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Iron-catalyzed efficient intermolecular amination of C(sp^3)-H bonds with bromamine-T as nitrene source

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[Fe(N4Py)(CH_3CN)](ClO_4)$_2$ can efficiently catalyze intermolecular nitrene insertion of sp^3 C–H bonds with bromamine-T as the nitrene source, forming the desired tosylprotected amines with NaBr as the by-product.

Nitrogen-containing compounds are abundant in nature and their importance applications in biology and medicine have been widely documented. Metal-mediated C-N bond formation via a C-H activation strategy is a highly attractive chemical process for synthesis of valuable nitrogen-containing compounds.[1] This C–H bond amination method can ideally install an amino group in an organic skeleton in a single step, avoiding tedious multiple-step functional group transformations. In recent years, complex of rhodium-,[2] ruthenium-,[3] copper-,[4] cobalt-catalyzed[5] this transformation with iminoiodance, azides, bromamine-T, and tosyloxycarbamates as the nitrene precursors have been reported. Ochiai and co-workers reported a method for the direct and chemoselective amination of aliphatic C–H bonds under metal-free conditions, in which N-triflylimino-λ^3-bromane functions as an active organonitrenoid species.[6] Very recently, there has been a surge of interest in developing iron catalysts for atom- and group-transfer reactions for the C-N bond formation because of the natural abundance and biocompatibility of iron.[7] In literature, oxoiron(IV) centers in nonheme ligand have been characterized in both enzymes[8] and model systems[9] and have been shown to efficiently catalyze the hydroxylation of C-H bonds.[10] Now, studies on nonheme iron-catalyzed amination of C(sp^3)−H bonds via nitrogen group insertion have emerged as a powerful methodology for C-N bond formation.[11] However, development of nonheme iron catalysts for intermolecular amination of C(sp^3)−H bonds remain a challenge. Complex [Fe(N4Py)(CH_3CN)](ClO_4)$_2$ (**1**) (N4Py = N,N-bis(2-pyridyl-methyl)bis(2-pyridyl)methylamine, Figure 1) was designed and synthesized by Que and co-workers, and has significent oxygen activation.[12] Imidoiron units are nitrogen analogues of oxoiron species. It should be capable of catalyze the amination of C-H bonds. In this paper, we reported that **1** is an efficient nonheme iron catalyst for intermolecular amination of the C(sp^3)−H bond using bromamine-T as nitrene source.

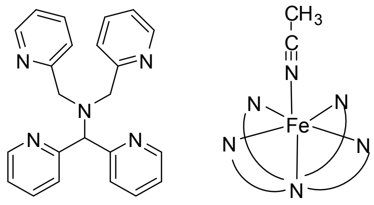
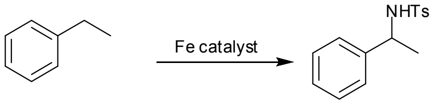


Figure 1. structure of N4Py and [Fe(N4Py)(CH3CN)]

Table 1. Optimization of conditions[a]



2a **3a**

Entry	Catalyst	N source	Solvent	*T* (°C)	Yield(%)
1	**1**	PhINTs	CH_3CN	80	12
2	**1**	TsNClNa	CH_3CN	80	NR[b]
3	**1**	TsNBrNa	CH_3CN	80	62
4	**1**	TsNBrNa	CH_3CN	40	76
5	**1**	TsNBrNa	CH_3CN	r.t.	71
6[c]	**1**	TsNBrNa	CH_3CN	80	81
7[c]	**1**	TsNBrNa	CH_2Cl_2	40	38
8[c]	**1**	TsNBrNa	DCE	80	46
9[c]	**1**	TsNBrNa	$CHCl_3$	60	21
10[c]	**1**	TsNBrNa	CH_3NO_2	80	55
11[c]	Fe(ClO_4)$_2$	TsNBrNa	CH_3CN	80	NR
12[c]	--	TsNBrNa	CH_3CN	80	NR

