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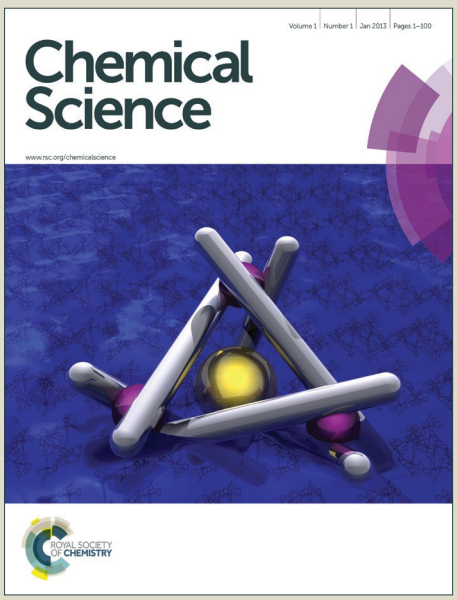

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Boronic Acid–DMAPO Cooperative Catalysis for Dehydrative Condensation between Carboxylic Acids and Amines

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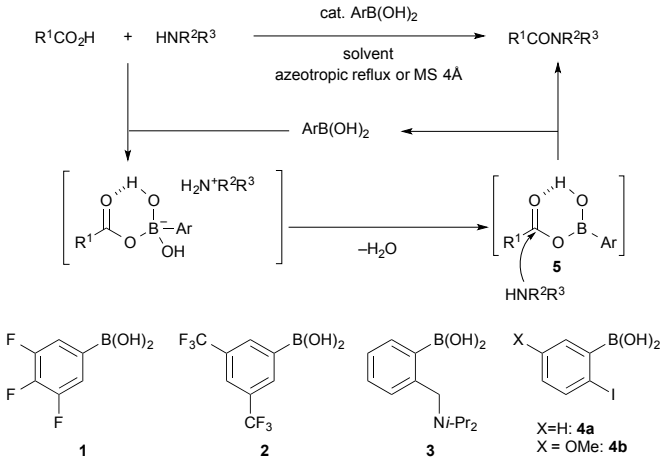
Arylboronic acid and 4-(*N*,*N*-dimethylamino)pyridine *N*-oxide (DMAPO) cooperatively catalyse the dehydrative condensation reaction between carboxylic acids and amines to give the corresponding amides under azeotropic reflux conditions. The cooperative use of them is much more effective than their individual use as catalyst, and chemoselectively promoted the amide condensation of (poly)conjugated carboxylic acids. The present method is readily practical and scalable, and has been applied to the synthesis of Sitagliptin and a drug candidate.

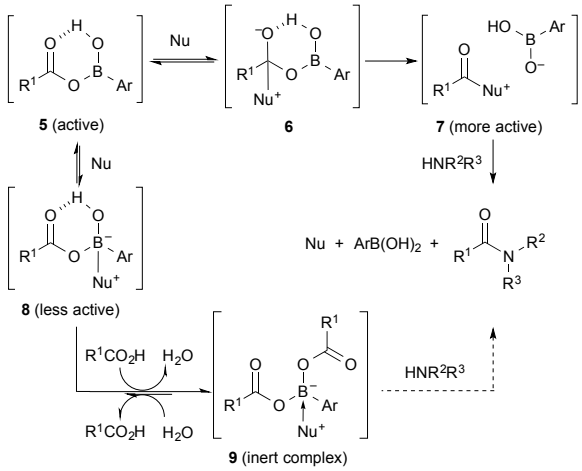
Introduction

The catalytic dehydrative condensation reaction between carboxylic acids and amines is one of the most ideal methods for synthesizing the corresponding amides.[1] In 1996, Yamamoto and Ishihara *et al.* reported the first example of the dehydrative amide condensation reaction catalysed by *meta*- or *para*-electron-deficient group-substituted phenylboronic acids such as 3,4,5-trifluorophenylboronic acid (**1**) (pK_a = 6.8)[2a] and 3,5-bis(trifluoromethyl)phenylboronic acid (**2**) (pK_a = 7.2)[2b] under azeotropic reflux conditions (Scheme 1).[3] These boronic acids are more acidic than phenylbornoic acid (pK_a = 8.8, 8.9).[2]



Scheme 1 Dehydrative condensation of carboxylic acids with amines catalysed by arylboronic acids and representative examples of catalysts.

