Very Important Publication

# Zirconium Oxide-Catalyzed Direct Amidation of Unactivated Esters under Continuous-Flow Conditions

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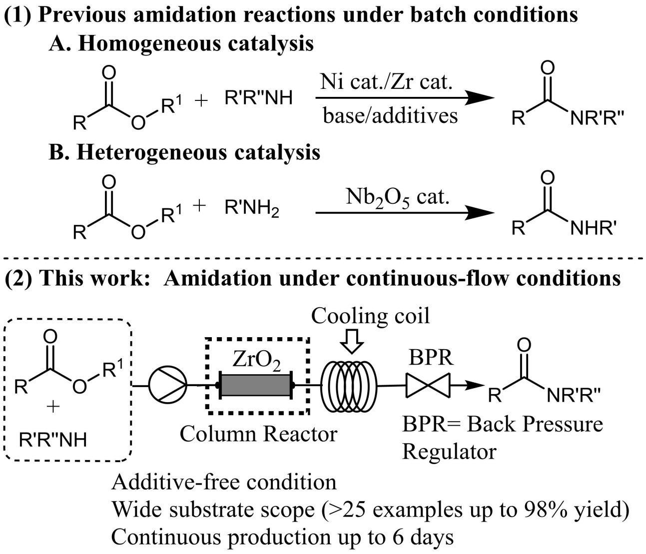
**Abstract:** A sustainable and environmentally benign direct amidation reaction of unactivated esters with amines has been developed in a continuous-flow system. A commercially available amorphous zirconium oxide was found to be an efficient catalyst for this reaction. While the typical amidation of esters with amines requires a stoichiometric amount of a promoter or metal activator, the present continuous-flow method enabled the direct amidation reaction under additive-free conditions with an extensive diversity towards various functional groups. High yields of the products were obtained with a nearly equimolar proportion of starting materials to reduce byproduct formation, which renders this process applicable for use in a sequential-flow system.

**Keywords:** amidation reaction; unactivated esters; amorphous zirconium oxide; additive-free conditions; continuous-flow method

Esters are one of the most important and ubiquitous functional groups in natural and synthetic organic compounds.[1] Therefore, the transformation of ester groups into other functional groups under mild and neutral conditions is particularly desirable in the context of organic synthesis. In particular, the direct amidation of esters with amines to give amides has received growing attention, since it generates an alcohol as the only co-product.[2] Moreover, the formation of amide bonds has been investigated intensively due to the importance of this functional group in peptides and proteins, in addition to its presence in various fine chemicals, polymers, and pharmaceuticals.[3]

Although several methods have been reported for the amidation of esters, the development of atom-economical green synthetic routes that do not generate waste or require the use of hazardous reagents remains a challenge.[4] Usually, the direct amidation reaction of esters with amines requires a stoichiometric amount of promoter or metal activator.[5] Unlike reactive carboxylic acid phenyl esters, the alkyl esters of carboxylic acids are inert substrates, and harsh reaction conditions are generally required to promote the amidation reaction.[6] Notable examples of some homogeneous catalytic systems have been developed for use in the ester-to-amide transformation, which involve combinations of metal alkoxides with additives, or the azeotropic removal of the alcohol co-product (Scheme 1(1), A and B).[7] However, these homogeneous catalytic systems do not tend to favor catalyst reuse, since catalyst-product separation can be challenging. To the best of our knowledge, the first heterogeneous $Nb_2O_5$ catalytic system for this type of reaction was developed by Shimizu and co-workers,[3a,b] where the required reaction time for the

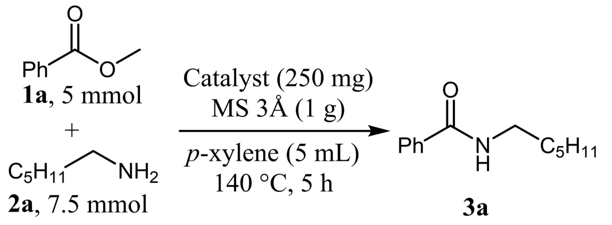


**Scheme 1.** State of art for the different approaches to the amidation of esters.

batch synthetic process was ~30 h at 140 °C (Scheme 1(1), B).

