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## COMMUNICATION

## Sodium methoxide: a simple but highly efficient catalyst for the direct amidation of esters†

Takashi Ohshima,<sup>a</sup> Yukiko Hayashi,<sup>b</sup> Kazushi Agura,<sup>a</sup> Yuka Fujii,<sup>b</sup> Asako Yoshiyama<sup>b</sup> and Kazushi Mashima<sup>a,b</sup>

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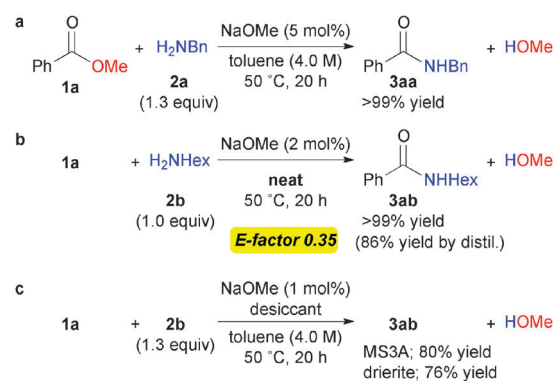
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A simple NaOMe catalyst provides superior accessibility to a wide variety of functionalized amides including peptides through direct amination of esters in an atom-economical and environmentally benign way.

Amides are one of the most ubiquitous and important functional groups in natural and synthetic organic compounds, and the amide bond formation has been intensively investigated in organic synthesis.<sup>1</sup> *In vivo*, protein synthesis (amide bond formation) is performed by ribosomes<sup>2</sup> and the key to this transformation is the catalytic amidation of esters. In the non-enzymatic amide formation, however, esters are viewed as an inert scaffold upon which traditional activation protocols are performed.<sup>1</sup> Unlike reactive phenolic esters, alkyl esters are inert substrates commonly used as protecting groups in peptide synthesis, and rather harsh reaction conditions, such as high temperature, high pressure, or the use of more than stoichiometric amounts of strongly basic reagents, are required to promote amidation. Thus, atom-economical “green” catalytic amide bond formation under mild conditions is in high demand. We searched for a non-enzymatic and rather simple catalyst for the amidation and herein report the first catalytic amidation of esters with amines using very simple NaOMe as the catalyst.

We began by screening nontoxic metal catalysts, minerals available *in vivo*, that mediate not only the amidation of esters with amines under mild conditions with high substrate generality, but also the peptide coupling reaction of chiral  $\alpha$ -amino esters. Although efficient catalytic systems based on inorganic ( $\text{Sb}(\text{OEt})_3$ <sup>3</sup> and  $\text{Zr}(\text{O}^i\text{Bu})_4\text{--HOAt}$ <sup>4</sup>) and organic catalysts (*N*-heterocyclic carbene,<sup>5</sup> DBU,<sup>6</sup> triazabicyclo[4.4.0]dec-5-ene,<sup>7</sup> and 1,2,4-triazole–DBU<sup>8</sup>) have been developed for the amidation of esters, and Ru-catalyzed dehydrogenative amidation<sup>9</sup> and aminolysis of

esters<sup>10</sup> have also been reported, these methods still have much room for improvement in terms of substrate generality and there are no examples of a catalytic peptide coupling reaction of chiral  $\alpha$ -amino esters. After testing several salts of group 1 elements (Li, Na, K) and group 2 elements (Mg, Ca) together with zinc,<sup>11</sup> which are abundant and essential minerals in life, we found that very simple NaOMe was a highly efficient catalyst.<sup>12</sup> Typically, in the presence of 5 mol% of NaOMe, the reaction of methyl benzoate (**1a**) with benzylamine (**2a**) proceeded smoothly at 50 °C to afford the corresponding amide **3aa** in quantitative yield (Scheme 1a). Not only sodium alkoxides, but also potassium alkoxides, had high catalytic activity, whereas lithium alkoxides and calcium alkoxides had poor activity. In addition, neither alkali metal carbonates nor alkaline-earth metal carbonates promoted the reaction. The NaOMe-catalyzed amidation of esters proceeded in various non-polar and polar solvents, such as hexane, THF, 1,4-dioxane, and NMP, except for alcohols and acetonitrile.<sup>12</sup> When both ester and amine were liquid, neat conditions were practically acceptable; for example, the reaction of **1a** with hexylamine (**2b**) without any solvents at 50 °C proceeded quite efficiently (>99% yield), and the subsequent direct distillation of the reaction mixture afforded pure amide **3ab** in 86% yield with an excellent environmental E-factor<sup>13</sup> of 0.35 (Scheme 1b). Moreover, the same reaction also proceeded at 25 °C (74% yield).<sup>12</sup> In contrast to transesterification,<sup>14</sup> which requires the removal of the resulting methanol, amidation in a shield-tube afforded



