol % of **BC** (entry 14). Other cyanides, such as $Zn(CN)_2$ and TMSCN, were ineffective (entries 15 and 16).

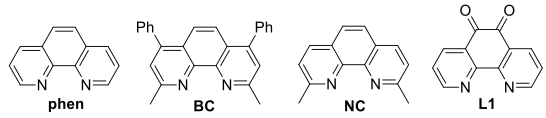
With the optimal conditions in hand (Table 1, entry 14), the scope of the cyanation was examined, and the results are summarized in Scheme 1 The reaction of TsCN with various *N*-fluorotosylamide derivatives afforded the desired $C_{sp}^3$−H cyanation products **2** in 30−85% yields. Noteworthy, as detailed in the Supporting Information, these N−F substrates **1** can be easily prepared by facile fluorination of the corresponding sulfonamides with NFSI with moderate to good yields (35−70%). For compounds **2a**, **2i**, and **2w** their constitution was unambiguously established by single-crystal X-ray analyses. In these reactions, tertiary inert C−H bonds,

**Table 1. Optimization of the $C_{sp}^3$−H Cyanation**[a]




**1a** **2a**

| entry | [Cu] (mol %) | ligand (mol %) | CN source (equiv) | temp (°C) | yield[b] (%) |
|---|---|---|---|---|---|
| 1[c] | CuBr (10) | - | TsCN (1.5) | 25 | trace |
| 2[c] | - | - | TsCN (1.5) | 25 | 0 |
| 3 | CuBr (10) | **Phen** (10) | TsCN (1.5) | 25 | 52 |
| 4 | CuBr (10) | **BC** (10) | TsCN (1.5) | 25 | 66 |
| 5 | CuBr (10) | **NC** (10) | TsCN (1.5) | 25 | 60 |
| 6 | CuBr (10) | **L1** (10) | TsCN (1.5) | 25 | 34 |
| 7 | CuCl (10) | **BC** (10) | TsCN (1.5) | 25 | 62 |
| 8 | CuI (10) | **BC** (10) | TsCN (1.5) | 25 | 58 |
| 9 | CuCN (10) | **BC** (10) | TsCN (1.5) | 25 | 68 |
| 10 | CuOAc (10) | **BC** (10) | TsCN (1.5) | 25 | 50 |
| 11 | $Cu(OTf)_2$ (10) | **BC** (10) | TsCN (1.5) | 25 | 36 |
| 12 | CuCN (10) | **BC** (10) | TsCN (1.5) | 60 | 76 |
| 13 | CuCN (10) | **BC** (10) | TsCN (2.0) | 60 | 73 |
| **14** | **CuCN (5)** | **BC (5)** | **TsCN (1.2)** | **60** | **78** |
| 15[c] | CuBr (10) | **BC** (10) | TMSCN (2.0) | 60 | 0 |
| 16[c] | CuBr (10) | **BC** (10) | $Zn(CN)_2$ (1.0) | 60 | 0 |




[a]Reactions were carried out with **1a** (0.2 mmol) in 1 mL of solvent under $N_2$ atmosphere, unless noted otherwise. [b]Isolated yield. [c]The reaction was performed for 24 h. **L1**: 1,10-phenanthroline-5,6-dione.

such as those in substrates **1b** and **1c**, were converted to yield **2b** and **2c** in 60% and 55% yield. The reaction worked well with five- and six-membered cyclic systems **2d** (56%), **2e** (66%). We then examined more challenging C−H cyanation at the secondary C−H bonds. Pleasingly, the radical cyanation of *N*-protected pentyl-, hexyl-, and heptylamine occurred with complete regiocontrol in good yields **2f−j** (52−71%). Additionally, the *N*-fluorotosylamide and *N*-fluorophenylsulfonamide (**1g**, **1h**) afforded the corresponding cyanation products **2g** (52%) and **2h** (65%). The secondary benzylic position was achieved with a lower yield **2k** (40%). As expected, remote cyanation beside an O atom was also achieved in good yield **2l** (73%). When *ε*-positions formed tertiary C−H **2m** (62%, regioselectivity = 4:1), **2n** (68%, regioselectivity = 2:1), or benzylic C−H bonds **2o** (63%, regioselectivity = 2:1), the 1,5-HAT and 1,6-HAT products were observed, while 1,5-HAT was slightly favored. In a ternary competition between *δ*/*ε* secondary C−H bonds and a *ζ* benzylic C−H bond, only the product of 1,5-HAT was observed **2p** (77%), rather than either 1,6- or 1,7-HAT. However, for the substrate with the *ε*-position bearing a methoxy substituent, the 1,5-HAT product was formed as a minor regioisomer along with the corresponding 1,6-HAT product (**2q**, 53% isolated yield, regioselectivity = 1:4).

