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$FeCl_3$ catalyzed sp^3 C–H amination: synthesis of aminals with arylamines and amides

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ABSTRACT

A simple and efficient amination of sp^3 C–H bonds adjacent to a nitrogen atom in amides was introduced. The reaction was catalyzed by cheap and low toxic iron salt and used arylamines as nitrogen source. It provides a straightforward construction of acyclic aminals under mild conditions.

C–N bond formation methodologies are intensively investigated, for since nitrogen is a key atom in natural product chemistry, pharmacy, and materials science. Compared with classical transformations that ranged from nucleophilic substitution of a leaving group to reductive amination of carbonyl groups, recently developed direct C–H amination reactions offer a potentially highly atom- and step-economical approach.[1] In the past decades, mainly three methodologies have been developed. One important methodology is direct C–H amination via metal-mediated nitrene intermediates (Scheme 1, route A).[2] In this route, highly active but sufficiently stable species should be required, such as azides,[2a–c] hypervalent iodines,[2d–g] and *N*-tosyloxycarbamates.[2h,i] The second flexible amination method is combined by two steps: direct C–H insertion or C–H activation by transition metals and thereafter coupling with N-atom (Scheme 1, route B).[3] In this route, the C–H bond should sit in a right position to be inserted by a transition metal, mostly under the help of chelating groups[3a–h] or allyl.[3i–m] Recently, a number of excellent oxidative functionalization of sp^3 C–H bonds adjacent to heteroatoms, double bonds, or phenyls has been developed.[4] Amination by this oxidative route is also greatly developed (Scheme 1, route C).[5] These reactions go through single-electron-transfer processes, and are promoted mostly by cheap and low toxic metals (Cu, Fe) or even no metal. Therefore, the route is more economical, simple, and efficient.

Alkylation of amines via oxidative sp^3 C–H bond activations has been reported by many groups. However, most of the amines were limited to amides, sulfonamides, azoles, or anilines with strong electron withdrawing-groups.[6] Alkylation of anilines remains an ongoing challenge. In 2012, Warren group[7] and our group[8] reported the benzylic and allylic C–H amination reactions with anilines. To the best of our knowledge, alkylation of anilines with sp^3 C–H bonds adjacent to a nitrogen atom via oxidative C–H bond activation is rarely realized, although it has been achieved in tandem cyclization reactions.[9] Maybe the acyclic aminals are more unstable than the cyclic ones. Aminal is found in a number of natural products,[10] and is recognized as a surrogate of imine and widely used as electrophile in the metal-catalyzed nucleophilic addition reactions.[11] Classical methods for preparing aminals are condensation reactions of amines with aldehydes. Herein we report a novel and efficient method for synthesizing acyclic aminals by the iron-catalyzed sp^3 C–H amination of lactams with arylamines under mild conditions.

Initially, $FeCl_3$/TBHP was applied to the reaction of aniline **1a** and 1-methylpyrrolidin-2-one **2a**. To our delight, the desired coupling product **3a** was isolated in 76% yield after 8 h at 75 °C (Table 1, entry 1). Elevated or lowered temperature did not give higher yield (Table 1, entries 2 and 3). When the chlorobenzene was added as solvent, the yield was decreased to 38% (Table 1, entry 4). When the reaction was conducted under air, the yield

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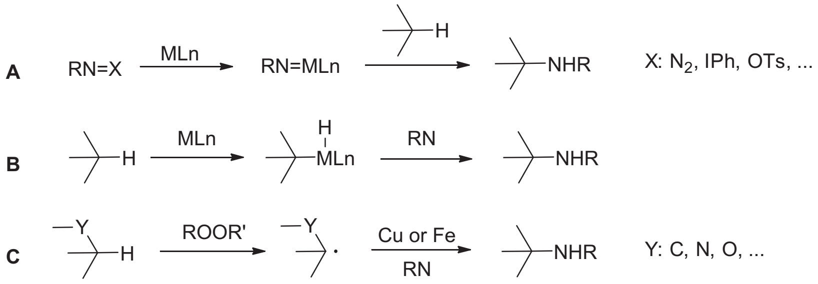
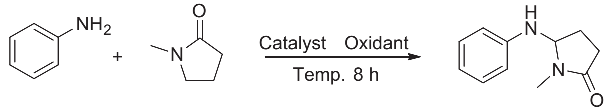


Scheme 1. Routes of C–H amination.