[a] ethylbenzene (0.3 mmol), nitrene source (0.45 mmol), catalyst (5 mol %),

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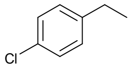
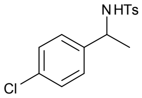
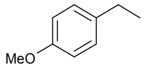
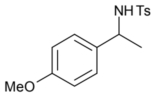
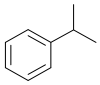
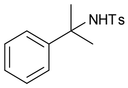
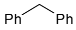
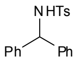
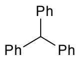
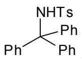
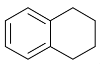
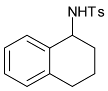
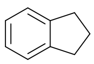
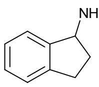
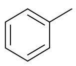
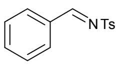
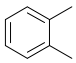
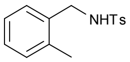
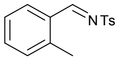
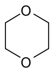
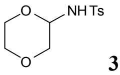
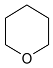
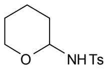
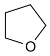
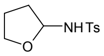
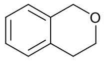
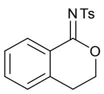
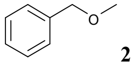
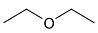
solvent (2 mL), 8 h. [b] NR = no reaction. [c] reaction time : 4 h.

Initially, we investigated the catalysis conditions, including optimization of nitrene sources, solvent and temperature. The results are summarized in Table 1. Using ethyl benzene **2a** as a model substrate, we systematically evaluated its catalytic C-H bond nitrene insertion with different nitrene sources catalyzed by complex **1**. The reagent PhINTs and related iminoiodane derivatives have been widely used as primary nitrene sources in amination of C–H bonds by iron catalysts.[11] Treatment of ethyl benzene with PhINTs (1.5 equiv.) in the presence of catalytic amount of [Fe(N4Py)(CH_3CN)](ClO_4)$_2$ (5 mol%) in acetonitrile under 80 °C for 8 h form the desired product **3a** in 12% yield (Table 1, entry 1). In contrast, using chloramine-T as nitrene sources, no reaction detected under similar reaction conditions (entry 2). We then examined the TsNBrNa (bromamine-T) as nitrene sources. Under similar reaction conditions, **1** catalyzed the amination to give **3a** in 62% yield (entry 3). The effects of temperature and solvent were also examined. The reaction in acetonitrile at 80 °C for 4 h gave the best result (entries 4-10, 81% yield). The yield of **3a** increased by decreasing the temperature (entry 3 with entry 4) and the reaction time (entry 3 with entry 6), because the product **3a** decomposed slowly at high temperature with iron salt under air. No decomposition of **3a** detected at 80 °C for 8 h, while 5% of **3a** decomposed with iron complex **1** at the same condition. When the amination reaction stopped, we found the iron complex **1** was decomposed and the free ligand N4Py can be isolated. So we added Fe(ClO_4)$_2$ • 6H_2O (5 mol%) into the acetonitrile solution of **3a**, 13% of **3a** decomposition was detected after 8 h at 80 °C under air. No reaction was observed in the absence of catalyst or with Fe(ClO_4)$_2$ as catalyst at 80 °C (entries 11, 12).

With the optimized conditions, we examined the substrate scope of [Fe(N4Py)(CH_3CN)](ClO_4)$_2$ catalyzed amination of C(sp^3)-H bonds with bromamine-T. As depicted in Table 2, a variety of sp^3 C−H bonds of benzylic and heterocycles reacted with bromamine-T in the presence of **1** to give corresponding products in good to excellent yields.

1 readily catalyzed amination with various substituted benzylic C-H bonds, including electron-donating or electron-withdrawing substituents on the aryl ring, to give the corresponding products in moderate to good yield (Table 2, entries 1-5). While 1,2,3,4-tetrahydronaphthalene **2g** and indan **2h** were employed, the corresponding isolated yield were 73% and 76% (entries 6, 7). In both of the cases, high chemoselectivity toward benzylic C–H bonds was observed. Notably, **1** can active the C-H bond of toluene. The reaction, however, didn't afford the corresponding amine product. Instead, the corresponding imine product **3i** was isolated in 80% yield (entry 8), presumably formed from the initial amine via a secondary reaction.[5] When *o*-xylene was used as the substrate, corresponding amine **3ja** and imine product **3jb** were obtained in 44% and 37% yields (entry 9). While only **3jb** was detected in 70% yield, when 2 equiv. TsNBrNa added into the reaction mixture. In cases of cycloethers, the amination reaction occurred at the position adjacent to O atoms (entries 10-12).

