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# Copper-Catalyzed Chemoselective (Amino)fluorosulfonylation of Hydrocarbons via Intramolecular Fluorine-Atom Transfer

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Cite This: https://doi.org/10.1021/acscatal.4c00116 Read Online

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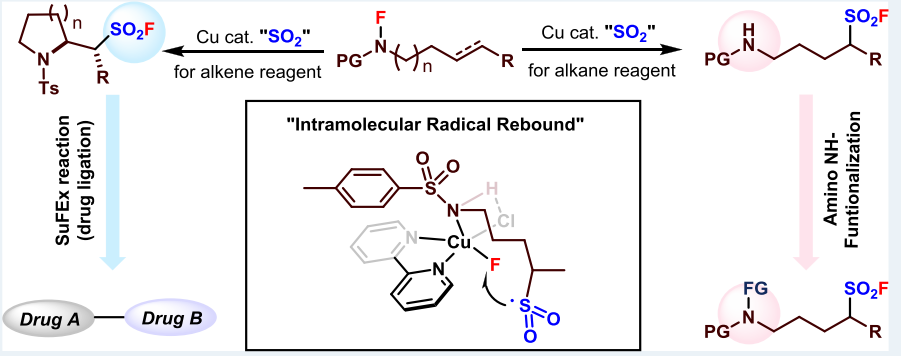



**ABSTRACT:** Sulfonyl fluorides have found increasing applications as functional molecules in chemistry and biology. We herein report a copper-catalyzed atom-economical access to two categories of sulfonyl fluorides through a radical relay strategy in the presence of an $SO_2$ surrogate. The aliphatic C($sp^3$)−H bond in *N*-fluoro-*N*-alkyl sulfonamides reacted via a 1,5-hydrogen atom transfer (HAT) process, affording alkanesulfonyl fluorides with a proximal amino group. On the other hand, utilizing substrates containing a proper C=C double bond resulted in intramolecular olefin aminofluorosulfonylation, allowing the synthesis of fluorosulfonyl-functionalized pyrrolidines and piperidines via atom-transfer radical addition (ATRA). Both reaction systems proceeded under mild conditions, requiring no additional fluorine source. Experimental and computational studies suggest that S−F coupling is likely achieved through an intramolecular radical-rebound pathway. By taking advantage of the SuFEx chemistry and multifunctionality of the products, the method is applicable to the late-stage modification of bioactive compounds, drug ligation chemistry, and organic synthesis.

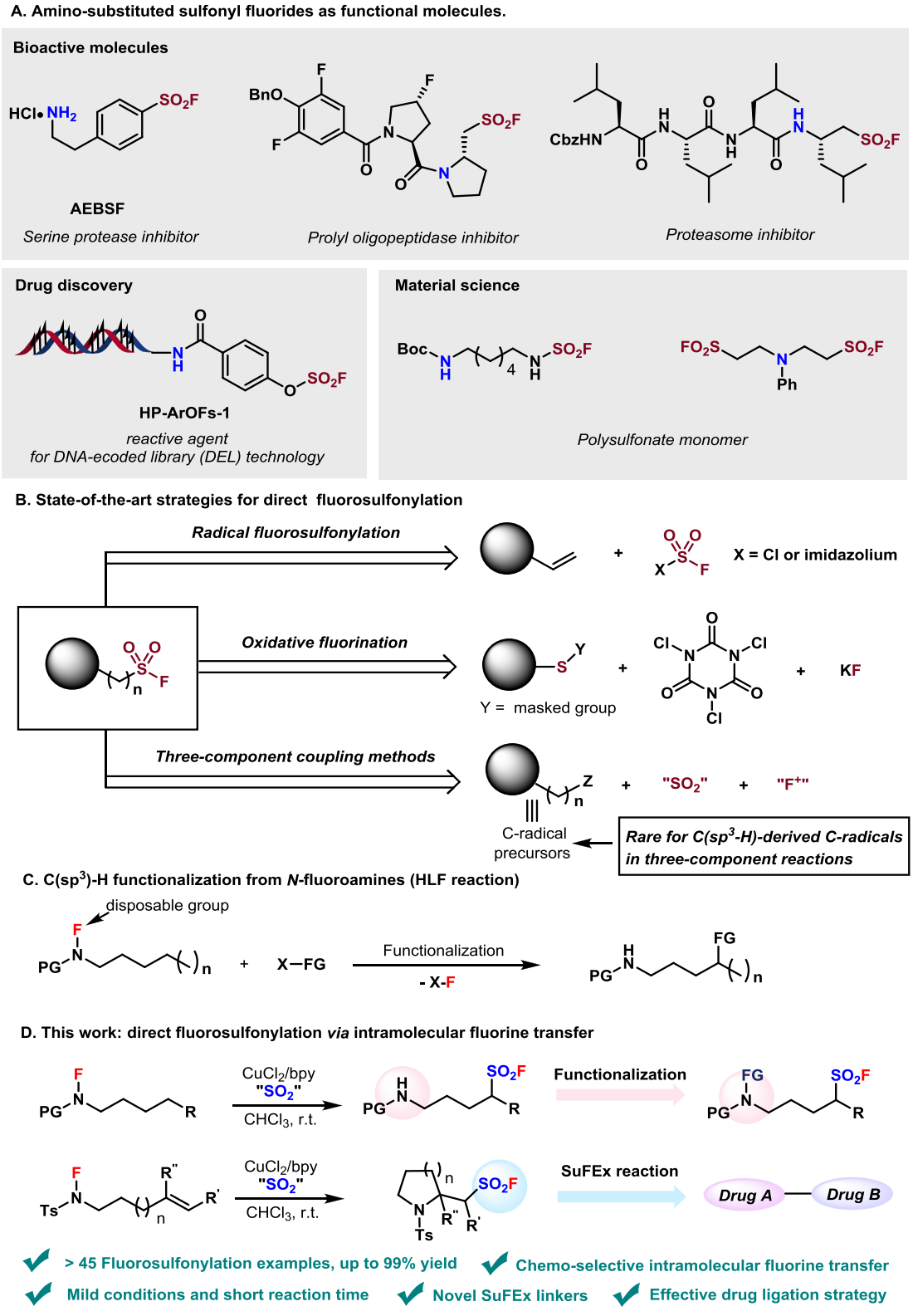
**KEYWORDS:** *fluorosulfonylation, fluorine atom transfer, amino alkanesulfonyl fluorides, SuFEx reactions, copper catalysis*

