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Ligand-free copper-catalyzed C(sp^3)–H imidation of aromatic and aliphatic methyl sulfides with N-fluorobenzenesulfonimide†

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A novel and efficient process has been developed for copper-catalyzed C(sp^3)–H direct imidation of methyl sulfides with N-fluorobenzenesulfonimide(NFSI). Without using any ligands, various methyl sulfides including aromatic and aliphatic methyl sulfides, can be transformed to the corresponding N-((phenylthio)methyl)-benzenesulfonamide derivatives in good to excellent yields.

Nitrogen-containing molecules are widely present in natural products, drug molecules, agrochemicals, and other chemical materials.[1] Among the large number of approaches developed for their synthesis,[2] the pathway through C–N bond formation has been of great interest to synthetic chemists. This is mainly due to the fact that the introduction of amino groups can facilitate the tuning of physicochemical properties of the molecules leading to biologically significant structures(Fig. 1).[3] Typical methods for C–N bond formation include Buchwald–Hartwig, Ullmann–Goldberg and Chan–Evans–Lam imidations, which are mostly transition metal catalyzed, and require pre-functionalization of starting materials.[4] Recently, a more concise and atom-economic alternative to such imidations has been investigated by direct C–H imidation of oxidized nitrogen reagents and carbon nucleophiles. This process is also transition metal-catalyzed, however avoids prefunctionalization of coupling partners, thus providing a more efficient and environmentally friendly approach for C–N bond formation.[5,6] However, the requirements of directing groups and a stoichiometric amount of oxidants have limited the wide application of these C–H imidation processes.

N-Fluorobenzenesulfonimide (NFSI), a commonly used fluorination reagent and nitrogen source,[7–16] has been recently employed in a variety of aminative functionalization reactions, such as imidations of aromatic C–H bond,[8] alkenes or unsaturated ketones,[9] alkyne[10] and benzylic or allylic C–H bond.[11–16] Various transition metals have been explored to catalyze direct imidation of C(sp^3)–H bonds with NFSI (Scheme 1). In 2010, a pioneering work on remote amide-directed palladium-catalyzed intermolecular highly selective benzylic C–H imidation with N-fluorobenzenesulfonimide was disclosed by Zhang's

group.[11] Liu's[12] group proposed a copper-catalyzed C(sp^3)–H imidation strategy for synthesizing various benzylic amines from benzylic hydrocarbons. The first biocompatible iron-catalyzed benzylic C(sp^3)–H imidation of methylarenes with NFSI have been achieved by Bao et al. (Scheme 1a).[13] Using palladium as catalyst has also been reported by Muñiz et al.[14] to catalyze intermolecular sequence consisting of the C–H activation, where amidation of methyl groups relied on NFSI as both oxidant and nitrogen sources. In addition, copper-catalyzed amidation of 8-methylquinolines with N-fluoroarylsulfonimides via C(sp^3)–H activation has been examined by Zheng et al. (Scheme 1b).[15] Furthermore, copper-catalyzed sequential C(sp^2)/C(sp^3)–H imidation of 2-vinylanilines has been performed with NFSI for the efficient synthesis of indole frameworks (Scheme 1c).[16]

Despite considerable progress in studying transition metal catalyzed C(sp^3)–H imidation reactions, limited effort has been made in the methyl C(sp^3)–H imidation of thioanisoles with NFSI. Xu and co-workers[17] reported the direct imidation of the methyl C(sp^3)–H bond of thioanisoles. However, the scope of substrates was limited to thioaromatics with low product yields. Recently, our group has developed a novel method for copper-catalyzed direct imidation of thiophene with NFSI, demonstrating a convenient and complementary approach to
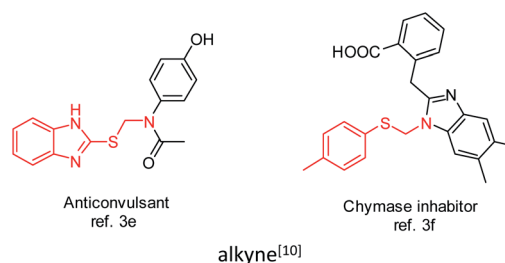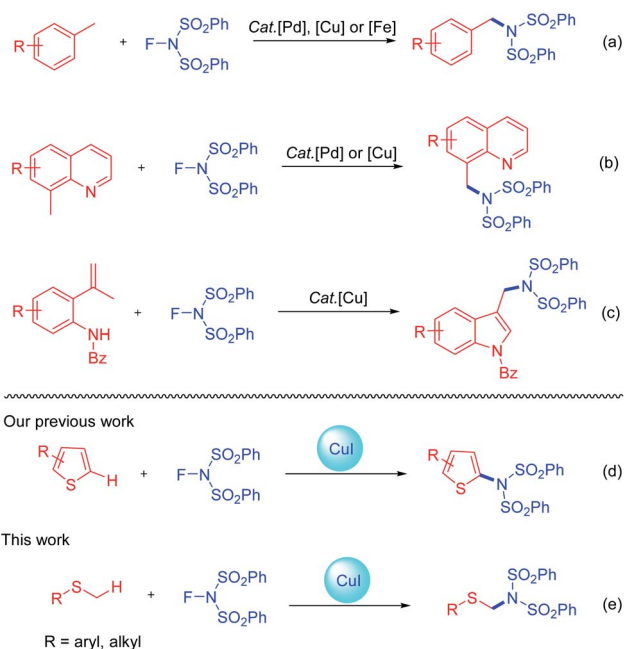
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Fig. 1 Representative examples of bioactive amides.

