Synthetic Methods

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Highly Regioselective Copper-Catalyzed Benzylic C–H Amination by *N*-Fluorobenzenesulfonimide**

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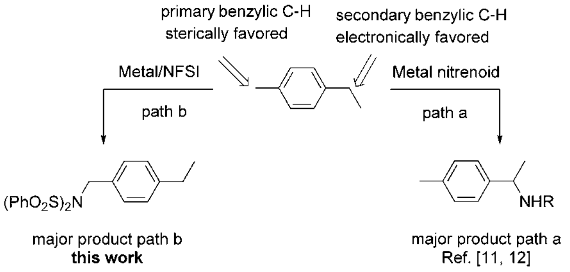
Amines are ubiquitous in both naturally occurring and man-made compounds which demonstrate high levels of biological activity.[1,2] Direct construction of a C–N bond through C–H amination is one of the most exciting and challenging fields in amine chemistry.[3,4] Direct aliphatic C–H amination has led to significant results arising from the discovery of metal nitrenoids,[5–8] but highly active free nitrene is unselective and uncontrollable. Recently, highly regioselective aliphatic C–H amination was realized by employing *N*-triflylimino-λ^3-bromane as the nitrogen source, and the selectivity for tertiary over secondary C–H bonds was observed.[9] Therefore, a delicate balance between reactivity and selectivity for direct C–H amination is very important, especially with regard to the choice of the nitrogen source.[9,10] Toluene and xylenes are among the basic organic raw materials and it is highly desirable to develop a general method for direct amination of their benzylic C–H bonds. However, because of the favored electronic effect of the secondary C–H bond (for example, the major product of path a in Scheme 1), the selective amination of primary C–H bonds, for example in 1-ethyl-4-methylbenzene, remains a great challenge.[11,12] In addition, to our knowledge, no efficient method exists for direct diamination of the two methyl groups in xylene. Even for the amination reactions of toluene, a large excess of toluene (15–500 equiv) is usually necessary.[10,13–15]



Scheme 1. Regioselectivity in benzylic C–H amination reactions.

The selective activation of benzylic C–H bonds in toluene is particularly important since the catalytic functionalization of toluene can yield industrially important chemicals such as benzyl alcohols, benzaldehydes, and benzoic acids. However, it is more difficult to achieve the benzylic C–H bond activation[16–18] because of the existence of four different C–H bonds (*ortho*, *meta*, *para*, and benzylic). Generally, metal-catalyzed C–H activating systems exhibit preferences for aromatic C–H bond activation over the benzylic C–H bond;[16–18] even the amination with nitrene as the nitrogen source ($AuCl_3$ as catalyst) provided aromatic C–H amination products.[19] Herein, highly selective copper-catalyzed benzylic C–H mono- and diamination reactions of a sterically hindered non-nitrene nitrogen source, *N*-fluorobenzenesulfonimide (NFSI), were efficiently realized. These reactions possess the advantage of avoiding the use of a large excess of benzylic substrates and the remarkable selectivity of primary over second C–H bonds (for example, the major product of path b in Scheme 1).

Recently, benzylic C–H bond arylation,[20,21] silylation,[22] and fluorination,[23] directed by *N*-oxide, pyridine, and quinoline, respectively, were realized. However, specific directing groups on the substrates are required to facilitate a C–H activation process, thus diminishing the general applicability of the methods. Our findings of the highly selective amide-directed, palladium-catalyzed C–H amination (*para* position) of *N*-phenylacetamides[24] and benzylic C–H amination of *N*-*p*-tolylacetamides[25] by commercially available NFSI enabled us to find a general method for directing-group-free benzylic C–H amination reaction through a suitable choice in the catalyst system. After careful screening (see the Supporting Information), we were pleased to find that *N*-benzyl-*N*-(phenylsulfonyl)benzenesulfonamide (**2a**) could be obtained in 80% yield from the reaction of toluene (**1a**, 1.0 mmol) with NFSI (1.1 equiv) in 1,2-dichloroethane (DCE, 3 mL) in the presence of CuCl (10 mol%) and 1,10-phenanthroline (phen; 5 mol%) at 110 °C in open air for 3.0 hours (Scheme 2). Similarly, **2a** was obtained in 80% yield under a nitrogen atmosphere. Interestingly, no aromatic C_{sp^2}–H functionalization product was observed as obtained in NFSI-promoted carboamination reactions of an alkene with toluene.[26] Notably, the above synthesis of benzylamine by using stoichiometric amounts of toluene and an aminating agent are rare.[27,28]

