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Fe-Catalyzed Oxidative Coupling of Heteroarenes and Methylamines

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Benzylic amines are ubiquitous structural constituents in pharmacologically important molecules with many interesting actions (Figure 1).[1] Classically, benzylic amines have

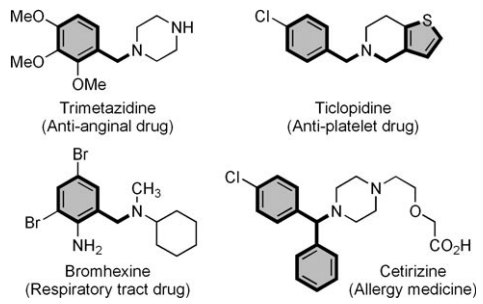

Figure 1. Representative drugs with benzylic amine structure.

been elaborated by the nucleophilic substitution reaction of amines with benzylic halides and related processes. With the advent of high-throughput chemistry, an efficient, straightforward, and diversity-oriented synthetic method toward this class of compounds is in high demand. As part of our program aimed at accessing privileged organic structures through direct C–H bond functionalization,[2,3] we attempted to develop a new catalyst for the synthesis of benzylic amines. Herein, we describe a new iron-based catalytic system for the oxidative C–H/C–H cross-coupling of electron-rich heteroarenes and methylamines.[4]

We embarked on the goal of developing new methods for benzylic amine synthesis taking inspiration from the important contributions of Murahashi[5] and Li[6], who clearly demonstrated that certain α-C–H bonds in amines can be oxidatively functionalized through the utilization of a transition metal such as ruthenium or copper.[7] For example, Murahashi has established that *tert*-butyldioxylation of α-C–H bonds of amines can be accomplished by treatment with *t*BuOOH in the presence of catalytic amounts of $RuCl_2(PPh_3)_3$.[8] Similarly, α-methoxylation (with MeOH)[9] and α-cyanation (with NaCN)[10] of tertiary amines can be carried out with related Ru catalyst/oxidant systems. Li has established that the combination of CuBr and a stoichiometric oxidant can promote the functionalization of α-C–H bonds of amines by various carbon nucleophiles such as terminal alkynes, nitroalkanes, and activated methylene compounds.[11] Although the precise mechanisms of these interesting catalytic processes remain unknown, metal-bound iminium species generated by the interaction of an amine and a transition metal have been proposed to be involved as key intermediates. Thus, we surmised that such iminium species could be trapped by nucleophilic heteroarenes furnishing the corresponding benzylic amines (Figure 2).[12]

We began our study by applying the catalytic conditions established by Murahashi, ($RuCl_3/O_2$) and Li (CuBr/*t*BuOOH) for the reaction of 3-methoxythiophene (**1A**) and *N*,*N*-dimethylbenzylamine (**2a**) (Table 1). Unfortunately, these conditions did not afford the expected C–H/C–H cou-

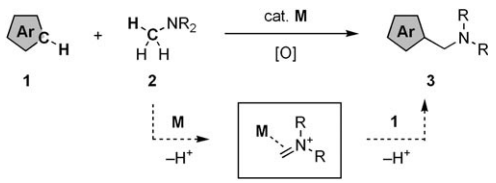

Figure 2. Synthesis of benzylic amines through oxidative cross-coupling reaction of arenes and methylamines.

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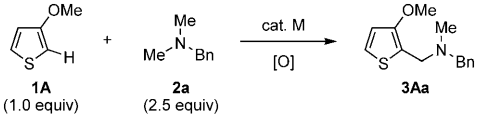
Table 1. Discovery of oxidative cross-coupling of heteroarenes and methylamines.

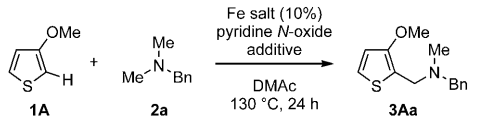


Conditions	Yield of **3Aa**
$RuCl_3$ (5%), O_2 (1 atm), MeOH/HOAc, 60°C, 12 h (Murahashi's conditions: Ref. [10])	<1%
CuBr (5%), *t*BuOOH (1.3 equiv), neat, 50°C, 12 h (Li's conditions: Ref. [12])	<1%
RuI_3 (5%), pyridine *N*-oxide (2 equiv), MeCONHMe, 130°C, 24 h	59%
$FeCl_2$ (10%), pyridine *N*-oxide (2 equiv), $MeCONMe_2$, 130°C, 24 h	24%

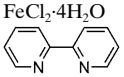
pling product **3Aa**. After extensive screening of conditions, a new ruthenium-based system was identified. In the presence of RuI_3 (5 mol%) and pyridine *N*-oxide (2 equiv), **1A** (1 equiv) and **2a** (2.5 equiv) underwent cross-coupling in MeCONHMe at 130°C to yield **3Aa** in 59% yield (Table 1). More interestingly, we also found that the combination of $FeCl_2$/C_5H_5N-O/$MeCONMe_2$ also promoted the desired coupling reaction, albeit with lower efficiency (24%).[13] It should be mentioned that Li and Li have recently reported that iron can catalyze the oxidative C–H/C–H cross-coupling of alkanes and 1,3-dicarbonyl compounds.[14–16]