Scheme 1 Methodologies for C(sp^3)–H imidation using NFSI.

Table 1 Optimization of the reaction conditions^{a,b}

Entry	Catalyst	Base (2 equiv.)	Solvent	Temperature (°C)	Yield ^{b}(%)
1	CuI	NaHCO$_3$	DCE	25	55
2	CuI	NaHCO$_3$	DCE	40	76
3	CuI	NaHCO$_3$	DCE	60	85
4	CuI	NaHCO$_3$	DCE	80	81
5	CuI	NaHCO$_3$	DCE	100	73
6	CuCl	NaHCO$_3$	DCE	60	76
7	CuBr	NaHCO$_3$	DCE	60	80
8	CuOAc	NaHCO$_3$	DCE	60	56
9	—	NaHCO$_3$	DCE	60	49
10	CuI	Na$_2$CO$_3$	DCE	60	10
11	CuI	NaOtBu	DCE	60	15
12	CuI	K$_2$CO$_3$	DCE	60	18
13	CuI	Cs$_2$CO$_3$	DCE	60	20
14	CuI	—	DCE	60	n. r.^{c}
15	CuI	NaHCO$_3$	CH$_3$CN	60	45
16	CuI	NaHCO$_3$	DCM	60	55
17	CuI	NaHCO$_3$	DMSO	60	n. r.^{c}
18	CuI	NaHCO$_3$	DMF	60	n. r.^{c}

^{a} Reactions were carried out on a 0.5 mmol scale in 3.0 mL of solvent with 1 equiv. of **1a**, 1.2 equiv. of **2**, 2 equiv. of base and 10 mol% of catalyst at 60 °C for 8 h. ^{b} Isolated yield after column chromatography. ^{c} n. r. = No reaction.

synthesizing the *gem*-thiazamethylene structural motifs exist in biologically active structures (Scheme 1d).[8h] Built on this development, the present study was extended to the direct C(sp^3)–H imidation of methyl sulfides with NFSI catalyzed with ligand-free copper catalysts (Scheme 1e), where both aromatic and aliphatic methyl sulfides were investigated. This strategy provides a facile and efficient process for transition metal-catalyzed C(sp^3)–H direct imidation of methyl sulfides.

Initially, the reaction of methyl(phenyl)sulfane **1a** with NFSI was carried out successfully by using CuI as a catalyst and NaHCO$_3$ as a base. In the presence of 10 mol% CuI and 2 equiv. of NaHCO$_3$, **1a** and with NFSI were under stirring in a reaction medium of 1,2-dichloroethane (DCE) at room temperature for 8 h, and the desired product **3a** was obtained in 55% yield (Table 1, entry 1). A brief eximidation of the temperature effect revealed that a temperature of 60 °C gave the highest yield of **3a**, *i.e.* 85% (Table 1, entries 2–4). A higher temperatures of 100 °C showed unfavorable effect on the product yield (Table 1, entry 5). By further examining more copper catalysts including CuCl, CuBr and CuOAc, no higher yields were observed (Table 1, entries 6–8). In the absence of copper catalyst, a 49% product yield was obtained (Table 1, entry 9). Different bases were also employed where NaHCO$_3$ was found to be the most suitable under identical conditions in the reaction process (Table 1, entries 3 and 10–13). In the absence of a base, no detectable product **3a** was obtained which indicated a crucial role that the base played in the reaction (Table 1, entry 14). The effect of solvent was then investigated with a range of solvents for this reaction including acetonitrile (CH$_3$CN), dichloromethane (DCM), dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF). It was found that, interestingly, the reaction proceeded in both CH$_3$CN and DCM whereas the use of DMSO and DMF failed to give the desired product (Table 1, entries 15–18).