Currently, to green and sustainable manufacturing, the pharmaceutical and fine chemical industries have been focusing on continuous-flow systems rather than conventional batch production methods. The continuous-flow reaction has substantial advantages over the batch reaction in terms of its efficiency, easy handling, scale-up with automatic control, high selectivity, reproducibility, direct use of intermediates without any purification, and, more importantly, in many cases, its superior safety and environmental compatibility.[8] The replacement of batch reactions with a continuous-flow manner is of particular interest.[9] We therefore envisioned establishing a new reaction under flow conditions, and herein report the general, fast, and high-yielding continuous-flow amidation of unactivated esters with amines using a heterogeneous $ZrO_2$ catalyst (Scheme 1(2)).

**Table 1.** Catalyst screening for the amidation reaction of methylbenzoate (**1 a**) with hexylamine (**2 a**) via the batch method.



| Entry | Catalyst | **3 a** (%)[a] |
|---|---|---|
| 1[b] | $Nb_2O_5$ | 6 |
| 2 | $TiO_2$ | 9 |
| 3 | $SiO_2$ | 6 |
| 4 | $CeO_2$ | 11 |
| 5 | $ZrO_{2\ \text{amorphous zirconia}}$ (ZrO–A) | 46 (93)[d] |
| 6[c] | ZrO-A | 27 (71)[d] |
| 7 | $ZrO_{2\ \text{crystalline zirconia}}$ (ZrO–C) | 45 (86)[d] |
| 8[e] | Nb/ZrO-A | 42 (76)[d] |
| 9[e] | $Nb/CeO_2$ | 34 |
| 10[e] | $Nb/TiO_2$ | 5 |
| 11[e] | $Nb/SiO_2$ | 12 |
| 12 | $Zr/CeO_2$ | 8 |
| 13 | Mont. K10 | 51 (84)[d] |
| 14[c] | Mont. K10 | 5 (9)[d] |
| 15 | $Zr^{4+}$–Mont. | 28 |
| 16 | $Na^{+}$–Mont. | 7 |
| 17 | $Nb^{5+}$–Mont. | 15 |
| 18 | Amberlyst-15 | 2 |

[a] GC yields were calculated using *n*-dodecane as an internal standard.

[b] $Nb_2O_5$ was prepared by the calcination of $Nb_2O_5{\cdot}nH_2O$ (CBMM) at 500 °C for 3 h under air.

[c] Reaction conducted without MS 3Å.

[d] The yields of **3 a** after a 16 h reaction time are shown in parentheses.

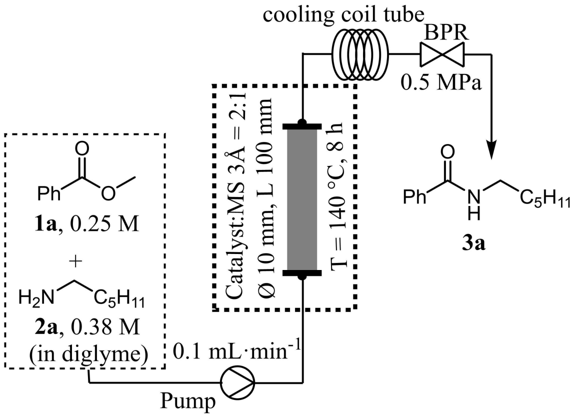
[e] Supported Nb and Zr catalysts (10 wt%) were prepared via a wet impregnation method from an aqueous solution of ammonium niobate(V) oxalate hydrate ($C_4H_4NNbO_9{\cdot}xH_2O$) and zirconium oxychloride hydrate ($ZrCl_2O\cdot 8H_2O$), respectively.

As a preliminary investigation, catalyst screening for the amidation reaction of methyl benzoate (**1 a**) with hexylamine (**2 a**) was performed under batch conditions, as shown in Table 1. The reaction was carried out using several commercially available Lewis and Brønsted acid catalysts, including $Nb_2O_5$, $TiO_2$, $SiO_2$ (CARiACT Q-10), amorphous zirconia (denoted as ZrO–A), crystalline zirconia (denoted as ZrO–C), $CeO_2$, Mont. K10, and Amberlyst-15. In addition, some supported and ion-exchanged Nb and Zr catalysts (Nb/ZrO–A, $Nb/CeO_2$, $Nb/TiO_2$, $Nb/SiO_2$, $Zr/CeO_2$, $Nb^{5+}$–Mont., and $Zr^{4+}$–Mont.) were prepared and their catalytic activities were compared with those of commercially available catalysts (Table 1). Among the examined catalysts, the Mont. K10 catalyst gave the highest yield of the desired product *N*-hexylbenzamide (**3 a**) within 5 h (51%, Table 1, entry 13). Other competitive catalysts were ZrO–A, ZrO–C, and Nb/ZrO–A, which afforded 46, 45, and 42% yields, respectively, within the same reaction time (Table 1, entries 5, 7–8). A longer reaction time of 16 h resulted in the amorphous zirconia catalyst (ZrO–A) giving the highest yield of **3 a** (93%), while the other crystalline zirconia (ZrO–C), Nb/ZrO–A, and Mont. K10 catalysts gave 86, 76, and 84% yields, respectively (Table 1, entries 5, 7, 8, 13). Furthermore, control experiments in the absence of molecular sieves (MS 3Å) indicated that Brønsted acidic Mont. K10 was less effective towards the amidation reaction compared to the Lewis acidic ZrO–A catalyst (Table 1, entries 6, 14). Therefore, to achieve the full conversion of **1 a** to **3 a** under batch conditions, it is suggested that molecular sieves play an important role in removing methanol (a co-product) from the reaction mixture. (see details in the Supporting Information (SI), Table S1). In addition, a catalytic activity drop by methanol has made a huge difference between Brønsted and Lewis acid catalysts.

