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Regioselective C−H Amidation of (Alkyl)arenes by Iron(II) Catalysis

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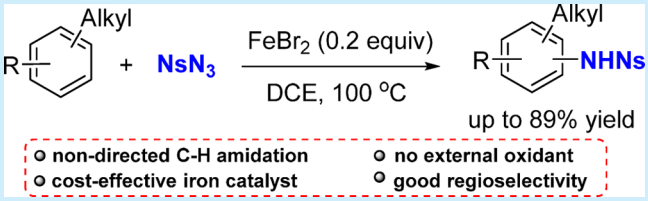
Supporting Information

ABSTRACT: A nondirected amidation reaction of aromatic C−H bond was developed under iron(II) catalysis, using sulfonyl azides as the nitrogen source. The reaction displayed a broad substrate scope and good regioselectivities in the aspects of aromatic ring vs alkyl chain and different aromatic position of (alkyl)arenes. This method provided a new protocol for the synthesis of some aromatic amines, which were hard to achieve in a previous report.



Direct C−H bond amination/amidation of aromatic molecules has been one of the most promising research topics in organic synthesis due to the amino functional groups on the aromatic rings widely existing in a variety of natural products, pharmaceuticals, or functional materials.[1,2] This method provides the convenience for simplifying the synthetic routes and diversifying complex molecules through directly introducing an amino functionality into the aromatic rings. Recently, two general strategies were presented on the basis of a selection of a nitrogen source in (i) amines or amides with external oxidants or (ii) preactivated nitrogen-containing compounds readily cleavaged by N−X bonds, such as *N*-chloroamines, *N*-hydroxycarbamates, *O*-acylhydroxylamines, nitrosobenzenes, and NFSI.[3,4] Among these reported approaches, organic azides are regarded as the environmentally benign nitrogen source and were extensively utilized for the direct amination/amidation of aromatic C−H bonds.[5] In this context, great progress has been made since Chang and co-workers successfully demonstrated and extended it through chelation-assisted C−H activation.[6] Accordingly, some representative examples were reported including Glorius and co-workers' Rh(III)/Cu(II)-cocatalyzed synthesis of 1*H*-indazoles,[7] the groups of Ackermann[8] and Jiao's[9] Ru-based catalytic systems, Kanai group's directed C(sp^2)−H amidation of indoles catalyzed by Cp*Co,[10] Zhu group's Cu-based catalytic systems,[11] and König and co-workers' visible-light C−H amidation of heteroarenes.[12] Additionally, our group also successfully expanded C−H amidation of cyclic *N*-sulfonyl ketimines by iridium(III) catalysis.[13] However, in most of these processes, the assistance of the directing groups and the catalysis of expensive transition metal are necessary for achieving C(sp^2)−H bond amination/amidation at their *ortho* position (Figure 1). On the other hand, in recent years, iron-catalyzed intramolecular C−H bond amination for the synthesis of N-heterocycles was also studied by preparing complex organic azides as the starting materials.[14]

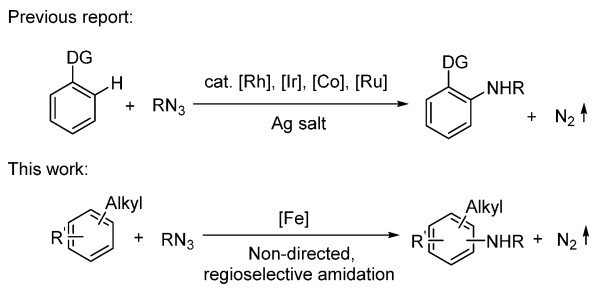


Figure 1. C−H amidation strategy.