In summary, the optimal reaction conditions were as follows: methyl(phenyl)sulfane **1a** (0.5 mmol), NFSI (1.2 equiv.), CuCl (0.1 equiv.) and NaHCO$_3$ (2.0 equiv.) at 60 °C in DCE (3 mL) for 8 h.

By applying the optimized reaction conditions, the generality and limitations of this ligand-free C–N bond formation were further investigated. The results are presented in Scheme 2. The reaction of NFSI and a variety of methyl(phenyl)sulfane derivatives **1** afforded the desired imidation products **3** in a range of 72–93% either electron electron-donating (**1b**, **1c**) or electron-withdrawing groups (**1d–1g**) at the para-position of the benzene ring, such as methy, OMe, halogens, or CN, reacted with NFSI effectively to give the desired benzenesulfonamides **3b–3g** in moderate to good yields (72–90%). Thioanisole substrates bearing methoxyl, bromo and chloro substituents at *meta*-position of the benzene ring were found to be good candidates for the imidation, where the corresponding products (**3h–3j**) were obtained in satisfactory yields (79–93%). Interestingly, (3,5-dichlorophenyl)(methyl)sulfane also afforded target product **3k** in a good yield (76%). Substrates bearing methoxyl (**1l**) or halogen (**1m–1p**) groups at *ortho*-position of the benzene ring were also successfully imidated with high yields (**3l–3p**). Both heterocyclic substrates 2-(methylthio)pyridine (**1q**) and 2-(methylthio)thiophene (**1r**) also worked nicely to deliver the imidation products with good to excellent yields (**3q–3r**, 83–84%). Likely due to the steric effect, ethyl(phenyl)sulfane **1s** did
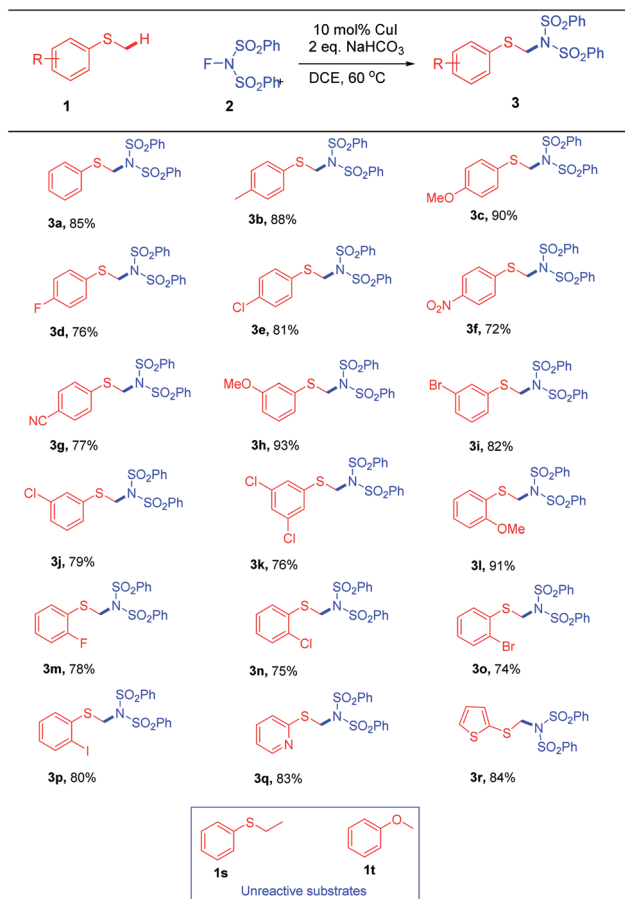
Scheme 2 Substrate Scope of Thioanisoles.[a,b] [a]Reactions were carried out on a 0.5 mmol scale in 3.0 mL of solvent with 1.0 equiv. of **1**, 1.2 equiv. of **2**, 2 equiv. of base and 10 mol% of catalyst at 60 °C for **8h**. [b] Isolated yield after column chromatography.
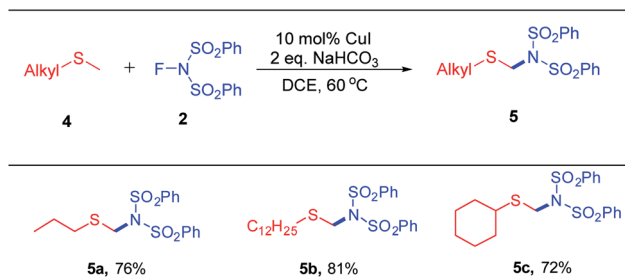
Scheme 3 Substrate scope of alkyl methyl sulfides.[a,b] [a]Reactions were carried out on a 0.5 mmol scale in 3.0 mL of solvent with 1.0 equiv. of **1**, 1.2 equiv. of **2**, 2 equiv. of base and 10 mol% of catalyst at 60 °C for **8h**. [b] Isolated yield after column chromatography.
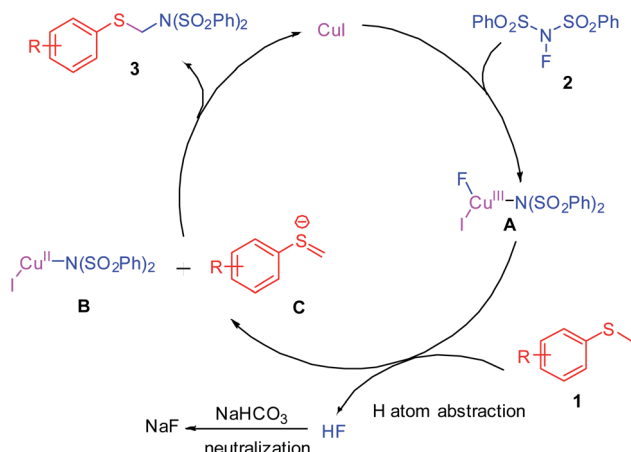
not provide imidated product under the optimized reaction conditions. Unfortunately, largely associated with the electronic effect, anisole **1t** also failed to afford the desired product.

