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ARTICLE

Direct oxidative amination of aromatic aldehydes with amines in continuous flow system using metal-free catalyst

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A novel method for metal-free oxidative amination of aromatic aldehydes and alcohols in the presence of H_2O_2/NaBr/H^+ within 25min in a continuous flow system has been developed. A series of different substrates were tested and the corresponding products were obtained in good yields.

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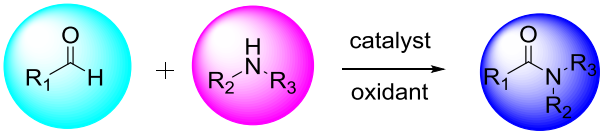
Introduction

General and convenient methods for the synthesis of amide are important in organic chemistry due to the extensive presence of amide units in natural products, pharmaceuticals, and polymers. [1] The reaction of an amine with carboxylic acid, which needs either more reactive derivatives [2] or coupling reagents [3] are the most common methods for the synthesis of amides. However, these methods have several common drawbacks. For example, it is poor atom-efficiency and it uses hazardous reagents which led to wastes that cause environmental problems. To overcome these problems, alternative methods for the synthesis of amide have been developed,[4] such as the name reactions like the Schmidt reaction,[5] the Beckmann rearrangement,[6] and Ugi reaction.[7] Other methods involve dehydrogenative amidation of alcohol [8], transamidation of primary amides [9], and oxidative amidation of aldehydes [10-14] have also been reported. During these methods above, oxidative amidation of aldehydes with amine is highly desirable since it uses cheap, abundant and less hazardous starting materials (Scheme 1).

In 1966, Nakagawa et al. first reported the oxidative amidation of aldehydes with amines by using nickel peroxide as the oxidant.[10] After that, several groups [11] have reported new methods for the direct synthesis of amides from aldehydes. However, these methods require the use of expensive transition metals as catalyst. Metal-free oxidative amidation of aldehydes with amines was first reported by Wolf et al. in 2007 by using TBHP as the oxidant.[12] Then more efficient catalytic methods using KI/TBHP [13] and NaI/TBHP [14] have also been reported. However, there are still drawbacks of these methodologies, such as the catalysts reported in literature are either expensive or involve a multistep synthesis and it often needs stoichiometric amounts of bases and sensitive reagents.

Molecular halogens and related reagents are well known oxidizing agents due to its simple operation and low cost. Recently, our group has researched the oxidation of alcohol to aldehyde in a continuous flow reactor with metal-free catalyst.[15] Then we continued to explore the oxidation amidation of alcohol to amide in a two-step continuous flow system with metal-free catalyst.[16] In the process, benzyl alcohol was firstly oxidized to aldehyde, which continued to react with amine under TBHP to form amide. Compared with traditional methods, this method is good enough from the economical and green chemistry points of view. However, it needs two different oxidants, which may cause the waste of material and low efficiency. The second step of the reaction needed 2 equiv number of TBHP, which was not environment friendly. And the system was not fit for primary amines, which limited the substrate scope. Then we intended to explore the more interesting and challenging oxidative amidations of aldehydes and alcohols with amines by using the same oxidant, which led to simple operation. The results are presented here.



Scheme 1 Oxidative amidation of aldehyde with amine

Results and Discussion

At the beginning, optimization studies were carried out by treating benzaldehyde with morpholine to form benzoyl morpholine **3a** in different reaction conditions. And the results were summarized in Table 1. The reaction with NaBr and without an oxidant did not get the product (Table 1, entry 1), whereas the reaction with H_2O_2 (30wt% in water) resulted in

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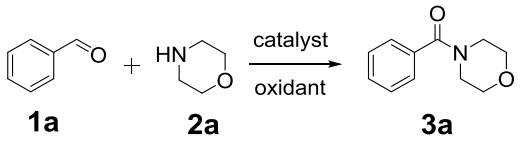
16% of the product (Table 1, entry 2). Under the similar conditions 10mol% NaBr and H_2O_2 provided 64% of the product (Table 1, entry 3). And when the equiv number of NaBr decreased to 5mol%, it almost had no effect on the yield of the product (Table 1, entries 3, 4). However, the equiv number of H_2O_2 had a great influence on the yield (Table 1, entries 4, 5 and 6).