After optimization of the batch conditions, we subsequently focused on the development of the flow amidation reaction using model substrates **1 a** and **2 a**. More specifically, a mixture of **1 a** (0.25 M) and **2 a** (0.38 M) was pumped at a flow rate of 0.1 mL·min$^{-1}$ through a SUS column (Ø 10 mm I.D × 100 mm L). The column was filled with a mixture of a catalyst and molecular sieves in a 2:1 ratio. Initially, solvent screening was performed using the optimal ZrO–A catalyst at 140 °C in a continuous flow system, where diethylene glycol dimethyl ether (diglyme) was found to be the best solvent for this reaction (80% yield of **3 a**; see details in SI, Table S2). Using other compatible catalysts from the batch reaction, the flow amidation reaction was performed, and the results are listed in Table 2. It was observed that the amidation reaction did not proceed in the absence of the catalyst (Table 2, entry 1), while the amorphous ZrO–A catalyst in the conversion of **1 a**, with a 80% yield of product being recovered after 8 h (Table 2, entry 2). In contrast, low yields were observed when the crystalline ZrO–C and calcined ZrO–A catalysts were employed (Table 2, entries 3–4), suggesting that crystallinity of zirconium species and/or its surface area are key factors for its catalytic activity. The Brønsted acidic Mont. K10 exhibited very low catalytic activity in the amidation reaction under continuous-flow conditions (Table 2, entry 5). We assume that this is due to the co-existence of methanol in a catalyst column which could not be removed by molecular sieves under continuous-flow conditions at elevated temperature.

Subsequently, optimization of the reaction conditions was carried out in the continuous-flow system using the ZrO–A catalyst (Table 3). Since the removal of methanol with molecular sieves was required during the batch reaction, optimization under flow conditions began with a high loading of molecular sieves (i. e., ~4 g ZrO–A and ~8 g MS 3 Å, Table 3, entry 1). Furthermore, the amidation reaction was also performed in the absence of molecular sieves (i. e., ~6 g ZrO–A, Table 3, entry 2). In contrast to the case of the

**Table 2.** Catalyst screening for the amidation reaction of **1 a** with **2 a** in a continuous-flow system.



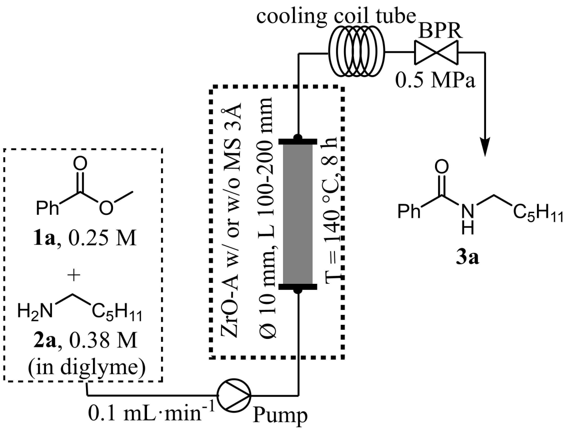
| Entry | Catalyst[a] | Conv. (%) | 3a (%)[b] |
|---|---|---|---|
| 1 | MS 3 Å | < 1% | 0 |
| 2 | ZrO–A | 86 | 80 |
| 3 | ZrO–C | 51 | 45 |
| 4[c] | ZrO–A | 47 | 38 |
| 5 | Mont. K10 | 16 | 12 |

[a] A catalyst:MS 3Å ratio of 4:2 (w/w) was used.

[b] Yields were determined by GC analysis using *n*-dodecane as an internal standard.

