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Iron-catalyzed aerobic oxidative amidation of tertiary amines with carboxylic acids

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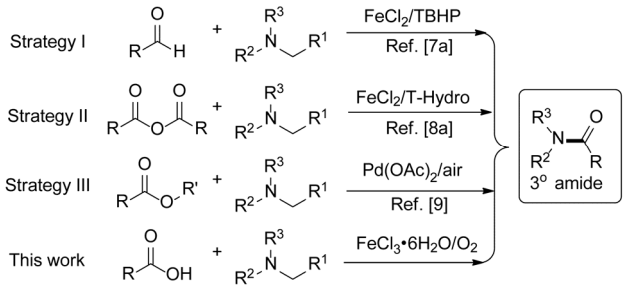
An oxidative amidation of tertiary amines with carboxylic acids has been developed in the presence of $FeCl_3 \cdot 6H_2O$ as catalyst and oxygen as oxidant. A variety of tertiary amides were obtained in good to excellent yields from inexpensive and readily available reagents. The possible reaction pathways were investigated.

amidation, tertiary amine, carboxylic acid, iron catalysis, oxidation

1 Introduction

Amide bond formation is one of the most often used reactions in the synthesis of natural products, pharmaceuticals and fine chemicals [1], because amide groups were contained in more than 25% of the known drugs contain in a survey [2]. The traditional method for the synthesis of amides is through the condensation of carboxylic acid and amine. The aid of coupling reagents usually results in mild reaction conditions and good yields. Recently, many catalytic transformations for the amide bond formation have been successfully developed, using alcohols [3], aldehydes [4], nitriles [5] and aryl halides [6] as carbonyl sources. Despite the rapid progress made using different carbonyl sources in recently years, the development of amide formation from tertiary amines is limited [7,8].

As tertiary amines are widely found in nature products and easily available from chemical companies, the development of amide formation from tertiary amines provides an attractive alternative (Scheme 1) [9]. Recently, we have demonstrated a new protocol for amide formation by an unconventional oxidative amidation between tertiary amines and aldehydes in the presence of a simple iron catalyst (Strategy I) [7a]. Furthermore, the application of anhydrides as acylation reagents successfully overcomes the decarbonylation problem of aliphatic aldehydes in Strategy I (Strategy II) [8a]. Recently, Bao and coworkers [9a] disclosed a novel reactions of perfluorophenyl carboxylates with tertiary amines by using $Pd(OAc)_2$ as catalyst and air as oxidant (Strategy III). However, the use of the expensive reagents limited the application of the method in amide synthesis. Therefore, a practical method for amide bond synthesis from tertiary amines is still highly desirable and valuable [10,11]. Herein, we wish to report an oxidative amidation of tertiary amines with carboxylic acids in the presence of simple iron salt as catalyst and oxygen as oxidant. The present study is complementary to amide synthesis



Scheme 1 Strategies for the amidation of tertiary amines.

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from tertiary amines, in which various carbonyl sources could be applied for tertiary amide synthesis.

2 Experimental

2.1 General information

^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometer (Switzerland) and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained at Bruker 100 MHz and referenced to the internal solvent signals (central peak is 77.0 ppm in $CDCl_3$). $CDCl_3$ was used as the NMR solvent. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. APEX II (Bruker Inc., Switzerland) was used for HR-MS and ESI-MS. IR spectra were recorded by a Nicolet 5MX-S infrared spectrometer (Thermo Electron, USA). Flash column chromatography was performed over silica gel 200–300. All reagents were weighed and handled in air at room temperature. Unless otherwise noted, all reactions were performed under a nitrogen atmosphere. All reagents were purchased from Alfa (USA), Acros (Belgium), Aldrich (USA), and TCI (Japan) and used without further purification.

2.2 Synthesis and characterization of the products 3

To a mixture of amine **1** (0.5 mmol), pivalic anhydride (1.0 mmol), carboxylic acid **2** (1.0 mmol), and $FeCl_3 \cdot 6H_2O$ (0.1 mmol), toluene (2.0 mL) was added under nitrogen at room temperature. Nitrogen flow was closed and oxygen was then introduced into the Schlenk tube via a needle from an oxygen balloon. The resulting mixture was stirred under 85 °C for 24 h. The temperature of reaction was cooled to room temperature and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether (*v*/*v*=1:10) as an eluent to afford the pure product **3** [8].