Table 1
Optimization of the reaction conditions[a]



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

Entry	Catalyst	Oxidant (1.5 equiv)	Temp (°C)	Yield[b] (%)
1	$FeCl_3$ (10%)	*t*-BuOOH[c]	75	76
2	$FeCl_3$ (10%)	*t*-BuOOH	60	62
3	$FeCl_3$ (10%)	*t*-BuOOH	100	29
4[d]	$FeCl_3$ (10%)	*t*-BuOOH	75	38
5[e]	$FeCl_3$ (10%)	*t*-BuOOH	75	32
6	—	*t*-BuOOH	75	6
7	$FeBr_3$ (10%)	*t*-BuOOH	75	41
8	$FeCl_3·6H_2O$ (10%)	*t*-BuOOH	75	47
9	$FeCl_2$ (10%)	*t*-BuOOH	75	51
10	$FeCl_2·4H_2O$ (10%)	*t*-BuOOH	75	41
11	$FeSO_4·7H_2O$ (10%)	*t*-BuOOH	75	43
12	$FeCl_2$ (3%)	*t*-BuOOH	75	73
13	$FeCl_2$ (1%)	*t*-BuOOH	75	69
14	$FeCl_3$ (3%)	*t*-BuOOH	75	63
15	CuBr (10%)	*t*-BuOOH	75	33
16	$Cu(OTf)_2$ (10%)	*t*-BuOOH	75	41
17	$ZrCl_4$ (10%)	*t*-BuOOH	75	22
18	$FeCl_3$ (10%)	(*t*-BuO)$_2$	75	9
19	$FeCl_3$ (10%)	30% H_2O_2	75	6
20	$FeCl_3$ (10%)	O_2	75	Trace

[a] Reaction conditions: Catalyst (0.05 mmol), oxidant (0.75 mmol), and substrate **1a** (0.5 mmol) in **2a** (2.0 mL, used as solvent also) for 8 h under nitrogen atmosphere.

[b] Isolated yield.

[c] 5-6 M in water.

[d] **2a** was 1.0 mmol and chlorobenzene is solvent.

[e] Under air atmosphere.

was sharply reduced (Table 1, entry 5). As a radical scavenger, O_2 may block this reaction. If no $FeCl_3$ was added, only 6% yield was obtained (Table 1, entry 6). Subsequently, other iron catalysts, such as $FeBr_3$, $FeCl_3·6H_2O$, $FeCl_2$, $FeCl_2·4H_2O$, and $FeSO_4·7H_2O$, were examined. No better than $FeCl_3$ catalyst was found (Table 1, entries 7–11). In view of Fe^{2+}/TBHP system well known as radical initiator combination in radical alkylation, we reduced the dosage of $FeCl_2$ from 10% to 3%. To our delight, the yield was increased from 51% to 73% (Table 1, entry 12). When the dosage of $FeCl_2$ was further reduced to 1%, the yield was lowered also (Table 1, entry 13). Reducing the amount of $FeCl_3$ to 3%, the yield was lower than $FeCl_2$'s (Table 1, entry 14). Other metal catalysts, such as CuBr, $Cu(OTf)_2$, and $ZrCl_4$, did not give a higher yield than $FeCl_3$ (Table 1, entries 15–17). Taking economic factor into account, $FeCl_3$ was selected as the best catalyst. Then a lot of oxidants were studied to enhance the yield of **3a** (Table 1, entries 18–20). No better than TBHP oxidant was found. Eventually, the satisfactory reaction conditions were: using the $FeCl_3$/TBHP as the oxidative system and carrying out the reaction at 75 °C under nitrogen atmosphere.