Sulfonyl fluorides ($RSO_2F$) exhibit a unique and attractive balance between reactivity and stability, justifying their privileged function in both chemistry and biology.[1] Since the discovery of "Sulfur(VI) Fluoride Exchange" (SuFEx), also known as the second-generation "click chemistry," by Sharpless and co-workers in 2014,[2] the application of sulfonyl fluorides has been increasingly extended to organic synthesis,[3] drug discovery,[4] chemical probes,[5] and material science[6] (Scheme 1A). However, the common synthetic approach to sulfonyl fluoride through the Cl/F exchange suffers from significant limitations due to the relative instability of many parent sulfonyl chlorides.[7] The growing demand for diversified $FSO_2$-containing structures calls for the development of more practical and convenient methodologies in this field.[8]

State-of-the-art synthetic strategies can be classified into three categories (Scheme 1B). (a) The products are synthesized via radical fluorosulfonylation of olefins under photoredox or electrochemical conditions using $FSO_2Cl$ and analogous reagents such as imidazolium sulfonyl fluoride salts.[9] However, this method ultimately necessitates the utilization of volatile toxic chemicals ($FSO_2Cl$ and $SO_2F_2$). (b) Alternatively, sulfur(II) precursors such as thiols, disulfides, sulfenyl phthalimides, or arylphosphorothiolates[10] can undergo oxidative fluorination, with KF being a fluoride source. The limitation of substrates and excessive oxidant usage hinder its further development. (c) A three-component method involving radical coupling of sulfur dioxide ($SO_2$) represents an attractive strategy. The three-component coupling between a carbon-based radical precursor, $SO_2$, and a fluorine source is advantageous owing to the flexibility and ready availability of the reagents, especially with the emergence of "solid $SO_2$" surrogates, such as 1,4-diazoniabicyclo[2.2.2]octane-1,4-disul-

Received: January 8, 2024
Revised: February 15, 2024
Accepted: February 15, 2024

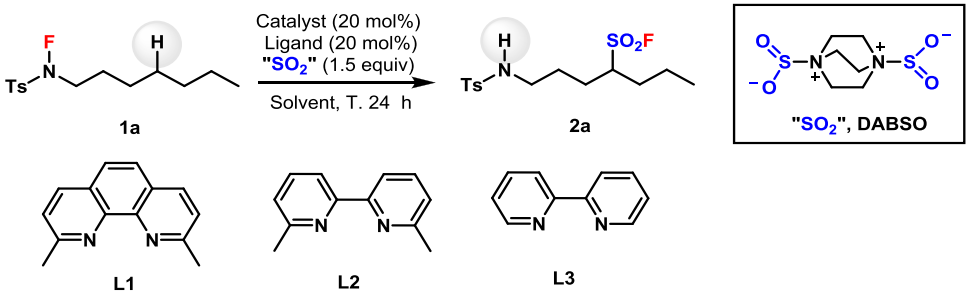
**Scheme 1. Synthesis and Application of Amino-Tethered Sulfonyl Fluorides: (A) Selected Examples of Amino-Tethered Sulfonyl Fluorides; (B) State-of-the-Art Strategies for Direct Fluorosulfonylation; (C) Common Methods of Functionalization of C($sp^3$)−H Bond via Hofmann−Löffler−Freytag (HLF) Reaction from *N*-fluoroamines; and (D) Direct Fluorosulfonylation Strategy through Chemoselective Fluorine Transfer (This Work) and Its Applications in Organic Synthesis and Drug Ligation**




finate (DABSO), $K_2S_2O_5$, $Na_2S_2O_4$, and $Na_2S_2O_5$.[11,12] The abundance of carbon-based radical precursors in both $sp^2$ and $sp^3$ categories[7d] further highlights the significance of this protocol. In fact, the most straightforward protocol for synthesizing alkanesulfonyl fluorides is the direct fluorosulfonylation of C($sp^3$)−H bonds. Nevertheless, because of the


https://doi.org/10.1021/acscatal.4c00116
ACS Catal. XXXX, XXX, XXX−XXX

**Table 1. Optimization of Conditions for the Preparation of Amino-Substituted Alkanesulfonyl Fluorides**[a]




| entries | cat | ligand | $T$/°C | solvent | yield of **2a** (%)[b] |
|---|---|---|---|---|---|
| 1 | CuCl | **L1** | 60 | DCE | 26 |
| 2 | $CuCl_2$ | **L1** | 60 | DCE | 35 |
| 3 | $CuCl_2$ | **L2** | 60 | DCE | 38 |
| 4 | $CuCl_2$ | **L3** | 60 | DCE | 46 |
| 5 | $CuCl_2$ | **L3** | r.t. | DCE | 50 |
| 6 | $CuCl_2$ | **L3** | r.t. | DCE | 50 |
| 7 | $CuCl_2$ | **L3** | r.t. | DMSO | trace |
| 8 | $CuCl_2$ | **L3** | r.t. | THF | trace |
| 9 | $CuCl_2$ | **L3** | r.t. | $CHCl_3$ | 57 |
| 10[c] | $CuCl_2$ | **L3** | r.t. | $CHCl_3$ | 63 |

[a]Reactions were carried out with **1a** (0.1 mmol) and "$SO_2$" (DABSO, 0.15 mmol), in 2 mL solvent under $N_2$ atmosphere. [b]Yields were determined by $^{19}F$ NMR analysis using (trifluoromethyl)benzene (Ph−$CF_3$) as an internal standard. [c]Reaction time: 4 h.

strong dissociation energy of C($sp^3$)−H bonds and challenges in controlling chemo- and regioselectivities,[13] this highly interesting strategy remains underexplored.