2.2.1 *N*-methyl-*N*-(*p*-tolyl)hexanamide (**3a**)

Isolated by flash column chromatography (ethyl acetate/petroleum ether, *v*/*v*=1:2, R_f=0.4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J*=8.0 Hz, 2H), 7.05 (d, *J*=8.2 Hz, 2H), 3.24 (s, 3H), 2.38 (s, 3H), 2.06 (t, *J*=7.6 Hz, 2H), 1.63–1.49 (m, 2H), 1.27–1.05 (m, 4H), 0.83 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 141.6, 137.4, 130.2, 127.0, 37.2, 33.9, 31.4, 25.2, 22.3, 21.0, 13.8 (see the Supporting Information online).

2.2.2 *N*-methyl-*N*-(*p*-tolyl)acetamide (**3b**)

Isolated by flash column chromatography (ethyl acetate/petroleum ether, *v*/*v*=1:2, R_f=0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J*=7.8 Hz, 2H), 7.04 (d, *J*=7.6 Hz, 2H), 3.21 (s, 3H), 2.35 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 142.0, 137.5, 130.2, 126.7, 37.1, 22.2, 20.9.

2.2.3 *N*-methyl-*N*-(*p*-tolyl)propionamide (**3c**)

Isolated by flash column chromatography (ethyl acetate/petroleum ether, *v*/*v*=1:2, R_f=0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J*=8.0 Hz, 2H), 7.06 (d, *J*=8.1 Hz, 2H), 3.24 (s, 3H), 2.37 (s, 3H), 2.08 (q, *J*=7.4 Hz, 2H), 1.04 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 141.6, 137.6, 130.3, 127.0, 37.3, 27.4, 21.0, 9.7.

2.2.4 *N*-methyl-*N*-(*p*-tolyl)benzamide (**3d**)

Isolated by flash column chromatography (ethyl acetate/petroleum ether, *v*/*v*=1:2, R_f=0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2H), 7.23 (m, 1H), 7.17 (m, 2H), 7.01 (d, *J*=8.1 Hz, 2H), 6.91 (d, *J*=8.2 Hz, 2H), 3.47 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 142.3, 136.2, 129.8, 129.7, 129.4, 128.6, 127.6, 126.6, 38.4, 20.9.

2.2.5 *N*,4-dimethyl-*N*-(*p*-tolyl)benzamide (**3e**)

Isolated by flash column chromatography (ethyl acetate/petroleum ether, *v*/*v*=1:2, R_f=0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J*=8.1 Hz, 2H), 7.01 (d, *J*=8.2 Hz, 2H), 6.96 (d, *J*=7.9 Hz, 2H), 6.92 (d, *J*=8.3 Hz, 2H), 3.46 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 142.5, 139.6, 136.1, 132.9, 129.7, 128.8, 128.3, 126.6, 38.6, 21.3, 20.9.

2.2.6 *N*-methyl-4-nitro-*N*-(*p*-tolyl)benzamide (**3f**)

Isolated by flash column chromatography (ethyl acetate/petroleum ether, *v*/*v*=1:2, R_f=0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J*=8.6 Hz, 2H), 7.45 (d, *J*=8.6 Hz, 2H), 7.02 (d, *J*=7.8 Hz, 2H), 6.91 (d, *J*=7.8 Hz, 2H), 3.49 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 147.8, 142.2, 141.1, 137.2, 130.1, 129.4, 126.6, 122.9, 38.2, 20.8.

2.2.7 *N*-methyl-*N*-(*p*-tolyl)cyclopentanecarboxamide (**3g**)

Isolated by flash column chromatography (ethyl acetate/petroleum ether, *v*/*v*=1:2, R_f=0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J*=8.1 Hz, 2H), 7.10 (d, *J*=8.2 Hz, 2H), 4.32 (m, 1H), 4.08–3.99 (m, 1H), 3.86–3.75 (m, 1H), 3.24 (s, 3H), 2.38 (s, 3H), 2.10–1.96 (m, 2H), 1.91–1.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 140.5, 137.8, 130.2, 127.2, 74.7, 69.4, 37.7, 30.1, 25.9, 21.0.

