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Copper-Catalyzed C–H Fluorination/Functionalization Sequence Enabling Benzylic C–H Cross Coupling with Diverse Nucleophiles

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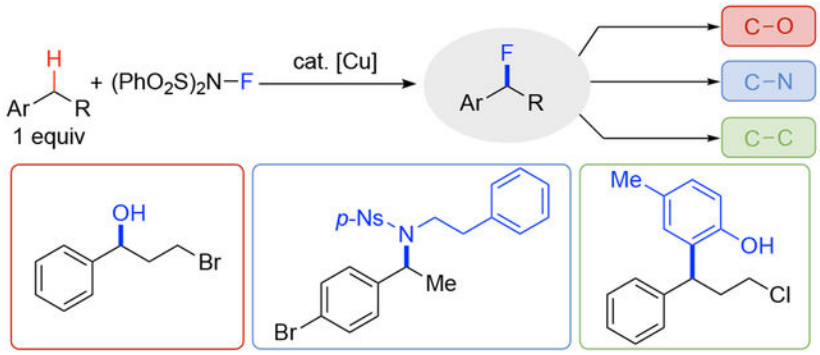
Abstract

Site-selective transformation of benzylic C–H bonds into diverse functional groups is achieved via Cu-catalyzed C–H fluorination with *N*-fluorobenzenesulfonimide (NFSI), followed by substitution of the resulting fluoride with various nucleophiles. The benzyl fluorides generated in these reactions are reactive electrophiles in the presence of hydrogen-bond donors or Lewis acids, allowing them to be used without isolation in C–O, C–N, and C–C coupling reactions.

Graphical Abstract



Medicinal chemistry and drug discovery efforts greatly benefit from synthetic coupling reactions that facilitate access to analogs of pharmaceutical building blocks and core structures. Functional groups that participate in efficient coupling, such as carboxylic acids, aryl halides, and boronic acids, provide the foundation for these methods.[1] Expansion of latent functionalities that participate in coupling could greatly increase the scope of synthetic diversity.[2] Benzylic C–H bonds are an appealing target in this context as they are prevalent in drug-like molecules and are susceptible to site-selective activation owing to their

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Supporting Information
Experimental procedures, characterization data, and NMR spectra.
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enhanced reactivity (e.g., reduced bond strength, higher acidity). Recent studies demonstrate that benzylic C–H substrates may be used as the limiting reagent in cross-coupling reactions with a number of different reaction partners, including alcohols,[3] amides[4], and arylboronic acids.[5] Cu catalysts in combination with *N*-fluorobenzenesulfonimide (NFSI) are particularly effective in these reactions as they exhibit unique selectivity for benzylic C–H bonds and promote a radical relay mechanism that enables coupling with diverse reaction partners (Scheme 1).[3a,4b,5a, 6] We recently discovered that a Cu/NFSI-based catalyst system switches selectivity, from C–N to C–F bond formation, when the reaction is conducted with $MeB(OH)_2$ as a redox buffer and Li_2CO_3 as a Brønsted base.[7] These observations provide the foundation for the present study in which we demonstrate a C–H fluorination/ substitution sequence that enables benzylic C–H cross-coupling with diverse oxygen, nitrogen, and carbon nucleophiles (Scheme 1). This strategy, which takes advantage of the intrinsic lability of benzyl monofluorides,[8,9] contrasts the many C–H fluorination efforts motivated by the inertness of the C–F bond.[10,11] This approach allows for successful benzylic C–H cross coupling with reaction partners that are oxidatively sensitive or otherwise incompatible with direct Cu/NFSI-catalyzed methods, thereby greatly expanding the synthetic scope and versatility of benzyl C–H cross coupling.

