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Iron-catalyzed direct amination of azoles using formamides or amines as nitrogen sources in air†

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A new iron-catalyzed, direct C–H amination of azoles at C2 has been developed by using formamides or amines as nitrogen sources. Imidazole is the only additive in the catalyst system and oxygen in air is employed during the transformation process.

Transition metal-catalyzed C–N formation is a powerful and efficient approach for C-amination in organic synthesis.[1] Outstanding results were obtained in hydroamination,[2] allylic amination,[3] palladium-catalyzed Buchwald–Hartwig coupling[4] and the copper-catalyzed Ullmann and Goldberg couplings.[5] Along with the increasing attention paid to C–H functionalization, studies about transition metal-catalyzed direct C–H amination have also sprung up.[1,6] These direct methods include nitrene C–H insertion[7] and Pd-catalyzed amination of sp^2 C–H bonds.[8]

Amino-substituted azoles are important scaffolds in medicinal chemistry.[9] Among the various approaches to these structures, direct C–H amination has been focused on for its atom economy. Inspiring progress regarding this synthetic method has occurred in past decade.[10] However, these methods always need high temperatures, a large amount of metal salts, additional oxidants, or a nitrogen atmosphere. Thus, we hoped to find a novel, mild and atom-economic method toward direct azole amination catalyzed by inexpensive and environmentally benign reagents. Some transition metal salts, especially easily available iron(III) salts, which may act as both Lewis acid and oxidant, have the potential to be suitable catalysts for this kind of amination. More recently, a communication was reported by Chang during the preparation of this manuscript. They developed the direct amination of azoles with amines by using a catalytic amount of cobalt or manganese salts.[11] However, the reaction needed the presence of a stoichiometric quantity of peroxide and an acid additive. Herein, we wish to introduce a new and mild catalytic system, which consists of just the iron(III) salt and imidazole under air, for direct amination.

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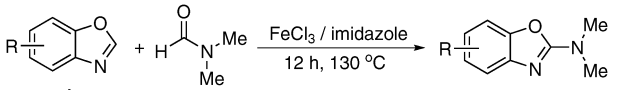
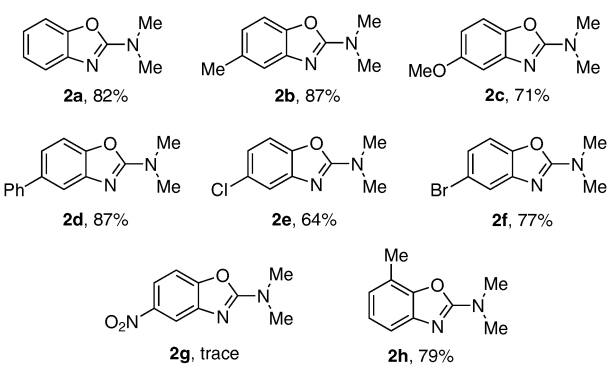
After the optimization of reaction conditions,[12] the 2-amino substituted product **2a** could be obtained from **1** and DMF in 82% yield (Table 1) without the use of any additional oxidant. Several substituted benzoxazoles were then applied to the decarbonylative amination under optimized conditions. As shown in Table 1, most of the benzoxazoles, especially with electro-donating substituents on the phenyl group, could react smoothly to give corresponding products with good yields (up to 87% for **2a–2f** and **2h**). However, benzoxazoles with strong electro-withdrawing substituents such as a nitro group (**1g**) could not progress well, and only a trace amount of product was obtained.

Azoles, other than benzoxazoles, with similar structures were employed for the reaction. Unfortunately, no product was found in the reaction involving benzothiazole, benzimidazole, 1-methylbenzimidazole, and phenyloxazoles. Nevertheless, exciting results were obtained in the reaction using 2-phenyl-1,3,4-oxadiazole (**3a**) as the substrate. As shown in Table 2, several 2-(substituted) phenyl-1,3,4-oxadiazoles could

Table 1 The iron-catalyzed decarbonylative amination of various benzoxazoles with DMF[a]