On the other hand, amino groups are ubiquitous in pharmaceuticals, and a diverse array of functional groups can be introduced by the manipulation of amines.[14] Therefore, compounds with both amino and fluorosulfonyl functionalities undoubtedly possess an advantage as potent reagents for various purposes (Scheme 1A). In this context, the Hofmann−Löffler−Freytag (HLF) reaction provides significant insights,[15] where a nitrogen radical undergoes 1,5-HAT to give a carbon-based radical through a six-membered ring transition state. This radical-triggered site-selective C($sp^3$)−H functionalization of N-fluorosulfonamides has been extensively studied for constructing carbon−carbon and carbon−heteroatom bonds.[16] We rationalized that by incorporating $SO_2$ as a radical acceptor and employing an intramolecular fluorine-atom transfer, we could establish a unified protocol to access amino-functionalized alkanesulfonyl fluorides in high chemo- and regioselectivities. While conceptually feasible, the implementation of this protocol remains challenging due to the potential competing reactions of N-fluorosulfonamide substrates that could lead to side products including nitrogen-containing heterocycles, unfluorinated sulfonamides, imines, and desaturated alkyl amines.[17] In addition, the chemoselectivity of the fluorine-atom transfer process needs to be improved as well. In most cases of N-directed C($sp^3$)−H bond functionalization using *N*-fluoroamides,[16] the fluorine atom typically participated as a disposable group that is not integrated into the product (Scheme 1C), as in HLF reactions. Cook and co-workers[18] and Ye and co-workers[19] recently reported *N*-fluoroamide-directed C($sp^3$)−H bond fluorination under Fe(II) and Co(II) catalysis, respectively. These few examples of intramolecular fluorine-atom transfer suggest that the key to our successful synthesis lies in streamlining multiple elementary steps including N-centered radical formation, the radical relay process, $SO_2$ insertion, and fluorine-atom transfer without any premature capture of radical intermediates. Herein, we present an efficient strategy to access amine- and aza-heterocycle-tethered sulfonyl fluorides (Scheme 1D). In the presence of a Cu(II) catalyst and DABSO, two classes of alkanesulfonyl fluorides with additional functionalities have been afforded under universal reaction conditions. The resulting multifunctional products were successfully employed for late-stage modification of bioactive molecules and drug ligation through SuFEx reactions.

We commenced our studies on direct fluorosulfonylation with *N*-fluoro-*N*-heptyl-4-methylbenzenesulfonamide (**1a**) for our proof-of-concept studies. In view of the recent progress in metal-catalyzed HLF reactions,[16] the reaction was initially conducted with CuCl as the catalyst and with 2,9-dimethyl-1,10-phenanthroline (**L1**) as the ligand. DABSO was designated as the $SO_2$ surrogate in dichloroethane (DCE) at 60 °C (Table 1, entry 1). The target $\delta$-fluorosulfonylation product **2a** was obtained in 26% yield. Various copper salts and ligands were then evaluated (entries 2−4, also see Table S1 in the Supporting Information). $CuCl_2$-bipyridyl provided an improved yield of the desired product (entry 4, 46%). Notably, similar yields were obtained at room temperature (entry 6). A series of single or mixed solvents were next assessed (entries 7−10; also see Table S3 in the Supporting Information), and product **2a** was obtained in 63% yield when $CHCl_3$ was used as the solvent. In contrast, a sluggish reaction occurred in ethereal or other polar solvents. Interestingly, the reaction yield was not affected when the reaction time was shortened to 4 h (entry 10).

With the optimized conditions in hand, we next examined the generality of this protocol (Table 2). The reaction exhibited remarkable compatibility with diverse linear and branched *N*-fluorosulfonamides, and several noteworthy observations were made. (1) *N*-Fluorosulfonamides bearing linear carbon chains of more than four $CH_2$ units afforded the $\delta$-fluorosulfonylation products in comparable yields (2b−2d, 42−51%), indicating that the length of the alkyl chain had