The present study began by testing the previously optimized fluorination conditions[7] with a variety of benzylic C–H substrates (Scheme 2). *para*-Bromoethylbenzene proceeds effectively in 81% to the corresponding benzyl fluoride product **1** (Scheme 2). Use of *ortho*-bromoethylbenzene resulted in low conversion of the starting material (<20%), presumably reflecting the deleterious steric or σ-electron withdrawing effect of the *o*-halogen on hydrogen atom transfer. Empirical modification of the conditions, including use of 4 equiv of NFSI, replacement of $MeB(OH)_2$ with B_2pin_2 as the reductant, and operating at 55 °C, led to a 50% yield of the desired product **2**. The modified conditions, either at 55 °C or 75 °C, also proved effective with other electron- deficient substrates (**2**, **4**, **5**, **6**, **9**, **13**, **17**, **19**), while the original conditions were favored for more reactive substrates (**3**, **7**, **8**, **10**, **11**, **12**, **14**). The latter group also includes celestolide, which underwent fluorination in 86% yield (**18**), and substrates with tertiary C–H bonds, leading to **23** and **24** in 92% and 84% yields. Overoxidation to ketone or styrene-derived side products, was observed with more activated C–H substrates, necessitating the identification of milder conditions (35 °C, 0.5 equiv $MeB(OH)_2$). These conditions allowed several benzyl fluorides to be obtained in good yield (**15**, **16**, **20**), including a bromochroman derivative. Methylarenes appear to favor C–H sulfonimidation rather than fluorination, as observed by the formation of **21** and **22**. A collection of other less successful substrates is provided in Table S9 of the Supporting Information, but, overall, these results show that the catalytic conditions may be tuned to access good fluorination reactivity for a broad range of benzylic C–H substrates.[12]

Complications were encountered during product isolation. Many of the products decomposed in the presence of silica gel, and even when stored in glass vessels. These observations belie the frequent incorporation of fluorine in organic molecules to inhibit reactivity at specific sites, for example, to slow drug metabolism.[10] Separately, benzylic monofluorides have been shown to undergo nucleophilic substitution in the presence of acids or hydrogen-bond donors.[8,9] These insights suggest that monofluorination of benzylic C–H

bonds is not a compelling end-goal for many substrates. On the other hand, they suggest that benzyl fluorides could serve as strategic intermediates in a sequential approach to benzylic C–H functionalization.

Efforts to explore sequential C–H fluorination/functionalization were initiated by testing hexafluoroisopropanol (HFIP, 10 equiv) as a hydrogen bond donor to activate the benzyl fluoride (Scheme 3).[9f] Initial results demonstrated conversion of benzyl fluorides to benzyl alcohols by including water as a nucleophile in the reaction mixture (**25**-**27**). Formation of **25** shows that hydrogen-bond activation supports displacement of the fluoride, even in the presence of a primary alkyl bromide. This fluorination/water-substitution sequence to access benzylic alcohols is noteworthy because C–H oxygenation strategies will typically proceed directly to ketones, reflecting the higher reactivity of alcohols relative to C–H bonds.[13]

Analogous efforts were effective for the formation of benzylic ethers and esters (**28**–**36**). For less nucleophilic alcohols, like *tert*-butanol, more forcing conditions were needed to form the product, using BF_3•OEt_2 as a Lewis acid catalyst (**28** and **33**).[9i] This approach also enabled reactivity with alcohols bearing Boc-pyrrolidine or pyridine substituents (**31** and **32**). These results expand the scope of accessible products relative to the recently reported method for direct Cu/NFSI-catalyzed benzylic etherification,[3a] which shows limited compatibility with basic heterocycles, such as pyridines, and Boc-protected pyrrolidines. Carboxylic acids were also effective coupling partners (**34**-**36**). These substrates have innate acidity, but the reactions were more effective with HFIP or BF_3 additives. The presence of allylic and benzylic C–H bonds in the carboxylic acids used to prepare **34** and **36** would likely complicate direct C–H carboxylation methods with these partners.

We then targeted C–N coupling reactions. Direct C–H amidation reactions typically feature primary sulfonamides or other stabilized ammonia surrogates capable of generating nitrenoid intermediates.[14] Few precedents exist for oxidative coupling of C–H bonds with carbamates or secondary sulfonamides.[4b,15] *tert*-Butyl carbamate itself proved to be an effective coupling partner when using BF_3•Et_2O to activate the benzyl fluoride (**37**). Then a range of secondary sulfonamides were shown to undergo effective displacement of the benzyl fluoride, with BF_3•Et_2O as an activator (**38**-**43**). The good reactivity with less nucleophilic, but more readily deprotected, nosylamides is noteworthy. Competitive Friedel-Crafts reactivity with chlorobenzene was observed in some of these reactions, but this complication was resolved by using dichloromethane as the solvent for the fluorination step (**40**-**43**).

The observation of Friedel-Crafts reactivity highlights opportunities for coupling with electron-rich arenes and other carbon nucleophiles that would not be compatible with a direct Cu/NFSI-catalyzed C–H coupling reaction. Such reactivity was demonstrated with phenols (**44**–**46**), *N*-sulfonyl indole (**47**-**48**), and a silyl enol ether and allyl silane (**49**-**50**).

