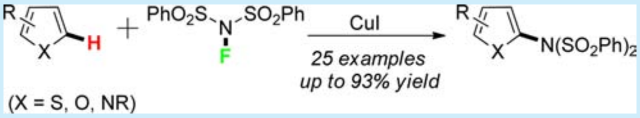
Copper-Catalyzed Direct Amidation of Heterocycles with *N*-Fluorobenzenesulfonimide

Sichang Wang, Zhangqin Ni, Xin Huang, Jichao Wang, and Yuanjiang Pan*

Department of Chemistry, Zhejiang University, Hangzhou 310027, People's Republic of China

Supporting Information

ABSTRACT: A highly efficient amidation reaction of heterocycles with *N*-fluorobenzenesulfonimide (NFSI) has been developed, presumably proceeding via C−H bond activation. Cuprous iodide was employed as the catalyst, and various α-amidated heterocycle derivatives have been generated in good to excellent yields. This chemistry endowed an economic method of synthesis of valuable amidated heterocycles through a direct C−N bond-coupling processes.



Transition-metal-catalyzed aryl C_{sp2}−N bond formation has been intensively studied over the past decade due to molecules containing arylamine and heteroarylamine units used in biology and pharmacy.[1,2]

So far, three major C−N bond formation approaches have been reported. One is traditional metal-mediated C−N coupling of aryl (pseudo)halides with amines, such as copper-mediated Ullmann and Goldberg type C−N bond formations[3] and palladium-catalyzed Buchwald−Hartwig amination/amidation (Scheme 1a).[4] However, this procedure not only generates stoichiometric amounts of byproducts but also needs high temperature and prefunctionalized arenes. Another procedure is direct C−H amination of arenes with amines in the presence of oxidants (Scheme 1b).[5−7] Special directing groups and stoichiometric oxidants are required in this atom-economical coupling, which diminish the general application of the method. The third strategy is direct C−N coupling of heteroarenes with preactivated amino precursors (Scheme 1c).[8] Nonetheless, this efficient and concise transformation has been reported. In 2004, Che and co-workers described amidation of C(sp2)−H bonds of heterocycles using ruthenium(II) porphyrin as catalyst and PhIdNTs as nitrogen source,[9] and in 2013, Ritter and co-workers disclosed the regioselective amidation of heteroarenes using *N*-fluorobenzenesulfonimide (NFSI) as nitrogen source and an

Scheme 1. Classical Strategies for C−N Coupling

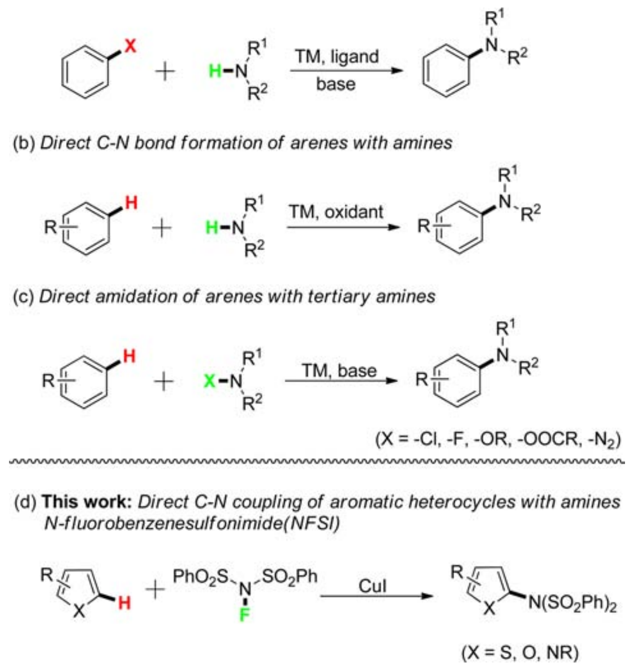
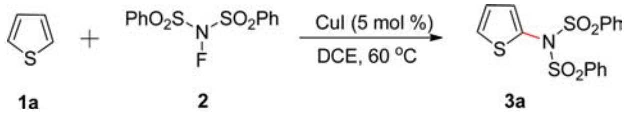