With the optimized reaction conditions in hand, we selected some substituted arylamines **1** to react with 1-methylpyrrolidin-2-one **2a** to explore the scope of the method (Table 2). Anilines with electron-donating groups did not work well (Table 2, entries 2–4). 4-Methoxyaniline **1d** only gave the corresponding product **3d** in 29% yield after the reaction temperature was reduced to 40 °C. Maybe the anilines or the corresponding products with electron-donating groups were not stable in this oxidizing reaction system. Anilines with electron-withdrawing groups worked comparatively well, and moderate yields were obtained (Table 2, entries 5–12). When *N*-methylaniline **1m** reacted with **2a**, the desired products **3m** was obtained in 20% yield, although *N*-de-alkylated product **3a** was isolated in 39% yield (Table 2, entry 13). Subsequently, the scope of the present transformation was further examined using different amides to react with aniline **1a**. 1-Ethylpyrrolidin-2-one **2b** and pyrrolidin-2-one **2c** gave the desired products in moderate yields (Table 2, entries 14 and 15). When the aniline **1a** and acyclic amide **2d** were treated with 1.0 equiv of NEt_3 in 90 °C, the desired product was also obtained in 50% yield after 3 h (Table 2, entry 16).

In this reaction, there should be two products, methylene C–H amination and methyl C–H amination products. However, the methylene C–H amination product is the major one. Maybe the secondary carbon radical intermediate was more stable than the primary carbon radical intermediate. When **1j** and **1k** reacted with **2a**, some methyl amination products **3j**′ and **3k**′ were generated (Table 2, entries 10 and 11). From ^1H NMR spectra the ratio of **3j** and **3j**′ could be determined as 17:3, and the **3k** and **3k**′ as 2:1.

According to all the above results, a plausible mechanism was proposed as shown in Scheme 2. Under the help of Fe^{2+} catalyst, TBHP was decomposed into *tert*-butoxyl radical and hydroxyl anion.[12] The *tert*-butoxyl radical abstracted an α-hydrogen atom and **A** was generated. The Fe^{3+} further oxidized **A** to give the iminium ion **B**. Nucleophilic addition of **2a** to **B** produced the desired coupling product **3a**.

In summary, we have introduced a simple and efficient methodology for the amination of sp^3 C–H bonds adjacent to a nitrogen atom in amides using arylamines. This reaction was catalyzed by cheap and low toxic $FeCl_3$ and used arylamines as nitrogen source. It provides a straightforward construction of acyclic aminals under mild conditions.

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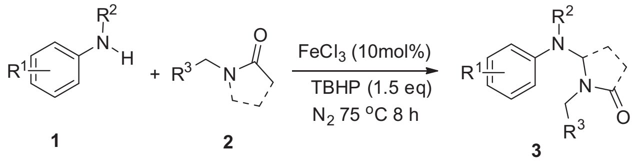
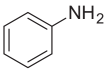
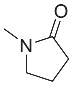
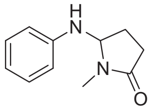
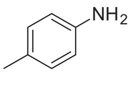
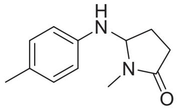
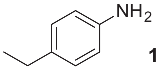
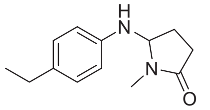
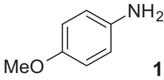
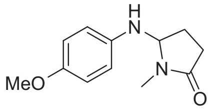
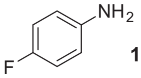
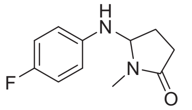
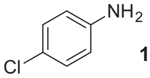
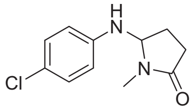
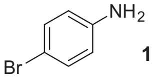
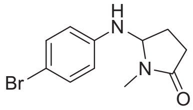
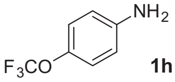
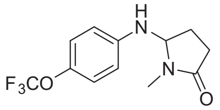
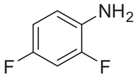
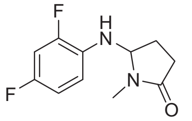
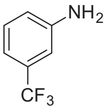
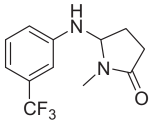
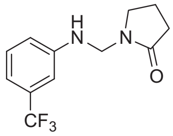
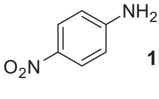
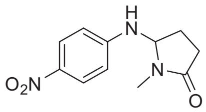
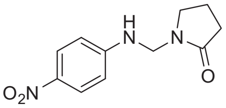
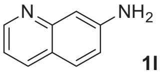
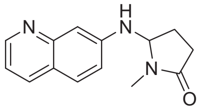
Table 2
Synthesis of aminals **3** with arylamines **1** and amides **2**[a]