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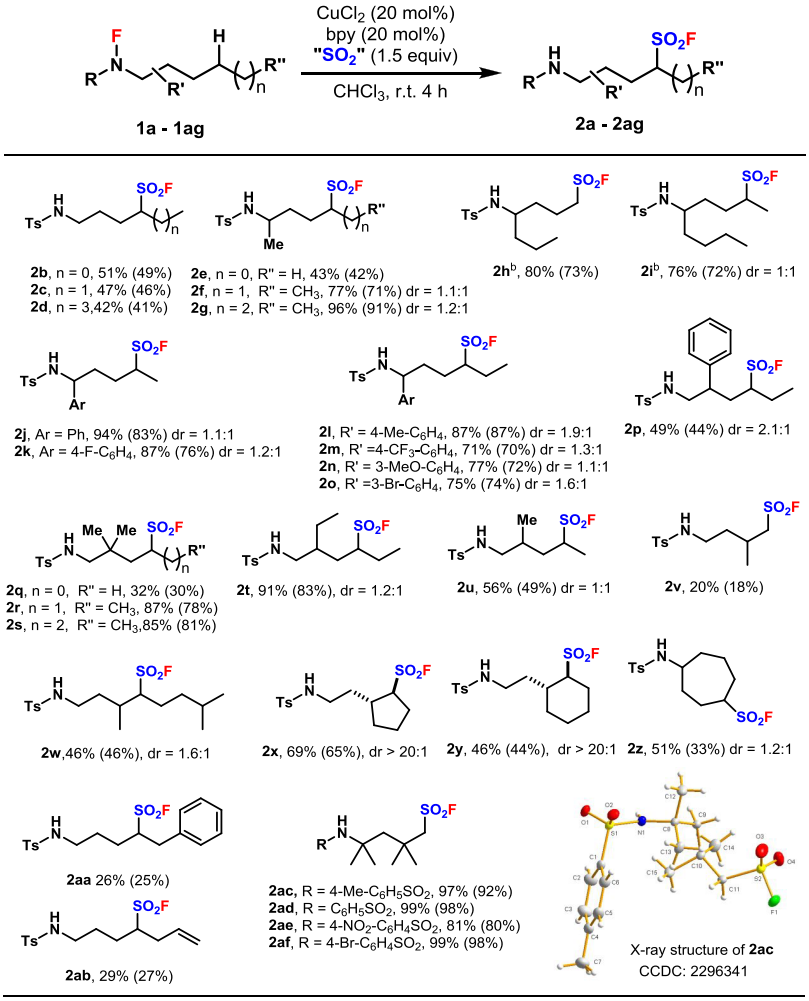
**Table 2. Reaction Scope of the Direct Fluorosulfonylation**[a]




[a]Reaction conditions: **1** (0.1 mmol), "$SO_2$" (DABSO, 0.15 mmol), $CuCl_2$ (0.02 mol), bpy (0.02 mol) in 2 mL $CHCl_3$ at r.t. for 4 h under $N_2$. Yields were determined by $^{19}F$ NMR analysis using Ph−$CF_3$ as an internal standard; isolated yields are shown in parentheses. [b]Reaction ran at 40 °C for 24 h.

minimal influence on the reaction performance. (2) Enhanced efficiency was observed when an $\alpha$-substituent was present. Introduction of an alkyl (1f−1i) or aryl (1j−1o) group to the $\alpha$-position afforded the sulfonyl fluorides with apparently higher yields (2f−2o, 77−96%) because the steric bulky substituents at $\alpha$-position suppressed the formation of side products. (3) The $\beta$ and $\gamma$ substituents exerted distinct effects on the chemoselectivity. While a single methyl group at the $\beta$ or $\gamma$ position had only a marginal impact on the reaction outcome (2u, 2w), bulkier groups such as *gem*-dimethyl (1r, 1s) and ethyl (1t) groups at the $\beta$ position caused a substantial increase of reaction efficiency (2r−2t, 85−91%). However, the substrate with a $\beta$-phenyl group reacted with only moderate yield (2p) due to the counteractive effect of cyclization preference. A similar trend was observed for the substrates containing a phenyl or alkenyl substituent attached to $\varepsilon$-carbon (2aa, 2ab). (4) Efficient fluorosulfonylation of C($sp^3$)−H bond within a cyclopentyl or cyclohexyl moiety was also achieved (2*x* and 2*y*, 69% and 46%, respectively) in excellent *trans*-selectivity (>20:1 dr), as a result of the steric repulsions between $FSO_2$ and the vicinal methylene group. In contrast, minimal stereoselectivity was observed when the C−H site was embedded in a seven-membered ring (2*z*). (5) The fluorosulfonylation of terminal C−H bonds is highly sensitive to the substitution pattern. While no desired products were obtained in the absence of any substituent, the introduction of methyl groups at the $\alpha$, $\beta$, or $\gamma$ position led to the isolation of the products in acceptable yields (2e, 2q, and 2v). Notably, *N*-fluorosulfonamide with gem-dimethyl at both $\alpha$ and $\gamma$ positions (1ac) gave an almost quantitative yield of the sulfonyl fluoride product 2ac. In this case, the reaction yields were only slightly affected by the different sulfonamide-protecting groups (1ad−1ae).