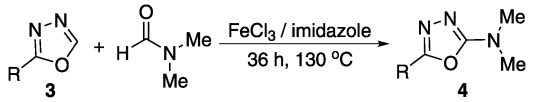


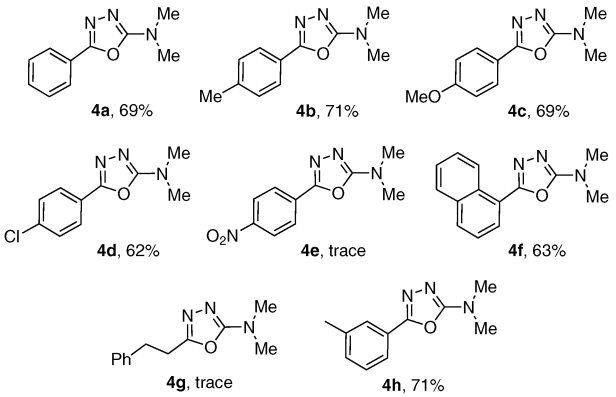
1 **2**



[a] Conditions: **1** (0.5 mmol), DMF (2 mL), $FeCl_3$ (0.25 equiv.), imidazole (2.0 equiv.), 130 °C, 12 h, under air. Yields were isolated yields.

Table 2 The iron-catalyzed decarbonylative amination of various 1,3,4-oxadiazoles with DMF[a]





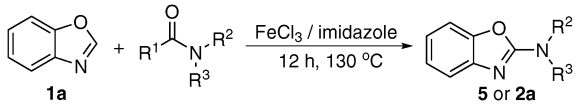
[a] Conditions: **3** (0.5 mmol), DMF (2 mL), $FeCl_3$ (0.5 equiv.), imidazole (2.0 equiv.), 130 °C, 36 h, under air. Yields were isolated yields.

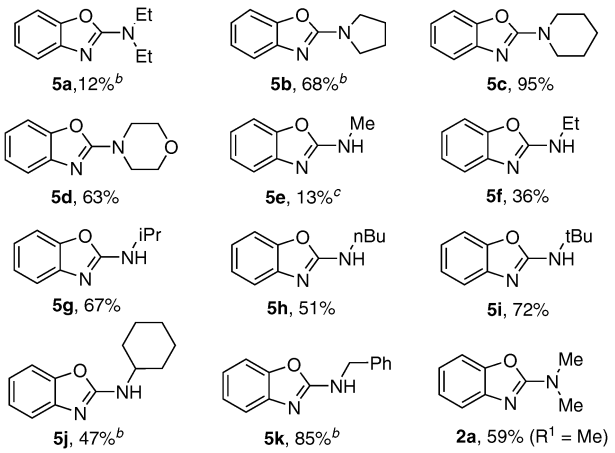
successfully react with DMF to give moderate to good yields (**4a–4d**, **4h**). Substrates with a β-naphthyl group also gave a comparable yield of 63% (**4f**). Comparing these to the reactions employing benzoxazoles, a longer reaction time (36 h) was needed and slightly lower yields (around 70%) were achieved. Similar to substrate **1g**, nitro-substituted 2-phenyl-1,3,4-oxadiazole **3e** was also hard to process in the reaction. The oxadiazole with an aliphatic substituent (**3g**) could not react smoothly, and only a trace amount of product was detected.

Subsequently, the scope of formamides with different amino moieties was expanded to test the generality of this synthetic protocol, and the results are summarized in Table 3. For *N*,*N*-disubstituted formamides, a cyclic amino moiety seemed to be critical for good results. The formamides derived from cyclic secondary amines, such as pyrrolidine, piperidine and morpholine, could give much higher yields (of **5b–5d**, respectively) than that derived from linear amine (*N*,*N*-diethylformamide, leading to **5a**). This might be attributed to the smaller steric hindrance on the N atom of the cyclic secondary amines. The best isolated yield was up to 95% (**5c**) in the reaction between benzoxazole and the piperdine-derived formamide. On the contrary, for the N-monosubstituted formamides, it's interesting to find that the more bulky groups on the N atom led to a better yield (**5e–5i**). Increasing the catalyst loading to 0.5 equiv., a reaction employing a formamide derived from benzylamine could give a related product in 85% yield (**5k**). Additionally, instead of DMF, *N*,*N*-dimethyl acetamide (DMA) was first employed for the reaction, and a moderate yield (59%) of product **2a** was obtained .