Entry	1	2	3	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	76
2	 **1b**	**2a**	 **3b**	37
3	 **1c**	**2a**	 **3c**	42
4[c]	 **1d**	**2a**	 **3d**	29
5	 **1e**	**2a**	 **3e**	63
6	 **1f**	**2a**	 **3f**	67
7	 **1g**	**2a**	 **3g**	81
8	 **1h**	**2a**	 **3h**	55
9	 **1i**	**2a**	 **3i**	50
10	 **1j**	**2a**	 +  **3j** **3j'**	60 (**3j**:**3j′** = 17:3)
11	 **1k**	**2a**	 +  **3k** **3k'**	56 (**3k**:**3k′** = 2:1)
12	 **1l**	**2a**	 **3l**	62

(*continued on next page*)

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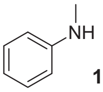
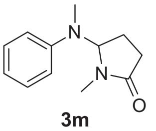
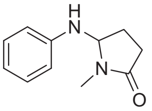
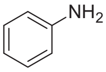
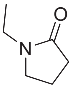
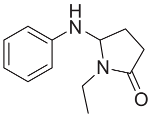
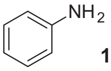
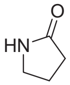
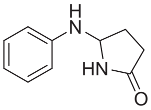
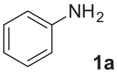
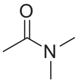
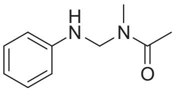
Table 2 (*continued*)

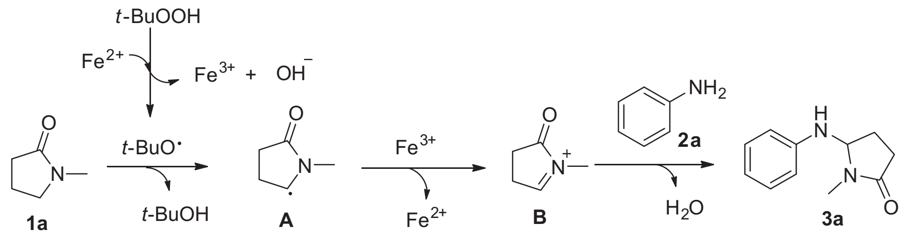
Entry	1	2	3	Yield[b] (%)
13	 **1m**	**2a**	 +  **3m** **3a**	**3m**:20 **3a**:39
14	 **1a**	 **2b**	 **3n**	52
15	 **1a**	 **2c**	 **3o**	53
16[d]	 **1a**	 **2d**	 **3p**	50

[a] Reaction conditions: FeCl$_3$ (0.05 mmol), TBHP (0.75 mmol, 5–6 M in water), and substrate **1** (0.5 mmol) in **2a** (2.0 mL, used as solvent also) in 75 °C for 8 h under nitrogen atmosphere.

[b] Isolated yield.

[c] The temperature is 40 °C.

[d] The reaction was conducted in 90 °C for 3 h with the additive of NEt$_3$ (0.5 mmol).



Scheme 2. A plausible mechanism.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.043.

References and notes

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