[c] The catalyst was calcined at 200 °C for 3 h in air prior to use.

**Table 3.** Optimization of the amidation reaction of **1 a** with **2 a** in a continuous-flow system.



| Entry | Temp. (°C) | Conv. (%) | 3a (%)[a] |
|---|---|---|---|
| Table 2, entry 2 | 140 | 86 | 80 |
| 1[b] | 140 | 85 | 81 |
| 2[c] | 140 | 85 | 80 |
| 3[c] | 150 | 93 | 91 |
| 4[c] | 160 | 99 | 98 |
| 5[c,d] | 160 | 99 | 98 |
| 6[c,d,e] | 160 | 99 | 98 |

[a] Yields were determined by GC using *n*-dodecane as an internal standard.

[b] A 10 mm × 200 mm column was used with a ZrO–A:MS 3Å ratio of 4:8 (w/w).

[c] Approximately 6 g of ZrO–A catalyst (without MS 3Å) was used in a Ø 10 mm × 100 mm column.

[d] [**1 a**] = 0.4 M.

[e] [**2 a**] = 1.2 equiv. of [**1 a**].

batch method, it was observed that the conversion and selectivity did not change significantly in the absence or presence of molecular sieves at 140 °C, even when an increased amount of catalyst was used. These results suggest that the molecular sieves have little influence on the continuous-flow system. To understand this in better detail, a control continuous-flow reaction between product **3 a** (0.25 M) and methanol (1.5 equiv.) was performed at 140 °C (see details in SI, Table S3), whereby a slow amide-to-ester transformation resulted in a 2.6% yield of ester **1 a**. This implies that ester **1 a** and amide **3 a** are in equilibrium at this temperature. Due to the continuous feeding of the reaction mixture, the molecular sieves were saturated with methanol, and at high temperatures, the activity of the molecular sieves was reduced, and so they were not required in the continuous-flow system. Thus, to accomplish the full conversion of **1 a** to the desired product, the reaction was conducted at higher temperature. Fortunately, a higher conversion was observed at higher temperatures, and a 98% yield of the product was obtained at 160 °C (Table 3, entry 4). Furthermore, the optimum concentration of **1 a** was found to be 0.4 M, and **2 a** was successfully reduced to 1.2 equiv. to the substrate (Table 3, entries 5–6; see details in SI, Table S4). In this case, the material balance for **1 a** was determined to be 99%, where the molar ratio of **1 a** to **2 a** was 1:1.2 (see details in SI, Table S5).

The durability and feasibility of the integrated catalyst column in the flow system were then tested over the long-time amidation of **1 a** under the optimized reaction conditions. The developed system produced amide **3 a** in yields of 94–98% over the course of a 140 h period (Figure 1). However, towards the end of the reaction, a gradual decrease in the yield was observed. This was attributed to the accumulation of a small amount of reactant or product on the catalyst surface. Following washing of the catalyst with diglyme at 160 °C for 5 h, its catalytic performance was regenerated, returning the product yield to 98% once again (see details in SI, Figure S3). These results indicate that our catalytic system should be highly suitable for application in a continuous-flow amidation reaction. In addition, a space-time yield (STY) of 7.03 $g h^{-1} dL^{-1}$ was achieved with a turnover frequency (TOF) of 3.3 $h^{-1}$.

