Sythetic Methods

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Regioselective Radical Aminofluorination of Styrenes**

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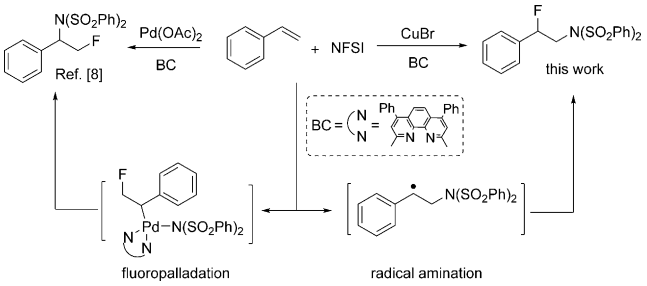
Abstract: *The copper-catalyzed radical aminofluorination of styrenes with N-fluorobenzenesulfonimide (NFSI) is realized with high regioselectivity, thus affording aminofluorination products with regioselectivities opposite that of the palladium-catalyzed and noncatalyzed processes. Preliminary mechanistic studies suggested the reaction went through a radical pathway and was supported by DFT calculations. In these reactions, NFSI is utilized as both a radical nitrogen source and radical fluorine source, thus rendering it an attractive reagent.*

Molecules containing vicinal amino and fluorine moieties constitute key building blocks for the synthesis of anticancer, anticholinergic, and anti-inflammatory drugs, as well as therapeutic β-peptides.[1] Tandem intramolecular amination cyclization followed by intermolecular fluorination of unsaturated carbon–carbon bonds has been proven to be an efficient way to construct nitrogen-containing heterocycles with vicinal amino and fluorine moieties.[2] In contrast, the addition reaction between unsaturated carbon–carbon bonds and compounds containing N–F bonds might provide a highly attractive strategy for direct and efficient construction, in an intermolecular fasion, of molecules containing vicinal amino and fluorine moieties.

N-Fluorobenzenesulfonimide (NFSI) contains a N–F bond and is widely used as an electrophilic fluorination agent.[3] Radical fluorine atom transfer reactions of NFSI have been also developed.[4] With NFSI as a nitrogen source, interesting amination reactions were discovered through possible nucleophilic,[5] electrophilic,[6] and radical[7] aminating processes. Given the multiple reaction modes of NFSI and our work on employing NFSI as a nitrogen source,[5b–d, 7a,b] we were prompted to investigate the challenging regioselective aminofluorination directly from unsaturated carbon–carbon bonds and NFSI. Recently, Liu and co-workers developed an efficient palladium-catalyzed aminofluorination of styrenes with NFSI by fluoropalladation (Scheme 1).[8] Herein, we report an efficient and highly regioselective copper-catalyzed radical aminofluorination reaction of styrenes with NFSI,



Scheme 1. Aminofluorination of styrene with NFSI.

wherein the regioselectivity is complementary to that of palladium catalysis (Scheme 1).

Novel synthetic methods for fluorine incorporation have been significantly developed because of the widespread use of fluorine-containing compounds in pharmaceutical and agrochemical industries.[1c,9] In comparison with nucleophilic or electrophilic fluorination, radical fluorination under benign conditions is far less explored. Very recently, the electrophilic fluorine sources NFSI and Selectfluor were effectively used to construct C–F bonds by radical fluorination, during which the generation of a C(sp^3)-centered radical was neccesary.[10] Accordingly, intermolecular hydrofluorination,[10a] phosphonofluorination,[10f] as well as intramolecular aminofluorination[10h] of alkenes were realized. However, to the best of our knowledge, intermolecular radical aminofluorination of alkenes has not been documented, and might be attributed to the lack of a convenient route for the generation of relatively stable nitrogen-centered radical species.[11–14] More recently, we developed copper-catalyzed aminocyanation and diamination reaction of alkenes by the efficient generation of nitrogen-centered radicals from NFSI, and subsequent radical addition reactions with alkenes.[7a] With this methodology, six-membered-ring sultams[7c] were consturcted and aminoazidation reaction of alkenes were also developed.[7e] Therefore, we reasoned that if fluorine transfer between the in situ generated C-centered radical intermediate and NFSI could occur, a novel radical amination initiated aminofluorination of styrenes would lead to a unique regioselectivity which would be different from previous work[8] (Scheme 1).

