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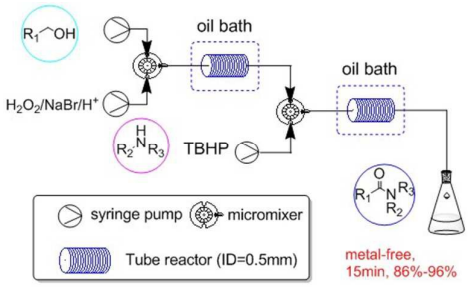
A two-step continuous flow synthesis of amides from alcohol using metal-free catalyst with good yield



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ARTICLE

A two-step continuous flow synthesis of amides from alcohol using metal-free catalyst

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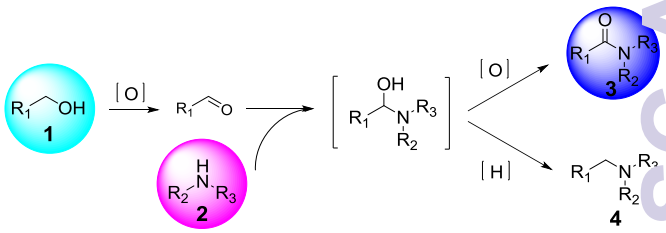
Metal-free oxidative amination of aromatic alcohols in the presence of TBHP provides convenient access to amides in 86–96% under mild reaction conditions within 15min in a two-step continuous flow reactor system. This method avoids expensive transition metal catalysts and integrates alcohol oxidation and amide bond formation, which are usually accomplished separately, into a single operation.

Introduction

The formation of amide bonds is one of the most important organic reactions due to the abundance of this functional group in natural products, polymers, and pharmaceuticals. [1, 2] The most frequently used amide formations involve the reaction of an amine (including ammonia) with activated carboxylic acid derivatives [3-7] or coupling with carboxylic acids mediated by a coupling reagent. [8] These existing methods have several common drawbacks, such as poor atom-efficiency, use of hazardous reagents, and generation of wastes that not only reduce process efficiency but also pose environmental problems. More recent approach, which is quite attractive in terms of green chemistry and economic considerations, has considered the use of oxidative amination from aldehydes. [9-16] However, these methods require the use of expensive transition metals as catalyst, and the use of aldehydes can be troublesome due to their inherent reactivity.

From the recent perspective of green chemistry, the development of efficient and practical amide formation reactions remains a great challenge. The direct amidation of alcohols with amines can be a potentially attractive method since it uses cheap, abundant and stable starting materials and has potential industrial, which can be applied in the synthesis of pharmaceutical intermediates or other products such as proline-derived amides. Recently, several groups [17-24] have reported catalytic amide formation from alcohols, using transition metal catalysts to oxidize the alcohol to the aldehyde in situ and then further oxidize the hemiaminal to the desired amide via the loss of 2 equiv of H_2. A common shortcoming of these methods is that expensive transition metal catalysts are required and amides are obtained in only moderate yields in some cases.

The coupling of an alcohol **1** with an amine **2** is expected to proceed via oxidation of the alcohol to an aldehyde and formation of an intermediate hemiaminal. Further oxidation of the hemiaminal would lead to the amide **3**, while elimination of water and return of hydrogen would provide amine **4** (Scheme 1). The balance between these pathways may be expected to favor amide formation in the presence of an oxidant or when the hemiaminal is stabilized. Generally, hemiaminals have low stability, either reverting to carbonyl compound and amine or undergoing dehydration. However, there are examples of isolated hemiaminals.[25, 26] From Scheme 1 we can see that alcohol oxidation and amide bond formation are usually accomplished separately, which involves three main consecutive steps: (1) activation-the oxidation of alcohols to form aldehydes; (2) bond construction-the coupling of aldehydes with amines to produce hemiaminals as reactive intermediates; (3) dehydrogenation-subsequent oxidation of hemiaminals to amides through H_2 liberation or H transfer to a hydrogen acceptor. A strategy to overcome the close "coupling" of the two oxidation steps is to design two separate reactions to achieve the same net transformation. However, the added complexity in multistep batch reactions, as compared with one-pot processes, can make such development efforts time-consuming and less efficient.



