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Heteroannulation of *N*-Fluoro-*N*-alkylsulfonamides with Terminal Alkynes via Remote C(sp^3)−H Functionalization

Long-Jin Zhong, Yang Li, De-Lie An, and Jin-Heng Li*

Cite This: *ACS Catal.* 2021, 11, 383−389 Read Online

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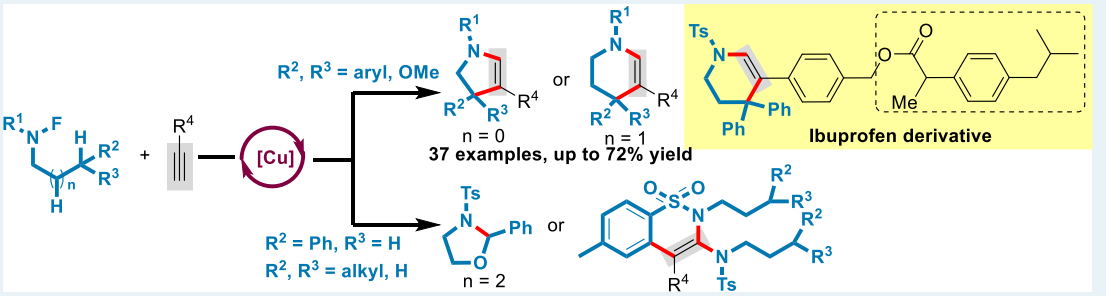


ABSTRACT: A copper-catalyzed divergent annulation of *N*-fluoro-*N*-alkylsulfonamides with terminal alkynes enabled by remote C(sp^3)−H functionalization for producing 2,3-dihydro-1*H*-pyrroles and 1,2,3,4-tetrahydropyridines is reported. Using a terminal alkyne to capture an amidyl radical forms a vinyl carbon-centered radical, which would sequentially undergo 1,5- or 1,6-hydrogen atom transfer (HAT) to site-selectively enable functionalization of the challenging C(sp^3)−H bonds at the β- or γ-position to the nitrogen atom in *N*-fluorosulfonamides, thus resulting in the *N*-fluorosulfonamides as three- or four-atom units to accomplish the (3 + 2) or (4 + 2) heteroannulation reactions.

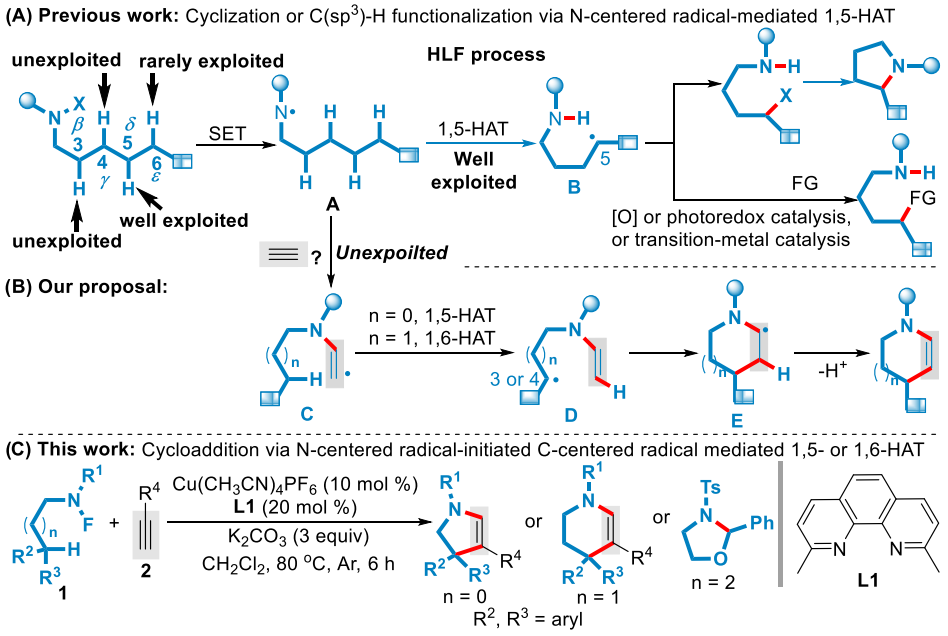
KEYWORDS: *copper, N-fluoro-N-alkylsulfonamides, alkynes, annulation, hydrogen atom transfer*

