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Reductive amination of tertiary anilines and aldehydes†

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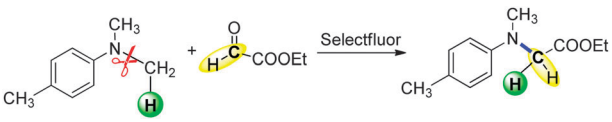
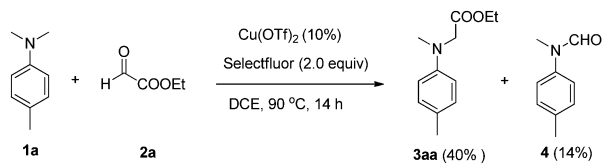
An unprecedented oxidant-mediated reductive amination of tertiary anilines and aldehydes without external reducing agents was developed *via* the nucleophilic attack of the oxygen atom of the carbonyl group to *in situ* generated iminium ions, in which tertiary anilines were used as both nitrogen source and reducing agent for the first time.

In the context of the synthesis of natural products,[1] bioactive compounds[2] or materials,[3] the development of novel C–N bond formation methodologies is a very important research field.[4] The reductive amination of amines and aldehydes or ketones constitutes one of the most efficient and direct routes to construct C–N bonds.[5] Primary or secondary amines have been successfully installed into the corresponding substrates *via* condensation and subsequent reduction,[5] whereas tertiary amines as nitrogen sources have rarely been studied in this area.[6] Harsh conditions were required for the additional C–N bond cleavage even in the presence of a transition-metal. For example, in 2002, Cho's group[6a] described ruthenium-catalyzed reductive amination of aldehydes with tertiary amines under a 10 atm CO atmosphere at 180 °C. In addition to nitrogen sources, reducing agents are also important factors in reductive amination. Over the past few decades, significant progress has been achieved,[5,7–9] in which internal reducing agents[7–9] are highly attractive because they make this procedure much more economical and environmentally friendly. Recently, Seidel's group[7,8] and Tunge's group[9] independently reported reductive amination of primary or secondary amines and aldehydes or ketones by employing tertiary amines (contained in substrates or *in situ* generated) to reduce carbonyl groups. Therefore, we envisaged that directly utilizing tertiary amines as both nitrogen source[6] and reducing agent[7–9] will provide a new method for reductive amination. Herein, Selectfluor-mediated, the first metal-free reductive amination of tertiary anilines and aldehydes was presented (Scheme 1).

Recently, we have developed various metal catalyzed C–N bond formation reactions directly from C–H bonds.[10] As part of our continuing effort towards the development of methodologies to construct C–N bonds,[11] we attempted amination of aldehydes and tertiary anilines.[12] Initially, we tested the reaction between *N*,*N*,4-trimetylanilide (**1a**, 0.4 mmol) and ethyl glyoxylate (**2a**, 0.8 mmol, 2.0 equiv.) in the presence of $Cu(OTf)_2$ (10%) and Selectfluor (0.8 mmol, 2.0 equiv.) in dichloroethane (DCE) under an air atmosphere eqn (1). After the reaction was performed at 90 °C for 14 hours, the *N*-methyl amino acid (NMA) derivative **3aa** was obtained in 40% yield along with 14% *N*-methyl-*N*-*p*-tolylformamide (**4**). Interestingly, when the reaction was performed under the same conditions but without employing the copper catalyst, similar results were obtained.



Scheme 1 Selectfluor-mediated reductive amination of tertiary anilines and aldehydes.



(1)

Encouraged by the successful synthesis of NMA derivatives widely existing in natural products and proteins,[13] we pursued our investigation with the metal-free reductive amination reaction condition screening (Table 1). Gratifyingly, under nitrogen atmosphere in anhydrous DCE, the desired product **3aa** was obtained in 72% yield and no oxidation product **4** was detected (Table 1, entry 1). In the absence of Selectfluor, no reaction occurred (Table 1, entry 2). With other F^+ reagents, such as *N*-fluoro-2,4,6-trimethylpyridinium tetrafluorobrate, *N*-fluoropyridinium tetrafluorobrate and *N*-fluoro-2,4,6-trimethylpyridinium triflate, **3aa** was obtained in 21%, 41% and 16% yields, respectively (Table 1, entries 3–5). When *N*-fluorobenzenesulfonimide (NFSI) was used as the oxidant, no desired **3aa** was obtained (Table 1, entry 6). Using other oxidants, such as *tert*-butyl hydroperoxide

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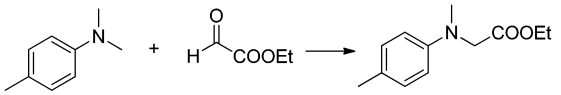
Table 1 Optimization of reaction conditions[a]