Scheme 1. Oxidative amidation of alcohol with amine

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The use of continuous flow microreactors provides a valuable platform for the development of multistep syntheses by integrating multiple unit operations into one single network and eliminating the handling of intermediate species. [27] The streamlined operation renders continuous scanning of reaction parameters and therefore enables fast screening of catalysts and rapid optimization of reaction conditions. At the same time, the modular nature of multistep syntheses in flow allows for the reaction parameters to be individually adjusted for each step and makes it possible to access a substantially larger operating space. In 2013, Jensen and co-workers [28] utilizing oxygen and urea hydrogen peroxide as oxidant to oxidize alcohol to amide in continuous flow reactor. However, the catalyst they used was Ru/Al_2O_3, and the reactor was complex. Here we report a two-step continuous flow reactor to integrate these two steps into a single operation, which are difficult to do this in batch.

Our group has researched the oxidation of alcohol to aldehyde in a continuous flow reactor with metal-free catalyst. [29] In the process, we used $H_2O_2/NaBr/H^+$ system as oxidant to oxidize benzyl alcohol to aldehyde, which could react with amines to form amides in the presence of an oxidant. Then we designed a two-step continuous flow reactor system, as shown in Figure 1. It consists of three syringe pumps, two T-piece micromixers and two microreactors. The volume of the syringe and two microreactors are 20mL, 1.96mL and 13.08mL, respectively. 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.

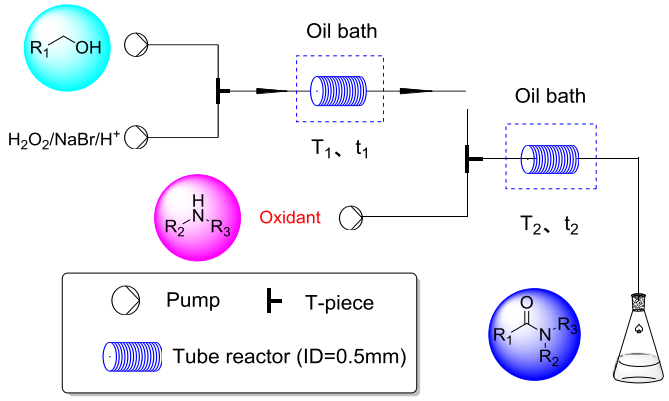
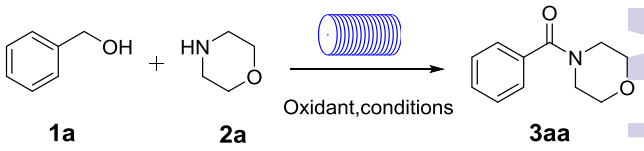


Figure 1. A two-step continuous flow reactor system

Results and Discussion

At the outset, a model reaction of benzyl alcohol **1a** and morpholine **2a** to form benzoyl morpholine **3aa** was chosen to identify the reaction system. As we had achieved the optimized conditions of benzyl alcohol to aldehyde, [29] which was the first step in this study, we would mainly optimize the second step according to the first step of this reaction. And the results of the optimization of the reaction conditions were summarized in Table 1. First of all, we continued to use the $H_2O_2/NaBr/H^+$ system as oxidant, and the corresponding product was obtained in 56% yield (Table 1, entry 1). To improve the yield of the product, other oxidants were tested. When we used TBHP (70wt% in water) as oxidant, the yield of the product was improved apparently (Table 1, entry 2). H_2O_2 and *m*-CPBA led to poor yield (Table 1, entry 3, 4). In the absence of oxidant, the product was obtained only in trace (Table 1, entry 5). Next, the temperature was investigated and we observed that whether increasing the temperature to 100˚C or reducing it to 50˚C, it led to a significant decrease in the amount of product **3aa**. Thus, 80˚C was regarded as the optimum temperature (Table 1, entry 2, 6, 7). The reaction time (Table 1, entry 2, 8, 9) and equiv number of oxidant (Table 1, entry 2, 10, 11) were also investigated, which led to best reaction conditions.