Table 2. **1** catalyzed C–H amination with bromamine-T[a]

Entry	Substrate	Product	Yield(%)[b]
1	 **2b**	 **3b**	78
2	 **2c**	 **3c**	76
3	 **2d**	 **3d**	69
4	 **2e**	 **3e**	82
5	 **2f**	 **3f**	86
6	 **2g**	 **3g**	73
7	 **2h**	 **3h**	76
8	 **2i**	 **3i**	80
9	 **2j**	 **3ja**  **3jb**	44 37
10	 **2k**	 **3k**	83
11	 **2l**	 **3l**	72
12	 **2m**	 **3m**	76
13	 **2n**	 **3n**	52
14	 **2o**	**3i**	70
15	 **2p**		NR[c]

[a] substrate (0.3 mmol), TsNBrNa (0.45 mmol), **1** (5 mol %), CH_3CN (2 mL),

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4 h. [b] isolated yield. [c] NR = no reaction.

The corresponding amination products were obtained in good yields. While **2n** was employed, the imine compound was detected as the only product in 52% yield (entry 13). We find that our standard condition was also effective for the amination of acyclic ether **2o** (entry 14). In the case, the hemiaminal products could not be isolated, since elimination of alcohol leading to imine **3i** was observed. The fact that hemiaminals are imine equivalents has been reported.[13] We also used the ethylether **2p** as substrate, but no reaction was detected (entry 15).

The catalyst loading for the amination reaction can be reduced to 3 mol % without significantly affecting the product yield. As an example, using ethyl benzene **2a** as substrate, **3a** was obtained in 79% yield under the same reaction conditions over 4 h. Moreover, the N4Py ligand is robust and can be reused for catalysis simply by addition of a new batch of $Fe(ClO_4)_2 \cdot 6H_2O$ to the reaction mixture. A solution containing **1** (3 mol %), TsNBrNa (0.45 mmol) and substrate **2a** (0.3 mmol) was stirred at 80 °C for 4 h. The substrate conversion of **2a** was 100% as detected by ^{1}H NMR spectroscopy. The catalysis stopped, presumably, **1** underwent demetalation to give free N4Py ligand. Without isolation of the ligand, a new batch of $Fe(ClO_4)_2 \cdot 6H_2O$ (3 mol %), TsNBrNa (1.5 equiv) and **2a** (0.3 mmol) was added to the reaction mixture, which was allowed to stir for another 4 h. The added $Fe(ClO_4)_2 \cdot 6H_2O$ reacted with the N4Py to regenerate complex **1** in situ, as evidenced by its absorption λ_{max} at 458 nm. The *in situ* generated **1** subsequently catalyzed the amination of **2a** to **3a.** This process was repeated 3 times to afford the **3a** with 75% yield after 3 runs.

Conclusions

In summary, we have demonstrated that the nonheme iron complex $[Fe(N4Py)(CH_3CN)](ClO_4)_2$ (**1**) is an active catalyst for the intermolecular amination of various C(sp3)−H bonds with bromamine-T at mild conditions. The benefit of using bromamine-T as the nitrene source was the innocent NaBr as the by-product. Efforts are underway to design and synthesize new nonheme iron complexes to further improve the scope and efficacy of the C–H amination system, including amination of unfunctional aliphatic carbon chains.

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Notes and references

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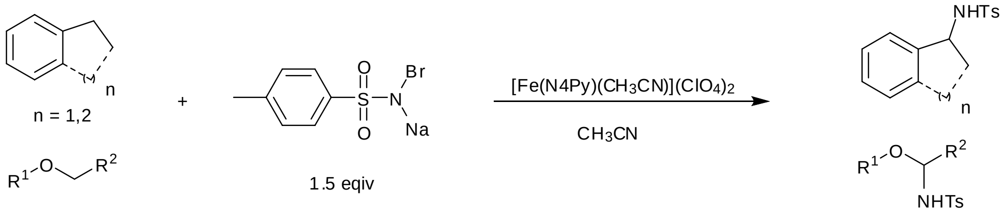

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