Table 1 Optimization of oxidative amidation for the synthesis of amide [a]



Entry	Catalyst (mmol)	Oxidant (mmol)	Yield (%) [b]
1	NaBr (0.1)	-	-
2	-	H_2O_2 (2)	16
3	NaBr (0.1)	H_2O_2 (2)	64
4	NaBr (0.05)	H_2O_2 (2)	62
5	NaBr (0.05)	H_2O_2 (1.5)	48
6	NaBr (0.05)	H_2O_2 (3)	64

[a] Reaction conditions: benzaldehyde (1mmol), morpholine (2mmol), sulphuric acid (1mol%), dioxane (3mL), 80 ˚C, 30h. [b] Isolated yield.

In In further study, both aromatic and aliphatic aldehydes were employed (Table 2). Moderate yield of benzaldehyde (Table 2, entry 1, "Batch" column) and 4-nitrobenzaldehyde (Table 2, entry 2, "Batch" column) were obtained. However, there was no product obtained of 4-methoxybenzaldehyde (Table 2, entry 3, "Batch" column) and 4-aminobenzaldehyde (Table 2, entry 4, "Batch" column), probably due to the reactivity between amines/alkoxys and hypobromite restrained the oxidation. And aliphatic aldehyde did not get the amide product, too (Table 2, entry 5, "Batch" column), which probably due to the low reactivity of aliphatic aldehyde. To overcome these problems in the oxidation process, continuous flow microreactors with benefits of high surface-to-volume ratio, efficient mass transfer and heat transfer, high selectivity was employed in this study.[17] In recent years, continuous flow technology has become increasingly popular in organic synthesis.[18] Owing to the high efficiency of heat and mass transmission, which contributes to reactivity of reactants, the reaction time will be shorten, and the reaction efficiency will be improved much more.

Then we designed an assembled continuous flow system, as shown in Figure 1. It consists of two syringe pumps, T-piece micromixer and microreactor. And the volume of the syringe and microreactor are 20mL, and 5mL, respectively. In the reaction process, the mole ratio of reactants and reaction time can be modulated by changing the flow rate of syringes. And the temperature was controlled by oil bath.

Table 2 The oxidation amidation of aldehydes with morpholine in batch and continuous flow systems

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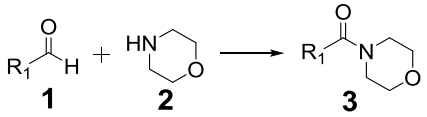
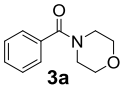
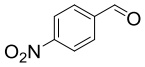
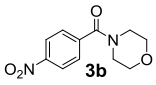
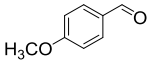
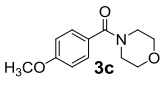
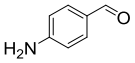
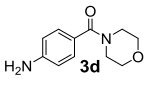
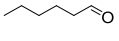
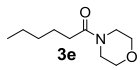


Entry	Aldehyde	Product	Yield (%) [c]	
			Batch [a]	Conti-flow [b]
1		 3a	62	96
2		 3b	58	94
3		 3c	NP [d]	93
4		 3d	NP	82
5		 3e	NP	NP

[a] Reaction conditions in batch: aldehyde (1mmol), morpholine (2mmol), NaBr (5mol%), sulphuric acid (1mol%), hydrogen peroxide (30wt% in water, 2mmol), dioxane (3mL), 80 ºC, 30 h. [b] Reaction conditions in continuous-flow system: solution A: 0.33M of aldehyde, 0.67M of hydrogen peroxide (30wt% in water), 5mol% of sodium bromide and 1mol% of sulphuric acid in dioxane, flow rate 0.1 mL/min; solution B: 0.67M of morpholine in the dioxane, flow rate 0.1 mL/min, 80ºC, 25min. [c] Isolated yield. [d] NP=No Product.

