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ortho-Substituent on 2,4-Bis(trifluoromethyl)phenylboronic Acid-Catalyzed Dehydrative Condensation between Carboxylic Acids and Amines†

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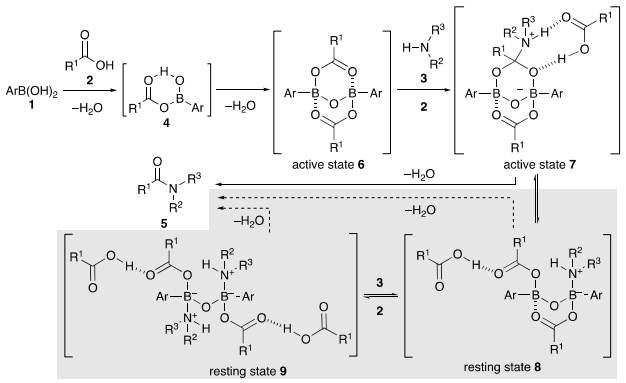
2,4-Bis(trifluoromethyl)phenylboronic acid is a highly effective catalyst for dehydrative amidation between carboxylic acids and amines. Mechanistic studies suggest that a 2:2 mixed anhydride is expected to be the only active species and the *ortho*-substituent of boronic acid plays a key role in preventing the coordination of amines to the boron atom of the active species, thus accelerating the amidation. This catalyst works for α-dipeptide synthesis.

The organoboron-catalyzed dehydrative condensation reaction between carboxylic acids and amines is one of the most ideal methods for synthesizing the corresponding amides.[1,2] In 1996, Yamamoto and Ishihara *et al.* reported the first example of the dehydrative amide condensation reaction catalyzed by *meta*- or *para*-electron-deficient group-substituted phenylboronic acids such as 3,4,5-trifluorophenylboronic acid (**1a**) and 3,5-bis(trifluoromethyl)phenylboronic acid (**1b**) under azeotropic reflux conditions (Scheme 1a).[2a] Over the past decade, the application of arylboronic acids bearing *ortho*-basic groups[3] has made it possible to more practical and mild conditions. However, the substrate scope is limited to simple ones, and especially the application of this reaction to α-dipeptide synthesis[2m,3g,h] remains a major issue.

Recently, other types of boron compounds like a DATB complex[4] and a borate ester[5] have been reported to be alternative powerful catalysts for direct amidations.[6] Although these new catalysts work fairly well on a broad range of substrates including for α-peptide formation, the key point in the design of boron catalysts for direct amidation is still unclear. We previously reported that carboxylic acid **2** might be activated through the generation of a 1:1 mixed anhydride **4**.[2a] In contrast, Whiting *et al*. more recently reported dimeric mixed anhydride **6** might be more preferable as a real active species based on their mechanistic study (Scheme 1).[7] If



Scheme 1 Amidation catalysis of **1** based on Whiting's proposed mechanism.[7]

substrate amine **3** directly attacks the acyl group of **6**, the corresponding amide **5** should be obtained through desired intermediate **7**. However, **3** can also coordinate to the boron center of **6** to give more stable tetrasubstituted boronate complexes **8** and **9**. We anticipated that suppression of their generation might increase the chance for amide formation.

Here, we report 2,4-bis(trifluoromethyl)phenylboronic acid (**1c**) as an extremely effective catalyst for direct amidation. This commercially available **1c** worked well for a wide range of substrates including amino acid substrates to construct α-dipeptides in higher yields with almost no epimerization. We propose that the *ortho*-monosubstituent of **1** sterically prevents the coordination of amine **3** to the boron atom of dimeric anhydride **6** to give **8** and **9**.

To clarify the importance of *ortho*-monosubstituent on arylboronic acid **1**, we initiated catalyst screening by considering amidation between ibuprofen (**2a**) and benzylamine (**3a**) in the presence of various arylboronic acid catalysts **1** and molecular sieves(MS) 3 Å at ambient temperature (Table 1). To our surprise, **1b** was totally ineffective (entry 1), while **1c** was quite powerful, and provided the desired amide product **5aa** in 64% yield (entry 2). On the other hand, 2,6-bis(trifluoromethyl)phenylboronic acid (**1d**) was useless in this transformation (entry 4). A lower

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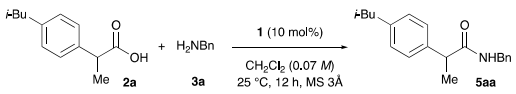
Table 1 Arylboronic acid **1**-catalyzed direct amidation between **2a** and **3a**[a]