Therefore, it is very desirable to explore cheaper and more efficient catalytic systems for direct C−H bond amidation of aromatic molecules by employing organic azides as a nitrogen source especially in the absence of directing groups. Our interest lies in the development of inexpensive, simple iron salt catalytic systems for the exploration of: (i) the selective C(sp^2)−H bond amidation of (alkyl)arenes and (ii) the regioselective C−H bond amidation of aromatic rings through electronic effect and steric control using sulfonyl azides as the environmentally benign nitrogen source (Figure 1). We herein report a method for the amidation of an aromatic C−H bond under iron catalysis using organic azides as the aminating

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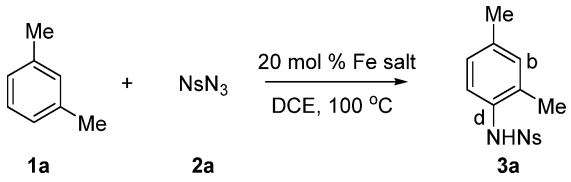
Org. Lett. XXXX, XXX, XXX−XXX

agents. The reaction displayed a broad substrate scope and good regioselectivities in the aspects of aromatic ring vs alkyl group and different aromatic position of (alkyl)arenes under the influence of electronic effect and steric hindrance.

To explore the possibility of C(sp^2)−H bond amidation of (alkyl)arenes and assess the selectivity of sp^2 vs sp^3 C−H bond functionalization, an initial study was conducted by employing *m*-xylene **1a** with 4-nitrobenzenesulfonazide (NsN_3) **2a** as the nitrogen source in the presence of iron(II) chloride. Interestingly, the product **3a** of C(sp^2)−H bond amidation was obtained in 70% isolated yield with an NMR ratio of 29:71 (b:d) (Table 1, entry 2). Furthermore, no multiamidation

Table 1. Optimization of the Reaction Conditions[a,b]



1a **2a** **3a**

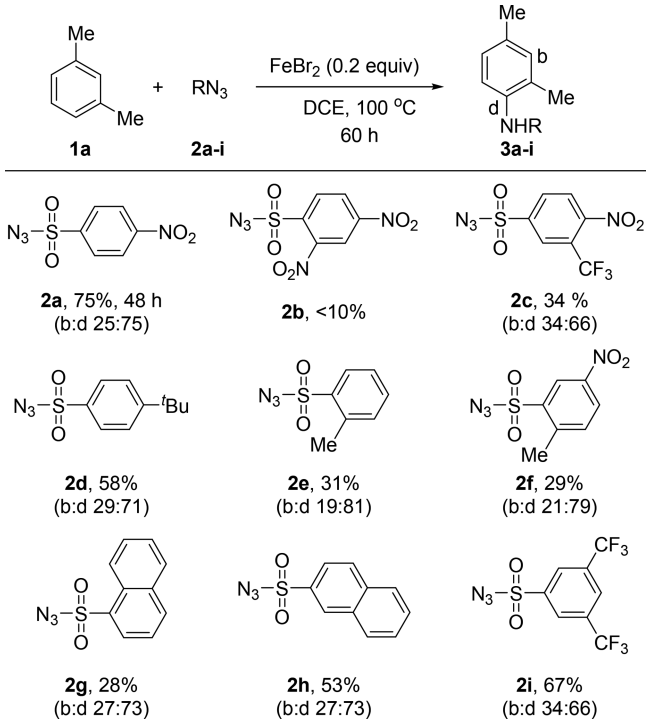
entry	catalyst	*t* (h)	yield (%)[b]	ratio (b:d)[c]
1	–	72	0	–
2	$FeCl_2$	72	70	29:71
3	$Fe(OAc)_2$	72	18	25:75
4	$Fe(OTf)_2$	72	12	23:77
5	$Fe(acac)_3$	72	7	27:73
6	$FeBr_2$	48	75	25:75
7[d]	$FeBr_2$	48	49	25:75
8[e]	$FeBr_2$	72	66	28:72
9[f]	$FeBr_2$	72	33	26:74
10[g]	$FeBr_2$	48	48	27:73
11[h]	$FeBr_2$	72	0	–
12[i]	$FeBr_2$	72	trace	–

