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Copper-Catalyzed Functionalization of Benzylic C–H Bonds with *N*Fluorobenzenesulfonimide (NFSI): Switch from C–N to C–F Bond Formation Promoted by a Redox Buffer and Brønsted Base

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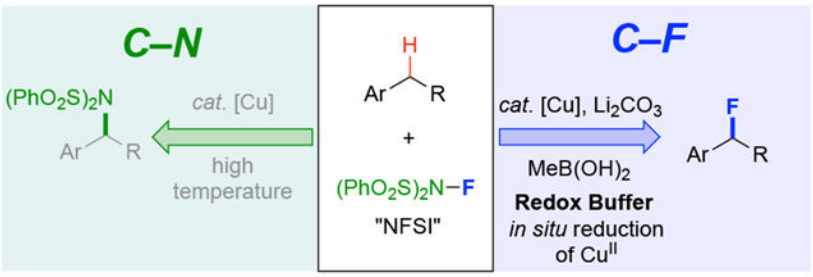
Abstract

A copper catalyst in combination with *N*-fluorobenzenesulfonimide (NFSI) has been reported to functionalize benzylic C–H bonds to the corresponding benzylic sulfonimides via C–N coupling. Here, we reported a closely related Cu-catalyzed method with NFSI that instead leads to C–F coupling. This switch in selectivity arises from changes to the reaction conditions (Cu:ligand ratio, temperature, addition of base) and further benefits from inclusion of $MeB(OH)_2$ in the reaction. $MeB(OH)_2$ is shown to serve as a "redox buffer" in the reaction, responsible for rescuing inactive Cu(II) for continued promotion of fluorination reactivity.

Graphical Abstract:



N–Fluorobenzenesulfonimide (NFSI) is a widely used reagent in organic synthesis. It is commonly used as a terminal oxidant in transition metal-catalyzed oxidations[1] and as a group-transfer reagent for sulfonylation, fluorination, and sulfonimidation of organic molecules.[2,3] The majority of these methods take advantage of the reactive N–F bond. For example, NFSI is commonly featured in electrophilic and radical fluorination of carbanions, carbon-centered radicals, and acidic C–H bonds,[4] while complementary methods and mechanisms have been identified for C–N bond formation with the sulfonimide group.[5] This bifurcation in reactivity between C–F and C–N bond formation is well documented in

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Supporting Information
Experimental procedures, characterization data, and NMR spectra.
The Supporting Information is available free of charge on the ACS Publications website.

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C(sp^2)–H functionalization of (hetero)arenes with NFSI (Scheme 1A).[3] We and others have recently been exploring Cu catalyzed methods for site-selective functionalization of benzylic C(sp^3)–H bonds.[6,7] These reactions employ NFSI in a radical-relay mechanism that enables oxidative C–H coupling with diverse nucleophilic partners, including cyanide, azide, trifluoromethyl, alcohols, and arylboronic acids (Scheme 1B). The earliest example of this reactivity featured direct transfer of the sulfonimide group from NFSI to the benzylic position (Scheme 1C, top).[6] Here, we show that variation of the Cu/NFSI C–H sulfonimidation reaction conditions leads to C–F rather than C– N bond formation, complementing other benzylic C–H fluorination methods in the literature.[8] Mechanistic studies provide insights into the origin of this switch in selectivity, highlighting the role of $MeB(OH)_2$ as a "redox buffer" and Li_2CO_3 as a Brønsted base in the reaction. Additional studies reveal the intrinsic lability of secondary benzylic fluorides, making them susceptible to nucleophilic substitution. The latter reactivity is noted here, but provides basis for a complementary effort, leading to a versatile new class of benzylic C–H cross-coupling reactions.[9]

The present study was initiated by investigating the original Cu/NFSI-catalyzed sulfonimidation reaction (Scheme 1C).[6] This reaction takes place at much higher temperatures than more recent Cu/NFSI reactions, which often proceed near room temperature.[7] Attempting the sulfonimidation of *p*-bromoethylbenzene at lower temperature led to low conversion, with a preference for C–N over C–F bond formation (Table 1, entry 2). The formation of a C–F bond could arise from reaction of an intermediate benzylic radical with a Cu^{II}–F species[10] or via a Cu-promoted radical-chain process involving NFSI.[8g, 11] Addition of $MeB(OH)_2$ as an in situ reductant for the Cu catalyst[7e] (see further discussion below) led to complete substrate conversion, but only moderate yield of the C–N product was observed, with no C–F product (Table 1, entry 3). Further variation of the conditions, however, including addition of Li_2CO_3 as a base, using PhCl as the solvent, and lowering the catalyst loading, led to C–H fluorination in good yield (81%, Table 1, entry 7), with no C–N product formation (see additional screening data in the Supporting Information). Difluorination of the benzylic position is the primary side reaction.