**Scheme 1** Amidation catalyzed by NaOMe. (a) NaOMe-catalyzed amidation in toluene. (b) NaOMe-catalyzed amidation under neat conditions. (c) 1 mol% of NaOMe-catalyzed amidation with a desiccant.

<sup>a</sup> Graduate School of Pharmaceutical Sciences, Kyushu University and CREST, JST, Fukuoka, Japan.  
E-mail: ohshima@phar.kyushu-u.ac.jp; Fax: +81 92 642 6650;  
Tel: +81 92 642 6650

<sup>b</sup> Department of Chemistry, Graduate School of Engineering Science, Osaka University and CREST, JST, Osaka, Japan.  
E-mail: mashima@chem.es.osaka-u.ac.jp; Fax: +81 6 6850 6245;  
Tel: +81 6 6850 6245

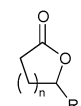
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the same good yield of **3ab**.<sup>12</sup> Surprisingly, addition of 5 mol% of water (1 equiv. to NaOMe) completely retarded the NaOMe-assisted amidation, and in fact, trace amounts of water crucially turned the catalyst system into a stoichiometric or sub-stoichiometric reaction as a consequence of saponification of the esters.<sup>12</sup> Anhydrous conditions were critically important to achieve high turnover frequency and maintain good reproducibility in association with the operational advantages. Thus, the addition of a desiccant, such as MS3A or Drierite, minimized catalyst loading to 1 mol% with 80 and 76% yields, respectively (Scheme 1c). Although alkali metal alkoxides such as NaOMe<sup>15</sup> and KOtBu<sup>16</sup> were previously reported to promote ester–amide exchange reactions, more than stoichiometric amounts or sub-stoichiometric amounts of these reagents were necessary. To the best of our knowledge, we present the first catalyst system for amide bond formation from esters and amines.

We evaluated the scope and limitations of the NaOMe-catalyzed amidation under the optimized conditions (Table 1). We examined various methyl esters as the substrates because isopropyl ester considerably decreased the yield, and tertiary butyl ester gave only a trace amount of the product. Methyl benzoates with electron-withdrawing substituents were good substrates, giving the corresponding amide in excellent yield (entries 1–3), whereas the reaction of electron-rich esters needed a longer reaction time

(44 h) to produce a good yield (entries 4 and 5). Amidation of methyl cinnamate (**1g**), a typical  $\alpha,\beta$ -unsaturated ester, proceeded efficiently without any side reaction, such as 1,4-addition, to yield amide **3gb** in 85% yield (entry 6). Alkanoates were also smoothly converted to the corresponding amide in high yield (entries 7–9). The amidation was somewhat sensitive to the congestion of substrates: the yield of sterically more demanding methyl cyclohexylcarboxylate (**1k**) was decreased to 62% (entry 10). Several lactones reacted to give the corresponding hydroxy amides in high yield (entries 14–17). Aiming at applying the present catalysis to peptide coupling, we first examined the compatibility of amide and carbamate functional groups. Reaction of an amide ester **1l** with hexylamine produced the desired benzyl hexyl amide **3lb** in 94% yield without any transamidated derivative (entry 11). Boc and Cbz groups were intact under the present mild reaction conditions (entries 12 and 13) (see also Table 2). Next, we investigated the scope and limitations of various amines. The amidation with primary amines, benzylamine and cyclohexylamine proceeded smoothly to give the corresponding amides in excellent yields (entries 18 and 19). Electronically more nucleophilic but also more sterically demanding secondary amines were also good substrates to give the corresponding amides in high yields (entries 20 and 21). In sharp contrast, aniline was an unsatisfactory substrate for the amidation (entry 22). Aminoethanol (**2g**) reacted chemoselectively with **1c** to give a hydroxy amide **3cg** in 70% yield along with the formation of an amino ester in 21% yield (entry 23).