Initially, the aminofluorination reaction between styrene (**1a**) and NFSI was investigated without employing a catalyst.[15] When the reaction of **1a** (0.5 mmol) and NFSI (1.2 equiv) was performed at 135 °C in 1,2-dichloroethane (DCE, 2 mL) for 10 hours, the aminofluorination product **2a** (same regioselectivity as with palladium as catalyst[8]) was obtained in 23 % yield upon isolation [Eq. (1)]. The aminofluorination product **3a** was not detected. In contrast, the reaction catalyzed by CuBr and bathocuproine (BC), as the ligand, delivered the aminofluorination product **3a** having the opposite regioselectivity.

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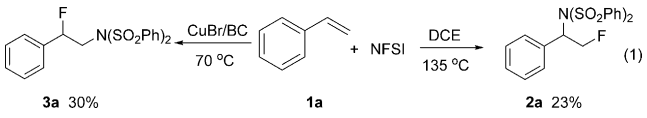
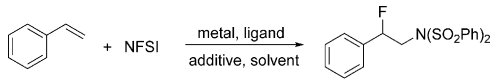


Thus, in the presence of 10 mol% CuBr and 5 mol% of BC, the reaction of **1a** (0.5 mmol) and NFSI (1.4 equiv) was performed in DCE (2 mL) at 70 °C for 10 hours under N_2, and the desired **3a** was obtained in 30% yield without the formation of **2a** (Table 1, entry 1). **3a** could also be obtained in 28% with neocuproin as the ligand, however, **3a** was not detected with 1,10-phenanthroline (Phen) or pyridine as ligands (entries 2–4). Intrigued by the reports on stabilization effects of Lewis acids on nitrogen-centered radicals,[16a] some Lewis acids were evaluated as additives to the reaction. It was discovered that addition of bis(pinacolato)diboron (B_2pin_2;[16b–d] 10 mol%) to the above reaction dramatically improved the yield of **3a** to 60% (entry 5). A control experiment in which CuBr was not present failed to afford any of the desired product (entry 6). With CuCl, CuCN, and $Cu(OTf)_2$ as the catalyst, **3a** was provided in 56, 48, and 35% yield, respectively (entries 7–9). With other metals, such as AgF, $Pd(OAc)_2$ and $Mn(OAc)_3$, **3a** was not observed (entries 10–12). Because of the observation of haloamination products (roughly the same amount compared to catalyst loading), AgF (10 mol%) was used to eliminate halide ions from the solution. Indeed, the yield of **3a** could be increased to 75% (entry 13). The yield was not affected by lowering the catalyst loading to 5 mol% copper and 2.5 mol% BC and B_2pin_2 (entry 14). Interestingly, when 1.0 equivalent of AgF was added, instead of 0.1 equivalents, **3a** was obtained in only 5% yield (entry 15). Other additives, such as $ZnCl_2$, $ZnBr_2$, and ZnI_2, also exhibited the corresponding Lewis acid effect with yields of **3a** ranging from 62 to 68% (entries 16–18). Of note is *n*-butyl fluoroborate, which also remarkably improved the yield to as high as 72% (entry 19).

With the optimized reaction conditions in hand (Table 1, entries 14 and 19), we then explored the scope and limitations of the above aminofluorination reaction and the results are summarized in Table 2. The reaction of NFSI with various