Several fundamental studies were undertaken to gain insights into the observed reactivity and the role of $MeB(OH)_2$ and other reaction components. Copper(I) is proposed to react with NFSI, forming a Cu^{II}–F species and an imidyl radical, •NSI (Scheme 1B). The imidyl radical can promote hydrogen atom transfer from the benzylic C–H bond, but it can react even more rapidly with another Cu^{I} center,[7e,12] generating a second equivalent of Cu^{II} and halting catalysis. To probe Cu/NFSI reactivity, NFSI was titrated into a solution of $BPhenCu^{I}(OAc)$ in PhCl (Bphen = bathophenanthroline). Nearly isosbestic behavior was observed by UV-visible spectroscopy, corresponding to oxidation of Cu^{I} to Cu^{II} species by NFSI (Figure 1A, step 1). Complete consumption of Cu^{I} was observed upon addition of 0.5 equiv of oxidant. This oxidation is rapid at room temperature, occurring on the timescale of mixing. Addition of NFSI beyond 0.5 equiv has no effect on the UV-visible spectrum, suggesting that Cu^{II} does not react further with NFSI.

The Cu^{II} species generated by NFSI is reduced by $MeB(OH)_2$. Addition of 5 equiv of $MeB(OH)_2$ to a solution of Cu^{II} generated from a combination of $BPhenCu^{I}(OAc)$ and 0.5

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equiv of NFSI in PhCl slowly regenerates Cu^{I} over approximately 1 h (Figure 1A, step 2). This process generates $Me–N(SO_2Ph)_2$ as a byproduct of the reaction, resembling the previously reported Chan-Lam amidation of alkylboronic acids[13] (see Figure S2).

The impact of $MeB(OH)_2$ on the catalytic reaction is clearly evident in Figure 1B. Virtually no reaction is observed in the absence of $MeB(OH)_2$. In contrast, full substrate conversion occurs in the presence of 2 equiv of $MeB(OH)_2$, leading to an 84% yield of the benzyl fluoride. This behavior is rationalized by the ability of $MeB(OH)_2$ to serve as a "redox buffer" for the Cu catalyst, slowly reducing Cu^{II} during the reaction. A mechanistic framework for these observations is illustrated in Figure 1C. Cu^{I} is oxidized rapidly to Cu^{II} by NFSI at the beginning of the reaction, but slow reduction of Cu^{II} by $MeB(OH)_2$ (dashed arrow, Figure 1C) generates small amounts of Cu^{I} that can react with additional NFSI. Generation of •NSI at this stage can lead to hydrogen atom transfer (HAT) from the benzylic C–H with only limited competitive quenching of •NSI by Cu^{I}, due to the low Cu^{I} concentration.

The synthetic scope of this reactivity is the focus of a separate study;[9] however, testing of representative substrates showed that isolation of benzyl monofluorides can be rather challenging, with poor mass balance and the appearance of new byproducts (see Supporting Information, Section V). Similar challenges are evident from previous C–H fluorination methods,[8] and other studies show that benzyl monofluorides undergo facile displacement in the presence of Brønsted and Lewis acids or hydrogen-bond donors.[14] The latter insights prompted us to assess the role of Li_2CO_3 in the reaction, which was also used in a previous benzylic C–H fluorination method.[8g] A time course for the optimized reaction conditions in Figure 1B (right) may be compared to the time course obtained without added Li_2CO_3 (Scheme 2A). The rate of substrate conversion is virtually identical in the presence and absence of Li_2CO_3; however, very little C–F product is observed after the first few hours of the reaction without Li_2CO_3, and the major products arise from C–O and C–N bond formation. NHSI is a strong acid and will build up as the fluorination reaction proceeds, and it could promote acidolysis of the benzyl fluoride.[15] In a control experiment, 1 equiv of NHSI was added to a solution of benzyl fluoride obtained from the catalytic reaction, following filtration through a silica plug to remove the Li_2CO_3. This reaction results in rapid formation of 1-phenylethanol (Scheme 2B). The hydroxy group presumably originates from adventitious water from the solvent or reagents present in the original reaction mixture. The net C–H fluorination/hydrolysis sequence resembles the recently reported C–H mesylation/hydrolysis strategy to achieve C–H hydroxylation, reported by Ritter and coworkers.[16]