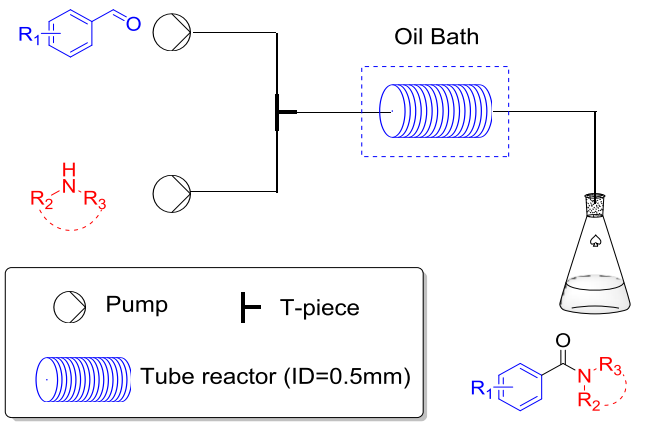


Figure 1 Continuous flow system

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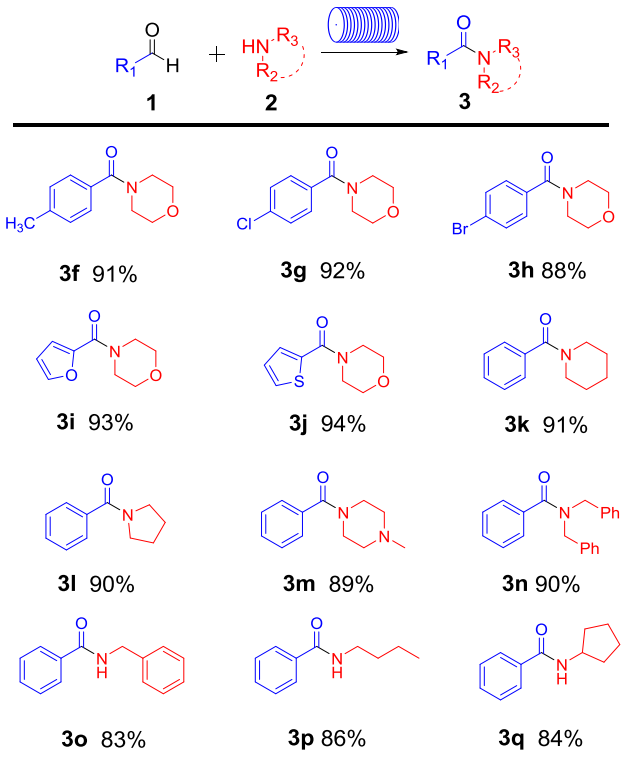
With an assembled continuous-flow system, all the reactions displayed in Table 2 were re-performed. Compared with batch condition, better reactivity and yield were realized (Table 2, entries 1, 2). What's more, 93% of **3c** and 82% of **3d** were obtained, which was inhibited in batch conditions (Table 2, entry 3). This proved that continuous-flow could improve the functional group compatibility of the oxidation. Unfortunately, reaction with aliphatic aldehyde was unsuccessful in continuous flow system, which due to the low reactivity (Table 2, entry 5).

Encouraged by these results, a library of amides was synthesized from various aldehydes and amines. The results were summarized in Table 3. Good to excellent yields were obtained in most cases. First of all, a wide range of arylaldehydes were used to react with morpholine. Both electron-rich and electron-deficient arylaldehydes provided good yield to corresponding product (Table 3, **3f**-**3h**). Similarly, heterocyclic aldehydes gave the corresponding benzoyl morpholine in good yields (Table 3, **3i** and **3j**). Then a variety of amines were also used to react with benzaldehyde to test the scope of substrates. Secondly amines reacted well in this system (Table 3, **3k**-**3n**). what's more, primary amines, which could not get the desired product in our previous study,[16] also had good reactivity (Table 3, **3o**-**3q**).

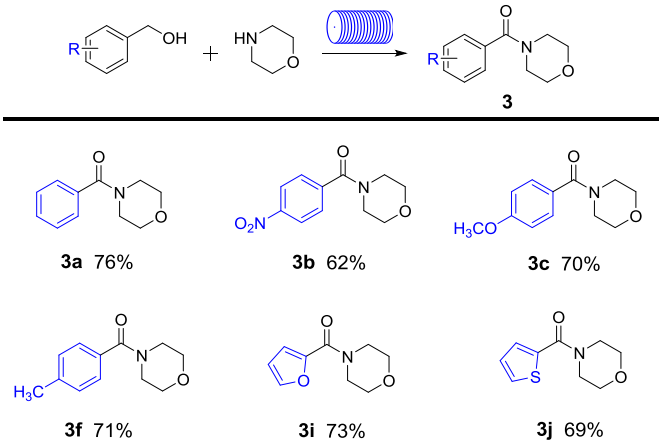
Table 3 The oxidation amidation of aldehydes with amines in continuous flow systems [a]



[a] Reaction conditions: solution A: 0.33M of aldehyde, 0.67M of hydrogen peroxide (30wt% in water), 5mol% of sodium bromide and 1mol% of sulphuric acid in dioxane, flow rate 0.1 mL/min; solution B: 0.67M of amine in the dioxane, flow rate 0.1 mL/min, 80˚C, 25min.