[a]Unless otherwise noted, the reactions were carried out at 100 °C using **1a** (1.00 mmol), **2a** (0.25 mmol), Fe salts (20 mol %), and DCE (1.0 mL), in N_2 atmosphere. [b]Isolated yields. [c]^{1}H NMR ratio. [d]80 °C. [e]The molar ratio of **1a** and **2a** (3:1). [f]The molar ratio of **1a** and **2a** (1:1.5). [g]10 mol % $FeBr_2$. [h]MeCN. [i]1,4-Dioxane.

product was detected. As shown in Table 1 (entries 3−6), other iron salts were also screened for this reaction. The desired product could be acquired in low yields (18%, 12%, and 7%) when $Fe(OAc)_2$, $Fe(OTf)_2$, and $Fe(acac)_3$ were used as the catalyst, respectively. To our delight, the use of $FeBr_2$ (20 mol %) as the catalyst was examined for this reaction at 100 °C for 48 h, leading to 75% yield with good regioselectivity (b:d = 25:75) in the different position of *m*-xylene **1a** (Table 1, entry 6). It is noteworthy that no amidation product was given in the absence of the iron catalyst (Table 1, entry 1). When the reaction temperature was decreased to 80 °C, only a moderate amount of desired product was obtained (Table 1, entry 6 vs 7). To inquire into the optimum molar ratio of *m*-xylene **1a** and NsN_3 **2a** used in the reaction, several control experiments were carried out by varying the different molar ratio. The results showed that 4.0 equiv of *m*-xylene **1a** to **2a** was most effective for this reaction (Table 1, entries 6, 8, and 9). We also observed a significant reduction of the catalytic efficiency with changing the catalytic quantity to 10 mol % (Table 1, entry 10). Various solvents were then tested for this reaction, but only DCE provided good yield, and no or a trace amount of the desired product was given if MeCN or 1,4-dioxane was used as the solvent (Table 1, entries 11 and 12). Therefore, the optimized reaction conditions are as follows: the reaction was performed using 20 mol % of $FeBr_2$, sulfonyl azide and 4.0 equiv of (alkyl)arene in dichloroethane at 100 °C.

Next, the scope and steric effect of structurally varied sulfonyl azides on the regioselective C−H bond amidation of *m*-xylene were investigated through adjusting the substituents of sulfonyl azides (Scheme 1). Moderate to good yields of the

Scheme 1. Effect of Structurally Varied Sulfonyl Azides on the Regioselective Amidation of *m*-Xylene[a,b]



[a]Unless otherwise noted, the reactions were carried out using **1a** (1.00 mmol), **2** (0.25 mmol), $FeBr_2$ (0.05 mmol, 20 mol %), and DCE (1.0 mL), in N_2, at 100 °C. [b]Isolated yields.

amidation products **3a−i** were provided with few exceptions. 4-Nitrobenzenesulfonyl azide **2a** is the suitable nitrogen source for this reaction, affording the desired product **3a** in 75% yield with good positional selectivity. The reaction reactivities obviously decreased if an electron-withdrawing group was added in the 2 or 3 position of the azide **2a** (compare **2b** and **2c** with **2a**). When the azide **2d** with a bulky *tert*-butyl group instead of a nitro one was used for this reaction, the slight lessening was observed in the amidation regioselectivity. Gratifyingly, the introduction of a congested methyl group at the *ortho* position such as sulfonyl azides **2e** and **2f** could increase the positional selectivity of the aromatic amidation. However, the use of other sulfonazides such as **2g**, **2h**, and **2i** could not augment the regioselectivity as presented in Scheme 1. Perhaps the joint influence of electronic factor and steric hindrance led to a subtle equilibrium, thus determining the relative rate and associated regioselectivity. Therefore, on considering the efficiency and selectivity of the reaction, NsN_3 was chosen to be our model amidation reagent for further investigation.