To further extend the scope of the imidation reaction, various alky methyl sulfides were also explored as the reactants (Scheme 3). It was demonstrated that both short chain methyl(propyl)sulfane (**4a**) and long chain dodecyl(methyl)sulfane

(**4b**) reacted well to afford the desired products in satisfactory yields (**5a** and **5b**). Moreover, cyclohexyl(methyl)sulfane (**4c**) smoothly participated in this reaction to give the desired imidated product in good yields (**5c**).

In order to demonstrate the synthetic utility of the reaction we developed, this imidation reaction was performed on a 7.0 mmol scale in the presence of 10 mol% of CuI catalyst, giving 2.9 g of the desired product **3i** in 83% yield under standard conditions (Scheme 4). Notably, **3i** could undergo an oxidation process in the presence of 3.0 equivalents of *m*-chloroperoxybenzoic acid (*m*-CPBA) to provide the sulfone **6** in 95% yield.

Based on the results and discussion above, a possible reaction pathway has been proposed as illustrated in Scheme 5, involving the formation of Cu(I), Cu(II), and Cu(III) complexes,[2d,17] although the exact reaction mechanism still remains to be elucidated. Initially, NFSI **2** oxidizes CuI to provide a Cu(III) species **A**. Next, the substrate **1** can attack **A** forming the key methylenethionium ions **C** and the Cu(II) species **B**. Finally, the methylenethionium ions **C** is oxidized by the Cu(II) species **B** to form the imidation product **3** and regenerate CuI for the next catalytic cycle. In this circle system, the addition of chemical equivalent base can clearly enhance increasing the product yield, where the neutralization of HF by NaHCO₃ is likely to accelerate the transformation from substrate **1** to intermediate **C**.

Scheme 4 Scaled-up study and application of **3i**.

Scheme 5 Plausible reaction pathway.

Conclusions

In conclusion, a novel and efficient process has been developed for copper-catalyzed C(sp³)–H direct imidation of methyl sulfides with NFSI. Various methyl sulfides, including aromatic

and aliphatic methyl sulfides, can be transformed to the corresponding N-((phenylthio)methyl)-benzenesulfonamide derivatives in good to excellent yields. Currently, the reaction mechanism and further applications of this imidation method are under active investigation in our laboratories.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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