Experimental and computational studies have been performed to gain mechanistic insights into this fluorosulfonylation system (Figure 1). Introduction of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) completely inhibited the reaction (Figure 1A-(1)), suggesting the intermediacy of organic radicals. More convincing evidence were obtained from the radical clock reaction (Figure 1A-(2)). In the radical clock reaction, only the ring-open sulfonyl fluoride product **2ag** was detected (54% yield), suggesting that the C-to-C radical relay is more rapid than the $SO_2$ trapping of the primary cyclopropylmethyl radical ($1.3 \times 10^8$ $s^{-1}$).[20] The radical-trapping studies using 1,1-diphenylethene further supported the intermediacy of the N-centered and S-centered radicals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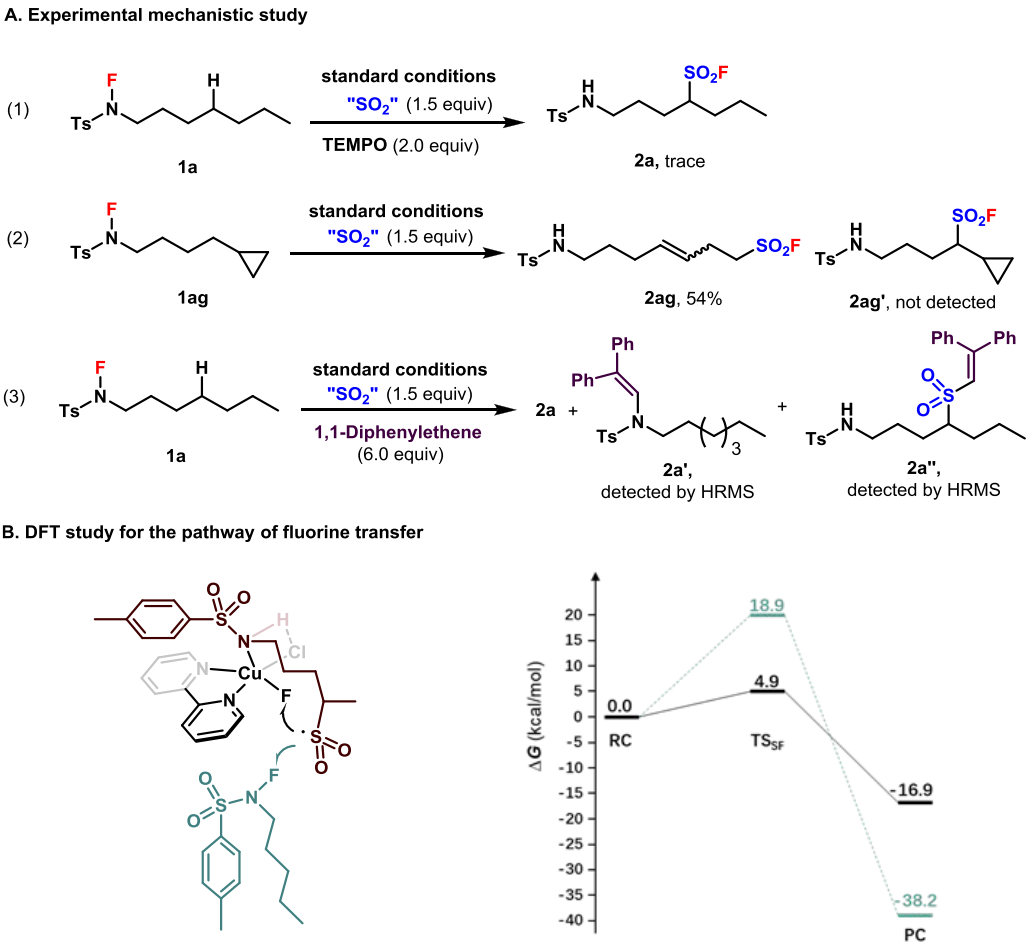


**Figure 1.** Mechanistic Studies: (A) Experimental mechanism studies. (B) DFT (B3LYP(D3BJ)/Def2-TZVPP//Def2-SVP) study for the pathway of fluorine transfer. Computational comparisons of F atom transfer from the Cu−F (black arrow) vs the substrate N−F (green arrow) to the sulfonyl radical. RC represents the reactant complex, TS represents the transition state, and PC represents the product complex.

(Figure 1A-(3)). Regarding the S−F bond formation event, two possible pathways have been considered, namely, the "intramolecular radical rebound" pathway[21] (black arrow in Figure 1B) and the intermolecular fluorine-atom transfer (FAT) pathway[22] (green arrow in Figure 1B). Our DFT studies revealed that the former pathway carries an activation barrier as low as 4.9 kcal/mol, whereas the latter one was identified with a much higher barrier (18.9 kcal/mol, Figure 1B). This result is consistent with the related reports by Cook and co-workers[18b] and is also in line with our crossover experimental findings (see the Supporting Information, Figure S1). Notably, no 1,5-fluorine-atom transfer product was detected under the standard conditions, suggesting a significantly greater level of complexity in the fluorine-atom transfer process compared to Cook's previous work.[18a]

Based on the experimental evidence and DFT calculations, we propose a plausible mechanism (Figure 2). Initially. the Cu(II) complex is reduced to Cu(I) chloride **A** in the presence of DABSO, which subsequently reacts with *N*-fluorosulfonylamide **1** via single-electron transfer to generate amidyl radical and Cu(II)-F species (**B**). Through a six-membered ring transition state, carbon-centered radical **C** is formed via intramolecular 1,5-HAT, followed by the capture of $SO_2$ affording S-centered radical intermediate **D**.[23] Finally, the fluorine transfer proceeds through an intramolecular radical rebound pathway leading to S−F bond formation, affording

