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A Direct Intramolecular C−H Amination Reaction Cocatalyzed by Copper(II) and Iron(III) as Part of an Efficient Route for the Synthesis of Pyrido[1,2-*a*]benzimidazoles from *N*-Aryl-2-aminopyridines

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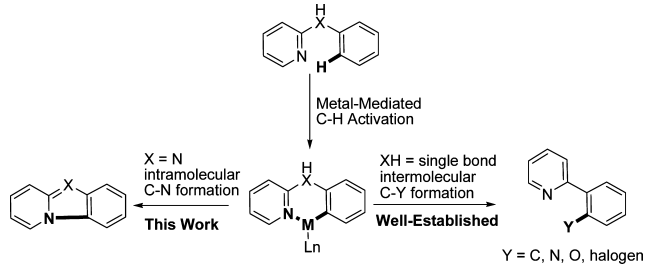
Abstract: A novel and efficient synthesis of pyrido[1,2-*a*]benzimidazoles through direct intramolecular aromatic C−H amination of *N*-aryl-2-aminopyridines has been developed. The reaction, cocatalyzed by $Cu(OAc)_2$ and $Fe(NO_3)_3\cdot 9H_2O$, is carried out in DMF under a dioxygen atmosphere. Diversified pyrido[1,2-*a*]benzimidazoles containing various substitution patterns are obtained in moderate to excellent yields by using this procedure. The results of mechanistic studies suggest that a Cu(III)-catalyzed electrophilic aromatic substitution (S_EAr) pathway is operating in this process. The unique role of iron(III) is believed to lie in its ability to facilitate formation of the more electrophilic Cu(III) species. In the absence of iron(III), a much less efficient and reversible Cu(II)-mediated S_EAr process takes place.

Direct C−H functionalization processes that feature atom economy and high bond-formation efficiencies have received substantial attention in recent years.[1] Compared with traditional strong acid-mediated heterocycle synthetic procedures, the strategy involving intramolecular C−H activation/C−heteroatom bond formation provides a complementary approach to the synthesis of heterocycles that is compatible with the increasing requirements for environmentally benign and efficient processes.[2] Although metal-catalyzed nitrene insertion into C−H bonds is a well-established methodology for formation of C−N bonds,[3] intramolecular amination via C−H activation was not realized until the pioneering research work by Buchwald in 2005.[4a] Since then, an increasing number of N-heterocycles, such as carbazoles,[4] benzimidazoles,[5] indazoles,[6] indolines,[7] and *N*-methoxylactams,[8] have been constructed by using this novel C−N bond-forming strategy. In this context, palladium catalysts together with stoichiometric or excess amounts of oxidants, such as $Cu(OAc)_2$, AgOAc, $PhI(OAc)_2$, $CeSO_4$, and/or F^+, have been used predominantly.[4,6−8] Much cheaper copper salts along with dioxygen as the terminal oxidant have been only rarely used in direct C−H activation/C−heteroatom bond-forming processes,[9] especially in intramolecular variants.[5,10] Below, we report the discovery of copper-catalyzed intramolecular C−H amination reactions of *N*-aryl-2-aminopyridines that produce pyrido[1,2-*a*]benzimidazoles and involve the unprecedented cooperative action of an iron(III) salt[11] and dioxygen as the terminal oxidant.

Owing to their antibacterial,[12] antitumor,[13] and antiviral activities,[14] considerable effort has been directed toward the synthesis of pyrido[1,2-*a*]benzimidazoles. However, the methods developed thus far suffer from the lengths of the preparative routes, the formation of regioisomeric mixtures of products, limited substrate scope, and/or unsatisfactory yields.[15] As a result, an efficient approach for the synthesis of these substances that has a wide functionality tolerance is highly desirable. To this end, we reasoned that the pyrido[1,2-*a*]benzimidazole nucleus could be constructed by direct intramolecular C−H amination reactions of readily available *N*-aryl-2-aminopyridines (Scheme 1), in which the pyridine moiety serves as a directing group as well as an intramolecular nucleophile.