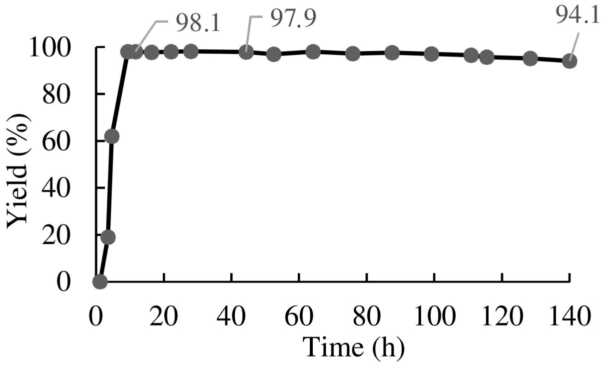
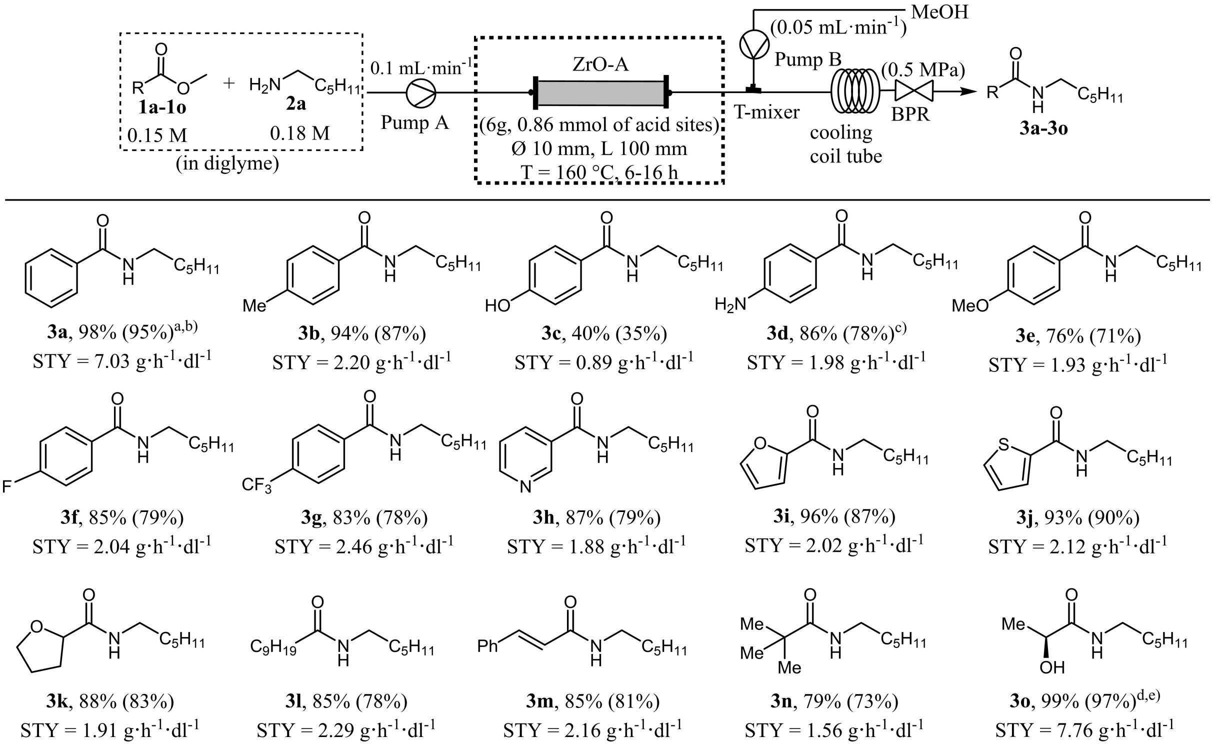


**Figure 1.** Investigation of the durability of the ZrO–A catalyst over a long-time amidation reaction. Reaction conditions: catalyst (6 g), methyl benzoate (**1 a**, 0.4 M), hexylamine (**2 a**, 0.48 M), *n*-dodecane (0.05 M), reactor temperature 160 °C, and flow rate 0.10 mL $min^{-1}$.

Following optimized conditions (Table 3, entry 6), substrate scopes were examined. Importantly, our catalytic system was found to be highly tolerant towards a wide range of sterically diverse ester and amine functionalities. The reaction scope with respect to the reaction of various esters (**1 a**–**1 o**) with **2 a** was examined (Scheme 2), where electron-donating (**1 b**–**1 e**) and withdrawing (**1 f**–**1 g**) substituents bearing benzoic acid esters were reacted efficiently to give their corresponding amides in isolated yields of 35–95%. Some heteroatom-containing aromatic and aliphatic esters (**1 h**–**1 k**) were also successfully transferred to their analogous amides in 79–90% isolated yields. Similarly, aliphatic esters such as a decanoate ester (**1 l**), a cinnamate ester (**1 m**), and a sterically hindered pivalate ester (**1 n**) were also well tolerated in this reaction to give their corresponding amides in high isolated yields (73–81%). Furthermore, the enantiopure L-methyllactate (**1 o**) was successfully converted to the corresponding enantiopure amide (**3 o**, 99%) with almost no racemization of the stereocenter (> 97% ee, see details in SI, Figure S31). It should be noted that this is the first successful example of a catalytic method for the preparation of enantiopure amides from challenging unactivated esters under continuous-flow conditions.