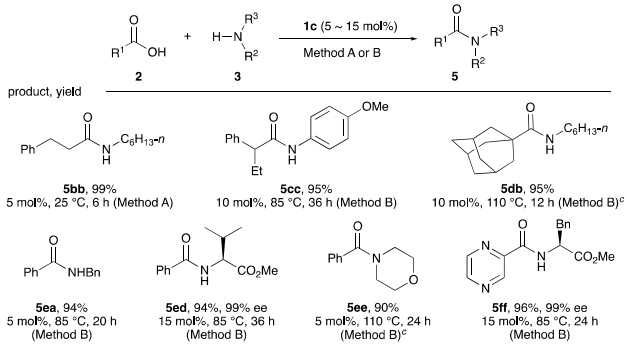
Entry	ArB(OH)$_2$ (**1**) Ar, **1**	Yield (%) of **5aa**	Entry	ArB(OH)$_2$ (**1**) Ar, **1**	Yield (%) of **5aa**
1	3,5-$(CF_3)_2$-C_6H_3, **1b**	<5	8	2-SF_5-C_6H_4, **1h**	<5
2	2,4-$(CF_3)_2$-C_6H_3, **1c**	64 (97[c])	9	2-Me-4-NO_2-C_6H_3, **1i**	31
3	2,4-$(CF_3)_2$-C_6H_3, **1c**	93[d]	10	2-Et-4-NO_2-C_6H_3, **1j**	39
4	2,6-$(CF_3)_2$-C_6H_3, **1d**	<5	11	2-*i*-Pr-4-NO_2-C_6H_3, **1k**	56
5	2-CF_3-C_6H_4, **1e**	42	12	2-(*i*-Pr_2NCH_2)-C_6H_4, **1l**	<5
6	2-Me-C_6H_4, **1f**	<5	13	2-I-5-MeO-C_6H_3, **1m**	46
7	2-NO_2-C_6H_4, **1g**	9	14	2-I-5-MeO-C_6H_3, **1m**	69[d]

[a] Reaction conditions: **2a** (0.5 mmol), **3a** (0.5 mmol) and **1** (10 mol %) were stirred at 25 °C for 12 h in dry dichloromethane containing powdered activated MS 3Å (1 g). [b] Yields of **5aa** were determined by ^{1}H-NMR. [c] Isolated yield of **5aa** after 18 h. [d] MS 4Å was used in place of MS 3Å. Reaction time was 20 h.

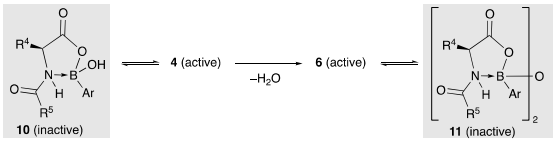
electron-deficiency of **1** reduced the yield of **5aa** (entries 2, 5 and 6, **1c** versus **1e, 1e** versus **1f**). Interestingly, other *ortho*-electron-deficient substituents like a nitro group (entry 7, **1g**) and pentafluorosulfanyl group (entry 8, **1h**) did not work, perhaps because coordination to boron[8] might decrease the activity or the *ortho*-substituents might be too sterically hindered. Next, the catalytic activities of **1i**, **1j** and **1k** with simple alkyl groups at *othro*-position were examined (entries 9–11). Surprisingly, catalytic activity improved as the size of the substituent increased. Nevertheless, **1c** was still more powerful than **1k** (entry 2 versus entry 11). Furthermore, **1c** showed superior catalytic activity to known boronic acids **1l**[3a] and **1m**[3d] regardless of the type of molecular sieves (3Å and 4Å) (entry 2 versus entries 12 and 13; entry 3 versus entry 14).[9]

Subsequently, we explored the substrate scope of direct amidation using **1c** as a catalyst (Table 2). The results showed that **1c** was effective for linear, α-branched, aromatic or heteroaromatic carboxylic acids **2** with aliphatic or aromatic

Table 2 Substrate scope for **1c**-catalyzed direct amidation[a,b]



[a] Method A: **2** (0.5 mmol), **3** (0.5 mmol) and **1c** were stirred at 25 °C for 12 h in dry toluene containing powdered activated molecular sieves 3 Å (1 g). [b] Method B: A solution of **2** (0.5 mmol), **3** (0.5 mmol), **1c** in fluorobenzene (bp. 85 °C) was heated to reflux with the removal of water by 1 g of activated MS 3Å (pellet). [c] Toluene (bp. 110.6 °C) was used instead of fluorobenzene.