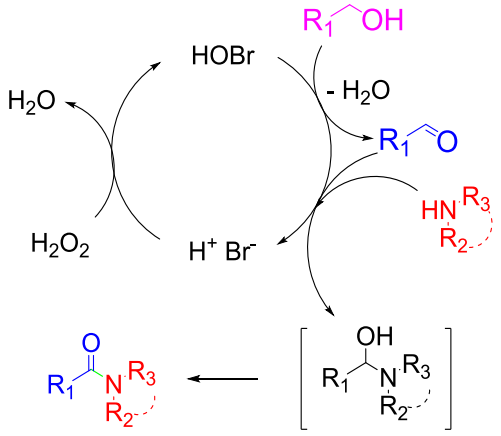
Then we have also researched the applicability of the present catalytic system to benzyl alcohol derivatives. And the results were shown in Table 4. Moderate to good yields were obtained with both electron-deficient and electron-rich benzyl alcohols (Table 4, **3a**-**3c**, **3f**). And heterocyclic alcohols gave the corresponding products in good yields (Table 3, **3i** and **3j**), too.

Table 4 The oxidation amidation of benzyl alcohols with morpholine in continuous flow system [a]



[a] Reaction conditions: solution A: 0.33M of benzyl alcohols, 0.67M of morpholine in dioxane, flow rate 0.1 mL/min; solution B: 1.67M of hydrogen peroxide (30wt% in water), 10mol% of sodium bromide and 1mol% of sulphuric acid in the dioxane, flow rate 0.1 mL/min, 80˚C, 25min. [b] Isolated yield.

On the basis of previous studies, [15, 16] a possible mechanism was proposed as shown in Scheme 2. Firstly, Br- was oxidized to form the hypobromous acid in the presence of hydrogen peroxide and acid. The reaction between aldehyde and amine may probably proceed through a hemiaminal intermediate, which can be further oxidized to the product amide by the generated hypobromous acid. And acid and Br- were reformatted to maintain the system circularly. In the case of direct amidation of benzyl alcohols, the reaction was expected to go through an aldehyde intermediate. To confirm this proposed mechanism, hydrobromic acid (40%, aq.), which was an important intermediate in the reaction pathway, was employed directly to replace Br^- source and sulfuric acid. A yield of 56% of amide was isolated in the model reaction, which supported the mechanism strongly.



Scheme 2 Proposed mechanism of the oxidative amination of aldehyde and alcohol

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Conclusions

In conclusion, we have developed a simple, general and straightforward method for the synthesis of the amide by oxidative coupling between an aldehyde/alcohol and an amine in continuous flow system. Compared with our previous work on the oxidative amination of alcohol to amide, this method is green and simple due to the use of one oxidant. And primary amines were also had good reactivity, which had no reactivity in our previous work. In this strategy, no external base or additive is required. And the reaction time is much shorter than that in batch. Moreover, the present methodology was metal-free. Formation of amides from alcohols, which is difficult to some extent, was also achieved in this study.

Experimental

General details

Reaction solvents were obtained commercially, and used without further purification. Commercial reagents were used as received. Reaction were monitored by thin-layer chromatography (TLC) on 0.25mm precoated Merck Silica Gel 60 F254, visualizing with ultraviolet light. $^{1}H/^{13}C$ NMR spectra were recorded on 400'54 ascend purchased from Bruker Biospin AG, operating at 400/100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. Flash column chromatography was performed on Merck Silica Gel 60 (200-300mesh) using petroleum ether and ethyl acetate.