Subsequently, we surveyed the scope of amine component (Scheme 3). More specifically, benzylic (**2 b**, **2 c**) and aliphatic primary amines (**2 d**), in addition to heteroatom-containing primary amines, such as furfuryl amine (**2 e**), thiophenmethylamine (**2 f**), and propanolamine (**2 g**), worked well under the standard reaction conditions to give the desired products in 50–88% isolated yield. On the other hand, non-nucleophilic aniline derivatives (**2 h**–**2 j**) and secondary aliphatic amines (**2 k**–**2 m**) were found to be less reactive towards the present catalytic system. Similarly, no racemization was observed during the synthesis of the optically active *N*-((*R*)-1-phenylethyl)-benzamide (**4 c**), as outlined in SI Figure S32. Moreover, we successfully developed a continuous-flow method for the direct synthesis of the antidepressant drug molecule Moclobemide[10] (Scheme 4), which elucidates an alternative, facile, and environmentally benign route for future applications.

In conclusion, we demonstrated an efficient route to convert esters into amides under continuous-flow conditions. The present flow system established an



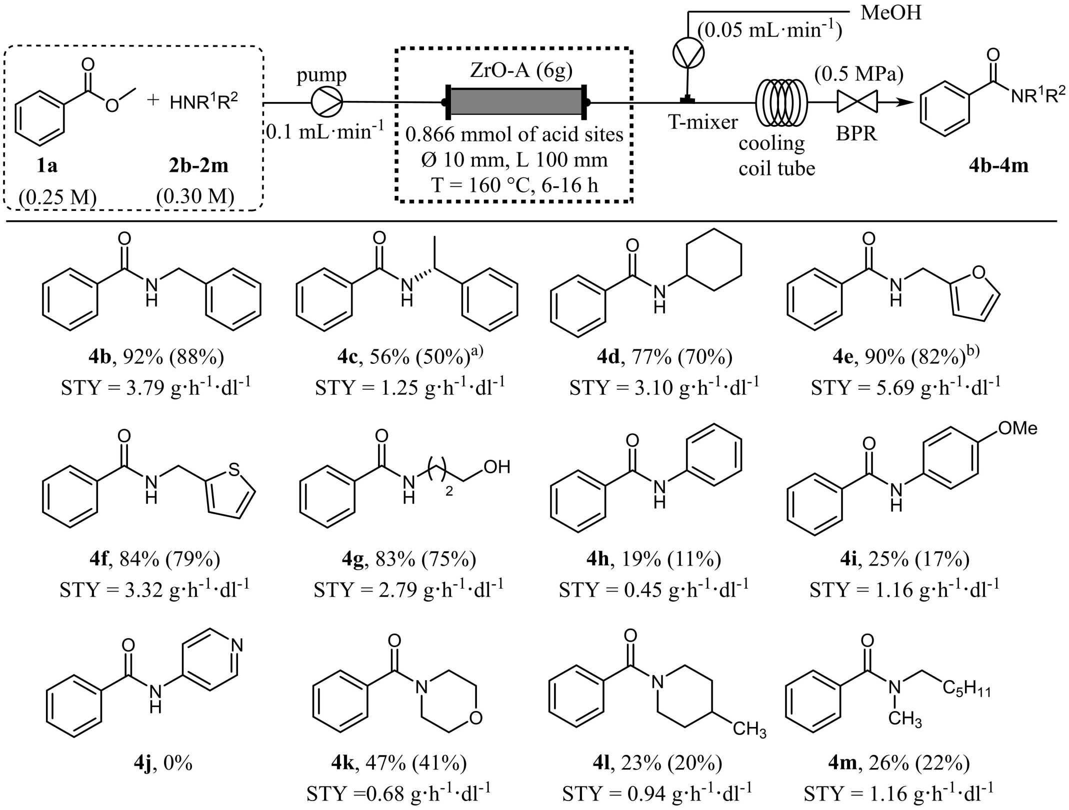
**Scheme 2.** The amidation of various esters with hexylamine. GC yields were determined using *n*-dodecane as an internal standard. Isolated yields are shown in parentheses. [a] 0.4 M Methylbenzoate and 0.5 M hexylamine were used. [b] No external solvent was passed through the T-mixer. [c] Ethyl ester was used instead of methyl ester. [d] >97% ee. [e] [**1o**] = 0.6 M, >99% ee, catalyst: Celite = 2:1 at reactor temperature of 150 °C.

alternative synthetic method for amides without any requirement for additives. More specifically, the reaction of unactivated esters with amines in the presence of an amorphous $ZrO_2$ catalyst was successful in producing various amides. The described methodology is broad in scope and proceeds using only 1.2 equivalents of the amine nucleophile. Thus, our method is preferably suited for the use in multi-step organic synthesis in the context of the material balance. Moreover, selective amide-bond formation was achieved in the presence of various functional groups, and without the racemization of the stereocenters of enantiopure substrates. Further study of this continuous-flow rection is currently ongoing in our laboratory, aiming an expansion of the scope as well as the process intensification toward practical synthesis of fine chemicals.

