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ARTICLE TYPE

# Multistep synthesis of amides from alcohols and amines in continuous flow microreactor systems using oxygen and urea hydrogen peroxide as oxidants

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By integrating a heterogeneous oxidation step, gas-liquid separation, and an oxidative amidation reaction to form a continuous system, a multistep synthetic protocol has been demonstrated to produce amides under mild conditions using alcohols and amines as the starting materials. The use of inexpensive oxygen and urea hydrogen peroxide as the only oxidants affords an economical and adaptable synthetic route for amides.

The amide linkage is an important functional group due to its extensive presence in natural products, pharmaceutical compounds, and synthetic polymers. Compared to the general synthetic methods based on the reaction between activated forms of carboxylic acids and amines, the synthesis of amides directly from alcohols and amines would be a desirable chemical transformation.<sup>1,2</sup> It would afford a highly economical synthetic route due to the availability and stability of the starting materials.

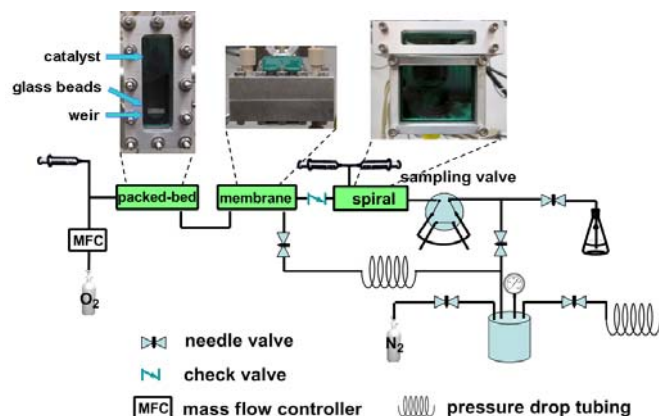
Only a limited number of systems have been developed so far to achieve this transformation, which are promoted by homogeneous or heterogeneous catalysts.<sup>1-3</sup> Ru- or Rh-based transition metal complexes,<sup>4-8</sup> Ag- or Au-based supported catalysts<sup>9,10</sup>, and Cu salt<sup>11</sup> have been used to directly convert alcohols and amines into amides. These synthetic protocols share a common underlying mechanism that 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<sub>2</sub> liberation or H transfer to a hydrogen acceptor. Since alcohols are less reactive and an increase in their oxidation level is required for this type of transformation, the synthetic strategies would involve oxidative activation of the alcohols. Another key feature of such strategies is that both oxidation steps, (1) and (3), are necessarily catalyzed by the same catalyst, making catalyst development extremely challenging. Additionally, the last step, which needs to regenerate the catalyst in order to render the process catalytic, usually produces gaseous hydrogen as a by-product or employs sacrificial hydrogen accepting reagents. This aspect poses additional challenges on system design to handle H<sub>2</sub> or on product isolation.

A strategy to overcome the close “coupling” of the two oxidation steps is to design two separate reactions to achieve the same net transformation. Such “decoupling” would allow each oxidation step to be carried out independently and therefore create more possibilities to improve the overall reaction, such as increase selectivity, improve efficiency, and lower environmental impact. In addition, the relatively larger number of well-established processes to convert alcohols into aldehydes<sup>12</sup> and aldehydes (with amines) into amides<sup>13</sup> provides a considerably wider design space to develop processes that would cover a broader range of substrates. However, the added complexity in multistep batch reactions, as compared with one-pot processes, can make such development efforts time-consuming and less efficient.

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.<sup>14-16</sup> 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. Furthermore, microreactors use minimum amounts of materials, which can be particularly beneficial when the systems involve expensive catalysts or reagents. Additionally, the temperature and pressure can be precisely controlled, leading to enhanced safety and higher selectivity.

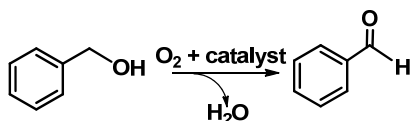
We present here a multistep synthetic protocol developed in continuous flow microreactor systems to directly convert aromatic alcohols and secondary amines into amides. The reaction system consists of three micro-system devices: (i) a packed-bed microreactor to catalytically oxidize alcohols into aldehydes using O<sub>2</sub> as the oxidant and Ru/Al<sub>2</sub>O<sub>3</sub> as the catalyst; (ii) a membrane separator to extract the residual O<sub>2</sub> out of the system; (iii) a spiral-channel microreactor to convert aldehydes and amines into amides using urea hydrogen peroxide (UHP) as the oxidant without any catalyst or promoter. The use of the membrane separator to remove the predominant gas phase allows for control of residence time for the spiral-channel reactor. Our system is continuously

operated under mild conditions with a total residence time of 45 min. The use of widely available alcohols and amines as starting materials and inexpensive oxidizing agents ( $O_2$  and UHP) offers an economical synthetic route to amides.