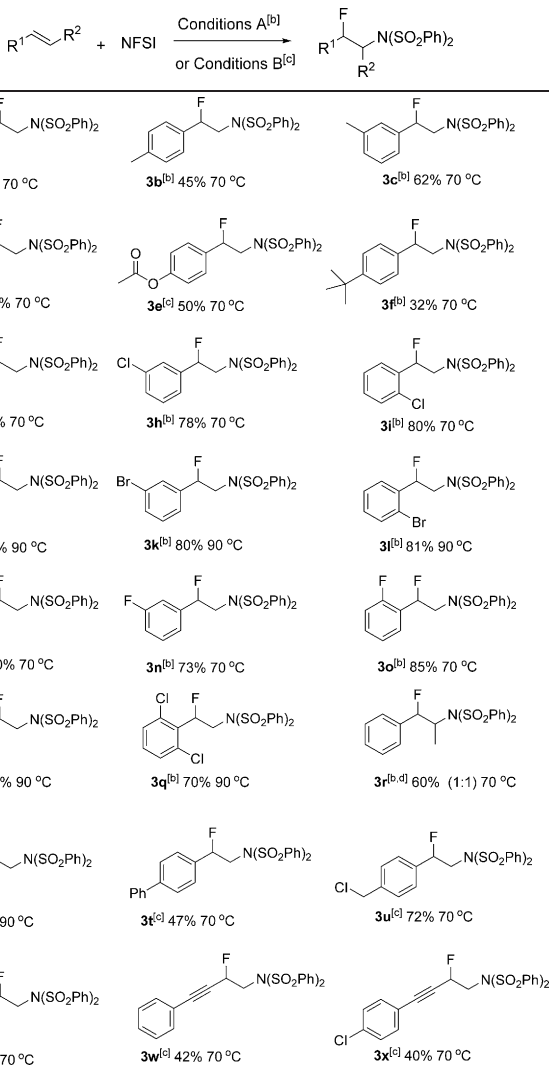
Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst	Ligand	Additive	*t* [h]	Yield [%][b]
1[c]	CuBr	BC	no	10	30
2[c]	CuBr	neocuproin	no	10	28
3[c]	CuBr	Phen	no	10	0
4[c]	CuBr	pyridine	no	10	0
5[c]	CuBr	BC	B_2pin_2	2	60
6[c]	No	BC	B_2pin_2	24	0
7[c]	CuCl	BC	B_2pin_2	2	56
8[c]	CuCN	BC	B_2pin_2	2	48
9[c]	$Cu(OTf)_2$	BC	B_2pin_2	2	35
10[c]	AgF	BC	B_2pin_2	10	0
11[c]	$Pd(OAc)_2$	BC	B_2pin_2	10	0
12[c]	$Mn(OAc)_3$	BC	B_2pin_2	10	0
13[c]	CuBr	BC	B_2pin_2/AgF	2	75
14[d]	CuBr	BC	B_2pin_2/AgF	4	75
15[e]	CuBr	BC	B_2pin_2/AgF	4	5
16[f]	CuBr	BC	$ZnCl_2$	4	68
17[f]	CuBr	BC	$ZnBr_2$	4	62
18[f]	CuBr	BC	ZnI_2	4	65
19[g]	CuBr	BC	*n*$BuBF_3K$	4	72

[a] Reactions were carried out with **1a** (0.5 mmol) and NFSI (1.4 equiv) in 2 mL DCE under N_2 atmosphere at 70 °C, unless otherwise noted. [b] Yield of the isolated product. [c] Catalyst (10 mol%), ligand (5 mol%), B_2pin_2 (10 mol%), AgF (10 mol%). [d] Catalyst (5 mol%), ligand (2.5 mol%), B_2pin_2 (5 mol%)/AgF (10 mol%). [e] Catalyst (5 mol%), ligand (2.5 mol%), B_2pin_2 (5 mol%)/AgF (100 mol%). [f] Catalyst (5 mol%), ligand (2.5 mol%), additive (5 mol%). [g] Catalyst (5 mol%), ligand (2.5 mol%), *n*$BuBF_3K$ (10 mol%).

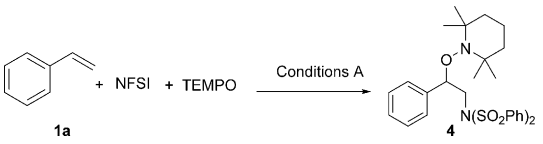
Table 2: Scope of the aminofluorination.[a]



[a] Yield is that of the isolated product. [b] Conditions A: **1** (0.5 mmol), NFSI (1.4 equiv), CuBr (5 mol%), BC (2.5 mol%), B_2pin_2 (5 mol%), AgF (10 mol%) and 2 mL DCE in sealed tube for 4 h under N_2 atmosphere. [c] Conditions B: **1** (0.5 mmol), NFSI (1.4 equiv), CuBr (5 mol%), BC (2.5 mol%), 10 mol% *n*$BuBF_3K$ and 2 mL DCE in sealed tube for 4 h under N_2 atmosphere. [d] The ratio of the two diastereisomers is given within parentheses.