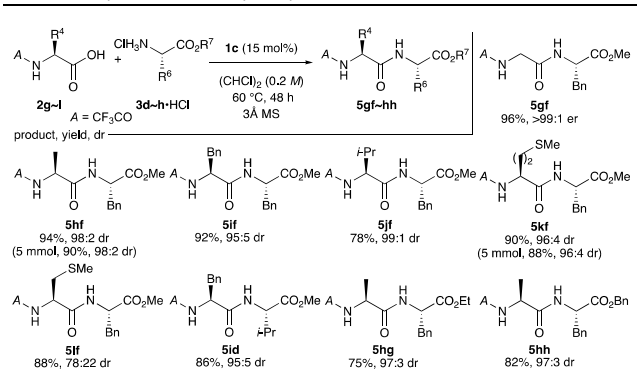
Scheme 2 Inactive complex formation on **1c**-catalyzed α-amino acid activation.

amines **3** to deliver the corresponding amides **5** in high yield at ambient temperature or acceptable elevated temperatures. Moreover, the condensation of pyrazinecarboxylic acid (**2f**) and *L*-phenylalanine methyl ester (**3f**) provided a key intermediate **5ff** for the synthesis of Bortezomib (Velcade®)[10] without any epimerization.

We then turned our attention to α-peptide synthesis. Although several boronic acids **1** have been reported to be applicable to α- or β-peptide synthesis, there is still room for improvement because of remaining problems, like low yield[2n,3g,h] and high catalyst loading.[2n] Similar to Hall's catalyst,[3h] **1c** was not effective with coordinatable *N*-Boc-, *N*-Cbz- or *N*-Fmoc-protected amino acids because of the possibility of generating stable inactive complex **10** or **11** (Scheme 2).[11] Recently, Shibasaki and Kumagai reported conventional *N*-protective groups (*N*-Fmoc and *N*-Boc) can be used in the DATB-catalyzed peptide synthesis at higher temperature.[4b] To inhibit catalyst complexation alternatively, we introduced more electron-deficient *N*-protecting groups to weaken the nucleophilicity of the amino moiety of amino acids. Due to its high reactivity, easy preparation and selective removability, an *N*-trifluoroacetyl moiety was found to be the most suitable. Notably, the catalytic activity of **1c** was superior to those of **1b** and **1m** even for α-dipeptide synthesis.[9,12]

Through further screening, we found that 1,2-dichloroethane was optimal solvent in α-dipeptide synthesis. As similar as Shibasaki and Kumagai *et al.*'s report,[4b] amino ester hydrochlorides were also proved to be more efficient than the amino esters in our catalysis. With regard to the substrate

Table 3 Direct amidations between *N*-trifluoromethyl protected L-amino acids and L-amino ester hydrochlorides catalyzed by **1c**[a]



[a] Unless otherwise noted: **2** (0.5 mmol), **3**•HCl (0.5 mmol) and **1c** were stirred at 60 °C for 48 h in 1,2-dichloroethane containing powdered activated MS 3Å (1 g). [b] Isolated yield. [c] Diastereomeric ratio (dr) was determined by ^{1}H NMR.

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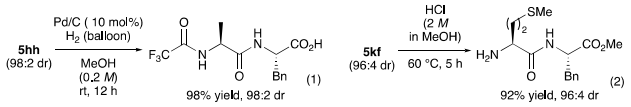
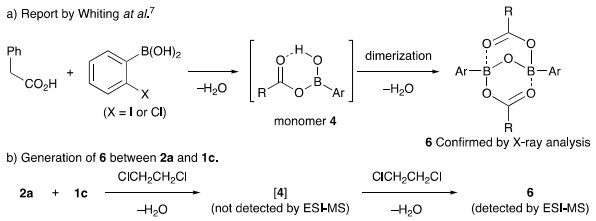


Scheme 3 Deprotection of α-dipeptides **5**.

scope, **1c** worked fairly well with *N*-trifluoroacetyl(A)-*L*-glycine (**2g**), *N*-A-*L*-alanine (**2h**), *N*-A-*L*-phenylalanine (**2i**), *N*-A-*L*-valine (**2j**), *N*-A-*L*-methionine (**2k**) to deliver α-dipeptides **5** in high yields with almost no epimerization (Table 3). However, extensive epimerization occurred with *N*-A-*L*-methylcysteine (**2l**) to produce **5lf** as a diastereomer mixture (78/22). The α-steric bulkiness of *L*-valine methyl ester hydrochloride (**3d**•HCl) and the bulky alkoxy groups of *L*-phenylalanine ester hydrochlorides **3g**•HCl and **3h**•HCl slightly decreased the yield of products **5id**, **5hg**, and **5hh**. This protocol is practical and scalable, and α-dipeptides **5hf** and **5kf** could be synthesized on a gram scale. Furthermore, the masked dipeptides were selectively deprotected under mild conditions (Scheme 3).