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	yield[b] (%)
1	CuI	DCE	25	52
2	CuI	DCE	40	76
3	CuI	DCE	60	88
4	CuCl	DCE	60	76
5	CuBr	DCE	60	80
6	CuCN	DCE	60	n.r.[c]
7	$CuCl_2$	DCE	60	56
8	CuI	DMSO	60	n.r.[c]
9	CuI	toluene	60	65
10	CuI	dioxane	60	30
11	CuI	CH_3CN	60	45
12	CuI	DCM	60	55
13	none	DCE	60	n.r.[c]

[a] Reactions were carried out on a 0.5 mmol scale in 3.0 mL of solvent with 1.0 equiv of **1a**, 1.2 equiv of **2**, and 5 mol % of catalyst for 8 h. [b] Isolated yield. [c] n.r. = no reaction.

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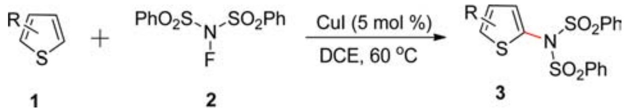
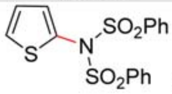
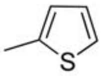
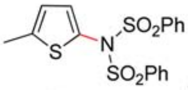
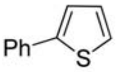
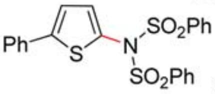
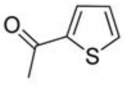
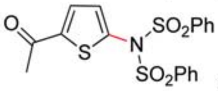
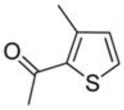
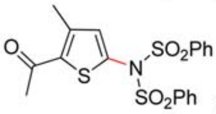
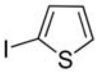
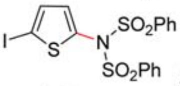
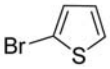
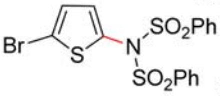
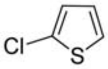
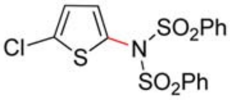
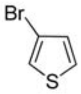
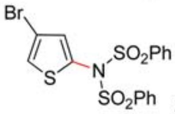
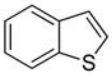
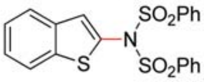
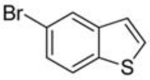
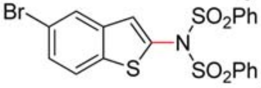
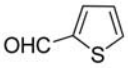
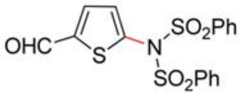
Table 2. Copper-Catalyzed Direct Amination of Various Thiophene Derivatives 1 with NFSI 2[a]

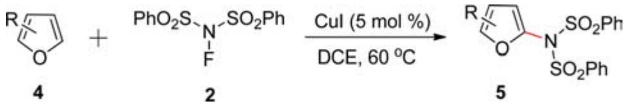


1 **2** **3**

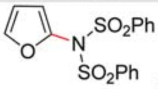
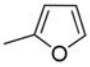
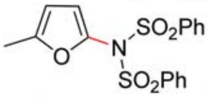
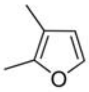
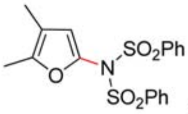
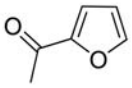
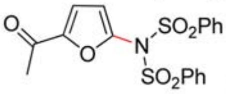
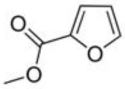
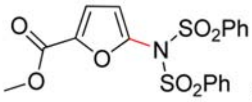
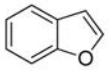
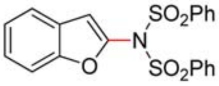
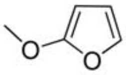
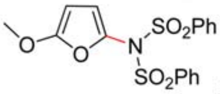
entry	substrate	product	yield (%)[b]
1		 **3a**	88
2		 **3b**	78
3		 **3c**	86
4		 **3d**	89
5		 **3e**	90
6		 **3f**	92
7		 **3g**	93
8		 **3h**	91
9		 **3i**	86
10		 **3j**	85
11		 **3k**	78
12		 **3l**	0

[a] Reactions were carried out on a 0.5 mmol scale in 3.0 mL sof olvent with 1.0 equiv of **1**, 1.2 equiv of **2**, and 5 mol % of CuI at 60 °C for 8 h. [b] Isolated yield after column chromatography.