Considering the obvious advantages of ubiquitous and cheap iron salts,[17] further optimization was conducted with the iron-based catalytic system (Table 2). The use of

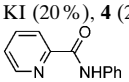
Table 2. Optimization of Fe-catalyzed coupling of **1A** and **2a**.[a]



Entry	Fe salt	Additive	Yield [%][b]
1	$FeCl_2$	–	24
2	$FeCl_2{\cdot}4H_2O$	–	24
3	FeF_2	–	9
4	$FeBr_2$	–	29
5	FeI_2	–	54 (53)
6	$FeCl_2{\cdot}4H_2O$	KI (20%)	46
7	$FeCl_2{\cdot}4H_2O$	KI (20%), bipy (10%)	60 (60)
8	$FeCl_2{\cdot}4H_2O$	KI (20%), **4** (20%)	64



bipy



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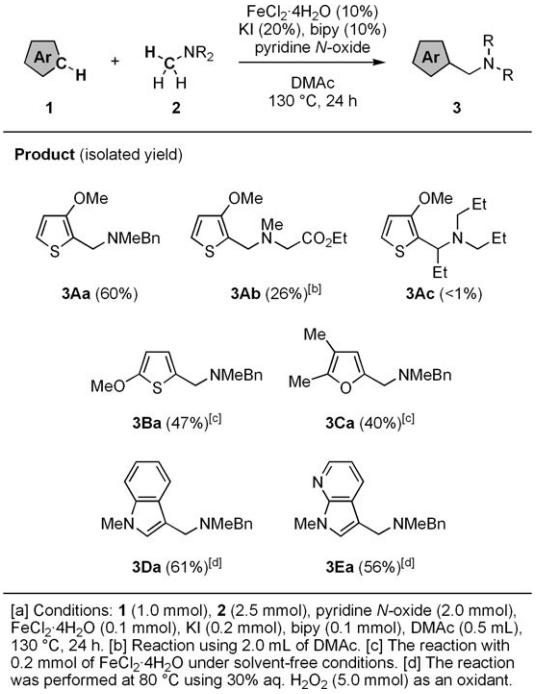
[a] Conditions: **1A** (1.0 mmol), **2a** (2.5 mmol), pyridine *N*-oxide (2.0 mmol), Fe salt (0.1 mmol), DMAc (0.5 mL), 130°C, 24 h. [b] Determined by GC analysis using *n*-undecane as an internal standard. Isolated yield is given in parenthesis.

$FeCl_2{\cdot}4H_2O$, which is considerably cheaper than its anhydrous form, provided **3Aa** in 24% yield (entry 2). Subsequent examination of various iron halides led to the finding that FeI_2 is a much better catalyst precursor, producing the coupling product in 54% yield (entry 5). Along these lines, we finally identified that the coupling proceeds equally well with $FeCl_2{\cdot}4H_2O$ catalyst when KI and 2,2′-bipyridyl (bipy) are added as additives (entry 7). Further examination by the addition of supporting ligands on iron also led to the finding that picolylamide **4** is superior to bipy furnishing **3Aa** in 64% yield (entry 8).

With a new iron-based catalytic system for the oxidative cross-coupling in hand, we next examined the cross-coupling using other substrates to gain a rough grasp of the scope of the current method (Figure 3). In this study, the



[a] Conditions: **1** (1.0 mmol), **2** (2.5 mmol), pyridine *N*-oxide (2.0 mmol), $FeCl_2{\cdot}4H_2O$ (0.1 mmol), KI (0.2 mmol), bipy (0.1 mmol), DMAc (0.5 mL), 130 °C, 24 h. [b] Reaction using 2.0 mL of DMAc. [c] The reaction with 0.2 mmol of $FeCl_2{\cdot}4H_2O$ under solvent-free conditions. [d] The reaction was performed at 80 °C using 30% aq. H_2O_2 (5.0 mmol) as an oxidant.

Figure 3. Substrate scope.[a]

optimized $FeCl_2{\cdot}4H_2O$/KI/bipy/C_5H_5N-O system was employed. Other than simple tertiary methylamines, *N*,*N*-dimethylglycine ethyl ester (**2b**) also reacted with **1A** at the methyl C–H bond giving **3Ab**. Interestingly, the coupling did not take place with trialkylamines such as tri(*n*-propyl)amine (**2c**). As exemplified in Figure 3, the present coupling reaction took place predominantly at *N*-methyl C–H bonds in the presence of other reactive bonds including the more acidic benzylic C–H (in **2a**) and the C–H bond α to the carbonyl group (in **2b**).[13] The high selectivity for "*N*-methyl" substituents is interesting considering that chemoselective demethylation of *N*-methyl tertiary amines is catalyzed by cytochrome P-450.[18]