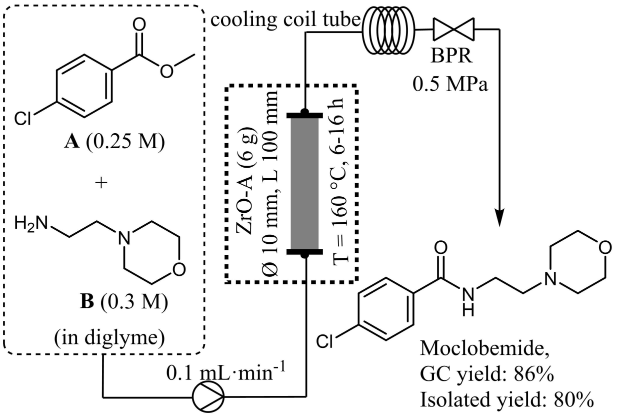
## Experimental Section

Typical procedure for catalytic amidation reaction in batch conditions: A Pyrex test-tube (30.0 mL) was charged with **1a** (5.0 mmol), **2a** (7.5 mmol), catalyst (250 mg), *p*-xylene (5.0 mL), and *n*-dodecane (0.2 mmol, an internal standard). A PTFE basket containing the molecular sieves (MS 3Å pellets, 0.5 g) was placed at the upper side of the reaction tube to remove the methanol formed as a co-product (see SI, Figure S2). The tube was equipped with a reflux condenser and was placed on an EYELA PPV-3000 ChemiStation. The reaction mixture was heated to 160 °C and stirred at 300 rpm for 5 h under aerobic conditions. After the designated reaction time, the reaction mixture was cooled to room temperature, ethyl acetate (3 mL) was added, and an aliquot was analyzed by GC (SHIMADZU GC-2014 instrument) with flame ionization detection using a DB-01 capillary column (30 m, 0.25 mm, 0.25 μm). A crude mixture was purified by column chromatography on silica gel 60 (spherical, 50–100 μm, Kanto Chemical Co., Ltd.) with hexane/ethyl acetate (70/30) as an eluent. An isolated product was analyzed by GC, GC-MS, $^1H$, and $^{13}C$ NMR spectroscopy.

Typical procedure for the continuous flow amidation reaction: A Ø 10 mm I.D × 100 mm L SUS column was filled with the ZrO–A catalyst (6 g, 0.86 mmol acid sites) and placed in an EYELA MCR-1000 flow reactor (SI, figure S1). Initially, diglyme was flowed through the column at a rate of 0.2 mL/min flow rate to purge out the internal gases at room temperature, and then with gradual heating to 160 °C for ~1 h. Subsequently, the flow rate was set to 0.1 mL/min with a 0.5 MPa back pressure. The reaction was initiated by changing the solvent flow to the reaction feed (stock solution of **1a** (0.40 M), **2a** (0.48 M), and *n*-dodecane (0.05 M) in diglyme) at a flow rate of 0.1 mL/min. The crude reaction mixture was collected from the outlet using a fraction collector (EYELA DC-1000), and the yield of product in each fraction was determined by GC



**Scheme 3.** Amidation of various amines with methylbenzoate. GC yields were determined using *n*-dodecane as an internal standard. Isolated yields are shown in parentheses. [a] **2 c** (99% ee) was used to give **4 c** in >99% ee. [b] [**1 a**] = 0.4 M and [**2 e**] = 0.48 M.



**Scheme 4.** Synthesis of anti-depressant drug from 4-chlorobenzoic acid methyl ester (**A**) and *N*-ethylaminomorpholine (**B**) under the continuous-flow conditions described herein.

analysis. The fractions containing the desired product were combined, mixed with water, and a crude product was extracted with ethyl acetate to remove any excess diglyme. The crude product was purified by column chromatography on silica gel 60 using hexane/ethyl acetate (70/30) as an eluent. An isolated yield was determined relative to the starting ester. The final pure product was characterized by $^1$H and $^{13}$C NMR spectroscopy.

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## References

[1] a) C. W. Cheung, M. L. Ploeger, X. Hu, *Nat. Commun.* **2017**, *8*, 14878; b) T. Ohshima, Y. Hayashi, K. Agura, Y. Fujii, A. Yoshiyama, K. Mashima, *Chem. Commun.* **2012**, *48*, 5434; c) M. B. Smith, *Compend. Org. Synth. Methods, Wiley, New York*, **2001**, *9*, 100; d) H. M. Riemenschneider, W. Bolt, *Ullmann's Encycl. Ind. Chem.* **2005**; e) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827–10852.