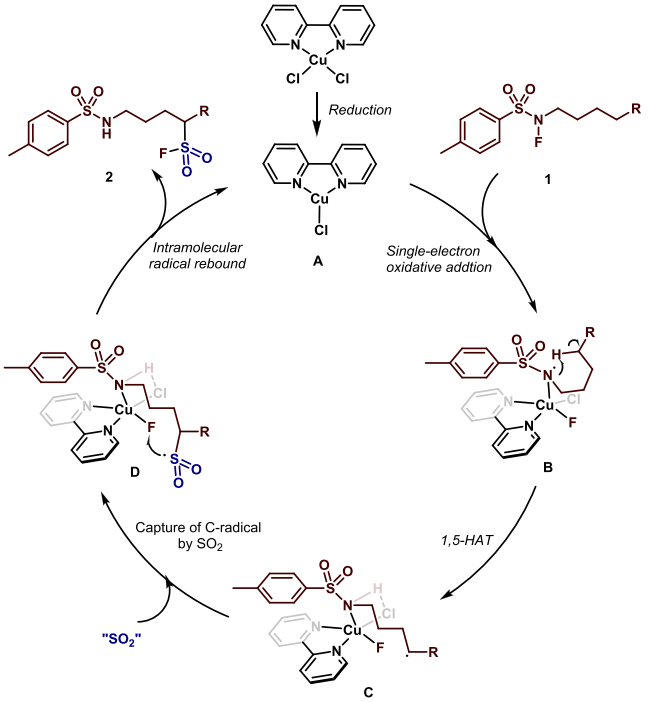


**Figure 2.** Proposed mechanism.


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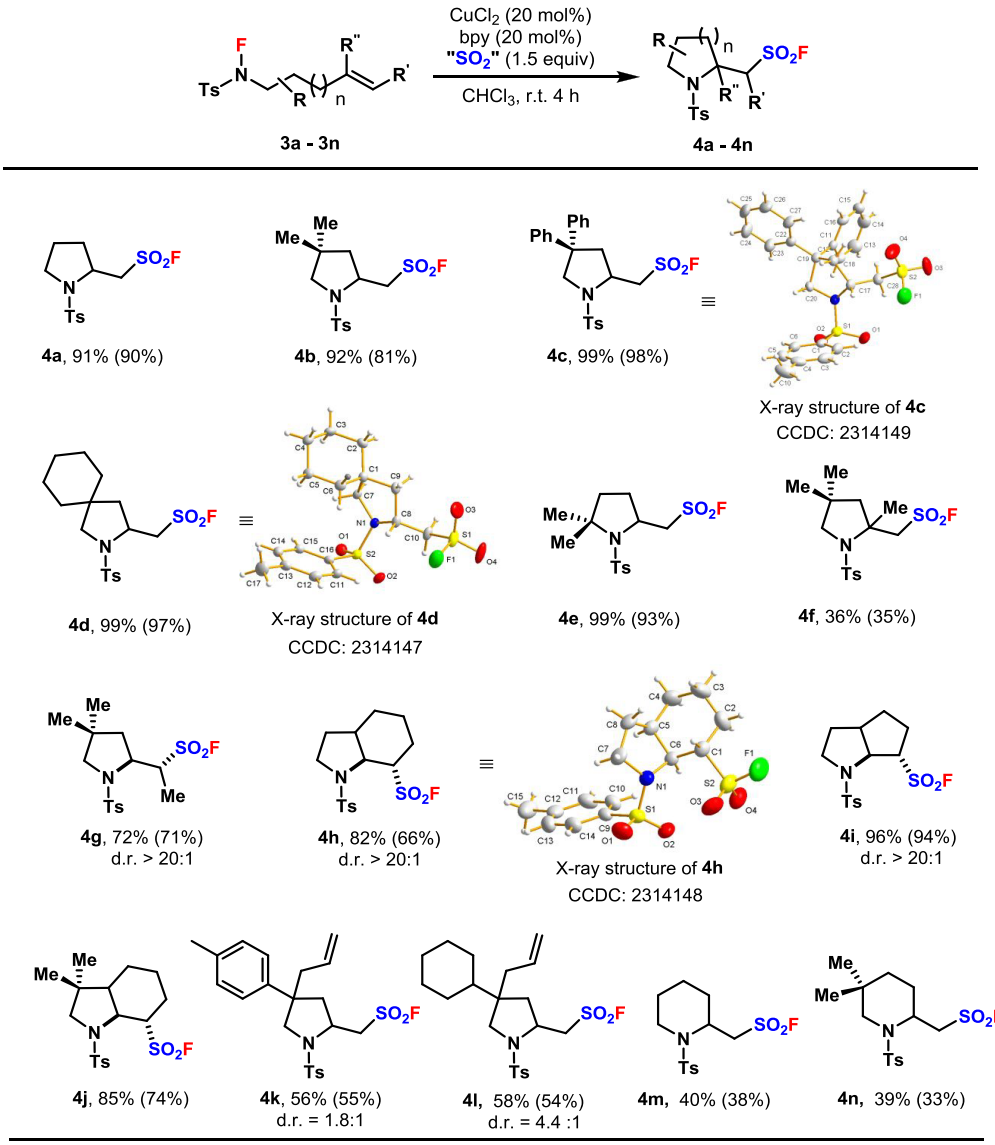
**Table 3. Reaction Scope of the Aminofluorosulfonylation of Olefins**[a]




[a]Reaction conditions: **3** (0.1 mmol), "$SO_2$" (DABSO, 0.15 mmol), $CuCl_2$ (0.02 mol), bpy (0.02 mol) in 2 mL $CHCl_3$ at r.t. for 4 h under $N_2$. Yields were determined by $^{19}F$ NMR analysis using Ph−$CF_3$ as an internal standard; isolated yields are shown in parentheses.

the desired product **2**. Throughout this process, fluorine-atom transfer exhibits high chemoselectivity.

To better explore the N-radical to C-radical formation, we envisioned another related system by aminofluorosulfonylation of olefins through atom-transfer radical addition (ATRA),[24] affording *β*-amino-substituted sulfonyl fluorides (Table 3). This task presents challenges since previous studies have shown that additional fluorine sources are usually essential.[24a] Gratifyingly, the same reaction conditions were fully applicable, and the desired aminofluorosulfonylation product (**4a**) was obtained in a nearly quantitative yield from the two-component reaction. In this case, the product was generated by 5-exo-dig cyclization of the N-radical to give a C-radical. Exploration of the substrate scope began with dialkyl-substituted *N*-fluoro-alkenylsulfonamides (**3b**−**3e**). The corresponding aminofluorosulfonylation products were obtained in excellent yields (92−99%). Notably, tertiary *N*-fluorosulfonamides **3e** were quantitatively transformed to *β*-amino-substituted sulfonyl fluoride **4e** without any loss in regio- or chemoselectivity. While the 1,1-disubstituted alkene **3f** was converted to the sulfonyl fluoride **4f** only in 36% yield due to the steric hindrance around the reactive site, the *N*-alkenyl sulfonamides with an internal alkene or cyclic alkenes afforded the corresponding products in high yields and excellent diastereoselectivities (**4h**−**4j**). The *trans* disposition of $FSO_2$ and the amino group in **4h** was confirmed by X-ray crystallography (CCDC 2314148). Interestingly, 3,3-diallyl substrates (**3k** and **3l**) also underwent aminofluorosulfonylation of one C=C double bond in moderate yields (56 and 58%, respectively), with the other terminal olefin untouched. Finally, we tested the reactivity of 5-hexen-1-amine substrates, and both the 6-exo-dig cyclization products (**4m** and **4n**) were obtained in moderate yields.