2.2.8 *N*-methyl-*N*-(*p*-tolyl)cyclopentanecarboxamide (**3h**)

Isolated by flash column chromatography (ethyl acetate/petroleum ether, *v*/*v*=1:2, R_f=0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J*=8.1 Hz, 2H), 7.04 (d, *J*=8.1 Hz, 2H), 3.21 (s, 3H), 2.38, (s, 3H), 2.28–2.33 (m, 1H), 1.41–1.57 (m, 1H), 0.90–1.01 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

182.1, 141.6, 137.5, 130.3, 126.9, 41.3, 37.5, 28.8, 26.9, 25.3.

2.2.9 *N*-(4-bromophenyl)-*N*-methylacetamide (**3i**)

Isolated by flash column chromatography (ethyl acetate/ petroleum ether, *v*/*v*=1:5, R_f=0.1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J*=8.4 Hz, 2H), 7.05 (d, *J*=8.4 Hz, 2H), 3.20 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 143.4, 132.8, 128.7, 121.2, 37.0, 22.3.

2.2.10 *N*-(4-(acetamidomethyl)phenyl)-*N*-methylacetamide (**3j**)

Isolated by flash column chromatography (ethyl acetate/ petroleum ether, *v*/*v*=1:5, R_f=0.1). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.34 (d, *J*=7.8 Hz, 2H), 7.16 (t, *J*=10.8 Hz, 2H), 6.54 (s, 1H), 4.45 (d, *J*=5.1 Hz, 2H), 3.20 (s, 3H), 2.03 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.2, 143.5, 138.2, 129.0, 127.1, 42.9, 37.1, 23.1, 22.3.

2.2.11 *N*-ethyl-*N*-phenylacetamide (**3k**)

Isolated by flash column chromatography (ethyl acetate/ petroleum ether, *v*/*v*=1:1, R_f=0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J*=7.5 Hz, 2H), 7.32 (t, *J*=7.3 Hz, 1H), 7.13 (d, *J*=7.3 Hz, 2H), 3.72 (t, *J*=7.2 Hz, 2H), 1.79 (s, 3H), 1.08 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 142.8, 129.6, 128.1, 127.8, 43.7, 22.8, 13.0.

2.2.12 *N*-(3-chlorophenyl)-*N*-methylacetamide (**3l**)

Isolated by flash column chromatography (ethyl acetate/ petroleum ether, *v*/*v*=1:1, R_f=0.4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 2H), 7.19 (s, 1H), 7.08 (d, *J*=7.4 Hz, 1H), 3.20 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ170.1, 145.6, 135.0, 130.6, 127.9, 127.4, 125.3, 77.3, 77.0, 76.7, 37.0, 22.4.

2.2.13 8-Acetyl-8-azabicyclo[3.2.1]octan-3-one (**3m**)

Isolated by flash column chromatography (ethyl acetate/ petroleum ether, *v*/*v*=1:1, R_f=0.3) [8]. ^{1}H NMR (400 MHz, $CDCl_3$) δ4.96–4.80 (m,1H), 4.44–4.33 (m, 1H), 2.76–2.62 (m, 1H), 2.58–2.47 (m, 1H), 2.46–2.27 (m, 2H), 2.22–1.93 (m, 5H), 1.83–1.71 (m, 1H), 1.70–1.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ207.1, 167.0, 54.3, 50.7, 49.5, 48.7, 29.8, 27.9, 21.5.

2.2.14 *N*-methyl-*N*-phenylacetamide (**3n**)

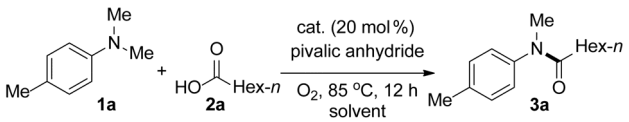
Isolated by flash column chromatography (ethyl acetate/ petroleum etner, *v*/*v*=1:1, R_f=0.3) [8]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J*=7.6 Hz, 2H), 7.31 (t, *J*=7.3 Hz, 1H), 7.16 (d, *J*=7.4 Hz, 2H), 3.24 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ170.4, 144.5, 129.6, 127.3, 127.0, 37.0, 22.3.