The generality of the C–H amination reaction was next examined. As described in Scheme 2, a broad range of toluene derivatives are compatible with this operationally

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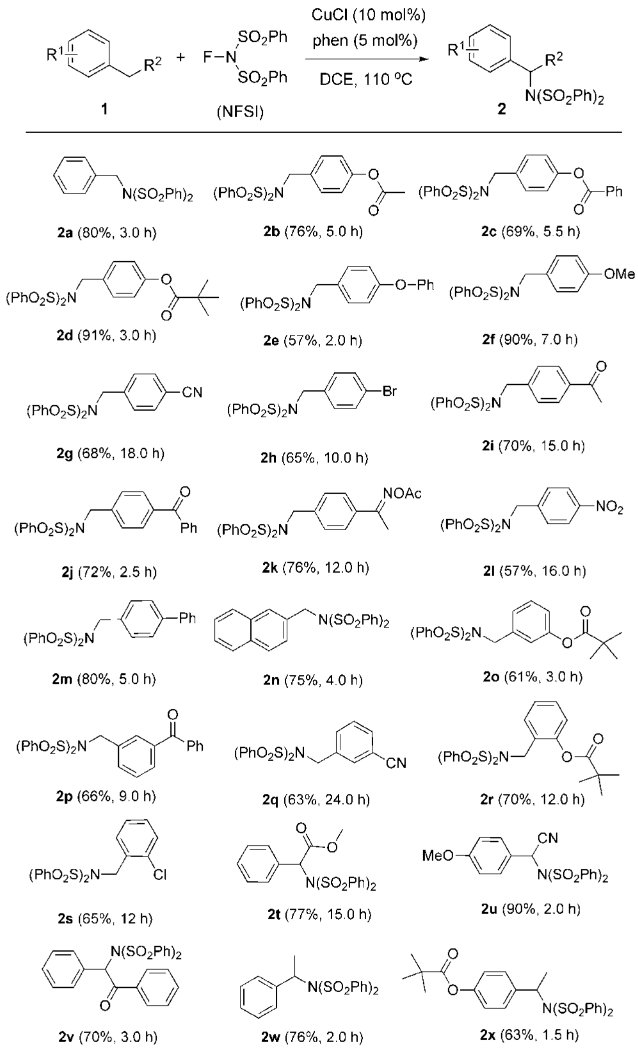
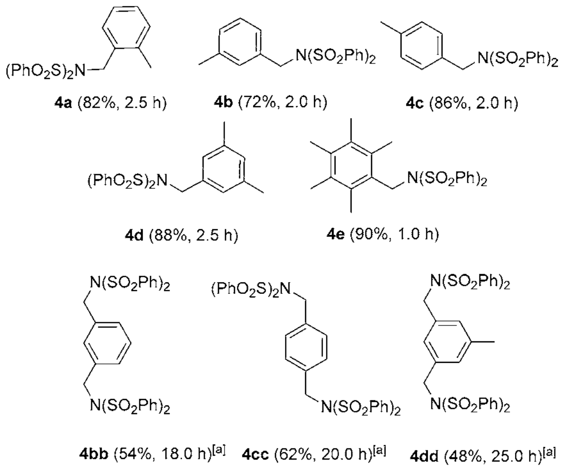


Scheme 2. Scope of the copper-catalyzed amination reaction using the toluene derivatives **1a–x** with NFSI. Unless otherwise noted, the reaction conditions are as follows: **1** (1.0 mmol), NFSI (1.1 equiv), and 1,2-dichloroethane (DCE, 3 mL) in the presence of CuCl (10 mol%) and phen (5 mol%) at 110 °C in open air.