Table 3. Copper-Catalyzed Direct Amination of Various Furan Derivatives 4 with NFSI 2[a]



4 **2** **5**

entry	substrate	product	yield (%)[b]
1		 **5a**	91
2		 **5b**	79
3		 **5c**	73
4		 **5d**	86
5		 **5e**	85
6		 **5f**	89
7		 **5g**	0

[a] Reactions were carried out on a 0.5 mmol scale in 3.0 mL of solvent with 1.0 equiv of **4**, 1.2 equiv of **2**, and 5 mol % of CuI at 60 °C for 8 h. [b] Isolated yield after column chromatography.

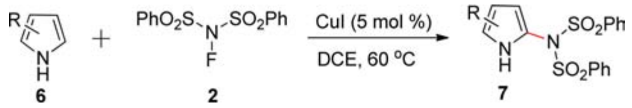
amine *N*-oxide ligated palladium complex as catalyst, in conjunction with silver cocatalyst.[11a]

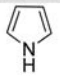
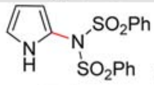
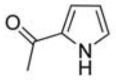
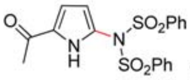
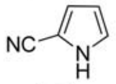
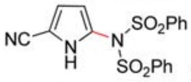
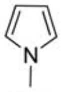
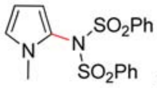
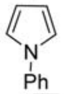
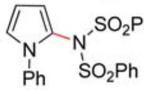
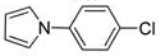
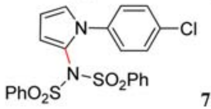
N-Fluorobenzenesulfonimide(NFSI), which was used as nitrogen source, has received increasing attention over the past decade.[10−12] Copper-mediated and palladium-catalyzed aryl C_{sp2}−N/C_{sp3}−N coupling of arenes with NFSI have been reported by Zhang and many others.[10,11] Although the coupling reactions between heterocycles and NFSI are known, examples of catalytic amidation of heteroarenes have rare precedents.[11a] We herein report the direct amidation of heteroarenes such as thiophene, furan, and pyrrole using cuprous iodide as a catalyst and NFSI as a nitrogen source (Scheme 1d).

Our investigation started with the coupling of thiophene (**1a**) with *N*-fluorobenzenesulfonimide (NFSI) (**2**) using cuprous iodide as the catalyst. Treatment of the thiophene with 1.2 equiv of NFSI and 5 mol % of CuI in DCE at room temperature for 8 h gave the C−N coupling product **3a** in 52% yield (Table 1, entry 1). It is noteworthy that when the temperature soared to 60 °C, the product was obtained in 88% yield (Table 1, entry 3). Several other copper catalysts, such as CuCl, CuBr, CuCN, and $CuCl_2$, were not superior to CuI (Table 1, entries 4−7). Solvent effect was also studied, (i.e., DMSO, toluene, dioxane, CH_3CN and CH_2Cl_2 (DCM)), which did not give improved results (Table 1, entries 8−12). Control experiments verified the necessity of the copper catalyst (entry 13). Therefore, we identified CuI (5 mol %)/DCE/60 °C as the best conditions, in which **3a** could be obtained in a yield of 88%.

Based on the above results, we first examined the substrate scope of various thiophene derivatives to react with NFSI under the optimized conditions, as shown in Table 2. When thiophene was used as a substrate, the Cu-catalyzed amidation with NFSI could afford 2-substituted product **3a** in 88% yield (entry 1). Gratifyingly, various regioselectively amidated thiophene derivatives were obtained regioselectively, and substratea which contained electron-rich or electron-poor groups were afforded in good to excellent yields (entries 2−12). Substrates bearing methyl (**1b**), phenyl (**1c**), ketone (**1d−e**), or halogen (**1f−i**) groups in the C2 or C3 position were also smoothly amidated