1a 2a 3aa

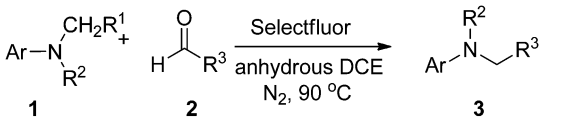
Entry	Oxidant	Solvent	Time (h)	Yield[b] (%)
1	Selectfluor	DCE	13	72
2	None	DCE	18	0
3	F^{+c}	DCE	12	21
4	F^{+d}	DCE	12	41
5	F^{+e}	DCE	12	16
6	NFSI	DCE	4	0
7	TBHP	DCE	4	0
8	O_2	DCE	18	0
9	$PhI(OAc)_2$	DCE	4	Trace
10	Selectfluor	THF	9	32
11	Selectfluor	DMF	9	Trace
12	Selectfluor	Toluene	9	Trace
13	Selectfluor	Acetonitrile	9	0
14[f]	**Selectfluor**	**DCE**	**9**	**79**

[a] Reactions were carried out with **1a** (0.4 mmol), **2a** (0.8 mmol, 2.0 equiv.), and oxidant (0.8 mmol, 2.0 equiv.) in 4 mL anhydrous solvent under nitrogen atmosphere at 90 °C unless specially mentioned. [b] Yield of the isolated product. [c] *N*-Fluoro-2,4,6-trimethylpyridinium tetrafluorobrate was used. [d] *N*-Fluoropyridinium tetrafluorobrate was used. [e] *N*-Fluoro-2,4,6-trimethylpyridinium triflate was used. [f] 1.6 mmol (4.0 equiv.) **2a** was used.

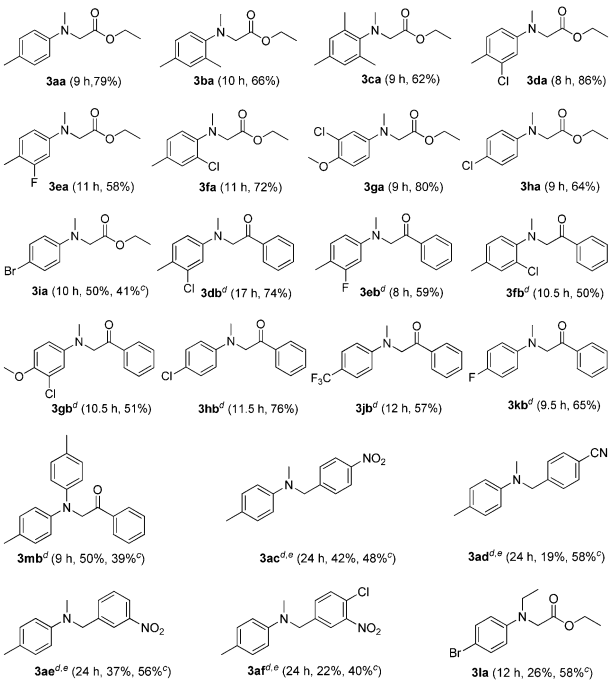
(TBHP) and O_2, the reaction could not occur (Table 1, entries 7 and 8). Changing the oxidant to $PhI(OAc)_2$, a trace amount of **3aa** was observed (Table 1, entry 9). With tetrahydrofuran (THF) as the solvent, **3aa** was obtained in 32% yield (Table 1, entry 10). Other solvents, for example, toluene and *N*,*N*-dimethylmethanamide (DMF), only gave a trace amount of **3aa** (Table 1, entries 11 and 12). Acetonitrile was not effective and no reaction occurred (Table 1, entry 13). Satisfactorily, upon increasing the feedstock of **2a** to 4.0 equiv. (1.6 mmol), the yield of **3aa** was increased to 79% (Table 1, entry 14).

With the optimized conditions in hand (Table 1, entry 14), the scope of the reductive amination was then examined and the results are summarized in Table 2. The reaction of ethyl glyoxylate (**2a**) with a variety of *p*-substituted *N*,*N*-dimethylaniline[14] **1a**–**1i** having an electron-donating group or an electron-withdrawing group could afford the corresponding NMA derivatives **3aa**–**3ia** in 50–86% yields. Notably, Cl and Br substituents on the phenyl ring were well tolerated, which offers an opportunity for further functionalization. With triethylamine as the substrate, no desired reductive amination product was obtained. Next, the scope of this reaction was investigated with respect to aldehydes **2**. Pleasingly, the reactions of 2-oxo-2-phenylacetaldehyde (**2b**) with tertiary anilines **1** could proceed smoothly and provided α-amino ketone derivatives constituting an important class of biologically active compounds.[15,16] Starting from tertiary anilines **1d**–**1h**, **1j**, **1k** and **1m**, α-amino ketones derivatives **3db**–**3hb**, **3jb**, **3kb** and **3mb** were obtained in 50–76% yields. No reaction occurred when 2-oxoacetic acid, 2-oxopropanal or 1-phenylpropane-1,2-dione was used as the substrate. It should be noteworthy that this reductive amination reaction provided an alternative efficient approach to obtain NMA[17] and α-amino ketone[18] derivatives. Furthermore, the new reductive amination protocol was applied to aromatic aldehydes, such as 4-nitrobenzaldehyde (**2c**), 4-formylbenzonitrile (**2d**), 3-nitrobenzaldehyde (**2e**) and 4-chloro-3-nitrobenzaldehyde (**2f**). The desired products **3ac**–**3af** could be obtained although the yields were relatively