The nitrogen-centered radical (NCR) chemistry has emerged as an important and popular research area because it can be capable of a wide range of chemical reactions to elaborate highly valuable nitrogen-based structures by the direct incorporation of nitrogen-containing functional groups.[1,2] In recent decades, considerable efforts have been devoted to the development of efficient and selective methods for the generation of NCRs and their subsequent synthetic applications. At present, three typical NCRs, including aminyl, amidyl, and iminyl radicals, have been intensively exploited,[1,2] and attractive method for their synthetic applications consists of the remote C(sp^3)−H functionalization reaction via hydrogen atom transfer (HAT).[1,3−6] Traditional approaches, namely, the Hofmann−Löffler−Freytag (HLF) reaction, generally proceed via the intramolecular cyclization of the linear acyclic *N*-halo-amines through the generation of the NCRs by the single-electron transfer (SET) and their subsequent 1,5-HAT.[1,3] However, such HLF methods suffer from limited unstable NCR precursors and relatively harsh reaction conditions, thus largely impeding the synthetic applications (Scheme 1A, top).[1,3] In recent years, significant progress has been made in the HLF field to selectively enable intermolecular remote C(sp^3)−H functionalization, such as atom transfer (e.g., halogenation),[4] Michael addition,[5] and cross-coupling,[6] by means of oxidant systems, photoredox catalysis or transition-metal catalysis (Scheme 1A, bottom). In general, these methods are achieved via the formation of aminyl radicals, followed by their HAT and the so-generated carbon radical functionalization, wherein the kinetically favored 1,5-HAT takes far more precedence over 1,3-HAT (enthalpic barrier), 1,4-HAT (enthalpic barrier), and 1,6-HAT (entropic barrier), attributed to the low energy cost of a preorganized six-membered cyclic transition state with a nearly linear C−H−N geometry.[1] Nevertheless, these advances are restricted to the functionalization of the remote C(sp^3)−H bond site at the δ-position to the nitrogen atom of the linear acyclic *N*-haloamines. To the best of our knowledge, however, functionalization of the remote C(sp^3)−H bond site at the β- or γ-position to the nitrogen atom of the *N*-haloamines remains an unexploited area. We imagined that if it would be possible to capture the NCRs with an active functional group, thereby lengthening the chain of radicals to drive the favored HAT at the original disfavored site in NCR precursors (Scheme 1B).

Received: September 3, 2020
Revised: December 10, 2020

https://dx.doi.org/10.1021/acscatal.0c03853
ACS Catal. 2021, 11, 383−389

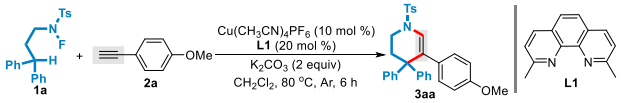
Scheme 1. Radical-Mediated Remote C−H Functionalization



Herein, we report a simple and general copper-catalyzed divergent annulation of *N*-fluorosulfonamides with terminal alkynes involving functionalization of the remote C(sp^3)−H bonds at the *β*- or *γ*-position to the nitrogen atom, in which the *N*-fluoro-sulfonamides serve as three- or four-atom units by cleavage of both the N−F bond and the C(sp^3)−H bond (Scheme 1C). This method constitutes a new domino strategy that the so-generated vinyl carbon-centered radical (CCR)[1g,7,8] from the reaction of the NCRs with alkynes selectively mediated 1,5-HAT and 1,6-HAT for producing 1,2,3,4-tetrahydropyridines and 2,3-dihydro-1*H*-pyrroles, both of which are frequent structural members of the occurrence of nitrogen heterocycles in the U.S. Food and Drug Administration (FDA)-approved pharmaceuticals.[9] Notably, the selectivity is subject to the reactivity of the C−H bonds in *N*-fluoro-sulfonamides. Using *N*-fluorosulfonamides possessing *gem*-diaryl groups at the *β*- or *γ*-position results in the (3 + 2) or (4 + 2) annulations with the C(sp^3)−H bonds via 1,5-HAT and 1,6-HAT, respectively, whereas in the case of *γ*-monoaryl-substituted or linear alkyl variants, other (4 + 2) annulation with the aryl C(sp^2)−H bonds of the arylsulfonamide moiety occurs to afford 2*H*-benzo[*e*][1,2]thiazine 1,1-dioxides.