3 Results and discussion

The reaction of 4-methyl-*N*,*N*-dimethylaniline **1a** with heptanoic acid **2a** was chosen as a model reaction to establish the reaction conditions (Table 1). First, a variety of metal salts were screened by the use of oxygen as oxidant (Entries 1–6). $FeCl_3 \cdot 6H_2O$ was found to be the best catalyst for the present oxidative amidation (Entry 1). The increasing amount of **2a** further improved the yield of **3a** to 67% yield (Entry 7). Next, the effect of solvents was investigated and other tested solvents such as DCE, H_2O and MeCN obviously retarded the efficiency of the desired transformation (Entries 8–10). Importantly, a 51% yield of **3a** was still achieved even in the presence of 2 mol% of $FeCl_3 \cdot 6H_2O$ (Entry 11). Finally, a 71% yield of **3a** was obtained when the reaction time was prolonged to 24 h (Entry 12). It is worth mentioning that only trace amount of **3a** (<5%) was observed in the absence of iron catalyst, indicating that iron catalyst is important in this reaction (Entry 13).

Subsequently, the scope of the substrates were investigated under the optimized reaction conditions (Tables 2 and 3). A range of carboxylic acids were examined and the results were shown in Table 2. To our satisfaction, both aliphatic and aromatic acids could be applied in this transformation. Good to excellent yields of aliphatic acids were reacted efficiently with **1a** (Entries 1 and 2). Moreover, various benzoic acid derivatives also reacted smoothly with **1a** (Entries 3–5). Benzoic acid with electron-donating group reacted efficiently with **1a** (Entry 4), whereas electron-withdrawing groups on the benzene ring reduced the efficiency of the oxidative amidation (Entry 5). Furthermore, the reaction of tetrahydrofuran-2-carboxylic acid **2h** with **1a** also led to the corresponding amide **3g**, albeit in a lower yield (Entry 6). And cyclohexanecarboxylic acid with **1a**

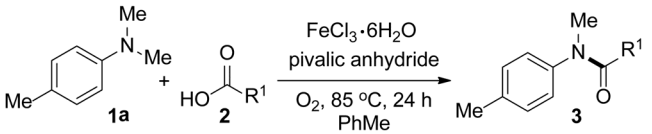
Table 1 Optimization of the reaction conditions [a]

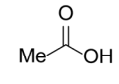
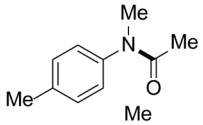
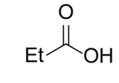
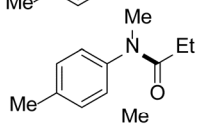
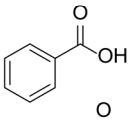
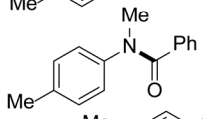
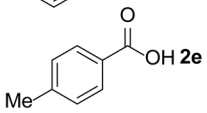
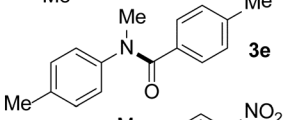
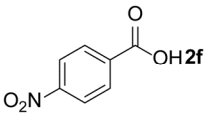
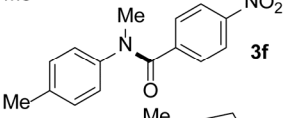
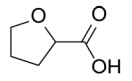
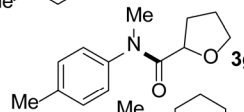
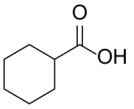
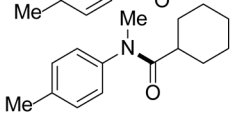