In2006, Whiting *et al.* reported that the *ortho*-Brønsted base-substituted phenylboronic acid such as 2-(*N*,*N*-diisopropylaminomethyl)phenylboronic acid (**3**) was an effective catalyst for the amide condensation of aromatic carboxylic acids under the same conditions as above.[1a,4] In 2008 and 2012, Hall *et al.* reported that 2-iodophenylboronic acid (**4a**) and 2-iodo-5- methoxyphenylboronic acid (**4b**) were also effective catalysts for the amide condensation in the presence of drying agents (activated molecular sieves 4Å) at lower temperature.[5] The *o*-iodo group of **4a** and **4b** assists the amide condensation catalysis as a weak base.[6] In addition to these boronic acids, boric acid,[7a,c] benzo[1,3,2]dioxaborol-2-ol,[7b] methylboronic acid,[7d] and some *o*-Brønsted base-substituted boronic acids[8] have been reported to be useful as amidation catalysts. However, the substrate scope is still quite limited. For example, hash conditions (higher temperature,



Scheme 2 Our proposal: Second activation of a mixed anhydride **5** with a nucleophilic additive (Nu) to generate a more active cationic intermediate **7**.

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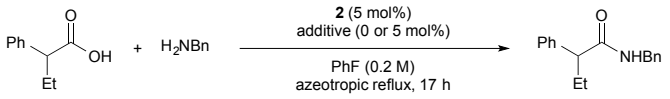
prolonged reaction time, excess amounts of substrates, increased amounts of catalysts, etc.) are required for sterically hindered α-branched carboxylic acids and conjugate carboxylic acids. In 2013, Whiting *et al.* discovered an interesting synergistic catalytic effect between *o*-tolylboronic acid (50 mol%) and *o*-nitrophenylboronic acid (50 mol%) in dipeptide synthesis.[3f] To the best of our knowledge, this is the first cooperative examples of two promoters for the direct amidation.[3f,9]

In the arylboronic acid catalysis, a mixed anhydride intermediate **5** is generated from carboxylic acid and arylboronic acid under azeotropic reflux conditions or in the presence of drying agents in the first stage (Schemes 1 and 2). This is the first activation of carboxylic acid. If a nucleophilic additive (Nu) reacts with **5** to generate a more active cationic intermediate **7**[10] (second activation) via a tetrahedral intermediate **6**, the amide condensation may proceed more rapidly. However, if Nu preferentially coordinates as a Lewis base to a boron atom of **5**, a less active species **8** is generated and the amide condensation may be suppressed. Here we report that arylboronic acids and *N*,*N*-dimethylaminopyridine *N*-oxide (DMAPO) cooperatively promote the dehydrative condensation between various carboxylic acids and amines.

Results and discussion

First, the amide condensation reaction between 2-phenylbutyric acid and benzylamine was examined in the presence of 5 mol% each of boronic acid **2** and a nucleophilic additive candidate under azeotropic reflux conditions in fluorobenzene (bp. 85 °C)[3f] for 17 h (Table 1). Boronic acid **2** did not promote this reaction in the absence of additive under these conditions (entry 1). Tertiary amines such as *N*,*N*-diisopropylethylamine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP)[11] were not effective as additives (entries 2 and 3). 4-Methoxypyridine *N*-oxide (MPO) was also less active (entry 4). In contrast, a more nucleophilic but weak base, DMAPO[12] was quite effective for the amide condensation (entry 5). However, more nucleophilic additive such as 4-(pyrrolidin-1-yl)pyridine *N*-oxide (PPYO) was less effective than DMAPO (entry 6),

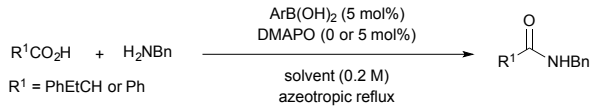
Table 1 Effects of additives on the dehydrative condensation between 2-phenylbutyric acid and benzylamine[a]