After the identification of the standard reaction conditions, we turned our attention to explore the scope of various

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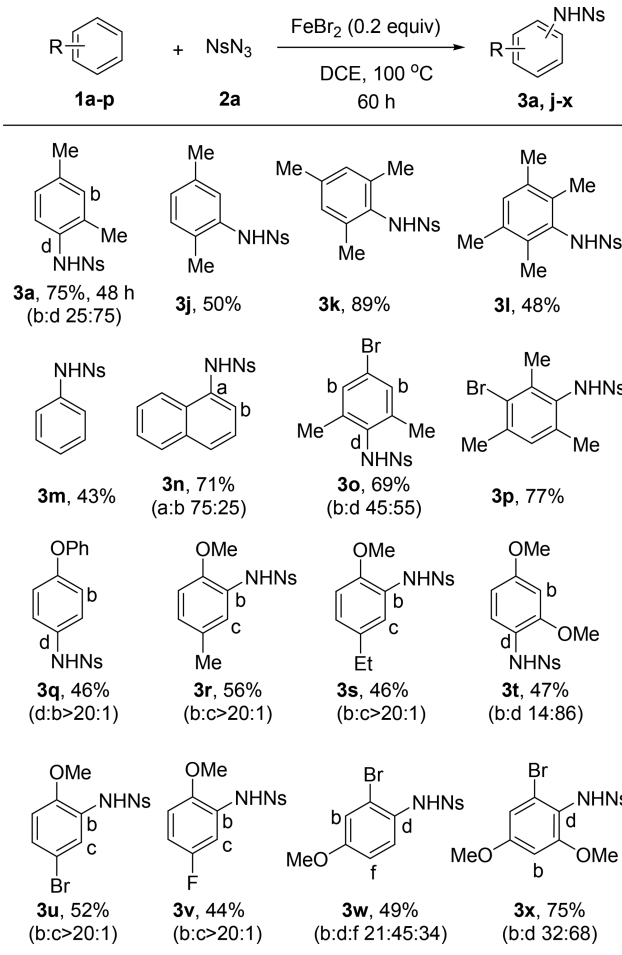
Org. Lett. XXXX, XXX, XXX−XXX

aromatic molecules for C(sp^2)−H bond amidation. As shown in Scheme 2, a broad range of simple (alkyl)arenes, aryl halides, and anisole derivatives could be transformed smoothly into the expected products in moderate to good yields (43%−89%) under the catalysis of cheap iron(II) bromide. For the aromatic ring containing alkyl substituents **1a−d**, **1g−h**, and **1j−k**, the amidation of the aromatic C−H bond is preferentially occurring in comparison to the benzylic C−H bond. Benzene **1e** and naphthalene **1f** as the most simple arene and polycyclic arene were also the suitable substrates for this reaction. In view of the low boiling point of benzene, the reaction was performed with no additional solvent (DCE). Encouraged by these results, an array of the functionized aromatic molecules with halides **1g−h** and **1m−p** and ether functional moieties **1i−p** were explored. The observation on the aminating regioselectivity of the simple substrates with different aromatic C−H bonds is consistent with the regular pattern of Friedel−Crafts reaction, whereas if a multi-substituted aromatic molecule was subjected to the standard reaction conditions, the aminating product at the unpredicted position can be obtained under the combined influence of electronic effect and steric hindrance. Aryl bromides **1g−h** and ethers **1i−p** were compatible with the catalytic system.

Scheme 2. Examination of Arene Scope[a,b]

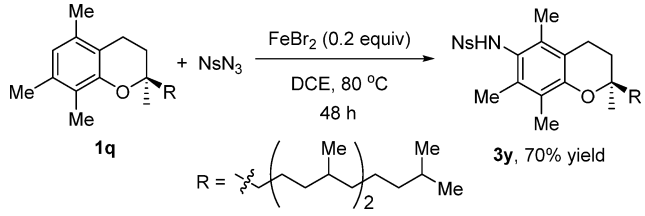


[a]Unless otherwise noted, the reactions were carried out using **1** (1.00 mmol), **2a** (0.25 mmol), $FeBr_2$ (0.05 mmol, 20 mol %), and DCE (1.0 mL), in N_2, at 100 °C. [b]Isolated yields based on 4-nitrobenzenesulfonazide **2a**.