Entry	Cat.	**2a** (equiv.)	Solvent	**3a** (%) [b]
1	$FeCl_3 \cdot 6H_2O$	1.0	PhMe	61(60)
2	$FeSO_4 \cdot 7H_2O$	1.0	PhMe	29(27)
3	$FeCl_3$	1.0	PhMe	51(51)
4	$FeCl_2$	1.0	PhMe	19(19)
5	$CoCl_2$	1.0	PhMe	39(37)
6	$CuCl_2$	1.0	PhMe	43(43)
7	$FeCl_3 \cdot 6H_2O$	2.0	PhMe	67(66)
8	$FeCl_3 \cdot 6H_2O$	2.0	DCE	<5
9	$FeCl_3 \cdot 6H_2O$	2.0	H_2O	15(15)
10	$FeCl_3 \cdot 6H_2O$	2.0	MeCN	10(10)
11 [c]	$FeCl_3 \cdot 6H_2O$	2.0	PhMe	51(50)
12 [d]	$FeCl_3 \cdot 6H_2O$	2.0	PhMe	71(71)
13		2.0	PhMe	<5

a) Conditions: **1a** (0.5 mmol), cat. (0.1 mmol), pivalic anhydride (1.0 mmol), O_2 balloon, and solvent (2 mL); unless otherwise noted; b) detected by ^{1}H NMR and based on **1a**, isolated yields were given in parentheses; c) $FeCl_3 \cdot 6H_2O$ (0.01 mmol); d) 24 h.

Table 2 Amidation of carboxylic acid with **1a** [a]

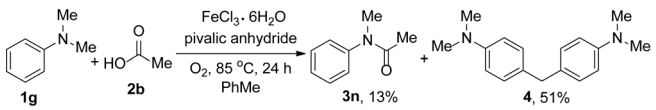


Entry	2	3	Yield [b]
1	 **2b**	 **3b**	89%
2	 **2c**	 **3c**	85%
3	 **2d**	 **3d**	50%
4	 **2e**	 **3e**	79%
5	 **2f**	 **3f**	50%
6	 **2h**	 **3g**	30%
7	 **2i**	 **3h**	51%

a) Conditions: **1a** (0.5 mmol), pivalic anhydride (1.0 mmol), **2** (1.0 mmol), $FeCl_3 \cdot 6H_2O$ (0.01 mmol), PhMe (2 mL) under oxygen; unless otherwise noted; b) isolated yields.

gave 51% yield of **3h** (Entry 7).

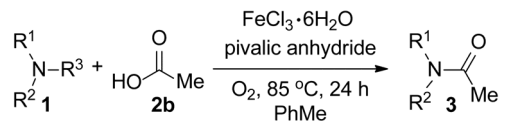
Furthermore, other tertiary amine derivatives were investigated by the use of acetic acid **2b** as a model acylation reagent under the optimized conditions (Table 3). Aniline with electron-withdrawing and electron-donating group such as **1b** and **1c** reacted smoothly with **2a** (Entries 1 and 2). Importantly, *N*,*N*-diethylaniline **1d** also reacted with **2a** smoothly to give the corresponding tertiary amide in a 53% yield (Entry 3). Substituent at meta-phenyl ring reduced the efficiency of the reaction due to the dimerization of **1e** (Entry 4). To our delight, the reaction of tropinone with acetic acid gave a 55% yield of **3l** (Entry 5). However, the reaction of *N*,*N*-dimethylaniline **1g** with **2b** led to **3n** and **4** in 13% and 51% yields, respectively (Eq. (1)) [12]:

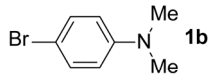
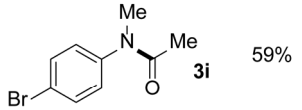
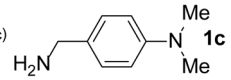
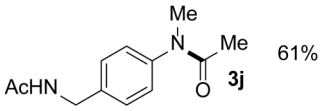
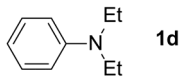
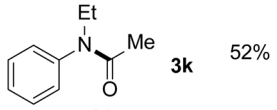
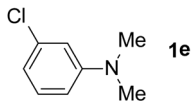
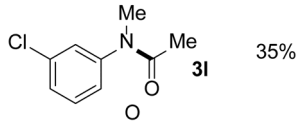
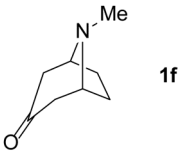
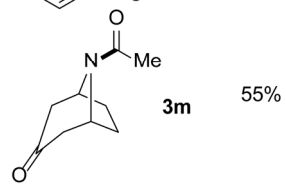