Table 2 The scope of reductive amination reaction[a,b]



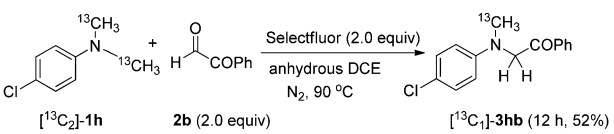
1 2 3



[a] Reactions were carried out with **1** (0.4 mmol), **2** (1.6 mmol, 4.0 equiv.), and Selectfluor (0.8 mmol, 2.0 equiv.) in 4 mL anhydrous DCE under a nitrogen atmosphere at 90 °C. [b] Yield of the isolated product. [c] Recovery of **1**. [d] 0.8 mmol (2.0 equiv.) aldehyde **2** was used. [e] Reactions were performed at 110 °C.

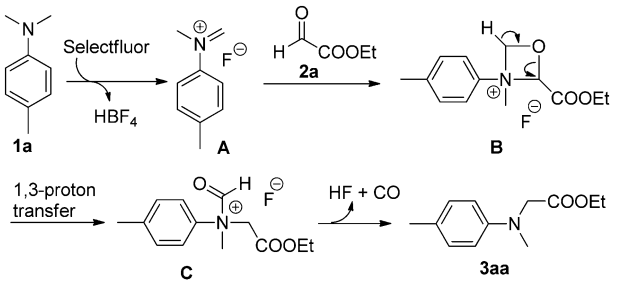
low (19–42%). Additionally, the reaction of 4-bromo-*N*,*N*-diethylaniline (**1l**) with **2a** afforded **3la** in 26% yield. Starting from 4-bromo-*N*-ethyl-*N*-methylaniline (**1n**), both reductive amination products **3ia** (16%) and **3la** (26%) were obtained after 12 h under optimal conditions.

To understand the reaction, both ^{13}C- and D-labelling experiments were performed. Firstly, [$^{13}C_2$]-**1h** and **2b** were subjected to the standard reaction conditions eqn (2). After 12 hours, the reductive amination product [$^{13}C_1$]-**3hb** was obtained in 52% yield. This result showed that the α-carbon atom of the ester group of [$^{13}C_1$]-**3hb** originated from aldehydes **2b**. It is worth noting that reduction of the carbonyl group could be efficiently realized in the presence of the oxidant Selectfluor. Then, the reaction of [D_6]-**1a** and **2a** was carried out and gave [D_4]-**3aa** in 50% yield eqn (3). This outcome clearly revealed that the tertiary anilines **1** served as a reducing agent. The two isotope labelling experiments demonstrated that tertiary anilines played a dual role in this unprecedented oxidant-mediated, metal-free reductive amination reaction.

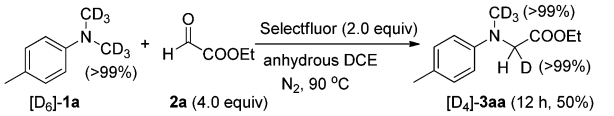


[$^{13}C_2$]-**1h** **2b** (2.0 equiv) [$^{13}C_1$]-**3hb** (12 h, 52%)

(2)



Scheme 2 Possible mechanism for the synthesis of *N*-methyl amino acid **3aa**.



(3)

Although the mechanistic details of this transformation are not very clear at the moment, based on the experimental results, the probable mechanism of the reductive amination is depicted in Scheme 2.[19] Firstly, *N*,*N*,4-trimethylaniline (**1a**) reacted with Selectfluor to form the iminium ion intermediate **A**.[20–22] In the next step, a key nucleophilic attack of the oxygen atom on the carbonyl group of **2a** to **A** takes place, providing a four-membered ammonium ylide **B**.[23] This step was supported by our theoretical calculation results.[19] Subsequent to 1,3-proton transfer, a new ammonium **C** was formed. Finally, the desired reductive amination product **3aa** was furnished along with the loss of carbon monoxide and hydrogen fluoride *via* thermal decomposition. It should be pointed out that the nucleophilic addition of the carbonyl group to iminium species as described in Scheme 2 has never been reported, although iminium intermediates generated by two-electron oxidation of amines have been extensively studied on their transformations by the addition of various nucleophiles.[24] Moreover, the metal-free reductive amination reaction between tertiary anilines and aldehydes is completely distinguished from the common reductive amination procedure.[5]

In summary, a novel oxidant-mediated direct reductive amination of tertiary anilines and aldehydes was developed, in which simple *N*,*N*-dialkylanilides acted as both nitrogen sources and reducing agents. The nucleophilic addition of carbonyl group to the *in situ* generated iminium ion intermediate was realized for the first time, which initiated the next intramolecular sequential amination and reduction. This protocol might open a new window for the construction of C–N bonds through reductive amination. Further studies on applying the dual role of tertiary amines to perform other aminative reactions are underway in our lab.

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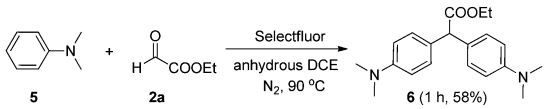

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