Our optimization investigations commenced with *N*-(3,3-diphenylpropyl)-*N*-fluoro-4-methylbenzenesulfonamide **1a** and 4-ethynylanisole **2a** because the electronic property of the aryl ring can activate the alkyl radical intermediate to initiate a new radical process (Table 1). Encouragingly, in treatment of sulfonamide **1a** with alkyne **2a**, 10 mol % $Cu(CH_3CN)_4PF_6$, 20 mol % 2,9-dimethyl-1,10-phenanthroline (**L1**), 3 equiv K_2CO_3, and CH_2Cl_2 as a solvent at 80 °C afforded smoothly the desired 1,2,3,4-tetrahydropyridine **3aa** in 67% yield (entry 1). It was noted that both Cu catalyst and ligand were essential for this reaction because in the absence of each no reaction was observed (entries 2 and 8). Further screening of the amount of $Cu(CH_3CN)_4PF_6$ experiments revealed 10 mol % as the optimum loading (entries 1−4). Other Cu catalysts, including CuCl, CuCN, and $Cu(OTf)_2$, displayed catalytic activity (entries 5−7), but all were inferior to that of $Cu(CH_3CN)_4PF_6$. This reaction was sensitive to solvents (entries 9−12). While only nonpolar solvents, such as CH_2Cl_2, $ClCH_2CH_2Cl$, toluene, and PhCl, were competent (entries 9−11), polar solvents, including 1,4-dioxane, $MeCONMe_2$ (DMA), and MeCN, had no reactivity (entry 12). We found that K_2CO_3 serves as a promotor, since the reaction could occur without bases, furnishing **3aa** in 38% yield (entry 13). However, other bases, such as $KHCO_3$ and Cs_2CO_3, had an impeding effect (entries 14 and 15). The optimal reaction temperature identified was 80 °C (entries 16 and 17). Intriguingly, the reaction was applicable to a scale up to 1

Table 1. Screening of Optimal Reaction Conditions[a]



entry	variation from the standard conditions	yield (%)
1	none	67
2	without $Cu(CH_3CN)_4PF_6$	0
3	$Cu(CH_3CN)_4PF_6$ (5 mol %)	32
4	$Cu(CH_3CN)_4PF_6$ (15 mol %)	66
5	CuCl instead of $Cu(CH_3CN)_4PF_6$	42
6	CuCN instead of $Cu(CH_3CN)_4PF_6$	55
7	$Cu(OTf)_2$ instead of $Cu(CH_3CN)_4PF_6$	57
8	without ligand L1	trace
9	$ClCH_2CH_2Cl$ instead of CH_2Cl_2	45
10	toluene instead of CH_2Cl_2	40
11	PhCl instead of CH_2Cl_2	35
12	1,4-dioxane, DMA or MeCN instead of CH_2Cl_2	trace
13	without K_2CO_3	38
14	$KHCO_3$ instead of K_2CO_3	<5
15	Cs_2CO_3 instead of K_2CO_3	28
16	at 70 °C	15
17	at 90 °C	65
18[b]	none	61

[a]Standard reaction conditions: **1a** (0.1 mmol), **2a** (3 equiv), $Cu(CH_3CN)_4PF_6$ (10 mol %), **L1** (20 mol %), K_2CO_3 (2 equiv), CH_2Cl_2 (2 mL), argon, 80 °C, and 6 h. [b]**1a** (1 mmol) and 24 h.