Compared to amides, such as DMF, most amines with higher molecular weights are suitable for direct use in the reaction. A preliminary study was carried out for the reaction between (phenyl)benzoxazole and several amines. After optimization of the reaction conditions, these reactions

Table 3 The iron-catalyzed decarbonylative amination of benzoxazole with amides[a]

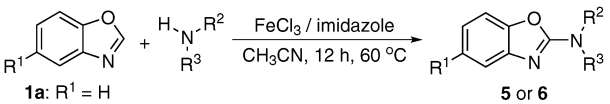


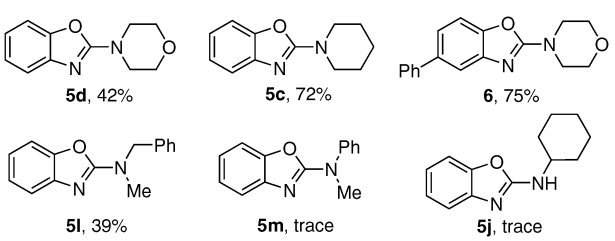


[a] Conditions: **1a** (0.5 mmol), amides (2 mL), $FeCl_3$ (0.25 equiv.), imidazole (2.0 equiv.), 130 °C, 12 h, R^1 = H, under air. Yields were isolated yields. [b] $FeCl_3$ (0.5 equiv.), 24 h. [c] $FeCl_3$ (0.75 equiv.), 24 h.

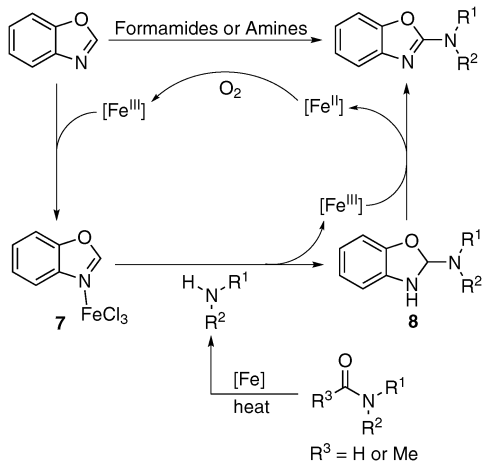
proceeded in acetonitrile in the presence of 1 equiv. of $FeCl_3$ at 60 °C.[12] As shown in Table 4, benzoxazole **1a** could react with morpholine to give product **5d** in 42% yield. Piperidine could give the related product **5c** with a much higher yield (72%). The phenyl substitution on the benzoxazole ring also benefited the reaction, and the reaction between **1d** and morpholine resulted in product **6** in 75% yield. This is the first example of iron-catalyzed direct C–H amination of azole-type substrates using an amine. However, non-cyclic amines seemed unsuitable for the reaction. Only *N*-methylbenzylamine could react with benzoxazole, leading to **5l** in poor yield.

Table 4 The iron-mediated direct amination of benzoxazole with amines[a]





[a] Conditions: **1** (1.5 equiv.), amine (0.5 mmol), $FeCl_3$ (1.0 equiv.), imidazole (2.0 equiv.), CH_3CN (2 mL) , 60 °C, 12 h. Yields of isolated product shown.



Scheme 1 A proposed pathway of the amination reaction.

In any case, this synthetic protocol might be a potential method for this type of direct amination.

Although systematic studies are required to elucidate the mechanistic details of the direct amination of benzoxazoles, a proposed mechanism is presented in Scheme 1. It is shown that benzoxazole was firstly attacked by a Lewis acid to form intermediate **7**. In the presence of imidazole, this formed an amine *in situ*, which acted as a nucleophile that could then attack the 2-position of benzoxazole to generate precursor **8**. Finally, oxidation of **8** led to the rearomatized product. We speculate that in this reaction, iron(III) species acted as the Lewis acid, which activated the C-2 position of the benzoxazole and oxidant, which completed the final rearomatization. Meanwhile, oxygen might mainly act as a co-oxidant to transfer iron(II) and regenerate the trivalent iron species. In the absence of oxygen, only a 30% yield was obtained in the reaction involving DMF with 0.5 equiv. of $FeCl_3$, and the yield increased to 74% in the presence of air (ESI†, Table S1, entries 11 and 17). Similarly, the reaction using morpholine as the substrate could also benefit from oxygen, and the use of an oxygen balloon could increase the yield from 42% (**5d**, Table 4) to 57%, while only a 14% yield was obtained in the absence of oxygen.† A radical scavenger effect was also investigated to study the reaction further by using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).† Results indicated that TEMPO only inhibited the decarbonylation of formamides, and it was possible that no radical was produced in the amination process.

In summary, a new catalytic system for decarbonylative coupling between azoles and formamides was developed. Moderate to good results were achieved for a series of substrates. In comparison with previously reported systems, more inexpensive and accessible iron salts were used as the catalyst, and relatively mild and easily handled reaction conditions, without additional oxidant, were employed. Moreover, instead of amides, several amines were also found to be beneficial for the direct amination. Further studies to elucidate the mechanism and to expand the synthetic scope of this reaction are currently under way.

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12 Optimization studies of the direct amination of benzoxazoles with formamides or amines were carried out. See ESI†.