General procedure for synthesis of compound 3a by benzaldehyde with morpholine: 0.01mol of benzaldehyde, H_2O_2 (30wt% in water, 0.02mol, 2eq), NaBr (5 mol%) and H_2SO_4 (1 mol%) were dissolved in 30mL dioxane, which was in syringe A. Morpholine (0.02mol, 2eq) was dissolves in 30mL dioxane, which was in syringe B. The flow rate of syringe A and B were both 0.1mL/min. And the temperature of the oil bath was set in 80˚C. The reaction liquid was collected, and dissolved in ethyl acetate, washed with H_2O. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the amide product **3a**.

General procedure for synthesis of compound 3a by benzyl alcohol with morpholine: 0.01mol of benzyl alcohol, morpholine (0.02mol, 2eq) were dissolved in 30mL dioxane, which was in syringe A. And H_2O_2 (30wt% in water, 0.05mol, 5eq), NaBr (10 mol%) and H_2SO_4 (1 mol%) were dissolves in 30mL dioxane, which was in syringe B. The flow rates of syringe A and B were both 0.1mL/min. And the temperature of the oil bath was set at 80˚C. The reaction liquid was collected, and dissolved in ethyl acetate, washed with H_2O. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the amide product **3a.**

Benzoyl morpholine (**3a**). White solid; 1.24g, 96% yield; m.p.=72-74 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 5H), 3.80–3.28 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.4, 134.3, 128.9, 127.5, 126.1, 65.9, 59.4, 20.0, 13.2; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}NO_2$ $[M+H]^+$ 192.1019, found 192.1040.

N-(4-Nitrobenzoyl)morpholine (**3b**). Light yellow solid; 1.43g, 94% yield; m.p.=101-102°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32–8.27 (m, 2H), 7.61–7.56 (m, 2H), 3.72 (d, *J* = 67.2 Hz, 6H), 3.39 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 147.5, 140.4, 127.1, 123.0, 65.7; HRMS (ESI) *m/z* calcd for $C_{11}H_{11}N_2O_4$ $[M+H]^+$ 237.0831, found 237.0857.

N-(4-Methoxybenzoyl)morpholine (**3c**). Yellow oil; 1.37g, 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2H), 6.94–6.89 (m, 2H), 3.84 (d, *J* = 3.2 Hz, 3H), 3.76–3.54 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 159.9, 128.2, 126.3, 112.8, 65.9, 54.3; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO_3$ $[M+H]^+$ 222.1085, found 222.1094.

N-(4-Aminobenzoyl)morpholine (**3d**). White solid; 1.12g, 82% yield; m.p.=131-132°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2H), 6.65–6.59 (m, 2H), 3.93 (s, 2H), 3.73–3.56 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 147.4, 128.4, 123.4, 113.2, 65.9, 59.4, 52.4, 20.0, 13.2; HRMS (ESI) *m/z* calcd for $C_{11}H_{14}N_2O_2$ $[M+H]^+$ 207.1089, found 207.1096.

N-(4-Methybenzoyl)morpholine (**3f**). Light yellow oil; 1.24g, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 3.69 (s, 8H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 139.1, 131.3, 128.1, 126.2, 65.9, 29.3, 20.4; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO_2$ $[M+H]^+$ 206.1136, found 206.1147.

N-(4-Chlorobenzoyl)morpholine (**3g**). White solid; 1.38g, 92% yield; m.p.=75-77 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (q, *J* = 8.5 Hz, 4H), 3.92–3.32 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 135.0, 132.6, 127.9, 127.6, 99.9, 65.8; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}ClNO_2$ $[M+H]^+$ 226.6720, found 226.6724.

N-(4-Bromobenzoyl)morpholine (**3h**). Light yellow solid; 1.58g, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2H), 7.31–7.27 (m, 2H), 3.86–3.31 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 133.1, 130.8, 127.8, 123.2, 65.8; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}BrNO_2$ $[M+H]^+$ 271.1260, found 271.1284.

2-Furanyl-4-morpholinylmethanone (**3i**). Yellow oil; 1.12g, 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.03 (dd, *J* = 3.5, 0.7 Hz, 1H), 6.49 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.82 (s, 4H), 3.77–3.72 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 146.7, 142.7, 115.8, 110.4, 65.9, 29.3; HRMS (ESI) *m/z* calcd for $C_9H_{11}NO_3$ $[M+H]^+$ 182.0772, found 182.0783.