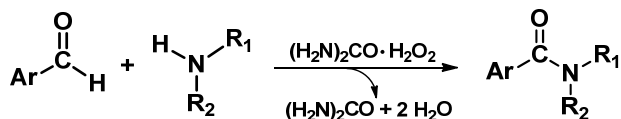


**Fig. 1** Diagram of the experimental setup for multistep synthesis of amides from alcohols and amines. Photos of the three micro-system devices (a packed-bed microreactor, a gas-liquid membrane separator, and a spiral-channel microreactor) are also shown.

The experimental setup (Fig. 1) consists of three micro-system devices: a packed-bed microreactor, a membrane separator, and a spiral-channel microreactor. The first reactor<sup>17</sup> is a silicon-Pyrex microreactor with a single-channel ( $27 \times 8 \times 0.6 \text{ mm}^3$ ). An array of pillars was fabricated downstream of the reactor with  $25 \text{ }\mu\text{m}$  intervals as a weir to hold the catalytic materials inside the channel. The stainless steel packaging chuck allows the device to be heated and pressurized. The separator<sup>18</sup> is constructed of two stainless steel chucks with a single channel ( $20 \times 2 \times 1 \text{ mm}^3$ ) on each piece. A piece of Zefluor membrane (Pall,  $0.5 \text{ }\mu\text{m}$  pore size) is sandwiched between the two pieces that are compressed together. It operated at ambient temperature in our experiments. The third device is a silicon-Pyrex microreactor ( $220 \text{ }\mu\text{L}$  in total volume) with a spiral channel.<sup>19</sup> The mixing and reaction zones are separated by a halo etched region.



**Scheme 1** Oxidation of benzyl alcohol to form benzaldehyde as a probe reaction for catalyst screening with the packed-bed microreactor using molecular oxygen as the oxidant.

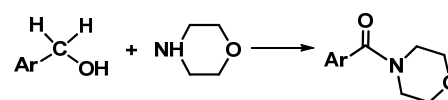


**Scheme 2** Amidation of aromatic aldehydes by secondary amines to form amides in the spiral-channel microreactor using urea hydrogen peroxide (UHP) as the oxidant. Ar: aromatic groups.

Each of the three unit operations—heterogeneous catalysis, separation, and amidation—was studied and optimized before forming a continuous network. Reaction parameters and

variables, including catalytic material, reaction temperature, concentrations of starting materials, back pressure, and residence time were varied in the optimization process. Specifically, using the catalytic oxidation of benzyl alcohol to form benzaldehyde as a probe reaction (Scheme 1), we studied a range of supported Pt-, Pd-, Au- and Ru-based catalytic materials and identified Ru/ $\text{Al}_2\text{O}_3$ -5wt% (Alfar Aesar)<sup>20</sup> to be the most efficient catalyst without any additives/promoters. A stable conversion of 95% was successfully obtained with the reaction running continuously for 24 h at  $80 \text{ }^\circ\text{C}$ . For the membrane separator, pressure control is crucial to achieve good separation.<sup>16, 18</sup> The back pressure at the outlet for the liquid phase was controlled by a stainless steel vessel that is connected to a high-pressure nitrogen cylinder and the pressure difference between the two outlets was provided by a pressure drop tubing ( $100 \text{ }\mu\text{m}$  ID). The liquid stream was fed into the spiral-channel microreactor where the aldehyde merged with urea hydrogen peroxide (UHP) and amine to produce amide (Scheme 2). The use of UHP is an improvement over our previous work<sup>13</sup> using aqueous  $\text{H}_2\text{O}_2$ , which decomposes over time to generate gas bubbles. UHP makes the process more stable, controllable, and adaptable.