**Table 1** NaOMe-catalyzed amidation with various esters and amines

$\text{R}^1-\text{C}(=\text{O})\text{OMe} \text{ (1)} + \text{HNR}^2\text{R}^3 \text{ (2)} \xrightarrow[\text{50 } ^\circ\text{C, Time}]{\text{NaOMe (5 mol\%)}} \text{R}^1-\text{C}(=\text{O})\text{NR}^2\text{R}^3 \text{ (3)}$			
Entry	Ester <b>1</b>	Amine <b>2</b>	Time/ Yield <sup>a</sup> h (%)
1	4-NC-C <sub>6</sub> H <sub>4</sub> -CO <sub>2</sub> Me ( <b>1b</b> )	H <sub>2</sub> N-Hex ( <b>2b</b> )	20 92
2	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -CO <sub>2</sub> Me ( <b>1c</b> )	<b>2b</b>	20 99
3	4-Cl-C <sub>6</sub> H <sub>4</sub> -CO <sub>2</sub> Me ( <b>1d</b> )	<b>2b</b>	20 93
4	4-Me-C <sub>6</sub> H <sub>4</sub> -CO <sub>2</sub> Me ( <b>1e</b> )	<b>2b</b>	44 85
5	4-MeO-C <sub>6</sub> H <sub>4</sub> -CO <sub>2</sub> Me ( <b>1f</b> )	<b>2b</b>	44 71
6	( <i>E</i> )-PhCH=CH-CO <sub>2</sub> Me ( <b>1g</b> )	<b>2b</b>	48 85
7	PhCH <sub>2</sub> CH <sub>2</sub> -CO <sub>2</sub> Me ( <b>1h</b> )	<b>2b</b>	20 94
8	C <sub>5</sub> H <sub>11</sub> -CO <sub>2</sub> Me ( <b>1i</b> )	<b>2b</b>	20 99
9	C <sub>11</sub> H <sub>23</sub> -CO <sub>2</sub> Me ( <b>1j</b> )	<b>2b</b>	24 99
10	<i>c</i> Hex-CO <sub>2</sub> Me ( <b>1k</b> )	<b>2b</b>	20 62
11 <sup>b</sup>	BnNHCO-CH <sub>2</sub> CH <sub>2</sub> -CO <sub>2</sub> Me ( <b>1l</b> )	<b>2b</b>	20 94
12	BocNH-CH <sub>2</sub> -CO <sub>2</sub> Me ( <b>1m</b> )	<b>2b</b>	20 88
13	CbzNH-CH <sub>2</sub> -CO <sub>2</sub> Me ( <b>1n</b> )	<b>2b</b>	26 97
14		<b>2b</b>	24 93
	<i>n</i> = 1, R = H ( <b>1o</b> )		
15	<i>n</i> = 1, R = Et ( <b>1p</b> )	<b>2b</b>	70 94
16	<i>n</i> = 2, R = H ( <b>1q</b> )	<b>2b</b>	20 95
17 <sup>c</sup>	<i>n</i> = 3, R = H ( <b>1r</b> )	<b>2b</b>	20 86
18	<b>1d</b>	H <sub>2</sub> N-Bn ( <b>2a</b> )	20 90
19	<b>1d</b>	H <sub>2</sub> N- <i>c</i> Hex ( <b>2c</b> )	20 93
20	<b>1d</b>	Piperidine ( <b>2d</b> )	36 94
21	<b>1d</b>	HN(Me)Bn ( <b>2e</b> )	26 87
22	<b>1d</b>	H <sub>2</sub> N-Ph ( <b>2f</b> )	120 7
23	<b>1d</b>	H <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> OH ( <b>2g</b> )	20 70 <sup>d</sup>