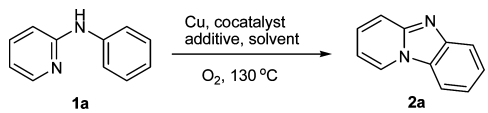
Scheme 1. Intramolecular C−H Activation/C−N Bond Formation



To test this hypothesis, a study of the reaction of *N*-phenyl-2-aminopyridine **1a** under Buchwald's carbazole synthesis conditions was conducted.[4a] Unfortunately, none of the expected product **2a** was formed in the reaction in toluene. However, conversion of **1a** to **2a** did take place when DMF was employed as the solvent (47%; Table 1, entries 1−2). A further investigation of the process revealed that the palladium catalyst was not needed since substoichiometric amounts of $Cu(OAc)_2$ alone catalyze the reaction with almost the same efficiency seen when the palladium catalyst was present (Table 1, entry 3). Moreover, the yield of **2a** increased to 81% when 10 mol % of iron salts were included in the reaction mixture, with $Fe(NO_3)_3\cdot 9H_2O$ being the most effective (Table 1, entries 4−6). Control experiments showed that iron salts themselves did not promote the reaction.[16] The yield of **2a** was further improved to 88% (Table 1, entry 7) when pivalic acid was utilized as an additive,[17] albeit an extended reaction time was required for complete consumption of **1a**. The amount of $Cu(OAc)_2$ employed to promote this reaction can be reduced to 20 mol % without a significant loss of yield with the requirement of longer reaction times (Table 1, entry 8).

Conditions involving 20 mol % of $Cu(OAc)_2$, 10 mol % of $Fe(NO_3)_3\cdot 9H_2O$, and 5.0 equiv of pivalic acid in DMF under a balloon pressure of O_2 at 130 °C were selected to explore the generality of this novel method for the synthesis of pyrido[1,2-*a*]benzimidazoles. The effects of substituents (R^2) on the aniline ring were examined first. Both electron-donating and electron-withdrawing groups in the *ortho* (Table 2, **2l**−**2n**) and *para* (Table 2, **2b**−**2g**) positions relative to the aniline nitrogen were well tolerated, and good to excellent yields of the corresponding substituted pyrido[1,2-*a*]benzimidazoles were obtained (68−84%).

Table 1. Optimization of the Reaction Conditions[a]

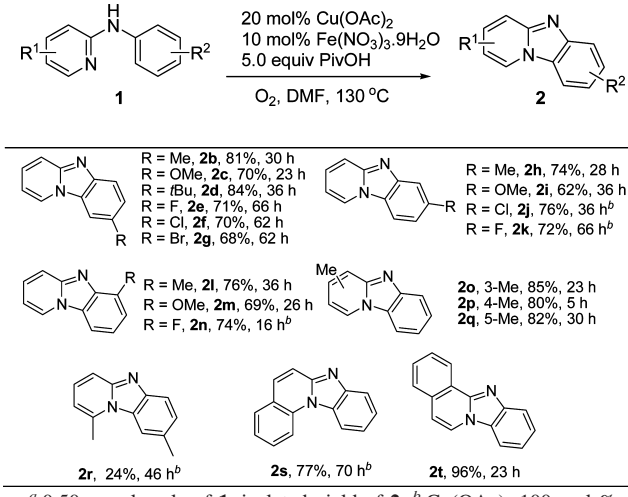


entry	catalyst	cocatalyst (equiv)[c]	solvent (equiv)	time (h)	yield (%)[d]
1[b]	$Pd(OAc)_2$ (0.1)	A (3.0)	toluene	12	trace
2[b]	$Pd(OAc)_2$ (0.1)	A (3.0)	DMF	12	47
3	$Cu(OAc)_2$ (0.5)	−	DMF	20	44
4	$Cu(OAc)_2$ (0.5)	B (0.1)	DMF	7	81
5	$Cu(OAc)_2$ (0.5)	C (0.1)	DMF	5	52
6	$Cu(OAc)_2$ (0.5)	D (0.1)	DMF	4	67
7[e]	**$Cu(OAc)_2$ (0.5)**	**B (0.1)**	**DMF**	**18**	**88**
8[e]	**$Cu(OAc)_2$ (0.2)**	**B (0.1)**	**DMF**	**28**	**82**

[a] Reaction conditions: **1a** (0.50 mmol), solvent (1.0 mL), O_2 balloon, 130 °C. [b] Under air. [c] A: $Cu(OAc)_2$; B: $Fe(NO_3)_3 \cdot 9H_2O$; C: $FeCl_3$; D: $Fe_2(SO_4)_3$. [d] Yield of isolated **2a**. [e] 5.0 equiv of PivOH was added.