[2] a) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451–3479; b) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

[3] a) M. A. Ali, S. M. A. H. Siddiki, K. Kon, K. I. Shimizu, *ChemCatChem* **2015**, *7*, 2705–2710; b) M. A. Ali,

S. M. A. H. Siddiki, W. Onudera, K. Kon, K. I. Shimizu, *ChemCatChem* **2015**, *7*, 3555–3561; c) C. G. McPherson, N. Caldwell, C. Jamieson, I. Simpson, A. J. B. Watson, *Org. Biomol. Chem.* **2017**, *15*, 3507–3518; d) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451–3479; e) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; f) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405–3415; g) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606–631; h) H. Lundberg, F. Tinnis, N. Selander, H. Adolfsson, *Chem. Soc. Rev.* **2014**, *43*, 2714–2742; i) T. W. Bousfield, K. P. R. Pearce, S. B. Nyamini, A. Angelis-Dimakis, J. E. Camp, *Green Chem.* **2019**, *21*, 3675–3681; j) G. Orsy, F. Fülöp, I. M. Mándity, *Catal. Sci. Technol.* **2020**, *10*, 7814–7818.

[4] a) B. Gnanaprakasam, D. Milstein, *J. Am. Chem. Soc.* **2011**, *133*, 1682–1685; b) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411–420.

[5] a) T. Shimizu, K. Osako, T. Nakata, *Tetrahedron Lett.* **1997**, *38*, 2685–2688; b) A. Basha, M. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, *18*, 4171–4172; c) T. Gustafsson, F. Pontén, P. H. Seeberger, *Chem. Commun.* **2008**, 1100–1102; d) C. Ferroud, M. Godart, S. Ung, H. Borderies, A. Guy, *Tetrahedron Lett.* **2008**, *49*, 3004–3008; e) J. L. Vrijdag, F. Delgado, N. Alonso, W. M. De Borggraeve, N. Pérez-Macias, J. Alcázar, *Chem. Commun.* **2014**, *50*, 15094–15097; f) T. Ooi, E. Tayama, M. Yamada, K. Maruoka, *Synlett* **1999**, 729–730; g) B. R. Kim, H. G. Lee, S. B. Kang, G. H. Sung, J. J. Kim, J. K. Park, S. G. Lee, Y. J. Yoon, *Synthesis (Stuttg).* **2012**, *44*, 42–50.

[6] T. Ohshima, Y. Hayashi, K. Agura, Y. Fujii, A. Yoshiyama, K. Mashima, *Chem. Commun.* **2012**, *48*, 5434–5436.

[7] a) R. M. De Figueiredo, J. S. Suppo, J. M. Campagne, *Chem. Rev.* **2016**, *116*, 12029–12122; b) T. Ben Halima, J. Masson-Makdissi, S. G. Newman, *Angew. Chem. Int. Ed.* **2018**, *57*, 12925–12929; c) H. Tsuji, H. Yamamoto, *J. Am. Chem. Soc.* **2016**, *138*, 14218–14221.

[8] a) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893; b) R. Gérardy, N. Emmanuel, T. Toupy, V. E. Kassin, N. N. Tshibalonza, M. Schmitz, J. C. M. Monbaliu, *Eur. J. Org. Chem.* **2018**, *2018*, 2301–2351.

[9] a) S. Kobayashi, *Chem. – An Asian J.* **2016**, *11*, 425–436; b) A. Tanimu, S. Jaenicke, K. Alhooshani, *Chem. Eng. J.* **2017**, *327*, 792–821; c) T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, *520*, 329–332.

[10] B. Fulton, P. Benfield, *Drugs* **1996**, *52*, 450–474.

# Zirconium Oxide-Catalyzed Direct Amidation of Unactivated Esters under Continuous-Flow Conditions

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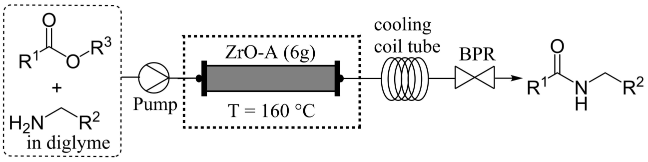

- High yield (up to 98%)
- Wide substrate scopes
- Additive free
- Continuous production (up to 6 days)