https://dx.doi.org/10.1021/acscatal.0c03853
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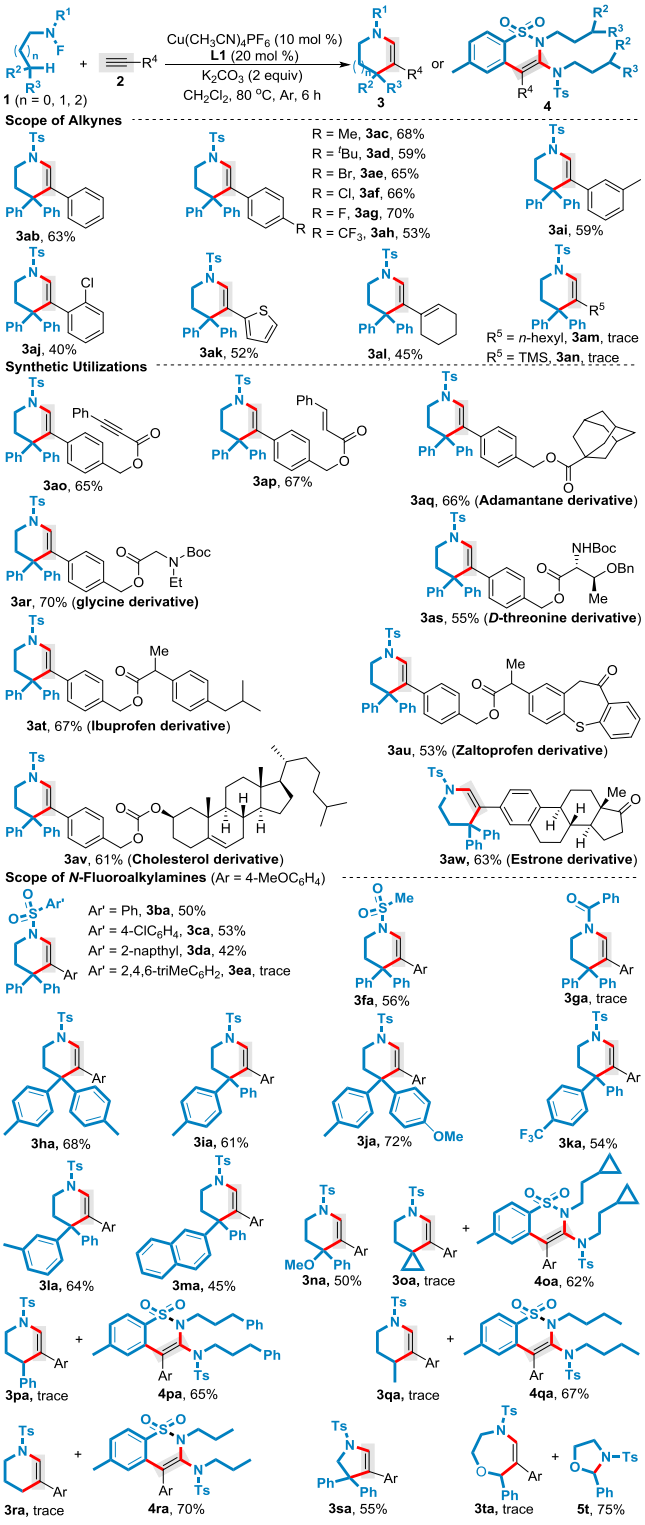
mmol of sulfonamide **1a**, giving **3aa** in satisfactory yield (entry 18).

With the optimal reaction conditions in hand, we turned our attention to evaluate the generality of this annulation protocol on a wide range of *N*-fluoro-sulfonamides **1** and terminal alkynes **2** (Scheme 2). Various arylalkynes **2b−l** and **2o−w** accommodate to the optimal conditions (**3ab−al and 3ao−aw**), but aliphatic alkyne **2m** and trimethylsilyl acetylene **2n** were inert (**3am−an**). For example, phenylacetylene **2b** was successfully used for this annulation, affording **3ab** in 63% yield. Several substituents, such as Me, bulky *t*-Bu, Br, Cl, F, and CF_3, on the aryl ring at the terminal alkyne, were well tolerated and 1,2,3,4-tetrahydropyridines **3ac−aj** were furnished in moderate to good yields.[10] Moreover, both the electronic property and steric hindrance affected this reaction. While alkyne **2c** bearing electron-donating Me group delivered **3ac** in 68% yield, alkynes **2d** and **2h** having a bulky *t*-Bu or an electron-withdrawing CF_3 group were converted to **3ad** and **3ah** in diminishing yields. Similarly, *m*-Me-substituted alkyne **2i** furnished **3ai** in moderate yield, and *o*-Cl-substituted alkyne **2j** gave **3aj** in a low yield. Notably, halogen atoms (e.g., Br, Cl, F) had no reactivity, thus providing a potential opportunity for their further functionalization. Both heteroaryl alkyne **2k** and 1,3-enyne **2l** were competent to furnish valuable functional-group-containing vectors **3ak** and **3al**. Encouragingly, the annulation protocol exhibited the translational potential in pharmaceutically relevant contexts as some frequently utilized functional groups (e.g., propiolate, cinnamate) and motifs (e.g., adamantane, amino esters, ibuprofen, zaltoprofen, cholesterol, estrone) commonly used in bioactive molecules were readily incorporated into the resulting 1,2,3,4-tetrahydropyridines **3ao−aw**.[11]