The results presented herein reveal an unusual switch in selectivity, from C–N to C–F bond formation, in Cu/NFSI-promoted oxidative functionalization of benzylic C–H bonds. Mechanistic studies show how two new reaction additives contribute to formation of the fluorination product. $MeB(OH)_2$ serves as a redox buffer[7e] that promotes steady-state reduction of Cu^{II} to the active Cu^{I} species during the catalytic reaction. Li_2CO_3 serves as a Brønsted base that prevents acid-promoted displacement of the fluoride during the reaction. While the observed substitutional lability of the products undermines the accessibility and practical utility of isolated benzyl monofluorides, this property introduces the possibility of using benzyl fluorides as strategic intermediates in a C–H fluorination/substitution sequence.

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Development and elaboration of the latter C–H cross-coupling strategy is the focus of a parallel report.[9]

Supplementary Material

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ACKNOWLEDGMENT

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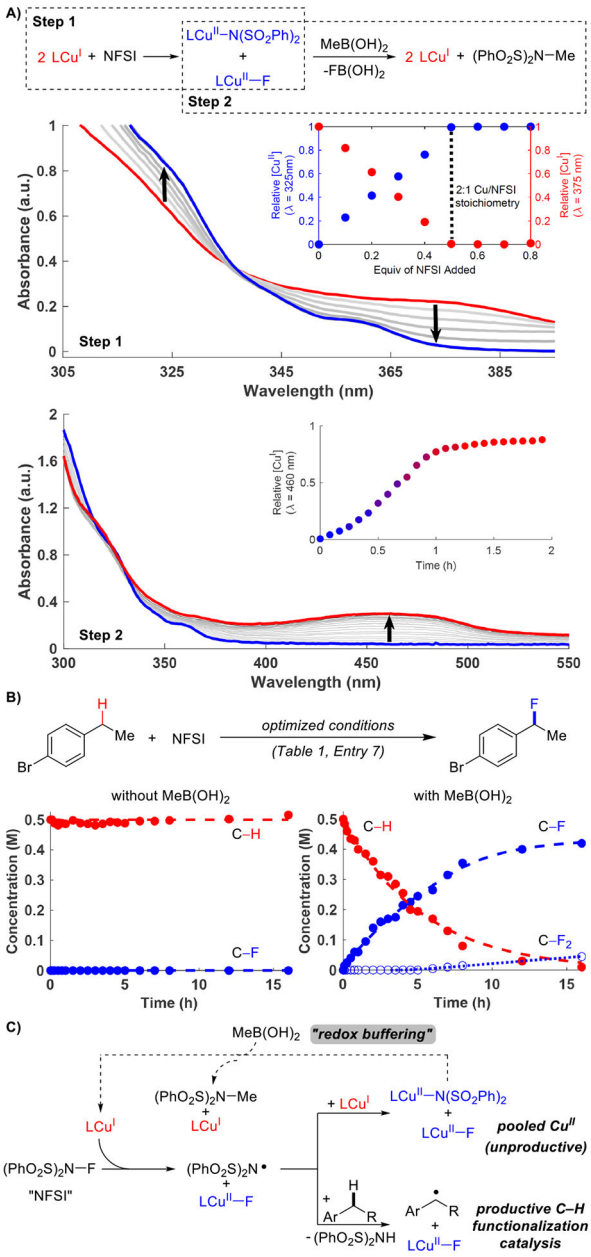

Figure 1. Fundamental insights into Cu/NFSI-catalyzed fluorination reactions.

A) Spectroscopic analysis of stoichiometric oxidation of Cu^{I} by NFSI and reduction of Cu^{II} by $MeB(OH)_2$. B) Reaction time course data demonstrating the effect of $MeB(OH)_2$ redox buffering in the catalytic fluorination reaction. C) Mechanism depicting the redox buffering role of $MeB(OH)_2$ in benzylic fluorination. Conditions: A) Step 1 – 0.33 mM $BPhenCu^{I}OAc$ + 0.1 equiv NFSI (×8) in PhCl. Step 2 – [Cu^{II}] (from 0.33 mM $BPhenCu^{I}(OAc)$ + 0.5 equiv NFSI) + 5 equiv $MeB(OH)_2$, 15 equiv Li_2CO_3 in PhCl. B) See Table 1, entry 7.