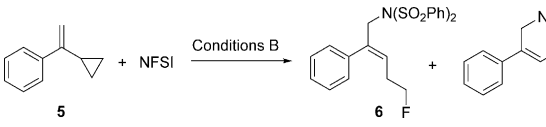
styrene derivatives afforded the desired aminofluorination products **3b–r** in yields within the range of 32–85%. In these reactions, the *ortho*-, *meta*-, and *para*-methyl styrenes afforded the corresponding **3b** (45%), **3c** (62%), and **3d** (70%). Other electron-donating groups such as *para-tert*-butyl, *para*-OAc, and *meta*-OMe styrenes afforded **3e** (50%), **3f** (32%), and **3v** (46%). Halo-substituted styrenes were tolerated in the aminofluorination reaction, thus affording the corresponding products (**3g–o**, **3q**, and **3s**) in good yields, even for the benzylic chloride **3u** (72%), which could be used for additional transformations. The electron-withdrawing 4-cyano styrene afforded **3p** in 73% yield. Starting from either (*E*)-prop-1-enylbenzene (**1r**) or (*Z*)-prop-1-enylbenzene (**1r′**), loss of configurational integrity was observed in the product, as both *trans*- and *cis*-aminofluorination products were obtained in a 1:1 ratio. 1,3-Enynes produced the alkynylated products **3w** and **3x**, in 42 and 40% yield, respectively, thus allowing further elaboratons. However, for unactivated olefins, such as 1-octene and allylbenzene, the desired products were not formed as the six-membered-ring sultam[7c] products were predominant.

To gain insight into the mechanism of this transformation, some mechanistic experiments were performed. In the presence of 1.0 equivalent of 2,6-di-*tert*-butyl-4-methylphenol (BHT), under the optimal reaction conditions A (Table 2), the reaction of **1a** failed to give any desired product. Moreover, when 1.0 equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) was added instead of BHT, the aminooxygenation product **4** was isolated in 20% yield [Eq. (2)]. In addition, under the standard reaction conditions A (Table 2), but using an O_2 atmosphere, the aminofluorination reaction of **1j** was investigated. After performing the reaction for 18 hours, the desired aminofluorination product **3j** was not observed and 30% 4-bromobenzaldehyde was obtained.[7a] Further evidence for a radical mechanism was demonstrated by the radical clock experiment with (1-



(2)

cyclopropylvinyl)benzene (**5**) as the substrate.[17] The reaction of **5** under the standard reaction conditions B (Table 2) produced the ring-opened products **6** and **7** in 30 and 4% yield, respectively [Eq. (3)]. These results supported the generation of a benzylic carbon radical intermediate.



(3)

To gain more understanding of the mechanism of this process, we sought to use density functional theory (DFT) calculations. Recently, an interesting hydrofluorination of alkenylarenes, which proceeds through a $Pd^{II}/^{IV}$ catalytic manifold, for the preparation of benzylic fluorides was developed by Gouverneur and co-workers.[18] Therefore, two mechanisms were proposed for this process, the radical mechanism mentioned above and a copper(III)-mediated pathway.[19] The possibilities of these mechanisms were interrogated computationally (Figure 1). The complex **Com** is formed from ligand, catalyst, and NFSI, thus setting the stage for the initial oxidative addition. The oxidative addition of copper(I) to the N–F bond gives a hexacoordinate copper(III) intermediate (**Int A**) with a barrier of 13.5 kcal mol^{-1}, and it could generate the copper(II)-stabilized radical **Int B** through a fast equilibration. The geometry of the corresponding transition-state **TS 1** is provided in Figure S1 in the Supporting Information. Upon fast complexation of styrene,