The scope of *N*-fluoro-sulfonamides **1** was subsequently explored. We found that the substitution effect of sulfonamides **1** affected the chemoselectivity. For various *N*-(3,3-diarylpropyl)-sulfonamides **1b−d** and **1h−m**, the (4 + 2) annulation reaction occurred, furnishing **3ba−da** and **3ha−ma** in moderate to high yields. Interestingly, the *N*-(3,3-diarylpropyl)-methylsulfonamides **1f** could convert to **3fa** in 56% yield. However, replacement of the sulfonyl groups by a Bz or 2,4,6-trimethylbenzenesulfonate group resulted in no annulation reaction, probably due to the electronic and/or steric hindrance effect (**3ea** and **3ga**). Surprisingly, a general (4 + 2) annulation with aryl C(sp^2)−H bonds of the arylsulfonamide moiety, not with the remote C(sp^3)−H bonds, took place to access important 2*H*-benzo[*e*][1,2]-thiazine 1,1-dioxides **4oa−ra**[12,13] when possessing an alkyl chain (e.g., 2-cyclopropylethyl, a propyl, or a butyl group) or a 3-phenylpropyl chain on the nitrogen atom. Encouragingly, the (3 + 2) annulation with the remote *β*−C(sp^3)−H bond occurred successfully to afford **3sa** when using *N*-(2,2-diphenylethyl)sulfonamide **1s**. For *N*-(2-(benzyloxy)ethyl)-sulfonamide **1t**, the intramolecular cyclization reaction occurred to generate **5t** not the desired annulation product **3ta** owing to the C(sp^3)−H bond activated by both the oxygen atom and the phenyl ring.

As shown in Scheme 3, without alkynes sulfonamide, **1a** underwent an intramolecular cyclization with the aryl C(sp^2)−H bond to afford 1,2,3,4-tetrahydroquinoline **6a** in 25% yield together with a defluorination product **7a** (eq 1). The reaction of sulfonamide **1a** with alkyne **2a** was restrained when using a radical inhibitor (e.g., TEMPO, hydroquinone, 2,6-di-*tert*-butyl-4-methylphenol) (eq 2). Meanwhile, with 1,1-diphenyl-

Scheme 2. Variations of the Sulfonamides (1) and Alkynes (2)[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (3 equiv), $Cu(CH_3CN)_4PF_6$ (10 mol %), **L1** (20 mol %), K_2CO_3 (2 equiv), CH_2Cl_2 (2 mL), argon, 80 °C, and 6 h.

ethylene or 1-(1-cyclopropylvinyl)-4-methoxybenzene as an additive, this (4 + 2) annulation reaction was confined, with the nitrogen radical intermediate **A** (Scheme 3) coupling with it to afford **8** in yield 48% and "radical clock experiments"

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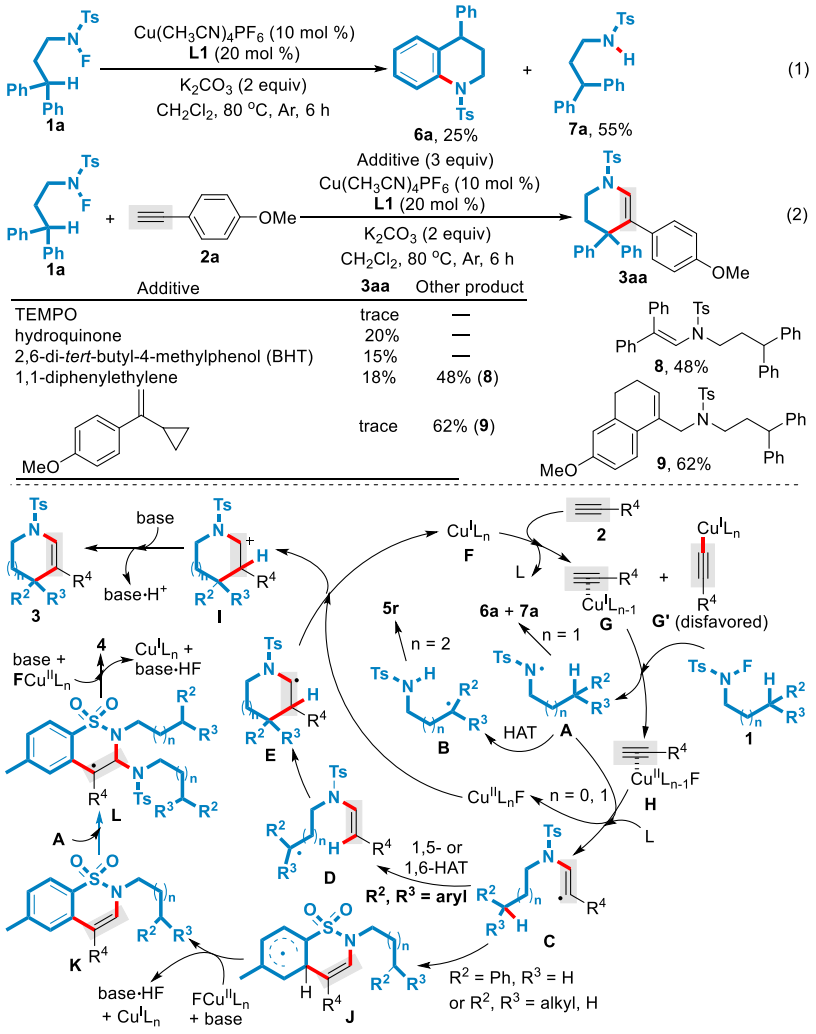
Scheme 3. Control Experiments and Possible Mechanisms