Each of the reactions highlighted above proceeds via a straightforward two-step protocol, without isolation of the benzyl fluoride intermediate. Following the fluorination step, sodium dithionite is added to quench any unreacted NFSI. The slurry is then diluted with dichloromethane and filtered. Subsequent addition of the nucleophile and HFIP/BF_3

promoter initiates the displacement reaction. As conveyed in several instances above, this two-step C–H cross-coupling sequence greatly expands the scope of useful reaction partners. Many of the electron-rich substrates and nucleophiles bearing oxidatively sensitive substituents would decompose or undergo deleterious side reactions with NFSI in a direct oxidative coupling reaction.[11c,16]

In summary, the results described above introduce a new strategy to achieve selective benzylic C–H cross-coupling with diverse reaction partners. The use of Cu/NFSI conditions that may be tuned to accommodate different substrate electronic properties allowed formation of benzyl fluorides that may be used without isolation as coupling partners to access products with new C(sp^3)–O, –N, and –C bonds. This method joins a number of emerging strategies for C(sp^3)–H cross-coupling that involve formation of strategic intermediates, such as xanthate esters, isocyanates, lactones, alkylboronates,[17] that allow rapid access to diversified products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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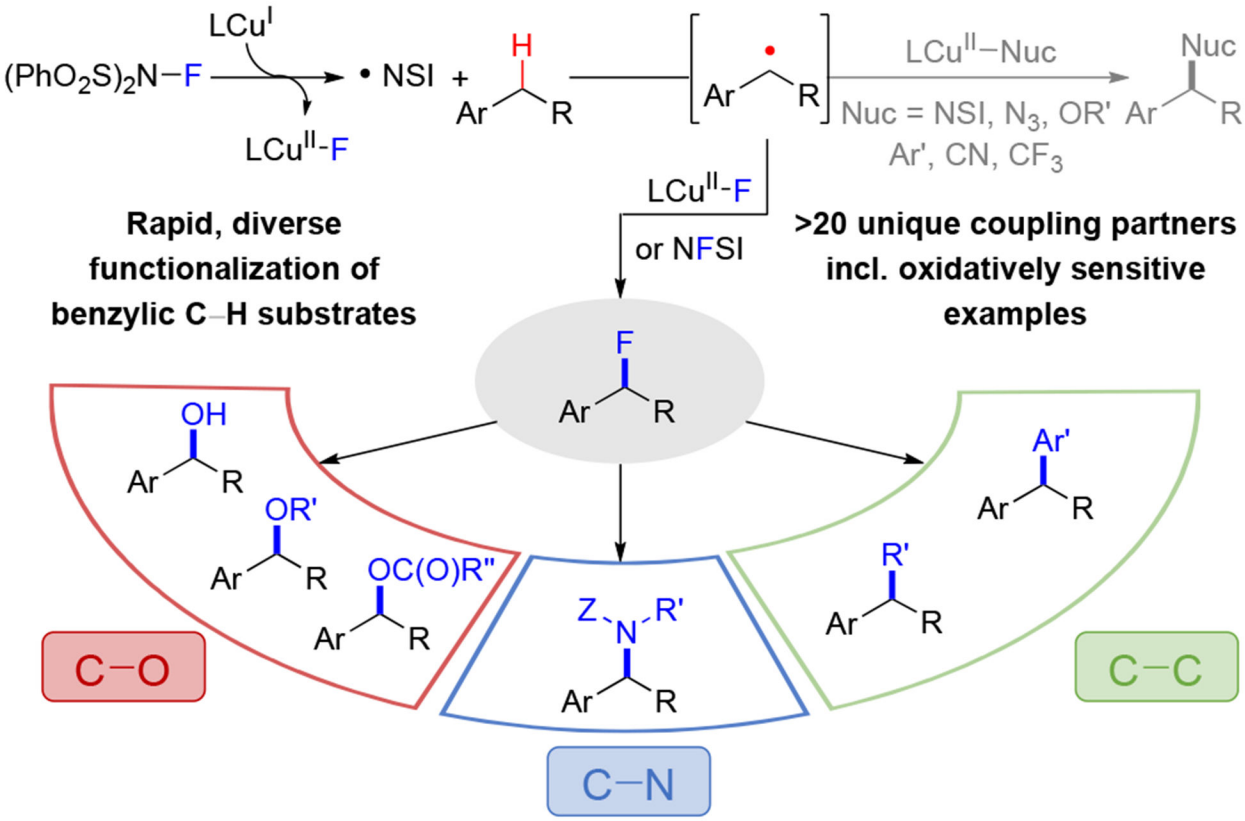
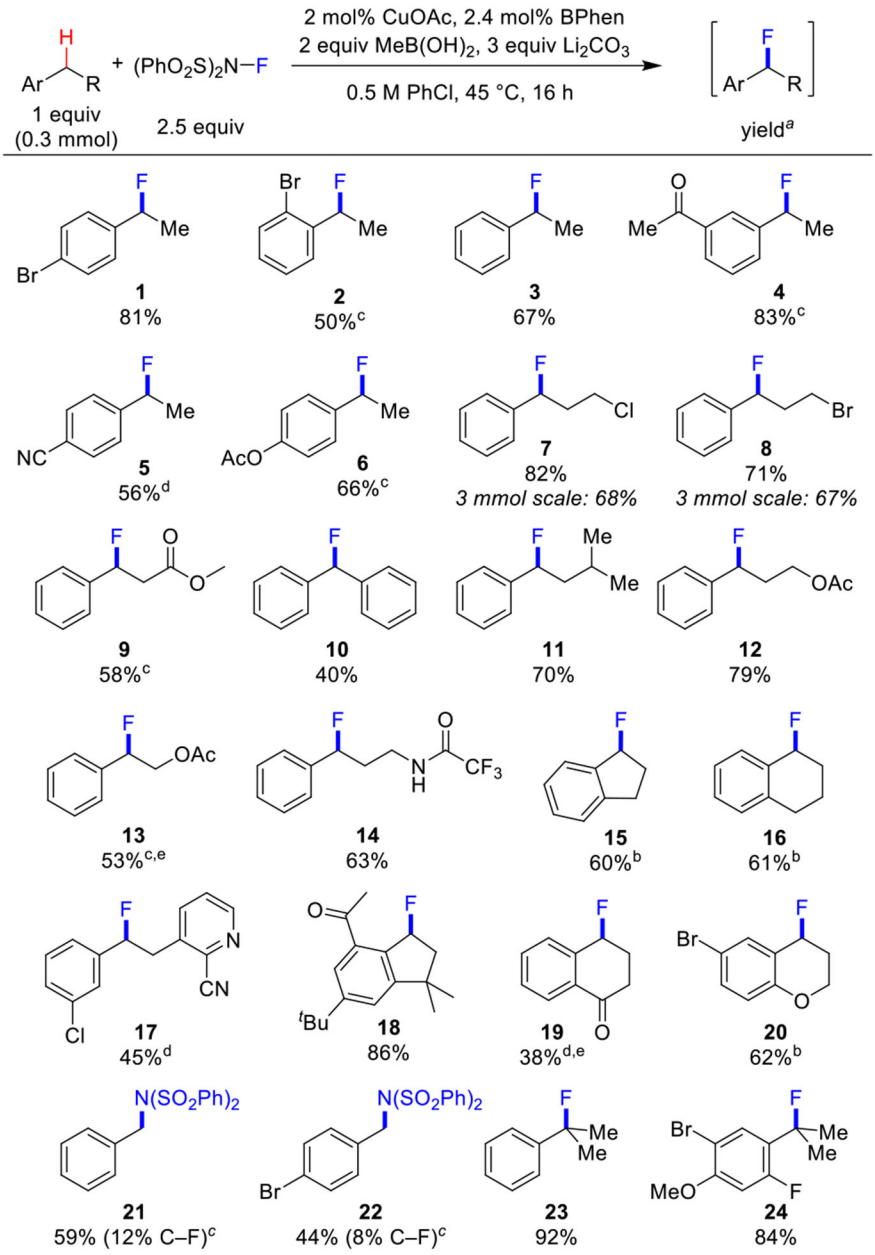
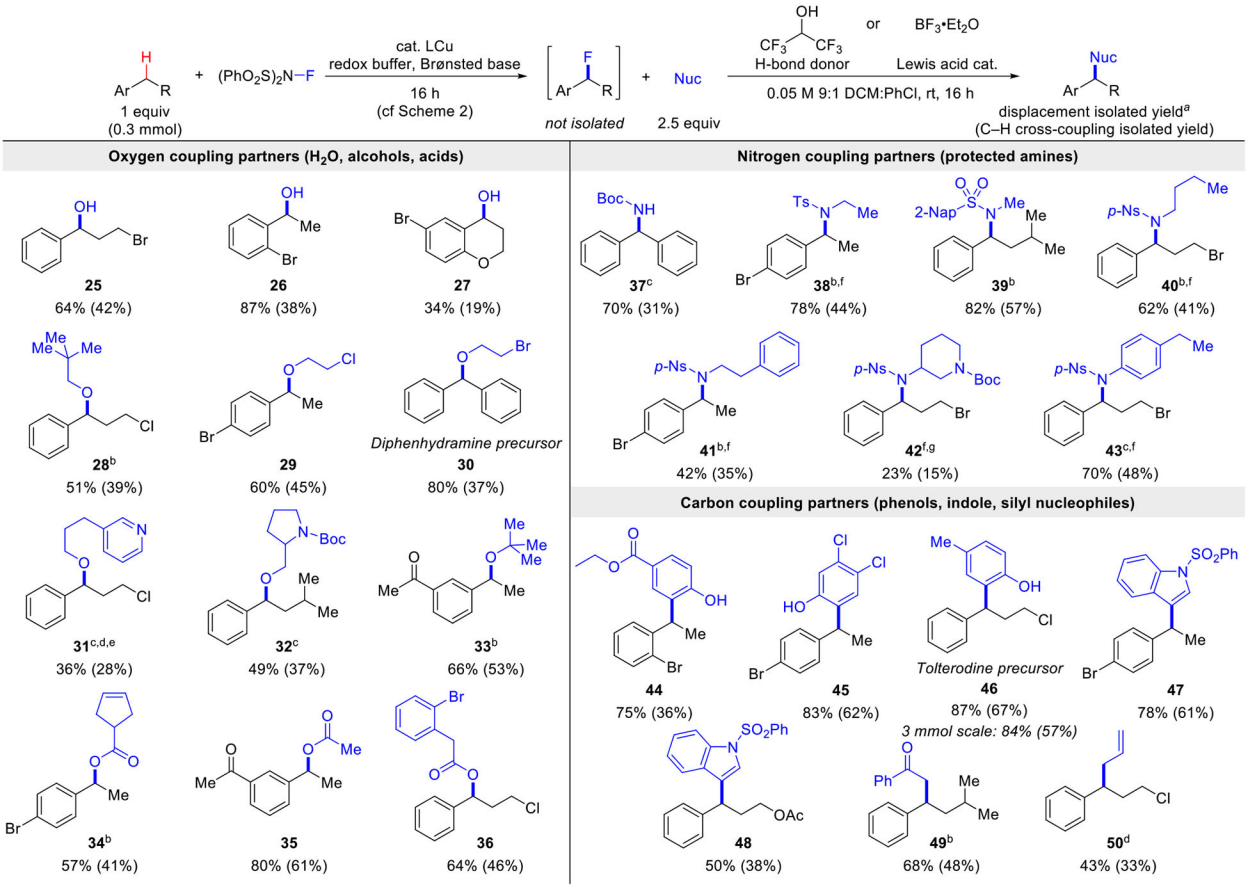