Entry	Additive	Yield[b] (%)	Entry	Additive	Yield[b] (%)
1	None	<5	4	MPO	<5
2	*i*-Pr_2EtN	<5	5	DMAPO	99
3	DMAP	<5	6	PPYO	27

[a] A solution of 2-phenbutyric acid (0.5 mmol) and benzylamine (0.5 mmol) in fluorobenzene was heated in the presence of **2** (5 mol%) and additive (0 or 5 mol%) under azeotropic reflux conditions. [b] Isolated yield.

Table 2 Cooperative effects of boronic acid–DMAPO on the dehydrative condensation reaction[a]



Entry	$ArB(OH)_2$	Yield[b,c] (%) of PhEtCHCONHBn	Yield[b,d] (%) of PhCONHBn
1	**2**	99 [<5]	97 [<5]
2	$PhB(OH)_2$	<5 [<5]	<5 [<5]
3	**4b**	92 [<5]	20 [8]
4	**3**	7 [15]	80 [95]

[a] 0.5 mmol of carboxylic acids and 0.5 mmol of benzylamine were used in the presence of 5 mol% of $ArB(OH)_2$ and 0 or 5 mol% of DMAPO. [b] The results when both catalysts were used are shown. For comparison, the results without DMAPO are shown in brackets. [c] Conditions: fluorobenzene (bp. 85 °C), 17 h. [d] Conditions: toluene (bp. 110 °C), 4 h.

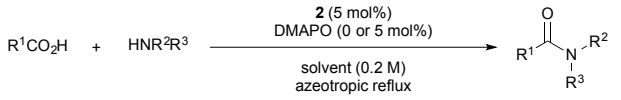
perhaps because the strong nucleophilicity of PPYO might reduce the activity of **7**.

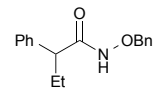
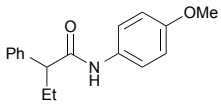
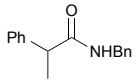
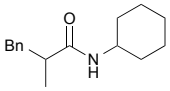
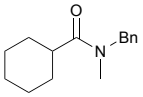
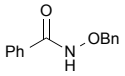
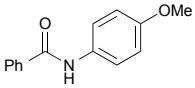
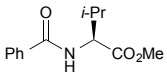
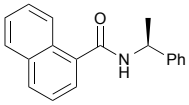
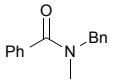
Next, the cooperative effects of several boronic acids (5 mol%) were compared in the condensation reaction between 2-phenylbutyric acid or benzoic acid and benzylamine in the presence of DMAPO (5 mol%) (Table 2). These less reactive carboxylic acids were not activated by the individual use of these boronic acids under the same conditions. As expected, **2**–DMAPO and **4b**–DMAPO efficiently activated 2-phenylbutyric acid (entries 1 and 3). Phenylboronic acid and **3** were almost inert, even in the presence of DMAPO (entries 2 and 4). Interestingly, **2**–DMAPO was more effective than **4b**–DMAPO for the amide condensation of benzoic acid (entries 1 and 3). While Whiting's catalyst **3** was quite effective for the amide condensation of benzoic acid, the catalytic activity of **3** was suppressed in the presence of DMAPO (entry 4).[13]

To explore the substrate scope of the cooperative catalyst, **2**–DMAPO, the amide condensation reactions of several less reactive α-branched carboxylic acids and arenecarboxylic acids were examined under azeotropic reflux conditions in fluorobenzene (bp. 85 °C) or toluene (bp. 110 °C). As shown in Table 3, in each example, these cooperative catalysts were much more effective than **2** alone, whose results are shown in brackets. Notably, not only aliphatic primary amines but also sterically hindered aliphatic secondary amines, less nucleophilic anilines and alkoxyamines reacted with these carboxylic acids. In particular, **2**–DMAPO was effective in the amidation of arenecarboxylic acids with sterically hindered amines in comparison with **3** and **4b** (entries 9–14). This cooperative method is scalable to practical volumes: the catalytic loading of **2**–DMAPO could be reduced to 2.5 mol% for the dehydrative condensation on 80 mmol scale (entry 4).