For a congener substrate in which the *ζ*-position had a methoxy substituent, only the 1,5-HAT product **2r** (62%) was obtained. The sterically bulky adamantyl substrate underwent



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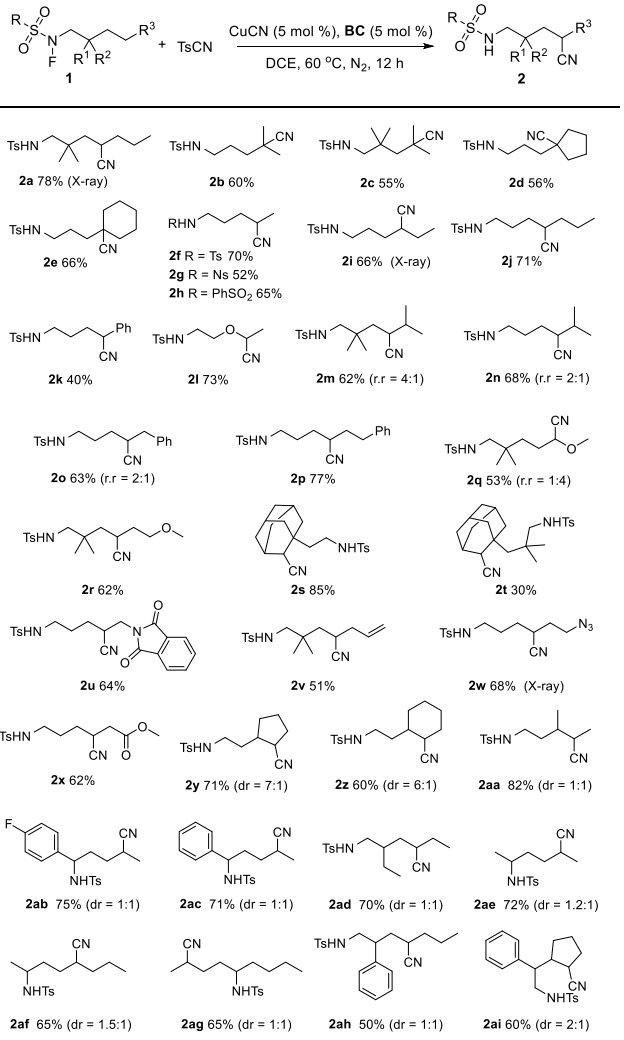
**Scheme 1. Scope of the $C_{sp}^3$–H Cyanation**[a,b]



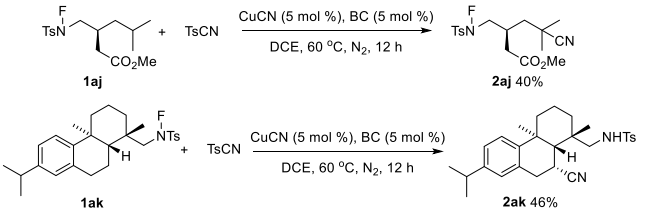

[a]Reactions were performed using **1** (0.2 mmol), TsCN (1.2 equiv), CuCN (0.05 equiv), **BC** (0.05 equiv), and 1 mL of absolute DCE at 60 °C under $N_2$ atmosphere for 12 h (TLC analysis indicated the full conversion of **1**), unless otherwise stated. [b]Yield of the isolated product.

remote C–H cyanation to afford the cyanation product in high yield **2s** (85%). Moreover, an adamantyl substrate having $\delta$-positions without a C–H bond afforded 30% cyanation product **2t** via 1,6-HAT. Functional groups, such as amide **2u** (64%), alkene **2v** (51%), azido **2w** (68%), and ester **2x** (62%), were all tolerated. For nonactivated, simple cyclohexyl and cyclopentyl groups, C–H cyanations achieved good yields with high stereoselectivity **2y** (71%, dr = 7:1), **2z** (60%, dr = 6:1). No stereoselectivity was observed (1,2-, 1,3-, and 1,4-stereoinduction) for intermolecular radical C–H cyanation in open-chain systems **2aa**–**ai** (50–82%).