<sup>a</sup> Isolated yield. <sup>b</sup> Toluene : THF (2 : 1) was used as a solvent. <sup>c</sup> Lactone **1r** was slowly added over 2 h. <sup>d</sup> 21% of amino ester was also obtained.

**Table 2** Additive screening for catalytic amidation of chiral  $\alpha$ -amino ester and substrate scope<sup>a</sup>

$\text{BocHN}-\text{CH}(\text{R}^4)-\text{C}(=\text{O})\text{OMe} \text{ (1)} + \text{H}_2\text{NBn} \text{ (2a)} \xrightarrow[\text{50 } ^\circ\text{C, 20 h}]{\text{NaOMe (5-10 mol\%)}} \text{BocHN}-\text{CH}(\text{R}^4)-\text{C}(=\text{O})\text{NHBn} \text{ (3)}$			
Entry	Additive <b>4</b>	pK <sub>a</sub>	Yield <sup>b</sup> ee <sup>c</sup> (%) (%)
1	Boc-Phe-OMe ( <b>1s</b> )	—	15.54 <sup>d</sup> 96
2	<b>1s</b>	CF <sub>3</sub> CF <sub>2</sub> OH ( <b>4a</b> )	12.43 91
3	<b>1s</b>	4-MeO-C <sub>6</sub> H <sub>4</sub> -OH ( <b>4b</b> )	10.20 89
4	<b>1s</b>	Ph-OH ( <b>4c</b> )	9.94 93
5	<b>1s</b>	2-MeO-C <sub>6</sub> H <sub>4</sub> -OH ( <b>4d</b> )	9.93 55
6	<b>1s</b>	4-Br-C <sub>6</sub> H <sub>4</sub> -OH ( <b>4e</b> )	9.34 73
7	<b>1s</b>	3-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -OH ( <b>4f</b> )	8.95 58
8	<b>1s</b>	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -OH ( <b>4g</b> )	8.68 49
9	<b>1s</b>	2-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -OH ( <b>4h</b> )	8.42 29
10	<b>1s</b>	4-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -OH ( <b>4i</b> )	7.14 22
11 <sup>e</sup>	<b>1s</b>	<b>4g</b>	8.68 81
12 <sup>e</sup>	Boc-Ala-OMe ( <b>1t</b> )	<b>4g</b>	8.68 80
13 <sup>f-h</sup>	Boc-Val-OMe ( <b>1u</b> )	<b>4g</b>	8.68 72
14 <sup>f,g</sup>	Boc-Leu-OMe ( <b>1v</b> )	<b>4g</b>	8.68 82
15 <sup>f,g</sup>	Boc-Pro-OMe ( <b>1w</b> )	<b>4g</b>	8.68 80
16 <sup>f</sup>	Boc-Met-OMe ( <b>1x</b> )	<b>4g</b>	8.68 80
17 <sup>f,g</sup>	Boc-Glu(OtBu)-OMe ( <b>1y</b> )	<b>4g</b>	8.68 84

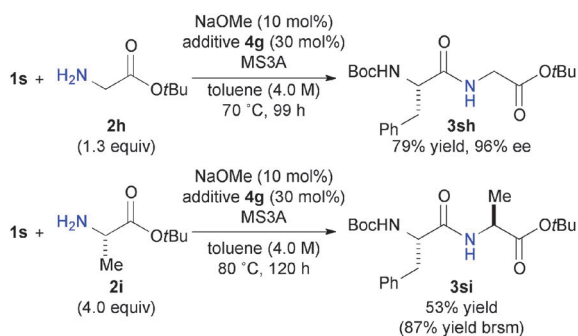
<sup>a</sup> 5 mol% of NaOMe and 10 mol% of **4** were used for entries 1–10 and 10 mol% of NaOMe and 30 mol% of **4g** were used for entries 11–17.