Our direct fluorosulfonylation protocol demonstrated good synthetic values (Scheme 2). Two reactions were readily scalable to a multimillimole scale, producing the desired products in 70 and 45% yields for **2ac** and **2a**, respectively (Scheme 2A). Additionally, this methodology enables the late-


https://doi.org/10.1021/acscatal.4c00116
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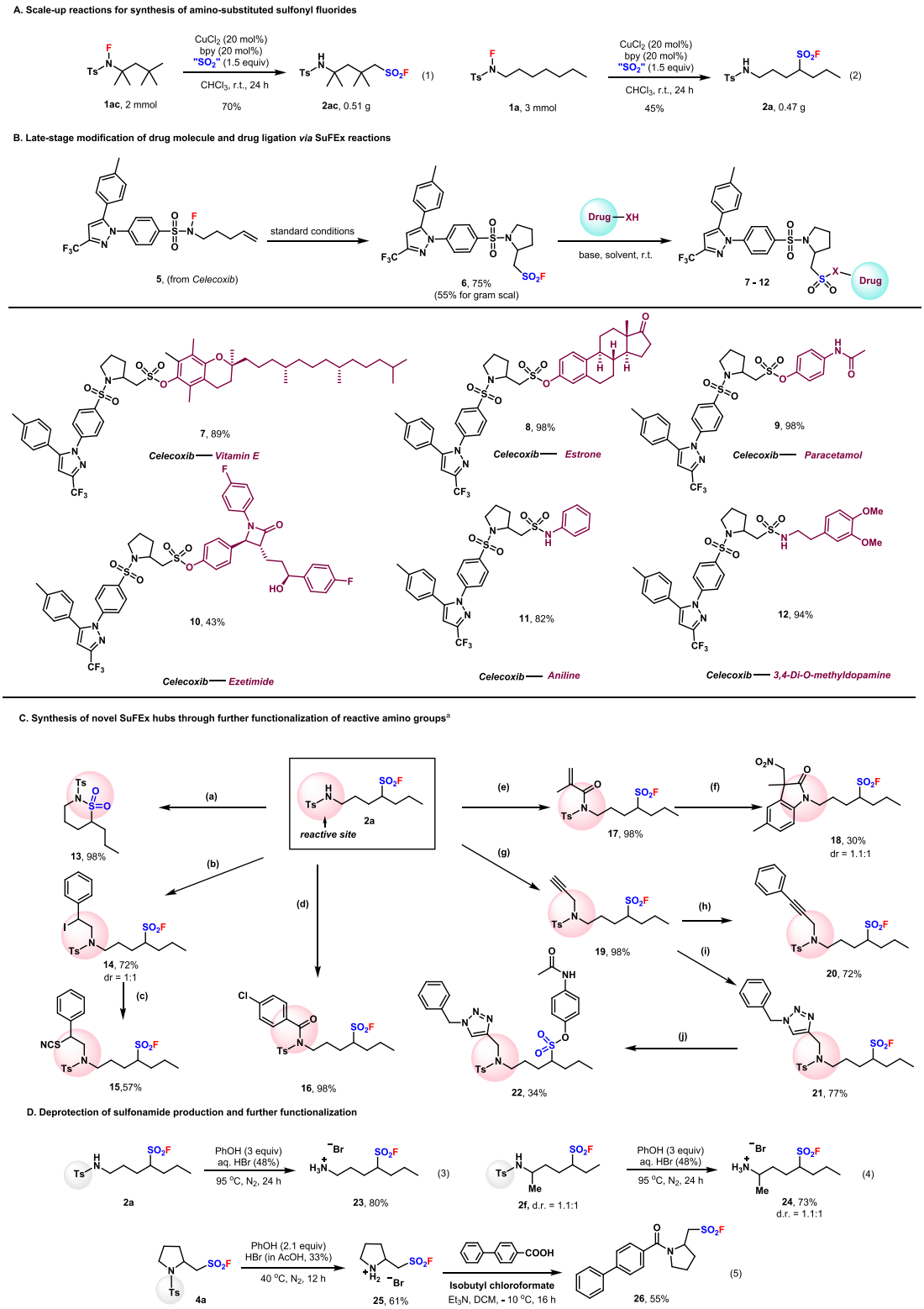
**Scheme 2. Diverse Synthetic Applications of the Fluorosulfonylation System: (A) Scale-up Reactions; (B) Drug Ligation through SuFEx Reactions; (C) Further Functionalization of the Amino Site; and (D) Deprotection of N-Sulfonyl Products.**[a]




[a]Reaction conditions of further functionalization of the amino site: (a) **2a**, NaH (1.5 equiv), in DMF at 0 °C to r.t. for 12 h; (b) **2a**, styrene (1.0 equiv), *N*-iodosuccinimide (1.0 equiv) in DMC, irradiation at 520 nm under $N_2$, at r.t. for 4 h; (c) **2a**, NaSCN (5 equiv) in MeCN at 70 °C for 24 h; (d) **2a**, R-$C_6H_4C(O)Cl$ (2.0 equiv), DMAP (10 mol %), $Et_3N$ (2.0 equiv) in DCM at r.t. for 12 h; (e) **2a**, methacryloyl chloride (2.0 equiv), DMAP (10 mol %). $Et_3N$ (2.0 equiv) in DCM at r.t. for 12 h; (f) **17**, $Na_2NO_2$ (2.0 equiv), $NaHCO_3$ (2.0 equiv), $K_2S_2O_8$ (2.0 equiv) in MeCN at 120 °C for 18 h; (g) **2a**, 3-bromoprop-1-yne (1.2 equiv), $K_2CO_3$ (2.0 equiv) in DMF at 0 °C to r.t. for 16 h; (h) **19**, PhI (2.5 equiv), $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (4 mol %), $Et_3N$ (6.0 equiv) in THF at r.t. for 12 h; (i) **19**, $BnN_3$ (1.2 equiv), CuI (2 mol %), 2,6-lutidine (1.0 equiv) in $H_2O$/$CH_3CN$ at r.t. for 24 h. (j) **21** (1.0 equiv), Acetaminophen (2.0 equiv), $Cs_2CO_3$ (2.0 equiv) in MeCN at r.t. for 24 h. All yields are isolated yields.