Table 1. Selected results for screening the optimized reaction conditions [a]



Entry	Oxidant	T_1 (˚C)	T_2 (˚C)	t_1 (min)	t_2 (min)	Yield(%) of **3aa** [b]
1	$H_2O_2/NaBr/H^+$	70	80	3	10	56
2	TBHP	70	80	3	10	94
3	H_2O_2	70	80	3	10	34
4	*m*-CPBA	70	80	3	10	16
5	-	70	80	3	10	trace
6	TBHP	70	100	3	10	76
7	TBHP	70	50	3	10	62
8[c]	TBHP	70	80	3	6.7	82
9[d]	TBHP	70	80	3	13.3	93
10[e]	TBHP	70	80	3	10	87
11[f]	TBHP	70	80	3	10	91

[a] Reaction conditions: solution A: 0.667M of **1a** in dioxane, flow rate 0.327 mL/min; solution B: 1.334M of H_2O_2, 2 mol% of NaBr and 1 mol% of H_2SO_4 in dioxane, flow rate 0.327mL/min; solution C: 0.667M of **2a**, 0.667M of oxidant in dioxane, flow rate 0.654mL/min, unless otherwise noted. [b] Isolated yield. [c] solution C: 0.334M of **2a**, 0.334M of TBHP in dioxane, flow rate 1.308mL/min. [d] solution C: 1.334M of **2a**, 1.334M of TBHP in dioxane, flow rate 0.327mL/min. [e] solution C: 0.667M of **2a**, 0.5M of TBHP in dioxane, flow rate 0.654mL/min. [f] solution C: 0.667M of **2a**, 1.0M of TBHP in dioxane, flow rate 0.654mL/min.

Optimized reaction conditions for a two-step continuous flow synthesis of benzoyl morpholine from benzyl alcohol have been obtained. Then we used the similar conditions to test the same reaction in batch. The yield of the product reached to 76%, which was lower than that in continuous flow system. And the reaction time in batch was 30h, which was much longer than 15min. Most importantly, the reaction in batch was much more troublesome. The two oxidation steps needed to accomplished separately, morpholine and TBHP in dioxane were added to the reaction liquid when benzyl alcohol was

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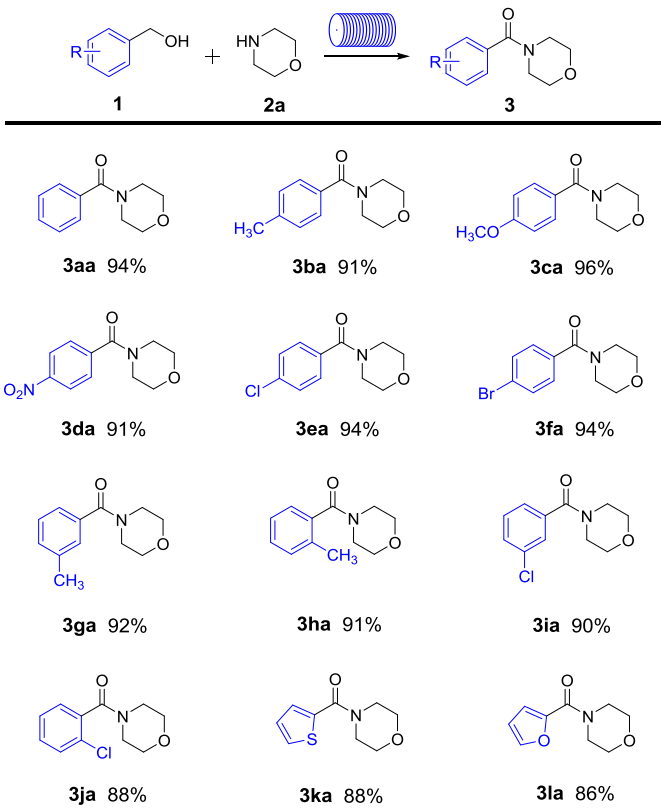
oxidized to benzaldehyde completely, which led to time-consuming and less efficient. From these results we can see that the continuous flow system was fit for the multistep reaction.