<sup>b</sup> Yield determined by HPLC analysis for entries 1–10 and isolated yield for entries 11–17. <sup>c</sup> Determined by chiral HPLC analysis. <sup>d</sup> pK<sub>a</sub> value of MeOH. <sup>e</sup> Reaction time was 72 h. <sup>f</sup> Reaction time was 99 h.

<sup>g</sup> Reaction temperature was 70 °C. <sup>h</sup> 4.0 equiv. of amine **2a** was used.

Because the amide and carbamate functional groups were intact, we next targeted the application of the NaOMe-catalyzed amidation to peptide-coupling reactions, in which epimerization of  $\alpha$ -amino acid derivatives was a major problem under such basic conditions. In fact, the reaction of Boc-Phe-OMe (**1s**, 99% ee) and **2a** under the optimized conditions resulted in epimerization of the corresponding benzyl amide **3sa** (Table 2, entry 1, 2% ee). This severe epimerization was successfully rectified by the addition of rather acidic alcohols such as 2,2,2-trifluoroethanol (entry 2) and various phenols (entries 3–11) to manipulate the basicity of NaOMe. As expected, both enantiomeric excess and yield of the product **3sa** correlated well with the  $pK_a$  values of the added alcohols;<sup>12</sup> the increased acidity of the added alcohol increased the enantiomeric excess of the product and decreased the yield. Among the tested conditions, a mixture of 10 mol% of NaOMe and 30 mol% of 4-trifluoromethylphenol (**4g**) was selected as the best catalytic condition to maintain a good balance between enantiomeric excess and yield of the product **3sa** (entry 11, 81%, 97% ee). With the optimized catalyst system for  $\alpha$ -amino esters in hand, we conducted catalytic amidation of various *N*-Boc protected chiral  $\alpha$ -amino esters with benzylamine (**2a**). The reactions of  $\alpha$ -alkyl substituted amino methyl esters **1t–w** afforded the corresponding amides in high yield without epimerization (entries 12–15). Furthermore, chiral  $\alpha$ -amino esters with functional groups in the side-chain could be used as substrates. A thioether functionality on the methionine (**1x**) did not disrupt the amidation reaction and the desired product **3xa** was obtained in good yield without epimerization (entry 16). The side-chain carboxyl group on glutamic acid protected by a standard tertiary butyl ester did not participate in the present NaOMe-catalyzed reaction, and only the main-chain methyl ester of Boc-Glu(OtBu)-OMe (**1y**) was converted to benzylamide (entry 17).

Furthermore, the NaOMe–**4g** catalyst system was successfully applied to a peptide coupling reaction of Boc-Phe-OMe (**1s**) and H-Gly-OtBu (**2h**) at 70 °C to afford dipeptide **3sh** in 79% yield with 96% ee (Scheme 2). Although the reactivity was lower than that of **2h**, this catalysis was also applicable to the reaction of **1s** and H-Ala-OtBu (**2i**), giving the corresponding coupling product **3si** in 53% yield along with the recovered **1s** (39%) and only trace amounts of byproducts (87% yield of **3si** based on recovered starting materials).



**Scheme 2** Peptide coupling reactions catalysed by NaOMe–**4g**.

To the best of our knowledge, this is the first example of a catalytic peptide coupling reaction without the need for enzymatic methods, and provides a new convenient synthetic protocol for the synthesis of various peptides with the advantages of being nontoxic, catalytic, and environmentally benign.

In conclusion, we present a simple, but highly efficient, NaOMe catalyst for the direct amidation of esters with amines with a wide variety of functional groups, as the first catalytic amidation reaction under mild conditions. Notably, the catalyst is a combination of NaOMe and 4-trifluoromethylphenol that serves as a unique artificial peptidyl transferase to mediate the peptide coupling reactions by precluding epimerization.

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