The boronic acid-catalysed condensation of relatively more reactive α-nonbranched carboxylic acids with sterically hindered secondary amines and less nucleophilic anilines proceeded even in the absence of DMAPO, as shown in brackets in Table 4.

Table 3 Cooperative effects of **2**–DMAPO on the dehydrative condensation of α-branched carboxylic acids and arenecarboxylic acids[a]

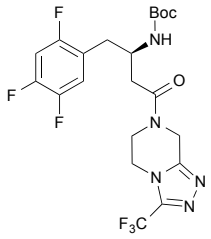
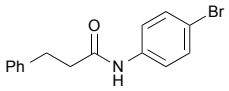


Entry	Amide	Solvent, Time	Yield (%)[b]
1[c]		PhF, 25 h	93 [<5]
2[c]		PhF, 17 h	90 [<5]
3		Benzene, 8 h	95 [<5]
4[d]		Toluene, 11 h	98
5		Toluene, 8 h	97 [<5]
6[c]		Toluene, 18 h	92 [<5]
7[c]		Toluene, 12 h	70 [23]
8		Toluene, 23 h	91 [19]
9[e]		PhF, 23 h	85[f] [30]
10[e,g]		PhF, 23 h	[2]
11[e,h]		PhF, 23 h	[17]
12		Toluene, 9 h	95 [<5]
13[g]		Toluene, 9 h	[39]
14[h]		Toluene, 9 h	[<5]
15		Toluene, 8 h	92 [32]

[a] Unless noted otherwise, 0.5 mmol of carboxylic acids and 0.5 mmol of amines were used in the presence of 5 mol% of **2** and 0 or 5 mol% of DMAPO. [b] The results when both catalysts were used are shown. For comparison, the results without DMAPO are shown in brackets. [c] 10 mol% of each of the catalysts was used. [d] 2.5 mol% of each of **2** and DMAPO was used on 80 mmol scale in 70 mL of toluene. [e] 15 mol% of each of the catalysts was used. [f] 99% ee. [g] **3** was used. [h] **4b** was used.

Nevertheless, the addition of DMAPO was also quite effective for these reactions. Interestingly, **4b** and phenylboronic acid were slightly more effective than **2** in the presence of DMAPO. In particular, the utility of inexpensive phenylboronic acid is industrially significant. This catalytic method is readily scalable. 2.5 g of *N*-Boc protected Sitagliptin,[14] an anti-diabetic drug, was obtained by the condensation on a 5 mmol scale (entry 4).

Table 4 Cooperative effects of boronic acid–DMAPO on the dehydrative condensation of α-nonbranched carboxylic acids[a]

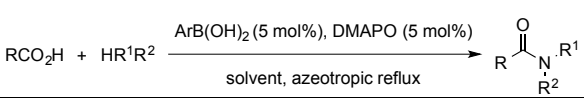
Entry	Amide	$ArB(OH)_2$	Solvent, Time	Yield (%)[b]
1[c]		**2**	PhF, 23 h	81 [55]
2[c]		$PhB(OH)_2$	PhF, 23 h	92 [50]
3[c]		**4b**	PhF, 23 h	98 [53]
4[d]		**4b**	PhF, 40 h	>99
5[c]		–	PhF, 23 h	<5 [<5]
6		$PhB(OH)_2$	PhH, 17 h	82 [44]

[a] Unless noted otherwise, 0.55 mmol of carboxylic acids and 0.50 mmol of amines were used in the presence of 5 mol% of $ArB(OH)_2$ and 0 or 5 mol% of DMAPO. The results when both catalysts were used are shown. For comparison, the results without DMAPO are shown in brackets. [c] 10 mol% of each of the catalysts was used. [d] The reaction was carried out at a 5 mmol scale.