Then we used a wide range of benzyl alcohols to test the substrate scope of this reaction. The results obtained are summarized in Table 2. Good to excellent yields were obtained in most cases. The TBHP-promoted oxidative amination provided convenient access to both electron-deficient and electron-rich arylamides (**3aa**-**3ja**). Similarly, heterocyclic alcohols **1k** and **1l** gave the corresponding benzoyl morpholine in good yields (**3ka**, **3la**).

Table 2. Scope of benzyl alcohol [a]

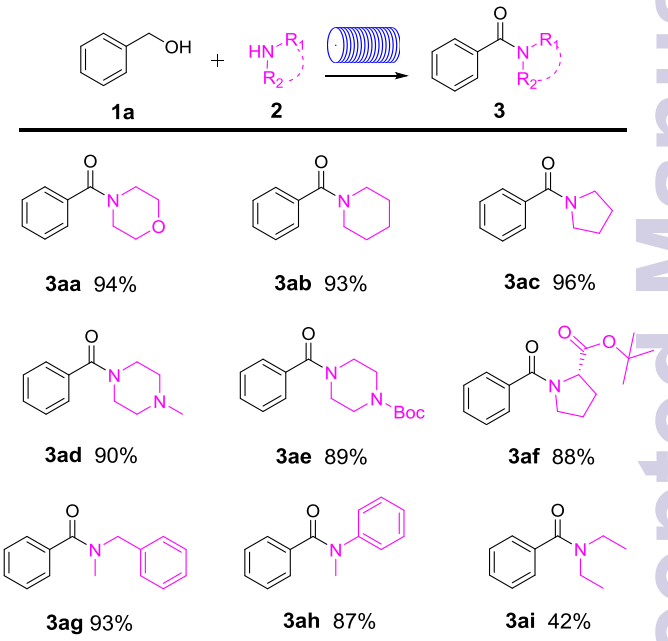


[a] Reaction conditions: solution A: 0.667M of **1a** in dioxane, flow rate 0.327 mL/min; solution B: 1.334M of H_2O_2, 2 mol% of NaBr and 1 mol% of H_2SO_4 in dioxane, flow rate 0.327mL/min, T_1 =70˚C; solution C: 0.667M of **2a**, 0.667M of oxidant in dioxane, flow rate 0.654mL/min, T_2 =80˚C.

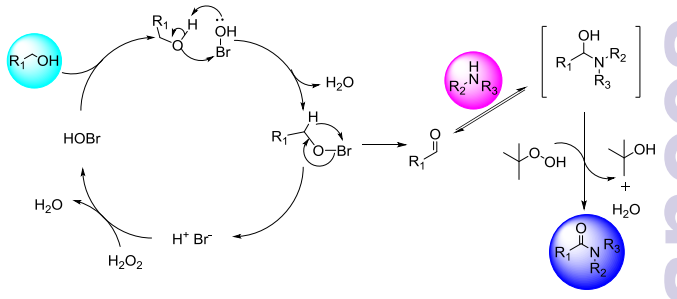
A wide range of secondary amines had also been used to test the substrate scope of the reaction, and the results were shown in Table 3. The formation of several benzamides occurred with excellent yields (**3aa**-**3ah**). However, only low yields (42%) were obtained when diethylamine was used (**3ai**). Importantly, proline-derived amides can be prepared in excellent yields (**3af**). And when primary amine was used, it could not get the amide product.

The mechanism of oxidative amidation of alcohol with amine can be divided into two steps (Scheme 2). [29] Initially, Br^- was oxidized to form the hypobromous acid in the presence of acid and hydrogen peroxide. The generated hypobromous acid subsequently reacted with the corresponding hydroxyl group to form the hypobromite intermediate, which yielded the corresponding carbonyl compounds via α-hydrogen elimination. Brønsted acid and Br^- were reformatted to maintain the system circularly. Then the carbonyl compounds reacted with amine to form an intermediate hemiaminal. And further oxidation of the hemiaminal leaded to the product amide.

Table 3. Scope of amine [a]



[a] Reaction conditions: solution A: 0.667M of **1a** in dioxane, flow rate 0.327 mL/min; solution B: 1.334M of H_2O_2, 2 mol% of NaBr and 1 mol% of H_2SO_4 in dioxane, flow rate 0.327mL/min, T_1 =70˚C; solution C: 0.667M of **2a**, 0.667M of oxidant in dioxane, flow rate 0.654mL/min, T_2 =80˚C.