It is noteworthy that a bromo-substituent remained intact under these reaction conditions (Table 2, **2g**), an observation that suggests further diversification of the process is possible. The reactions were sluggish when electron-deficient *m*-chloro and *m*-fluoro substituted substrates (**1j** and **1k**) were employed. In these cases, an increase in catalyst loading to 100 mol % was necessary in order to produce the corresponding products **2j** and **2k** efficiently. In reactions in which two regioisomeric products could be formed (Table 2, **2h**−**2k**), only the less sterically hindered products were generated.

Table 2. Synthesis of Substituted Pyrido[1,2-*a*]benzimidazoles[a]

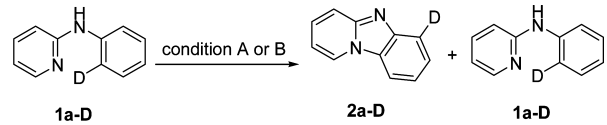


[a] 0.50 mmol scale of **1**, isolated yield of **2**. [b] $Cu(OAc)_2$ 100 mol %.

Reactions of *N*-aryl-2-aminopyridines with substituents at all of the four pyridine ring positions (R^1) were also examined. When the pyridine moiety was substituted with electron-withdrawing groups, such as F, Cl, and CN, the starting materials cannot be consumed completely under the standard reaction conditions. On the other hand, substrates with methyl groups at all positions undergo the reaction efficiently (Table 2, **2o**−**2q**) except when a methyl group is present at the position next to the pyridine ring nitrogen (Table 2, **2r**). In this instance, steric interference of the adjacent methyl with coordination of copper to the pyridine nitrogen might be responsible for the unexpectedly low yield observed. Additionally, *N*-phenyl-2-aminoquinoline and *N*-phenyl-2-aminoisoquinoline were ideal substrates whose reactions led to the benzo-fused pyrido[1,2-*a*]benzimidazoles **2s** and **2t** in good and excellent yields, respectively.

A plausible reaction mechanism, especially one that highlights the critical and unique role played by iron(III), was proposed based on the following observations. First, a competition reaction using excess amounts of $Cu(OAc)_2$ was carried out. The yield of **2a** diminished dramatically to 58% when $Fe(NO_3)_3 \cdot 9H_2O$ was absent, even when 200 mol % of $Cu(OAc)_2$ was employed under otherwise identical conditions. This result indicates that reoxidation of Cu(I) to Cu(II) is not or at least not the only role of iron(III). Second, deuterium incorporation in the product **2a-D** and recovered **1a-D** was monitored at the middle and end of reactions of the monodeuteriated substrate **1a-D** under both iron and iron-free conditions (Table 3). Deuterium incorporation in recovered **1a-D** was found to decrease to 70% after a reaction time of 2 h when iron(III) was absent, while the deuterium content of the recovered reactant remained unchanged (>95%) when the iron salt was present in the reaction mixture. Analysis of the deuteration rate of 2**a-D** showed that the process was associated with a primary H/D kinetic isotope effect ($k_H/k_D = 2.4$)[16] when iron(III) was present. The results demonstrate that the aromatic C−H activation reaction is reversible and that H−D exchange takes place under the iron-free conditions. In contrast, C−H bond cleavage is the rate-determining step and the process is irreversible in the presence of iron(III).

Table 3. Deuteration Study



cond.	time (h)	**2a-D** (%)[b]	deut. rate of **2a** (%)[c]	**1a-D** (%)[b]	deut. rate of **1a** (%)[c]
A	2	65	71	29	>95
B	2	16	55	81	70
A	18	88	70	0	−
B	18	27	33	−	−

[a] Condition A: **1a-D** (0.5 mmol, D% > 95%), $Cu(OAc)_2$, 50 mol %, $Fe(NO_3)_3 \cdot 9H_2O$ 10 mol %. Condition B: same as condition A but without $Fe(NO_3)_3 \cdot 9H_2O$. [b] Yield of isolated **2**. [c] The deuteration rate was determined by ^1H NMR.