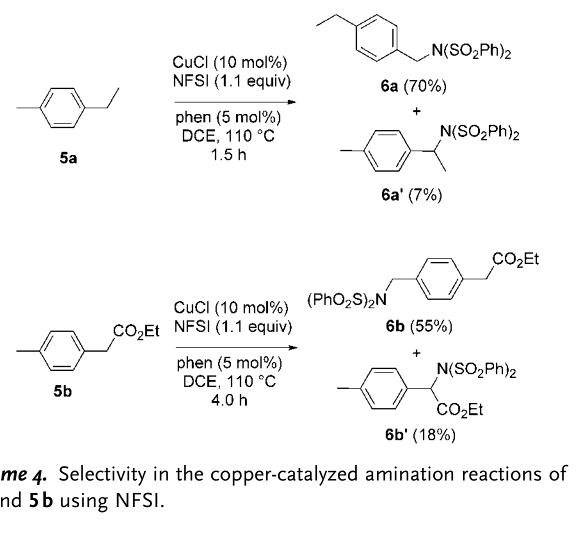
simple copper-catalyzed C–H amination reaction. Substrates with various electron-donating and electron-withdrawing functional groups at the *para* position of the benzene ring can give the corresponding benzylamines **2b–m** in good to high yields. Remarkably, the reaction can tolerate toluene substrates bearing electron-withdrawing groups on the benzene ring (see products **2g**, **2i–l**). In the case of toluene bearing a variety of typical functional groups at the *meta* position, the corresponding benzylamines **2o–q** were also be obtained in good yields. Under the general reaction conditions described above, benzylamines **2r** and **2s** were produced in good yield from 2-methylnaphthalene *o*-tolyl pivalate and 1-chloro-2-methylbenzene, respectively. The generality of the reaction was additionally demonstrated by its application to the synthesis of 2-phenylglycine (**2t**), 2-amino-2-phenylacetonitrile (**2u**), and 2-amino-1,2-diphenylethanone (**2v**) through C_{sp^3}–H amination adjacent to either a carbonyl or cyano group of the active methylene compounds. In addition, 1-phenylethanamine (**2w**), and 4-(1-aminoethyl)phenyl pivalate (**2x**) were also obtained in good yields from ethylbenzene and 4-ethylphenyl pivalate, respectively.

The CuCl/phen catalytic system could also be applied to the amination of the *o*-, *m*-, and *p*-xylene (**3a–c**), mesitylene (**3d**), and hexamethylbenzene (**3e**). By using the general reaction conditions described in Scheme 2, the corresponding monoamination products **4a–e** were synthesized in high yields (Scheme 3). The above results show that **3e** having six methyl groups on the benzene ring reacted at the fastest rate to deliver **4e**. In addition, it was found that the reaction of **3b–d** also gave the corresponding diamines **4bb–dd** in moderate yields under the optimal reaction conditions (Scheme 3) albeit it with 5.0 equivalents of NFSI. The successful diamination of xylene provides the simplest access to benzylic diamines, which are the important units in polyamides and molecular cages.[29,30]



Scheme 3. Scope of the copper-catalyzed amination reaction using **3a–e** with NFSI. [a] Used 5.0 equiv of NFSI for **4bb–dd**.

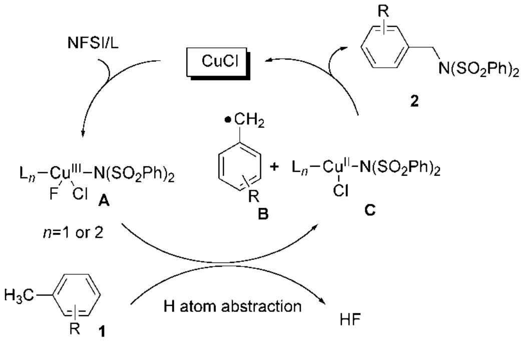
The above results clearly show the efficiency and generality of this amination method (Schemes 2 and 3). Next, the selectivity of the reaction was studied (Scheme 4). Under



Scheme 4. Selectivity in the copper-catalyzed amination reactions of **5a** and **5b** using NFSI.