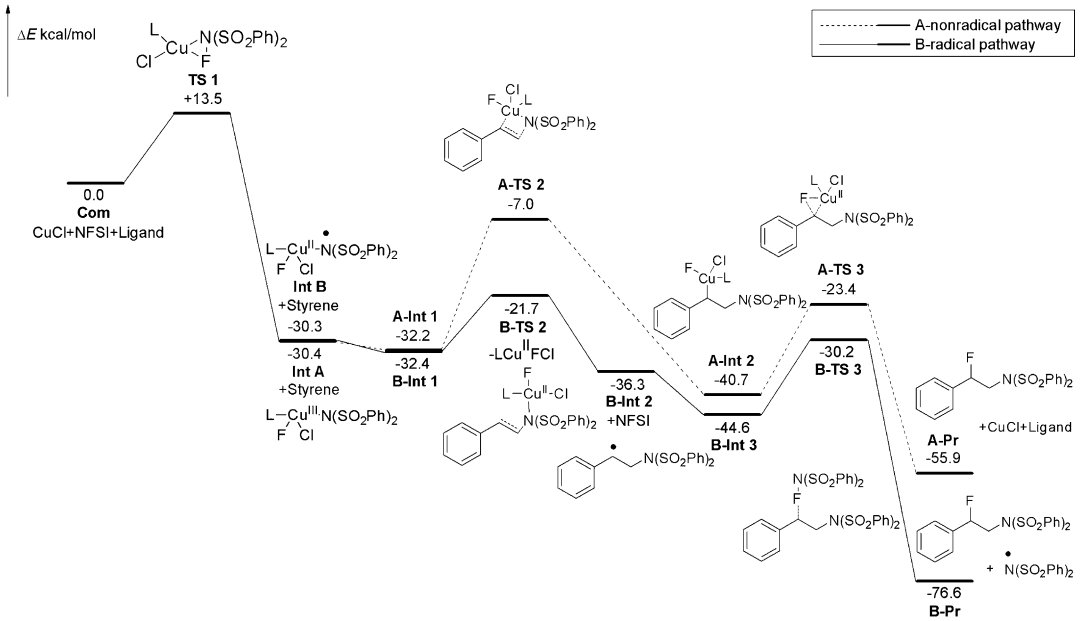
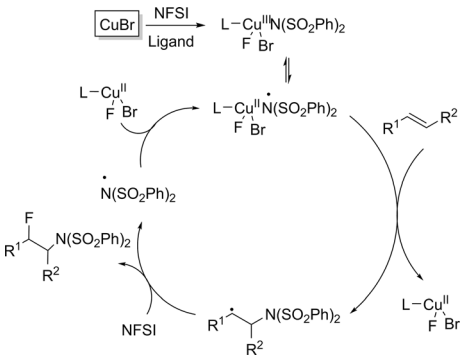


Figure 1. Energy profile obtained at the B3LYP/6-31G* level of theory. All the energies are in kcal mol^{-1}.

concerted aminocupration of **Int A** with styrene proceeds with an energy barrier of 25.2 kcal mol^{-1} to afford **A-Int 2**. In contrast, radical addition of **Int B** to styrene leads to **B-Int 2** with a much lower energy barrier of 10.7 kcal mol^{-1}. The aminofluorination product could be formed by reductive elimination from **A-Int 2** with a barrier of 17.3 kcal mol^{-1}. For the radical process, fluorine transfer from NFSI to the C radical via **B-TS 3** (formed from the interaction between **B-TS 2** and NFSI, see the Supporting Information) furnishes the aminofluorination product and has a lower activation energy of 14.4 kcal mol^{-1}. At this juncture, the interaction between the N radical and the copper(II) regenerates **Int B** to continue the radical pathway B. In both the styrene insertion and fluorine-transfer steps, lower activation barriers were found for the radical process, thus corroborating the experimental observations. A possible mechanism, based on the above results, is proposed as shown in Scheme 2.



Scheme 2. A plausible mechanism of styrene aminofluorination.

In summary, we have developed a novel copper-catalyzed regioselective radical aminofluorination reaction between styrenes and NFSI. To our knowledge, this is the first example employing NFSI as both radical nitrogen source and radical fluorine source, thus making it an attractive reagent for synthetic purposes. Further studies are underway in our lab.

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Communications

Sythetic Methods

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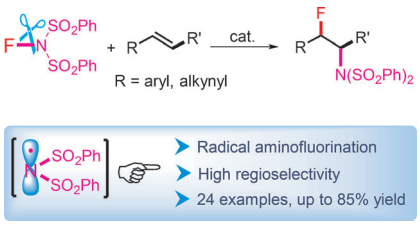
Regioselective Radical Aminofluorination of Styrenes



Double agent: The copper-catalyzed radical aminofluorination of styrenes with *N*-fluorobenzenesulfonimide (NFSI) is realized with high regioselectivity, thus affording aminofluorination products with regioselectivities opposite to those of the palladium-catalyzed and noncatalyzed processes. NFSI reacts under N–F bond homolysis and is utilized as both a radical nitrogen source and radical fluorine source.