Although the simple (unsubstituted) thiophene was found to be a poor heteroarene coupling partner, 2-methoxythiophene (**1B**) reacted with **2a** to give the corresponding benzylic amine **3Ba** in 47% yield (Figure 3). Similarly, 2,3-dimethylfuran (**1C**) cross-coupled with **2a** in 40% yield. In all of these examples, the coupling proceeded selectively at the α-position of the thiophene or furan ring. Further investiga-

tion of alternative heteroarenes uncovered that the coupling using indoles results in a complex mixture under the influence of the $FeCl_2{\cdot}4H_2O$/KI/bipy/C_5H_5N-O system. After reinvestigating the conditions, it was found that the use of aqueous H_2O_2 solution (30%) in place of pyridine *N*-oxide furnishes the desired cross-coupling product at lower temperature (80°C). For example, the coupling of *N*-methylindole (**1D**) and **2a** afforded **3Da** in 61% isolated yield. Similarly, the reaction using *N*-methyl-7-azaindole (**1E**) provided the corresponding aminomethylated product **3Ea** in 56% yield.

Having developed a new protocol for making benzylic amines from readily available coupling partners (heteroarenes and methylamines), we next surmised that a pharmaceutical relavant structure can be created by our method. Given that benzazepines and their bioisosteres are potent ligands for σ- and NMDA receptors,[19] we examined the intramolecular C–H/C–H coupling for the generation of benzazepine-like bicyclic nitrogen heterocycles (Figure 4). Thus

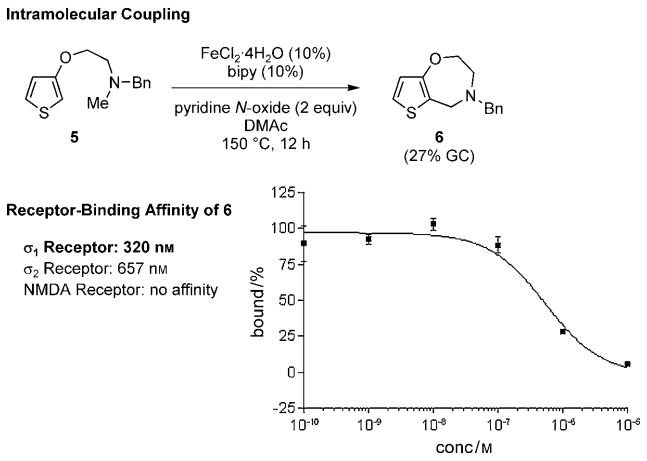


Figure 4. Intramolecular C–H/C–H coupling leading to a new σ_1-receptor ligand.

the thiophene **5** having a tethered methylamino group was prepared and subjected to the Fe-catalyzed reaction. Although the efficiency was not satisfactory under the current conditions, the target bicyclic product **6** was formed in 27% GC yield (isolated in 7% yield after extensive purification suitable for biological testing). The low efficiency might arise from the general difficulty of cyclizing a seven-membered ring.

Nevertheless, with the target compound **6** in hand, we investigated its affinity and selectivity towards σ_1, σ_2, and NMDA receptors. The receptor binding affinities were determined by competition experiments with radioligands; [^{3}H]-(+)-pentazocine (σ_1 receptor), [^{3}H]-di-*o*-tolylguanidine (σ_2 receptor), and [^{3}H]-MK-801 (NMDA receptor). Compound **6** showed affinity toward σ_1 receptors (K_i = 320 nM) and σ_2 receptors (K_i = 657 nM), while there was essentially no affinity toward the NMDA receptor (the inhibition at 1 mM was 17%). Though not excellent, a good binding affinity of **6** toward σ_1 receptor is promising as a lead for further optimization.[20]

In summary, we have developed a new iron-based catalytic system for the oxidative cross-coupling of electron-rich heteroarenes and methylamines. The successful identification of a new ligand family for the σ_1 receptor speaks well for the potential of the present iron catalysis in a range of applications. Future work will be devoted to mechanistic investigations and the development of highly active second-generation catalyst.

Experimental Section

Typical Procedure for Fe-Catalyzed Oxidative Coupling of Heteroarenes and Methylamines

A 20 mL glass vessel equipped with a J. Young O-ring tap and containing a magnetic stirring bar was dried with a heatgun under vacuum and filled with argon after cooling to room temperature. To this vessel were added $FeCl_2{\cdot}4H_2O$ (19.8 mg, 0.10 mmol), KI (33.4 mg, 0.20 mmol), 2,2′-bipyridyl (15.6 mg, 0.10 mmol), pyridine *N*-oxide (190.2 mg, 2.0 mmol), 3-methoxythiophene (**1A**: 114.2 mg, 1.0 mmol), *N*,*N*-dimethylbenzylamine (**2a**: 338.0 mg, 2.5 mmol), and *N*,*N*-dimethylacetamide (DMAc: 0.5 mL). The vessel was sealed with an O-ring tap and then heated at 130°C for 24 h in an 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, Et_2O (2 mL) was added to the mixture, followed by filtration through Celite (washed with Et_2O). The filtrate was washed with water (5 mL × 3) and brine (5 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/EtOAc = 3:1) to afford **3Aa** (147.9 mg, 60% yield) as a colorless oil.

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Keywords: C–H functionalization · heterocycles · iron · cross-coupling · oxidation

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