Scheme 2. Proposed mechanism of the oxidative amination of alcohol

Conclusions

In summary, we have developed an efficient and direct synthesis of amides from alcohols in continuous flow system. This transition-metal-free strategy provides a practical synthesis of various amides and integrates alcohol oxidation and amide bond formation, which are usually accomplished separately, into a single operation. It also clearly shows the major advantage of continuous multistep systems to allow chemical or reaction parameters to be independently

adjusted, hence providing a larger design space for developing chemical reactions or systems.

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 $F_{254,}$ visualizing with ultraviolet light. $^1H/^{13}C$ 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 3: 0.02mol of benzyl alcohol 1 was dissolved in 30mL dioxane, which was in syringe A. And H_2O_2 (30wt% in water, 0.04mol, 2eq), NaBr (2 mol%) and H_2SO_4 (1 mol%) were dissolved in 30mL dioxane, which was in syringe B. Secondary amine 2 (0.02mol, 2eq) and TBHP (70wt% in water, 0.02mol, 2eq) were dissolves in 30mL dioxane, which was in syringe C. The flow rate of syringe A, B and C were 0.327mL/min, 0.327mL/min, and 0.654mL/min, respectively. And the temperature of the two oil baths was set in 70˚C and 80˚C, respectively. 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 **3**.

Benzoyl morpholine (**3aa**).[23] White solid, ^1H NMR(400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 5H), 3.80–3.28 (m, 8H). HRMS (ESI) m/z calcd for $C_{11}H_{13}NO_2$ $[M+H]^+$ 192.1019, found 192.1040.

N-(4-Methybenzoyl)morpholine (**3ba**).[23] Light yellow oil. ^1H 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 169.64, 139.08, 131.31, 128.13, 126.21, 65.90, 29.30, 20.37.

N-(4-Methoxybenzoyl)morpholine (**3ca**).[23] Yellow oil. ^1H 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 169.43, 159.90, 128.19, 126.32, 112.78, 65.92, 54.35.

N-(4-Nitrobenzoyl)morpholine (**3da**).[10] Light yellow solid. ^1H NMR(400 MHz, $CDCl_3$) δ 8.34–8.26 (m, 2H), 7.62–7.55 (m, 2H), 3.87–3.31 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.04, 147.49, 140.41, 127.13, 122.96, 65.73.

N-(4-Chlorobenzoyl)morpholine (**3ea**).[30] White solid. ^1H 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 168.37, 135.03, 132.61, 127.86, 127.65, 99.96, 65.83.

N-(4-Bromobenzoyl)morpholine (**3fa**).[31] Light yellow solid. ^1H 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 168.38, 133.08, 130.82, 127.83, 123.25, 65.81.

N-(3-Methybenzoyl)morpholine (**3ga**).[32] Light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.18 (m, 1H), 7.14 (dt, *J* = 10.8, 5.5 Hz, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 3.87–3.19 (m, 8H), 2.28 (d, *J* = 8.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.59, 137.47, 134.28, 129.54, 127.34, 126.67, 122.95, 65.87, 47.15, 41.44, 20.34.

N-(2-Methybenzoyl)morpholine (**3ha**).[32] Light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.17 (m, 1H), 7.17–7.10 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 3.79–3.65 (m, 4H), 3.49 (s, 2H), 3.16 (d, *J* = 4.5 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.07, 134.61, 133.15, 129.48, 128.03, 124.98, 124.80, 65.94, 46.23, 40.88, 25.88, 17.99.

N-(3-Chlorobenzoyl)morpholine (**3ia**).[30] Colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 3H), 7.23–7.17 (m, 1H), 3.83–3.23 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 136.02, 133.64, 129.00, 128.97, 126.26, 124.14, 65.77, 46.9, 41.45, 25.88.