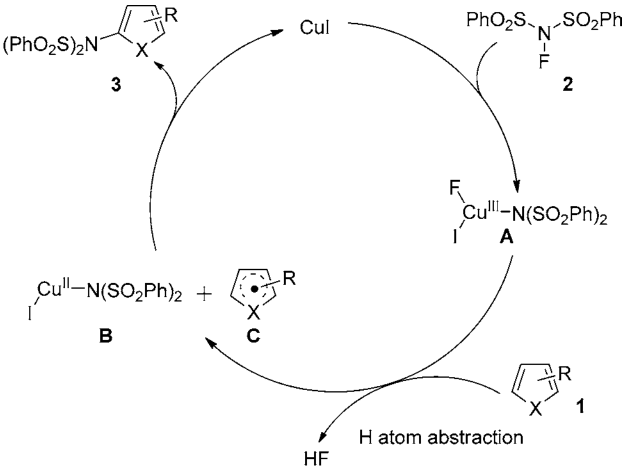
Table 4. Copper-Catalyzed Direct Amination of Various Pyrrole Derivatives 6 with NFSI 2[a]



entry	substrate	product	yield (%)[b]
1		 7a	86
2		 7b	88
3		 7c	85
4		 7d	83
5		 7e	76
6		 7f	78

[a]Reactions were carried out on a 0.5 mmol scale in 3.0 mL of solvent with 1.0 equiv of **6**, 1.2 equiv of **2**, and 5 mol % of CuI at 60 °C for 8 h. [b]Isolated yield after column chromatography.

Scheme 2. Proposed Mechanism



with high yields (entries 2–9). In addition, while benzothiophene derivatives were used as substrates, regioselective amidated products were also obtained in good yield (entries 10 and 11). However, thiophene-2-carbaldehyde could not afford any desired product (entry 13).

We then applied our protocol to furans to prepare 2- or 5-amidated furan derivatives, as shown in Table 3. While furan was used as a substrate, the corresponding 2-amidation furan was afforded in 91% yield (entry 1). Substrates bearing electron-donating groups such as methyl or dimethyl underwent this amidation in good yield (entries 2 and 3). On the other hand, substrates bearing electron-withdrawing groups such as ketone or ester increased the reactivity and afforded products in excellent yield (entries 4 and 5). Furthermore, benzofuran also reacted with NFSI to afford 2-substituted amidation product in 89% yield. Unfortunately, because of the electronic effect, 2-methoxyfuran did not afford the corresponding product.

In order to broaden the substrate scale, various pyrrole derivatives were also tested under the optimized conditions (Table4). It was found that substrates which bear electron-withdrawing or -donating groups or *N*-substituted substrates were totally tolerated in this reaction (entries 1–6). For example, 2-ketone and 2-cyan pyrrole derivatives could go through this reaction perfectly to give amido pyrroles **7b** and **7c** with good yields (entries 2 and 3). In addition, *N*-substituted pyrroles could also be amidated fluently under standard conditions to give desired products **7d–f** with 76–83% yields.

Although the exact reaction mechanism of this new process is still unclear at this stage, the most plausible pathway would involve the formation of Cu(I), Cu(II), and Cu(III) complexes (Scheme 2).[10,13] Initially, NFSI **2** oxidizes CuI to provide a Cu(III) species **A**.[13c] Then, the substrate **1** can attack **A** forming the heterocycle radical intermediate **C** and the Cu(II) species **B**. Ultimately, the heterocycle radical **C** is oxidized by the Cu(II) species **B** to form the amination product **3** and regenerate CuI for the next catalytic cycle.[10a]

In conclusion, we have developed a novel and useful approach for copper-catalyzed direct amidation of heterocycles. This transformation used *N*-fluorobenzenesulfonimide(NFSI) as the amine source, and a series of heterocycle substrates were selectively amidated in high yields with excellent functional group tolerance. Further mechanistic studies and use of this reaction in organic synthesis are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, and spectra of ^{1}H NMR, ^{13}C NMR, MS, and HRMS for new products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: panyuangjiang@zju.edu.cn.

Notes

The authors declare no competing financial interest.

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