**Table 1** Multistep synthesis of amides in continuous flow microreactor systems from aromatic alcohols and morpholine using  $O_2$  and urea hydrogen peroxide as oxidants<sup>d</sup>

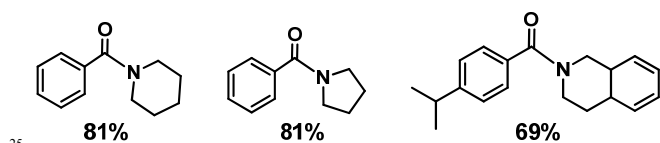


Entry	Alcohol	T ( $^\circ\text{C}$ ) <sup>b</sup>	Conversion (%) <sup>c</sup>	Yield (%) <sup>d</sup>
1		100	95	86
2		110	86	81
3		100	>99	90 <sup>e</sup>
4		120	>99	94
5		130	97	88
6		110	>99	79
7		130	97	79
8 <sup>f</sup>		130	>99	89
9 <sup>f</sup>		110	96	69
10		120	>99	97
11		90	>99	79
12		120	>99	81

<sup>a</sup> Reaction conditions are as follows. Packed-bed microreactor:  $5 \text{ }\mu\text{L}/\text{min}$  flow rate for alcohol ( $0.1 \text{ M}$  in acetonitrile),  $200 \text{ }\mu\text{L}/\text{min}$  flow rate for gaseous oxygen,  $80 \text{ }^\circ\text{C}$ . The estimated residence time based on the total flow rate is  $19 \text{ s}$ . Spiral-channel microreactor:  $2.5 \text{ }\mu\text{L}/\text{min}$  flow rate for both morpholine ( $4\text{M}$  in acetonitrile) and UHP ( $2\text{M}$  in dimethyl sulfoxide),  $90$ - $130 \text{ }^\circ\text{C}$ ,  $22 \text{ min}$  residence time, unless otherwise indicated.

<sup>b</sup> Reaction temperature for the spiral-channel microreactor. <sup>c</sup> GC conversion. <sup>d</sup> GC yield. <sup>e</sup> Isolated yield: 84% (see ESI<sup>†</sup> for details). <sup>f</sup> Initial reagent concentrations:  $8\text{M}$  for morpholine and  $4\text{M}$  for UHP.

The substrate scope of this multistep methodology was determined by investigating different types of alcohols and amines to produce the corresponding amides. We have found that our strategy is suitable to prepare a wide range of amides starting from aromatic alcohols (Table 1). The reactions with morpholine were performed under mild conditions with the temperature for the packed-bed reactor at 80 °C and that for the spiral-channel reactor at 90-130 °C. Functional groups on the phenyl ring do not significantly affect the reaction (Entries 1-9). Excellent conversion was achieved with yields ranging from 69 to 94%. The main by-product is the corresponding aldehyde, with yields in the range of 2-15%. Our synthetic protocol can be extended to heterocyclic aromatic alcohols (Entries 10-12) under similar reaction conditions with good to excellent yield toward the corresponding amides. Allylic alcohols were also investigated as potential substrates and lower yield was obtained. For example, although 95% of cinnamyl alcohol was converted into cinnamaldehyde, the amidation step was less efficient, resulting in the amide yield of 67%. Aliphatic alcohols, however, are not compatible with our system. In addition, this process can be applied to other secondary amines, including piperidine, pyrrolidine, and 1,2,3,4-tetrahydroisoquinoline, to form amides under similar conditions (Fig. 2).



**Fig. 2** Amides synthesized with the multistep continuous flow system utilizing piperidine, pyrrolidine, or 1,2,3,4-tetrahydroisoquinoline. The reaction temperature for the amidation step is 110 °C with the other conditions the same as those for morpholine.

For the purpose of establishing a workup protocol for our multistep synthesis to determine the isolated yield toward the amide products, 32 samples were collected and combined within a total reaction period of 24 h using 4-chlorobenzyl alcohol and morpholine as the starting materials (Table 1, Entry 3). No catalyst deactivation was observed and quantitative gas-liquid separation was achieved through the process. The obtained product mixture underwent extraction, concentration, column chromatography, and solvent evaporation to yield 4-(4-chlorobenzoyl)morpholine with the yield of 84% (see ESI<sup>†</sup> for details).

The underlying reaction mechanism involves aldehyde as an intermediate species that couples with amine to form amide with the assistance of H<sub>2</sub>O<sub>2</sub> that is released from the urea hydrogen peroxide adduct under our reaction conditions. This coupling step is a direct adaptation of our previous method<sup>13</sup> for oxidative amidation of aromatic aldehydes, with H<sub>2</sub>O<sub>2</sub> being replaced by urea hydrogen peroxide, further demonstrating the versatility of this continuous multistep synthetic strategy.

In summary, the integration of a heterogeneous oxidation step, gas-liquid separation, and an oxidative amidation reaction represents an effective protocol for amide synthesis under mild conditions using alcohols and amines as the

starting materials. The use of inexpensive oxygen and urea hydrogen peroxide as the only oxidants affords a more economical and adaptable synthetic route. 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. Despite sharing the same general mechanistic features, this approach differs considerably from previous and current research efforts on developing catalysts that promotes both the activation of alcohols and amidation of the resultant aldehydes in one pot. By decoupling the key reaction steps, such continuous systems provide new opportunities for organic synthesis in general, building upon the extensive literature on conversion of various functional groups.