N-(2-Chlorobenzoyl)morpholine (**3ja**).[30] Light yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.38 (m, 1H), 7.37–7.27 (m, 3H), 3.89 (ddd, *J* = 16.6, 11.3, 5.6 Hz, 1H), 3.83–3.73 (m, 3H), 3.73–3.65 (m, 1H), 3.63–3.55 (m, 1H), 3.34–3.16 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.95, 134.37, 129.35, 129.32, 128.6, 126.83, 126.28, 65.80, 65.71, 46.10, 41.05.

4-Morpholinyl-2-thienylmethanone (**3ka**).[32] Light yellow oil. ^1H 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 162.63, 135.57, 127.94, 127.85, 125.75, 65.82, 59.36, 20.03, 13.18.

2-Furanyl-4-morpholinylmethanone (**3la**).[23] Yellow oil. ^1H 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 158.11, 146.76, 142.76, 115.81, 110.38, 65.96, 29.30.

Benzoylpiperidine (**3ab**).[23] Colourless oil. ^1H 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 169.29, 135.51, 128.32, 127.37, 125.76, 47.75, 42.11, 25.44, 24.61, 23.57.

Benzoylpyrrolidine (**3ac**).[23] Colourless oil. ^1H NMR(400 MHz, $CDCl_3$) δ 7.51–7.26 (m, 5H), 3.56 (s, 2H), 3.36 (s, 2H), 1.84 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.74, 136.17, 128.76, 127.22, 126.05, 48.57, 45.16, 25.36, 23.51.

1-Benzoyl-4-methylpiperazine (**3ad**).[33] Yellow oil. ^1H NMR(400 MHz, $CDCl_3$) δ 7.59–7.27 (m, 5H), 3.74 (s, 2H), 3.58–3.24 (m, 2H), 2.65–2.12(m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.36, 169.33, 134.73, 128.68, 127.46, 126.01, 54.16, 53.62, 46.50, 44.89, 40.92, 20.48.

1-Benzoyl-4-Bocpiperazine (**3ae**).[33] White solid. ^1H NMR(400 MHz, $CDCl_3$) δ 7.46–7.34 (m, 5H), 3.73 (s, 2H), 3.41 (s, 6H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.60, 153.55, 134.47, 128.90, 127.58, 126.02, 79.34, 46.34, 42.85, 27.35.

(S)-tert-Butyl-N-benzoylprolinate (**3af**).[34] White solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.31 (dd, *J* = 15.5, 6.6 Hz, 5H), 4.48 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.72 (t, *J* = 6.5 Hz, 1H), 3.55 (dt, *J* = 13.8, 7.0 Hz, 1H), 3.43 (dd, *J* = 13.1, 8.7 Hz, 1H), 1.99–1.87 (m, 4H), 1.43 (s, 9H), 1.33–1.13 (m, 18H); ^1C

NMR (101 MHz, $CDCl_3$) δ 170.44, 168.52, 138.26, 135.51, 129.01,128.66, 127.29, 127.21, 126.19, 125.77, 113.05, 80.29, 61.02, 58.93, 48.93, 45.65, 32.81, 30.91, 29.12, 28.68, 28.43, 28.34, 27.01, 26.73, 24.36, 21.67, 21.67, 13.10.

N-Benzyl-N-methylbenzamide (**3ag**).[33] Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.00 (m, 10H), 4.67 (s, 1H), 4.42 (s, 1H), 2.85 (d, *J* = 69.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.91, 136.02, 135.58, 135.21, 128.58, 127.72, 127.40, 127.14, 126.53, 125.86, 54.13, 49.75, 35.97, 32.14, 28.65.

N-Methyl-N-phenylbenzamide (**3ah**).[35] Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 7.9, 6.6 Hz, 2H), 7.16–7.02 (m, 6H), 6.95 (d, *J* = 7.6 Hz, 2H), 3.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.64, 143.88, 134.90, 128.55, 128.10, 127.67, 126.68, 125.87, 125.45, 37.36.

N,N-Diethylbenzamide (**3ai**).[35] Colourless oil. ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.60–7.30 (m, 5H), 3.54 (s, 2H), 3.25 (s, 2H), 1.27–0.98 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.32, 136.24, 128.08, 127.37, 125.26, 42.26, 38.25, 30.49, 29.12, 13.18, 11.89.

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