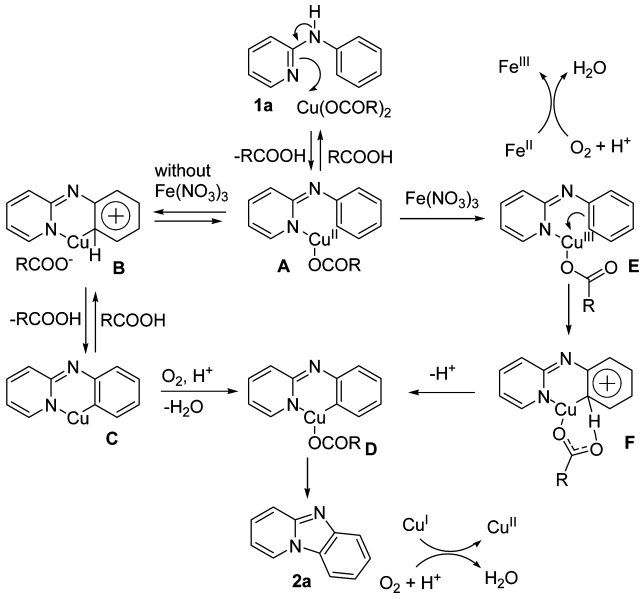
Finally, the relative reactivity of substrates with electron-rich and electron-poor groups was examined.[16] Substrates with electron-donating groups at both of the *meta* and *para* positions of the aniline ring were observed to react faster than those with electron-withdrawing groups at the same positions. However, electron-withdrawing groups in the *meta* position retarded the reaction rate much more than those at the *para* position. The results suggest that an electrophilic aromatic substitution (S_EAr) mechanism is likely operating in this process.[18,5,10]

Based on the above observations, the mechanisms depicted in Scheme 2 are proposed for reactions in the presence and absence of iron salts. In the absence of iron(III), a Cu(II) adduct **A** is formed initially, followed by electrophilic aromatic substitution to form a Cu(II) intermediate **C**. Reversible protonation of **C** occurs before it is oxidized to a reactive Cu(III) intermediate **D**. Reductive elimination delivers the product **2a** with concurrent formation of Cu(I), and Cu(II) is regenerated by O_2 oxidation to close the catalytic cycle.[19]

In the presence of iron(III), the Cu(II) adduct **A** is oxidized to a more electrophilic Cu(III) intermediate **E**,[20] which undergoes the following electrophilic substitution process more readily. Elimination of the aromatic proton yields intermediate **D** via a six-membered transition state **F**. The primary H/D kinetic isotope effect

noted above shows that this step is rate-limiting. Reductive elimination then takes place quickly before reversible protonation occurs.

Scheme 2. Proposed Mechanism with and without Iron Salt



In summary, the results of the studies described above demonstrate the feasibility of a novel and efficient approach for the preparation of pyrido[1,2-*a*]benzimidazoles by using direct intramolecular aromatic C−H amination of *N*-aryl-2-aminopyridines, a process that is cocatalyzed by inexpensive $Cu(OAc)_2$ and $Fe(NO_3)_3 \cdot 9H_2O$. In this process, the pyridinyl nitrogen in the substrates acts as both a directing group and nucleophile. Diversified pyrido[1,2-*a*]benzimidazoles with substituents at different positions are generated in moderate to excellent yields. However, electron-withdrawing substituents in the *meta* position of the aniline ring and any position of the pyridine ring are unfavorable. In addition, mechanistic studies, aimed at uncovering the unique role played by iron(III), were performed. The results suggest that iron(III) aids the reaction by enabling formation of the more electrophilic Cu(III) species which facilitates the subsequent S_EAr process. The unprecedented copper/iron cocatalysis system will undoubtedly extend applications of direct C−H functionalization reactions in which replacement of more expensive metal catalysts is desired.

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Supporting Information Available: Experimental and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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