https://doi.org/10.1021/acscatal.4c00116
ACS Catal. XXXX, XXX, XXX−XXX

stage modification of biologically active molecules by the facile manipulation of the $FSO_2$ moiety. For example, pyrrolidin-2-yl-substituted sulfonyl fluoride carrying a *Celecoxib* structure was synthesized in 75% yield (55% yield for a scale-up reaction). Furthermore, the $FSO_2$ group within the molecule exhibits inherent reactivity toward nucleophiles and allows the ligation of two drugs via SuFEx reactions. Scheme 2B illustrates the successful connection of *Celecoxib* with drugs containing phenolic hydroxyl groups such as *Vitamin E* (**7**), *Estrone* (**8**), *Paracetamol* (**9**), and *Ezetimibe* (**10**) and drugs containing amino groups such as simple aniline (**11**) and 3,4-*di-O-methyldopamin* (**12**) under mild conditions. The sulfonyl fluoride products in Table 2 are also distinguished by the presence of a reactive amino site, which enables further functionalization to deliver a wide range of value-added chemicals. Versatile reactivity of **2a** is demonstrated in Scheme 2C. Treatment with NaH led to an intramolecular SuFEx reaction, producing a six-member sultam **13** in quantitative yield. It is worth noting that analogous cyclic sulfonamides were found as drug molecules for treating Parkinson's or Alzheimer's disease.[25] Furthermore, when a mixture of **2a**, *N*-iodosuccinimide (NIS), and olefin was irradiated with green LED light ($\lambda$ = 520 nm),[14d] iodoamination product **14** was obtained in high yield. Interestingly, the benzylic iodides could be further transformed through nucleophilic substitution reactions. For instance, treatment of **14** with NaSCN resulted in the formation of sulfonyl fluoride containing a 1,2-amino thiocyanato motif (**15**) in 57% yield. In addition, treatment of **2a** with acid chloride afforded a series of corresponding amide (**16**) without any self-cyclization product being detected. This late-stage functionalization protocol also allowed for the introduction of olefin (**17**) into SuFEx hubs, which demonstrates broad prospects in chemical probe development and organic synthesis.[26] Similarly, compound **19** containing an *N*-2-propyn-1-yl group can be simply synthesized from the reaction of **2a** with propargyl bromide. The alkynyl group in this molecule can integrate alkyne−azide "click" reaction and SuFEx "click" reaction (1,2,3-triazole **21** was formed through alkyne−azide "click" reaction of **19** with (azidomethyl)-benzene,[27] which underwent a subsequent SuFEx "click" reaction with acetaminophen affording **22**). It also underwent Sonogashira coupling to give compound **20** in 72% yield. Last of all, the sulfonyl fluoride products in Tables 2 and 3 were subjected to treatment with strong acids, such as HBr, resulting in the cleavage of sulfonamides while preserving the integrity of $FSO_2$ groups (Scheme 2D). The resulting deprotected amine **25** can be further functionalized for the synthesis of high-value compounds such as amides carrying the $FSO_2$ moiety (**26**).

In conclusion, we realized for the first time the direct fluorosulfonylation of *N*-fluorosulfonamide substrates through chemoselective intramolecular fluorine-atom transfer. Two reaction systems have been developed. On one hand, *N*-fluoro-*N*-alkylsulfonamide substrates reacted via a 1,5-HAT process en route to site-selective fluorosulfonylation of aliphatic C($sp^3$)−H bonds, affording diverse alkanesulfonyl fluorides with a reactive amino substituent. On the other hand, aminofluorosulfonylation of C=C double bonds has been achieved for *N*-fluorosulfonamides bearing a proximal olefin, allowing high-yielding synthesis of pyrrolidin-2-yl- and piperidin-2-yl-substituted sulfonyl fluorides. Mechanistic investigations confirmed a radical relay process in these transformations, and the fluorine transfer proceeds through an intramolecular radical rebound pathway involving a Cu(II)−F intermediate. This methodology not only demonstrated its potential applications in late-stage modification of bioactive molecules but also showcased compatibility with SuFEx reactions for drug ligation purposes. Furthermore, various newly developed amino-substituted alkanesulfonyl fluorides can be readily transformed into highly valuable aliphatic sulfonyl fluorides, thereby offering promising opportunities for drug design, as well as facilitating organic syntheses.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c00116.

Crystallographic data for **2ac** (CIF)
Crystallographic data for **4c** (CIF)
Crystallographic data for **4d** (CIF)
Crystallographic data for **4h** (CIF)
Experimental procedures and methods, mechanistic study details, synthesis of the substrates, and spectroscopic data for the new compounds (PDF)

### Accession Codes

Deposition numbers 2296341, 2314147, 2314148, and 2314149 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support for this work was provided by the National Natural Science Foundation of China (22201162 and 22371175), Science Foundation for Outstanding Young Scholars of Shandong Province (No. 2022HWYQ-0057), and the Qilu Young Scholars Program of Shandong University. This work is dedicated to Prof. Dr. Xiaoyan Li on the occasion of her 60th birthday.

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https://doi.org/10.1021/acscatal.4c00116
*ACS Catal.* XXXX, XXX, XXX−XXX