product **9** in yield 62% (eq 2). These results support the generation of the NCR intermediate. On the basis of the present experiments and the literature precedents,[1,3−7] we propose that this annulation protocol catalyzed by the active Cu^{I}-alkyne complex species, which is generated by the coordination of the Cu^{I} species with ligand and alkyne **2**, proceeds via initial generation of the NCR **A** by the splitting of the N−F bond in *N*-fluorosulfonamide **1** (Scheme 3).[1−6] In comparison with the Liu group's work,[6l] the formation of the alkynyl-Cu^{I} species under the present conditions is disfavored as the current reaction could occur without bases (entry 13; Table 1). The addition of the NCR **A** across the C≡C bond in alkyne **2** forms the vinyl CCR intermediate **C** and the Cu^{II} species. The intermediate **C** can undergo two pathways depending on the substitution effect of the *β*- or *γ*-position to the nitrogen atom. The electronic effect of two *gem*-aryl groups can activate the C(sp^3)−H bonds and facilitate the HAT process to produce the sp^3-hybridized CCR **D**, followed by the cyclization of the intermediate **D** with the inherent C=C bond to access the product **3** by the generation of the radical intermediate **E** and its subsequent single-electron oxidation/deprotonation.

In the case of *γ*-monoaryl-substituted or linear alkyl variants, the superior reactivity of the aryl C(sp^2)−H bond of the arylsulfonamide moiety over that of the C(sp^3)−H bonds results in the direct annulation with the aryl C(sp^2)−H bond in **C** to provide the phenyl radical intermediate **J**. The intermediate **J** undergoes single-electron oxidation by the Cu^{II} species and then deprotonation to produce the intermediate **K**. Finally, the intermediate **K** performs the second addition with the NCR **A**, single-electron oxidation, and deprotonation to afford product **4**.

In conclusion, we have developed the first copper-catalyzed (3 + 2) or (4 + 2) annulation of *N*-fluorosulfonamides with terminal alkynes involving remote C(sp^3)−H functionalization. This reaction can be applied to the late-stage modification of pharmaceutical and natural product derivatives by the incorporation of the tetrahydropyridine ring system into their molecular environment. More importantly, this simple and general HAT strategy enables a radical translocation from the NCR to the in situ generated CCR by overcoming the enthalpic/entropic barrier, which is introduced into the remote C(sp^3)−H functionalization reaction for the control of site selectivity. Upon the activity of the Cu catalytic system, the challenging C(sp^3)−H bonds at the *β*- or *γ*-position to the nitrogen atom in NCR precursors are selectively functionalized simply through the in situ lengthening of the chain of radicals, which may be considered as a new door toward site-selectivity-controllable remote C−H functionalization reaction.

https://dx.doi.org/10.1021/acscatal.0c03853
ACS Catal. 2021, 11, 383−389

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization of all compounds, NMR spectra, and X-ray data for **3ac** (CCDC 1985807) (PDF)

Crystal structure of **3ac** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Jin-Heng Li − *State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, China; Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China; Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research (Ministry of Education), Hunan Normal University, Changsha 410081, China; State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China;* orcid.org/0000-0001-7215-7152; Email: jhli@hnu.edu.cn

Authors

Long-Jin Zhong − *State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, China*

Yang Li − *Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China*

De-Lie An − *State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c03853

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21625203 and 21871126), the Opening Fund of KLCBTCMR, Ministry of Education (No. KLCBTCMR18-02), and the Jiangxi Province Science and Technology Project (No. 20182BCB22007) for financial support.

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