Furthermore, diphenyl ether **1i** can react with NsN_3 to furnish the regiospecific product at the 4-position. If anisole derivatives **1j−k** and **1m,n** containing a *para* substituent such as methyl, ethyl, Br, or F were used, the amidation selectively occurred at the more electron-rich *ortho* site. The result comparison between **1g** and **1p** also confirmed the inconsistency with Friedel−Crafts pattern.

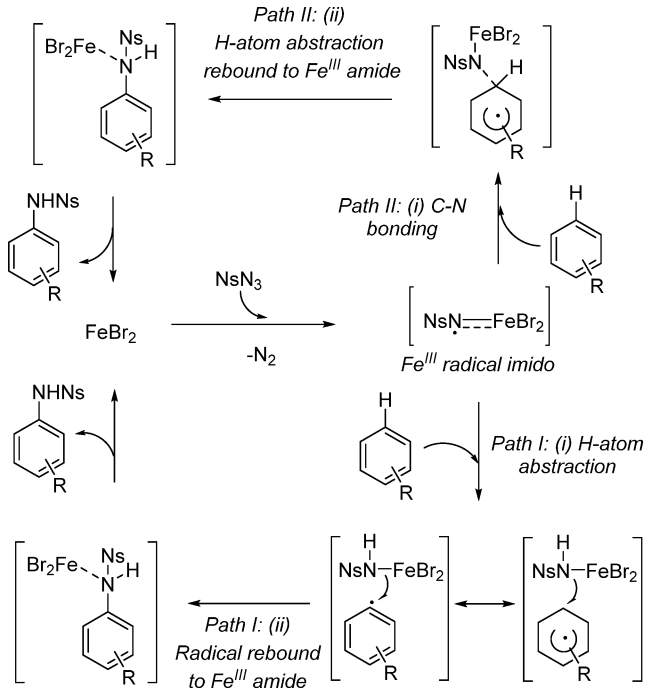
Subsequently, the application of aromatic C−H bond amidation to the modification of biologically complex molecules is explored as well. α-Tocopherol derivative **1q** was selected as the typical representative. It is gratifying that the desired product **3y** was obtained in good yields at 80 °C for 48 h (Scheme 3).

Scheme 3. Aromatic C−H Amidation of α-Tocopherol Derivative 1q



Addition of TEMPO significantly inhibited the reaction, which indicated that radicals might be involved in the C−N bond formation. On the basis of the experimental results and literature reports,[14] two possible reaction pathways were proposed as presented in Scheme 4. First, the interaction of iron(II) bromide with NsN_3 formed the Fe(III) radical imido intermediate. Next, this active species reacted with arene via (1) H atom abstraction, then radical rebound to the Fe(III) amide, or (2) C−N bonding, then H atom abstraction rebound to Fe(III) amide, thus leading to the formation of an amidation

Scheme 4. Plausible Reaction Mechanism



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Org. Lett. XXXX, XXX, XXX−XXX

product. Of course, up to now we still have no more evidence to support which mechanism this reaction undergoes.

In conclusion, we have developed an iron-catalyzed reaction for the conversion of an aromatic C−H to C−N bond with sulfonyl azides as the aminating source in the absence of a directing group. The reaction displayed the broad substrate scope and good regioselectivities in two aspects of (i) aromatic ring vs alkyl group and (ii) different aromatic position of (alkyl)arenes. This method provided a new protocol for the synthesis of some aromatic amines, which are hard to achieve in a previous report. In addition, a plausible reaction mechanism was proposed. The exploration of a new catalytic system to increase the regioselectivity, further application to the synthesis of biologically active complex molecules, and detailed mechanism studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00697.

Synthetic procedures, mechanistic studies, and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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