Scheme 1.
C–H Cross-Coupling via a Benzyl Fluoride



Scheme 2. Cu/NFSI Fluorination of Benzylic C–H Bonds

[a]^{1}H or ^{19}F NMR yields; $CH2Br_2$ or $PhCF_3$ as internal standard. [b]35 °C, 0.5 equiv $MeB(OH)_2$. [c]55 °C, 1 mol% Cu/1.2 mol% BPhen, 4 equiv NFSI, 1 equiv B_2pin_2 instead of $MeB(OH)_2$. [d]75 °C 1 mol% Cu/1.2 mol% BPhen, 4 equiv NFSI, 1 equiv B_2pin_2 instead of $MeB(OH)_2$. [e]Acetone solvent.



Scheme 3. Benzylic C–H Cross-Coupling to C–O, C–N, and C–C Bonds via a Benzyl Fluoride

[a]Reaction uses 10 equiv HFIP as a H-bond donor. Isolated yields calculated with respect to the ^{1}H NMR yield of the benzyl fluoride (or the C–H substrate, in parentheses). [b]10 mol% BF_3•Et_2O used instead of HFIP. [c]50 mol% BF_3•Et_2O used instead of HFIP [d]Both HFIP and BF_3•Et_2O used. [e]2.5 equiv MsOH added to the nucleophile. [f]Used dichloromethane as the fluorination reaction solvent. [g]1.5 equiv BF_3•Et_2O used instead of HFIP. Isolated as the amine.