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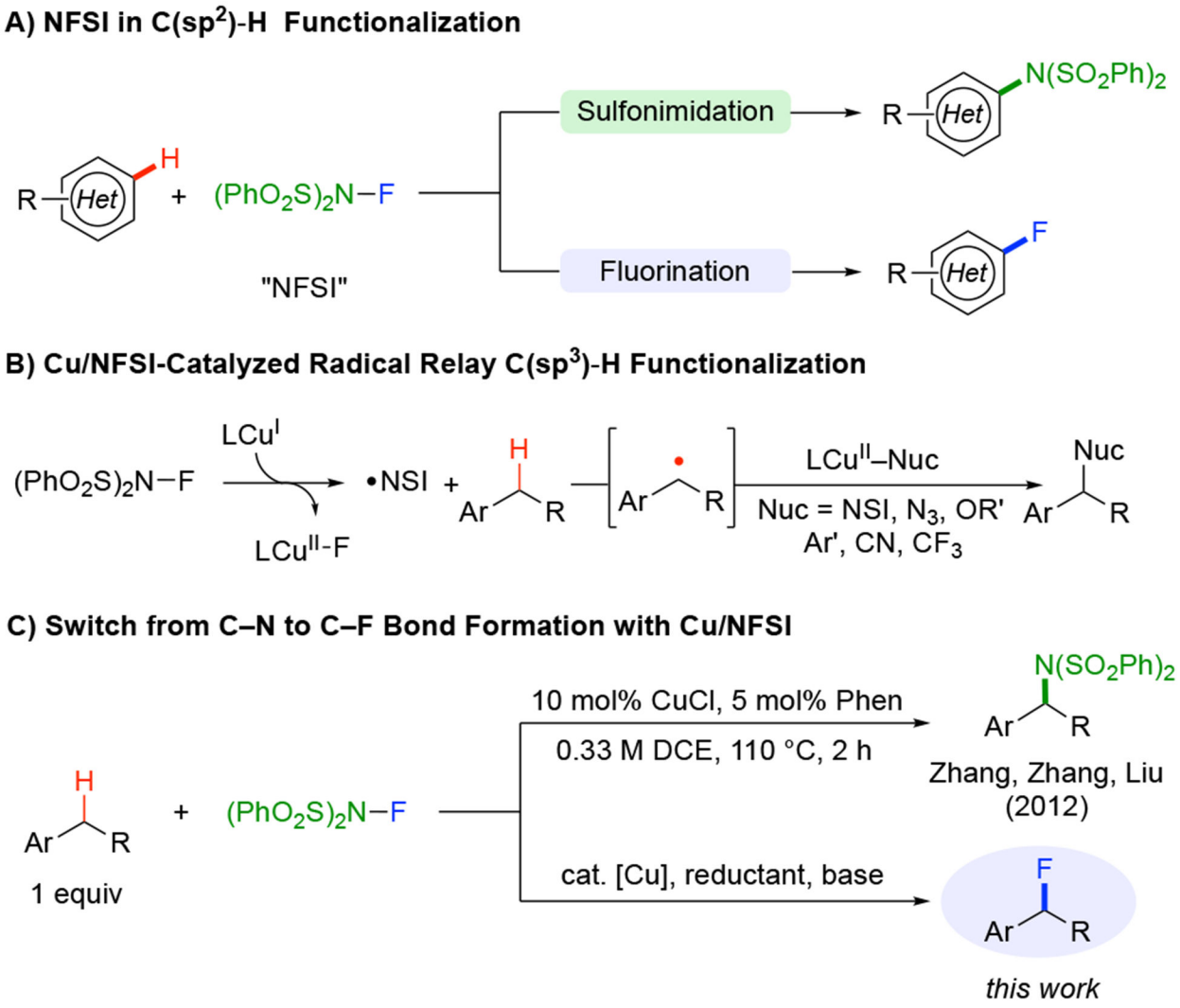

Scheme 1.

C–N to C–F Bond Formation when Using NFSI in C(sp^2) and C(sp^3) C–H Functionalization