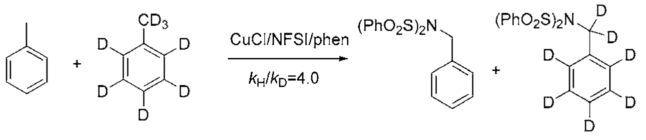
identical reaction conditions as those described in Scheme 2, *N*-(4-*e*thylbenzyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**6a**) and *N*-(phenylsulfonyl)-*N*-(1-*p*-tolylethyl)benzenesulfonamide (**6a′**) were obtained after 1.5 hours in 77% total yield in a ratio of 10:1 from 1-ethyl-4-methylbenzene (**5a**). Moreover, similar selectivity was also observed from reaction of ethyl 2-*p*-tolylacetate (**5b**; giving **6b** and **6b′** in 73% total yield with 3:1 ratio). The results shown in Scheme 4 (**6a/6a′** and **6b/6b′**) indicate the remarkable preference for primary over second C–H bonds in the amination reaction; this preference is in sharp contrast to the previous reports.[11,12]

Although the mechanistic details of this transformation are not clear at the moment, we presently favor the catalytic cycle involving Cu^{I}, Cu^{II}, and Cu^{III} species (Scheme 5). In the presence of ligands, the oxidation of CuCl with NFSI provides the Cu^{III} complex **A**, which abstracts a benzylic hydrogen atom[14,31] from substrate **1** to give the benzylic radical intermediate **B** and the Cu^{II} species **C**. The subsequent oxidation of the benzylic radical by the Cu^{II} species **C** leads to the formation of the amination product **2** along with CuCl for the next catalytic cycle.[32] The remarkable amination selectivity favoring the benzylic methyl C–H bond could originate from the last amination step involving the key sterically hindered nitrogen source. Considering the steric effect, we also performed the amination reaction of cumene, and an unidentified mixture of products was obtained. Furthermore, the isotope effect ($k_H/k_D = 4.0$; Scheme 6, the reaction was performed under the optimal reaction conditions) implies the benzylic hydrogen abstraction might be involved in the rate-limiting step.



Scheme 5. A putative mechanism of benzylic C–H amination. L = ligand.

Herein, we have described a highly selective benzylic C–H amination reaction by using an in situ generated sterically hindered Cu^{III} complex. The remarkable preference for primary over second C–H bonds is realized for the first time. Although the mild *N*-benzenesulfonate removal strategy for this nitrogen source needs to be additionally explored, we anticipate that the general copper-catalyzed, directing-group-free benzylic C–H amination reaction will have an impact on C–H amination pathways and should prompt the investigation of metal complex catalysts for benzylic C–H functionalization such as C–C and C–O cross-coupling reactions.



Scheme 6. The kinetic deuterium isotope effect for reactions between toluene and NFSI.

Experimental Section

In a 25 mL round-bottomed flask, toluene **1a** (0.106 mL, 1 mmol), CuCl (9.90 mg, 0.10 mmol), NFSI (346.5 mg, 1.10 mmol), and 1,10-phenanthroline (9.90 mg, 0.05 mmol) were dissolved in 3.0 mL DCE. The reaction mixture was stirred at 110 °C for 3 h (monitored by TLC). After the reaction was quenched by water, the mixture was extracted with CH_2Cl_2 (5.0 mL × 3), and the combined extracts were washed with $NaHCO_3$ (aq) (5.0 mL) and brine (5.0 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes 1:1) to give compound **2a** (309 mg, 80%) as a white solid.

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[32] To gain additional evidence for the proposed mechanism, ESI(+)(−)-MS experiments were performed: see the Supporting Information.