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## Notes and references

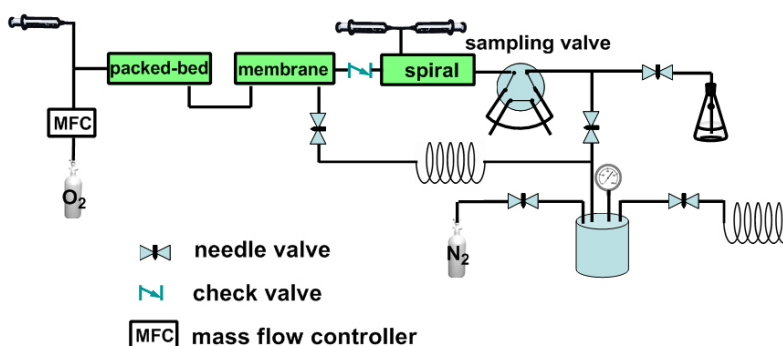
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- <sup>†</sup> Electronic Supplementary Information (ESI) available: Experimental setup and product isolation. See DOI: 10.1039/b000000x/
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## Multistep synthesis of amides from alcohols and amines in continuous flow microreactor systems using oxygen and urea hydrogen peroxide as oxidants

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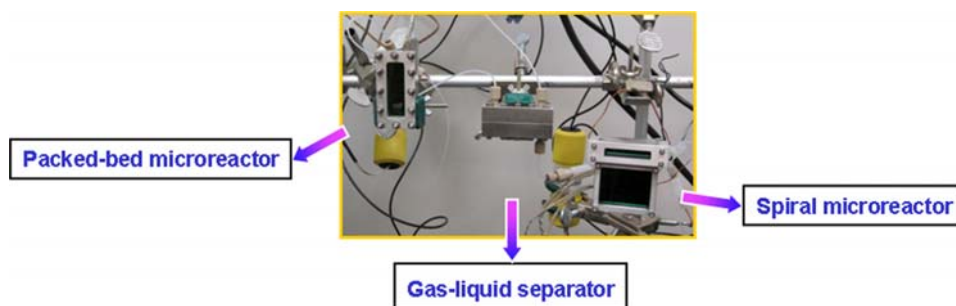
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### Construction of microreactor systems



**Figure S1** Diagram of the experimental setup for multistep synthesis of amides from alcohols and amines.

The experimental setup (Figure S1) consists of three micro-system devices (Figure S2): a packed-bed microreactor, a membrane separator, and a spiral-channel microreactor. The first reactor is a silicon-Pyrex microreactor with a single-channel ( $27 \times 8 \times 0.6 \text{ mm}^3$ ). An array of pillars was fabricated downstream of the reactor with  $25 \mu\text{m}$  intervals as a weir to hold the catalytic materials inside the channel. The stainless steel packaging chuck allows the device to be heated and pressurized. The separator is constructed of two stainless steel chucks with a single channel ( $20 \times 2 \times 1 \text{ mm}^3$ ) on each piece. A piece of Zefluor membrane is sandwiched between the two pieces that are compressed together. The third device is a silicon-Pyrex microreactor ( $220 \mu\text{L}$  in total volume) with a spiral channel. The mixing and reaction zones are separated by a halo etched region.



**Figure S2** Photo of the three micro-system devices forming a continuous network.

### ***Product isolation***

The product (Table 1, Entry 3), 4-(4-chlorobenzoyl)morpholine, was isolated following a procedure described below. The reaction mixture was collected by combining 32 samples from the same stock solutions running continuously for a total reaction time of 24 h. Water was then added followed by extraction using dichloromethane for 4 times. The organic layers were combined and concentrated under vacuum. Purification was performed with column chromatography (silica gel, dichloromethane:ethyl acetate 5:1 for first column and hexane:ethyl acetate 4:5 for second column) and the solvent was removed under vacuum to give light yellow crystals. Nuclear Magnetic Resonance spectra were obtained on a Bruker 400 MHz instrument with deuterated chloroform as the solvent. Chemical shifts of  $^1\text{H}$  were relative to the residual chloroform and those of  $^{13}\text{C}$  to deuterated chloroform.  $^1\text{H}$  NMR:  $\delta$  3.30-3.90 (m, 8H), 7.30-7.39 (m, 4H);  $^{13}\text{C}$  NMR:  $\delta$  67.0, 128.9, 129.1, 133.8, 136.2, 169.6.