The results in Tables 1–4 suggest that both the nucleophilicity of the additive and the Lewis acidity and steric effect of the boronic acid are important in the cooperative catalysis with an $ArB(OH)_2$–nucleophilic base (Table 5). The reactivity was higher in the order arenecarboxylic acid, α-branched carboxylic acids, and α-nonbranched carboxylic acid. As results, **2** was more effective for arenecarboxylic acid and α-branched carboxylic acids. On the other hand, **4b** and phenylboronic acid were more effective for α-nonbranched carboxylic acids.

The amide condensation reaction should occur through active intermediate **6** (Scheme 2). However, not only **6** but also undesired complex **8** would be generated in an equilibrium mixture. Complex **8** might be converted to more stable complex **9**, which was inert for the amide condensation. In fact, the generation of inert complex **9** was ascertained by ^{11}B and ^{1}H NMR analysis in the amidation of less-hindered carboxylic acids.[15] And also the chemical structure of the cyclic complex prepared from **2**, phthalic acid, and DMAPO was determined to be **9z** by X-ray diffraction analysis (Fig. 1).[16]

Table 5 Relationship between the Cooperative Effects of Boronic Acid–DMAPO and the Reactivity of Carboxylic Acids



RCO_2H	Catalytic activity of $ArB(OH)_2$–DMAPO		
	2	**4b**	$PhB(OH)_2$
$ArCO_2H$	High	Low	Low
$R^3R^4CHCO_2H$	High	Good	Low
$R^3CH_2CO_2H$	Good	High	High

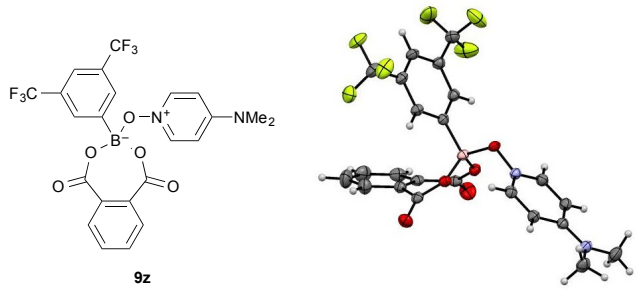
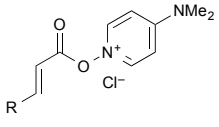


Fig. 1 X ray-structure of **9z**.

For sterically hindered carboxylic acids such as arenecarboxylic acids and α-branched carboxylic acids, desired intermediate **7** was preferentially generated. Thus, *o*-nonsubstituted and *m*- or *p*-electron-deficient group-substituted phenylboronic acids such as **1** and **2** were more suitable. In contrast, for sterically less hindered α-nonbranched carboxylic acids, undesired complex **9** was generated more easily. In addition, the strong Lewis acidity of **2** helped to stabilize **9** by the tight coordination of DMAPO to the boron centre. This is why **4b** and phenylboronic acid were slightly more effective than **2** for the condensation of α-nonbranched carboxylic acids. Not only Lewis acidity but also bulkiness of *o*-substituents of boronic acids might suppress the generation and stability of **9**. It is noted that the effect of DMAPO was no striking at ambient temperature. Heating conditions were required to accelerate the equilibrium between **6** and **8**.

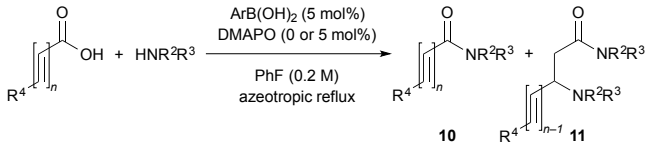
The utility of the cooperative catalysts is also demonstrated for the selective amide condensation of β-substituted acrylic acids to give the corresponding amides **10** (Table 6). The production of Michael adducts **11** was fairly minimized. In contrast, when boronic acids were used in the absence of DMAPO, the yield and the selectivity of **10** were moderate. Control experiments ascertained that **10** (*n* = 1) was selectively given from **13**,[17] and **11** (*n* = 1) was not given from **10** (*n* = 1) but **14**. Amide **10c** is known to be a potential antimitotic agent, especially for brain cancers (entry 6).[18] The cooperative catalysts were effective for the selective amide condensation of not only β-substituted acrylic acids but also polyconjugated carboxylic acids and but-2-ynoic acid (entries 12–17).