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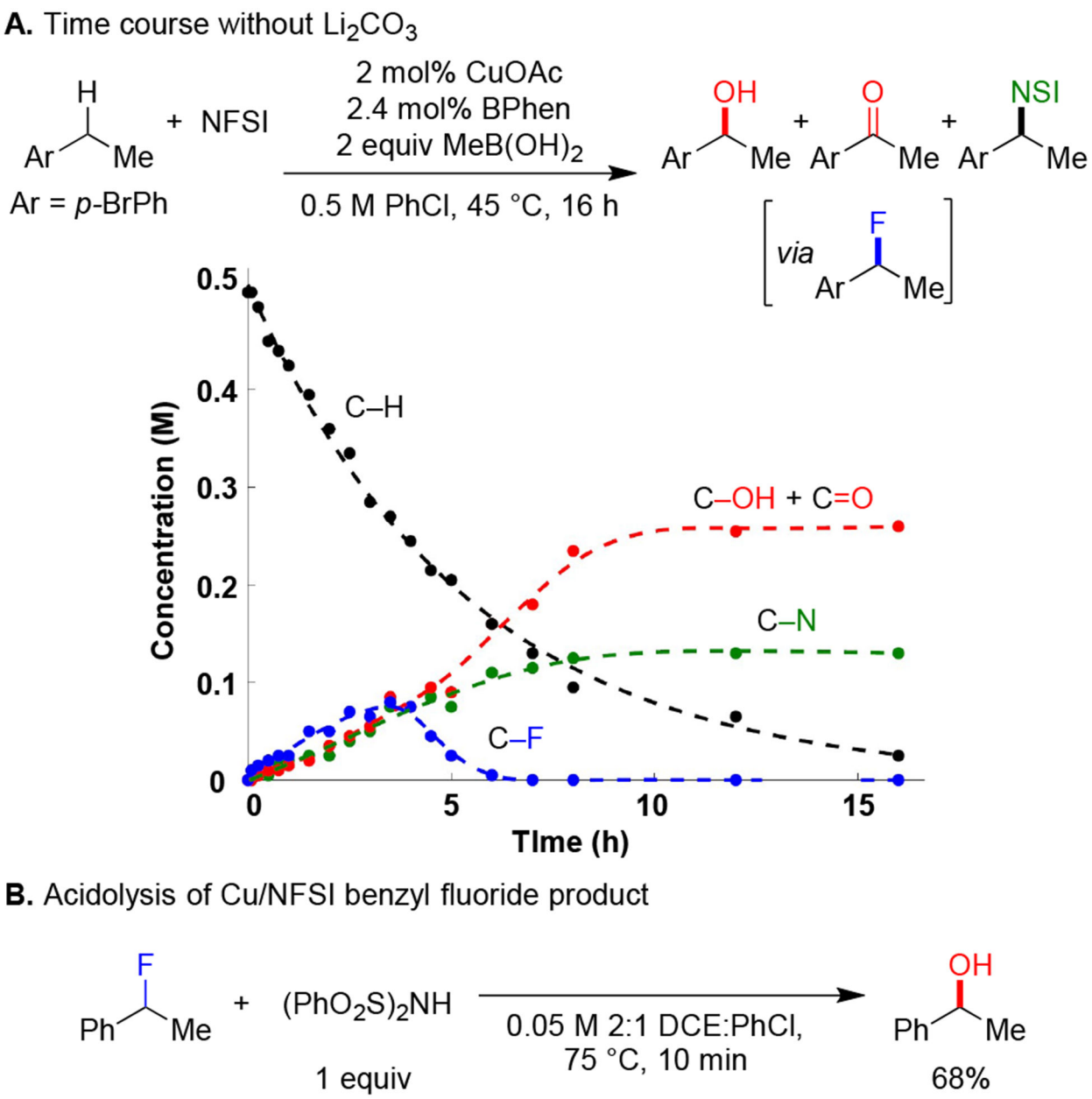

Scheme 2.
Li_2CO_3 Effect on Benzyl Fluoride Lability

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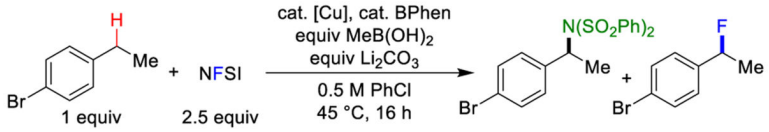
Table 1.

Fluorination Reaction Optimizations



entry	[Cu] (mol%)	BPhen (mol%)	$MeB(OH)_2$ (equiv)	$Li2CO_3$ (equiv)	Conv (%)	C–N (%)	C–F $(CF2)^a$ (%)
$1^{b,c}$	CuCl (10)	*see* Scheme 1A *for conditions*			nd	76	nd
2^c	CuCl (10)	5	-	-	24	19	4
3^c	CuCl (10)	5	2	-	100	42	-
4^c	CuCl (10)	5	2	3	100	44	21 (4)
5	CuCl (10)	5	2	3	100	25	40 (6)
6	CuCl (2)	1	2	3	86	4	74 (4)
7	CuOAc (2)	2.4	2	3	100	-	81 (11)

[a] 0.3 mmol scale. ^1H NMR yields; int. std. = CH2Br2.

[b] Reported results with ethylbenzene (ref. 6).

[c] 1,2-dichloroethane (DCE) used as the solvent.