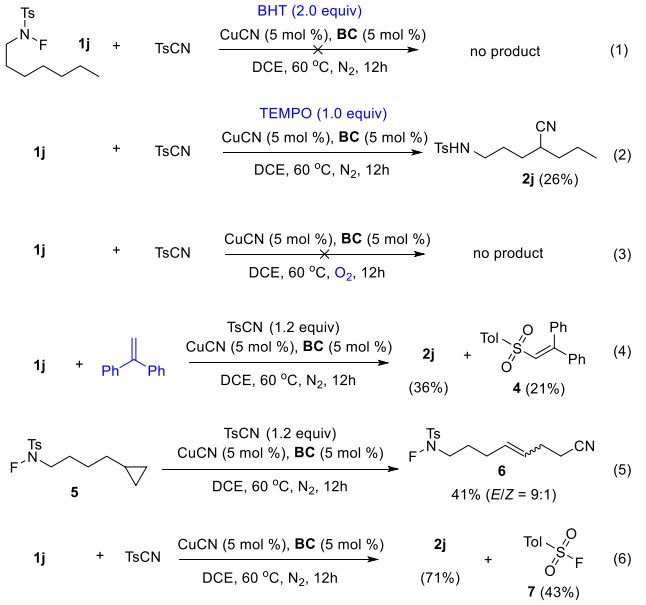
Finally, we tested more complex bioactively relevant compounds **1aj** (from pregabalin)[19] and **1ak** (from (+)-dehydroabietylamine),[20] which afforded cyanation products **2aj** and **2ak** in 40% and 46% yields, respectively. Notably, the regioselective C10-cyanation product **2ak** showed complete diastereocontrol (Scheme 2).

A series of control experiments were conducted to obtain insight into the reaction mechanism (Scheme 3). First, in the presence of 2.0 equiv of 2,6-di-*tert*-butyl-4-methylphenol

**Scheme 2. Late-Stage Functionalization of Natural Product Derivatives**




**Scheme 3. Mechanistic Investigation**




(BHT), cyanation was completely inhibited under the standard reaction conditions (eq 1). Second, when 1 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added, the yield of **2j** decreased to 26% (eq 2). Additionally, no product was observed when the reaction was run under $O_2$ atmosphere (eq 3). These results indicated that the reaction might work through a radical mechanism.

Moreover, the desired cyanation product **2j** was only obtained in 36% yield along with 21% radical addition–elimination product **4**, while 1.0 equiv of ethene-1,1-diyldibenzene was added to the reaction as a radical scavenger (eq 4). This demonstrated that TsCN might take part in a cyano group transfer process to give the cyanation product and benzenesulfonyl radical.[17b,21] Furthermore, a "radical clock" experiment with cyclopropane **5** delivered the ring-opened cyanation product **6** (eq 5), indicating an intramolecular 1,5-HAT process might be involved. The cyanation of **1j** afforded cyanation product **2j** in 71% yield, and the *p*-toluenesulfonyl fluoride could also be isolated in 43% yield (eq 6). The reason for generating *p*-toluenesulfonyl fluoride will be explained below.

On the basis of these preliminary studies, a plausible mechanism was proposed (Figure 2). Initially, ligand coordinated Cu(I) reduction of *N*-fluoro-tosylamide **1** by a single-electron-transfer mechanism produced $FCu(II)CNL_n$ **A** and amidyl radical **B**. Subsequently, amidyl radical **B** underwent intramolecular 1,5-HAT to afford the carbon-centered radical **C**. Subsequent trapping by TsCN provided the observed $C_{sp}^3$–H cyanation product **2** and the formation of



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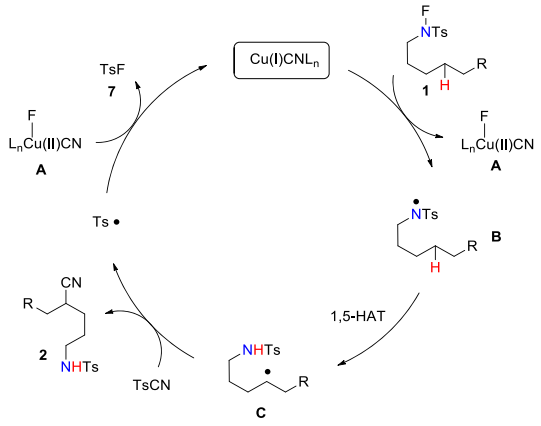


**Figure 2.** Proposed Mechanism.

*p*-toluenesulfonyl radical at the same time. Finally, interaction of FCu(II)CNL$_n$ **A** with *p*-toluenesulfonyl radical gave rise to TsF as well as regenerated the active Cu(I)CNL$_n$.

In summary, we report an unprecedented Cu-catalyzed intermolecular alkyl $C_{sp}^3$–H cyanation of *N*-fluorotosylamide derivatives for the first time, enabling the preparation of versatile nitrile compounds under mild reaction condition. The reaction overrides the common preference for intramolecular amination within the classic Hofmann–Löffler–Freytag manifold and can be used for the late-stage functionalization of natural product derivatives. Application of the current strategy to asymmetric version is underway 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.9b00553.

Details of experimental procedures, $^1$H and $^{13}$C NMR spectra, as well as the X-ray data of compounds **2a**, **2i**, and **2w** (PDF)

### Accession Codes

CCDC 1890184–1890186 contain 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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