(1)

In order to clarify the possible reaction pathways, the

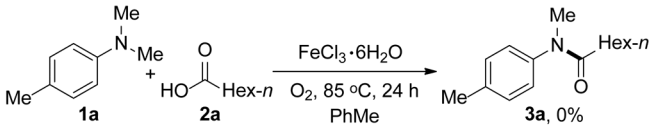
Table 3 Amidation of tertiary amines with acetic acid [a]



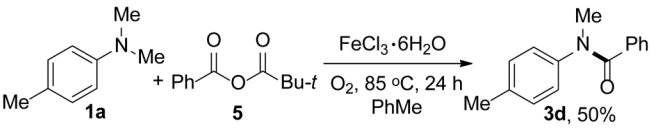
Entry	1	3	Yield [b]
1	 **1b**	 **3i**	59%
2 [c]	 **1c**	 **3j**	61%
3	 **1d**	 **3k**	52%
4	 **1e**	 **3l**	35%
5	 **1f**	 **3m**	55%

a) Conditions: **1** (0.5 mmol), pivalic anhydride (1.0 mmol), **2a** (1.0 mmol), $FeCl_3 \cdot 6H_2O$ (0.01 mmol), PhMe (2 mL) under oxygen; unless otherwise noted; b) isolated yields; c) pivalic anhydride (2.0 mmol), **2a** (2.0 mmol).

role of pivalic anhydride was studied. The amide **3a** was not detected by ^{1}H NMR in the absence of pivalic anhydride (Eq. (2)). Furthermore, when 2.0 equivalent of benzoic pivalic anhydride **5** [13] was added into the reaction under our standard conditions, the desired product **3d** was obtained in a 50% yield (Eq. (3)). The results indicated that a mixed anhydride like **5** generated by the reaction of carboxylic acid **2** with pivalic anhydride in situ acts an active acylation reagent.

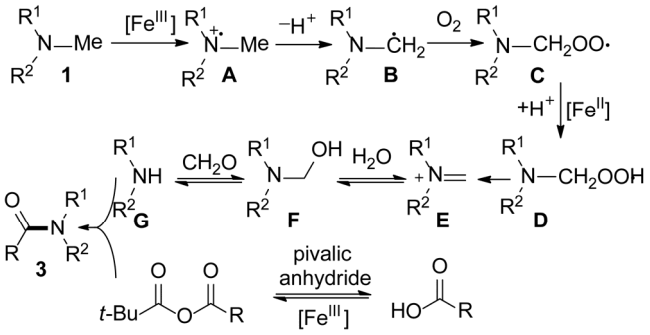


(2)



(3)

Accordingly, a tentative mechanism for the present transformation is proposed (Scheme 2). The oxidation of amine **1** gives amine radical **A**. Followed by the deprotonation, an



Scheme 2 A tentative mechanism for iron-catalyzed aerobic oxidative amidation of tertiary amines with carboxylic acids.

α-amino radical **B** is generated [14]. The termination of **B** with molecular oxygen furnishes a peroxide intermediate **C** [9b,9c], followed by the reduction to furnish a peroxide intermediate **D**. The iminium intermediate **E** can be formed via the elimination of **D**. Then the secondary amine **G** is formed by hydrolysis of **E** via **F**. Finally, the in situ generated **G** immediately reacts with the mixed anhydride which is formed by carboxylic acids with pivalic anhydride to give the desired amide **3**. It is worthwhile to note that: (1) iron catalyst most likely also plays an important role as Lewis acid catalyst for the formation of the mixed anhydride in the last step, because ferric iron salts showed higher activity than ferrous irons (Table 1, Entries 1–4); (2) the rapid reaction of **G** and mixed anhydride ensures the equilibrium toward the **G** formation efficiently and prevent excessive oxidation of secondary amine **G** [8a].

4 Conclusions

In summary, a new and practical method for the synthesis of tertiary amide had been developed. Carboxylic acid was successfully applied as an acylation reagent in the oxidative amidation of tertiary amines, which presents a complement to the previous method. The method is also highlighted by the use of $FeCl_3 \cdot 6H_2O$ as catalyst and oxygen as oxidant.

Supporting information

The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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