4-Morpholinyl-2-thienylmethanone (**3j**). Light yellow oil; 1.23g, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.22 (dd, *J* = 3.6, 1.0 Hz, 1H), 6.97 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.71–3.63 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 135.6, 127.9, 127.8, 125.7, 65.8, 59.4, 20.0, 13.2; HRMS (ESI) *m/z* calcd for $C_9H_{11}NO_2S$ $[M+H]^+$ 198.0544, found 198.0568.

Benzoylpiperidine (**3k**). Colourless oil; 1.14g, 91% yield; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.31(s, 5H), 3.63 (s, 2H), 3.27 (s, 2H), 1.70–1.35 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 135.5,

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128.3, 127.4, 125.7, 47.7, 42.1, 25.4, 24.6, 23.6; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO$ $[M+H]^+$ 190.1187, found 190.1192.

Benzoylpyrrolidine (**3l**). Colourless oil; 1.05g, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dt, *J* = 8.5, 3.7 Hz, 2H), 7.35–7.28 (m, 3H), 3.46 (d, *J* = 81.7 Hz, 4H), 1.84 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 136.2, 128.7, 127.2, 126.0, 48.6, 45.2, 25.4, 23.5; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}NO$ $[M+H]^+$ 176.1031, found 176.1045.

1-Benzoyl-4-methylpiperazine (**3m**). Yellow oil; 1.21g, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 3.74 (s, 2H), 3.34 (s, 2H), 2.55–2.27 (m, 4H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 169.3, 134.7, 128.7, 127.5, 126.0, 54.2, 53.6, 46.5, 44.9, 40.9, 20.5; HRMS (ESI) *m/z* calcd for $C_{12}H_{16}N_2O$ $[M+H]^+$ 205.1296, found 205.1305.

N,N-Dibenzylbenzamide (**3n**). White solid; 1.80g, 90% yield; m.p.=113-114 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.11 (m, 15H), 4.70 (s, 2H), 4.40 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 136.9, 136.4, 136.2, 129.7, 128.8, 128.6, 128.4, 127.6, 127.0, 126.7, 51.6, 46.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}NO$ $[M+H]^+$ 302.1500, found 302.1509.

N-Benzylbenzamide (**3o**). White solid; 1.16g, 83% yield; m.p.=104-106 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.2 Hz, 2H), 7.53–7.20 (m, 8H), 6.48 (s, 1H), 4.64 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 138.2, 134.4, 131.5, 128.8, 128.6, 127.9, 127.6, 127.0, 44.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{13}NO$ $[M+H]^+$ 212.1031, found 212.1084.

N-Butylbenzamide (**3p**). White solid; 1.01g, 86% yield; m.p.=41-43 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 93.1, 13.0 Hz, 2H), 7.48–7.09 (m, 3H), 6.22 (d, *J* = 75.4 Hz, 1H), 3.53–3.11 (m, 2H), 1.58 (dt, *J* = 14.0, 7.0 Hz, 2H), 1.39 (dd, *J* = 14.5, 7.2 Hz, 2H), 0.94 (dd, *J* = 9.2, 5.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 134.9, 131.2, 128.5, 126.8, 39.8, 31.7, 20.2, 13.8; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NO$ $[M+H]^+$ 178.1187, found 178.1189.

N-Cyclopentylbenzamide (**3q**). White solid; 1.05g, 84% yield; m.p.=133-134 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.70 (m, 2H), 7.51–7.35 (m, 3H), 6.11 (s, 1H), 4.45–4.34 (m, 1H), 2.08 (td, *J* = 11.4, 6.1 Hz, 2H), 1.78–1.59 (m, 4H), 1.49 (td, *J* = 12.5, 6.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 135.0, 131.2, 128.5, 126.8, 51.7, 33.2, 23.8; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO$ $[M+H]^+$ 190.1187, found 190.1192.

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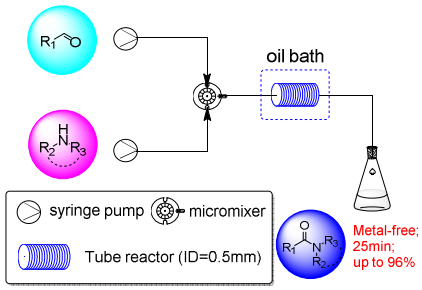
Metal-free oxidative amination of aromatic aldehydes with amines in continuous flow system under mild reaction conditions.



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