Conclusions

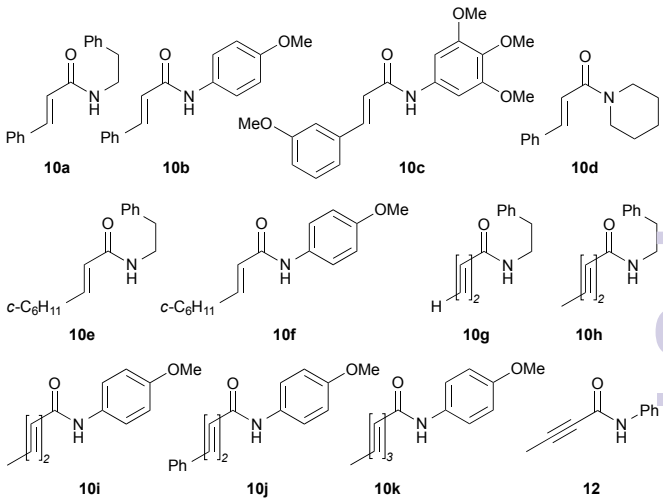
In conclusion, this new cooperative catalytic system is quite effective for the amidation reaction of less reactive carboxylic acids such as sterically hindered α-branched carboxylic acids and arenecarboxylic acids and the chemoselective amidation reaction of conjugated carboxylic acids. Based on the NMR spectral and X-ray diffraction analyses of inert species **9**, preliminary mechanism was proposed. Further mechanistic study is in progress. We believe that these findings will trigger further development of high-performance amidation catalysts.

Table 6 Cooperative effects of boronic acid–DMAPO on the dehydrative condensation of conjugated carboxylic acids[a]



Entry	$ArB(OH)_2$	Time (h)	Product **10** or **12**	
			Yield (%)[b]	Selectivity (%)[b]
1	**2**	12	**10a**, 87 [42]	93 [74][c]
2	**4b**	10	**10a**, 82 [79]	94 [91][c]
3	$PhB(OH)_2$	12	**10a**, 15 [4]	95 [78][c]
4	**2**	15	**10b**, 77 [17]	89 [30][c]
5	**4b**	16	**10b**, 65 [29]	89 [47][c]
6[d,e]	**2**	15	**10c**, 96 [49]	96 [64][c]
7	**2**	38	**10d**, 90 [78]	>95 [>95][c]
8	**2**	8	**10e**, 68 [19]	82 [37][c]
9	**4b**	7	**10e**, 72 [62]	84 [78][c]
10[d]	$PhB(OH)_2$	19	**10e**, 81 [56]	92 [76][c]
11[d]	$PhB(OH)_2$	22	**10f**, 73 [32]	96 [55][c]
12[d]	**2**	16	**10g**, 98 [45]	>99 [45][f]
13[d]	**2**	16	**10h**, 97 [69]	>99 [79][f]
14[d]	**2**	16	**10i**, 73 [<5]	97 [<5][f]
15[d]	**2**	23	**10j**, 92 [–]	>99 [50][f]
16[d]	**2**	24	**10k**, 99 [25]	>99 [56][f]
17[d]	**2**	14	**12**, 98 [46]	>99 [82][f]

[a] Unless noted otherwise, 0.5 mmol of carboxylic acids and 0.5 mmol of amines were used in the presence of 5 mol% of $ArB(OH)_2$ and 0 or 5 mol% of DMAPO. [b] The results when both catalysts were used are shown. For comparison, the results without DMAPO are shown in brackets. [c] β-Aminoamide **11** (*n* = 1) was obtained as a sole minor product. [d] 10 mol% of each of the catalysts was used. [e] Toluene was used as a solvent. [f] Several minor products including **11** were obtained.



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Notes and references

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17 Intermediate **13** was prepared from DMAPO and the corresponding acryl chloride. The reaction of **13** with amine gave **10** as a sole product. See the SI for details.

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