Recently, Whiting successfully obtained the crystal structures of dimeric anhydride **6** between 2-phenylacetic acid and 2-halophenylboronic acids (Scheme 4).[7] Based on this report,[7] we also detected **6** from a reaction mixture of **1c** and ibuprofen **2a** by electrospray ionisation mass spectrometry (ESI-MS). In contrast, monomeric anhydride **4** was not detected by ESI-MS. Although these ESI-MS experiments are not enough as evidence for generation of **6**, it is expected that an active species of **1c**-catalysis as well as those of 2-halophenylboronic acid-catalysis are **6**, which may be generated *via* **4**.

To better understand the problems with each catalyst, we examined the reaction rates of the generation of active species **6** from ibuprofen **2a** with **1**, and the reaction rates between the active species with benzylamine **3a** to give amide **5aa** (Table 4). To our surprise, representative **1b**, **1l** and **1m** demonstrated similar activities for the generation of **6**, while showing lower or no activities for amidations. Furthermore, **1d** and **1f** failed to provide active species under the same conditions, perhaps because of steric hindrance or low Lewis acidity. Moreover, boroxine (cyclic trimer) of **1c** also provided comparable result in formation of **6** as the single form. We also found that formation of boroxine under dehydrative conditions was quite fast (<5 min), so that not only **1** but also its boroxine should be effective as catalysts.[13] These results reveal that the activation step and the amidation step are both crucial for the overall reaction, and **1c** is superior in the amidation step.



Scheme 4 Analysis of active species **6** by X-ray diffraction[7] and ESI-MS.

Table 4 Generation of dimeric anhydride **6** and activities for amidation

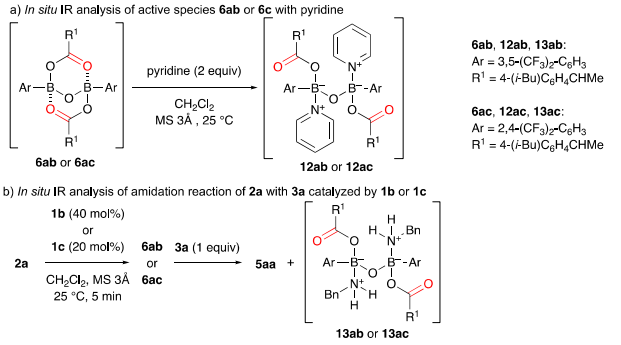
Entry	1	Yield (%) of **6**[a]	Yield (%) of **5aa**[a,b]	Entry	1	Yield (%) of **6**[a]	Yield (%) of **5aa**[a,b]
1	**1b**	**6ab**, 88	<5	4	**1f**	**6af**, 13	–
2	**1c**	**6ac**, 85	41	5	**1l**	**6al**, 84	<5
3	**1d**	**6ad**, 9	–	6	**1m**	**6am**, 82	16

[a] Determined based on ^{1}H NMR analysis. [b] Purities of **6** used in the amidation step were >95%.

According to Marcelli's theoretical calculations, the high catalytic activity of 2-iodophenylboronic acid can be attributed to the electronic effect in which an "I•••H–O" hydrogen bond stabilizes monoacyl boronate **4**.[14] Hall *et al.* have proposed a similar mechanism.[3h] On the other hand, Guo *et al.* proposed that the orbital overlap between a sp^2 orbital of the iodine atom and the *p* orbital of the boron atom may stabilize the complex after amine addition.[15] Our experimental results show that not only these electronic effects but also the steric effect of an *ortho*-substituent should be important for enhancing the catalytic activities.

To clarify the possibility that the *ortho*-substituent of boronic acid **1** plays a key role in preventing the coordination of amines to the boron atom of dimeric anhydride **6**, we examined the coordination effect between **6** and pyridine by *in situ* IR through observation of the stretching vibration of the carbonyl groups (Scheme 5a). As a consequence, 74% of **6ab** (1589 cm^{-1}) turned to a new peak at 1693 cm^{-1} within 3 minutes after pyridine was added. Since the new peak is different from any reference peaks,[16] we proposed that it should be the coordinate complex **12ab**. On the other hand, only 36% of **6ac** changed to the chelate complex (1697 cm^{-1}). Similar results were observed in the catalytic amidation between **2a** and benzyl amine **3a** (Scheme 5b). Through pre-mixing, **6ab** was formed quickly, while no amide (also confirmed by ^{1}H NMR) but a new coordinate complex **13ab** at 1678 cm^{-1} was observed.

In the **1c**-catalyzed amidation reaction, amide **5aa** was gradually generated instead of an ate-complex **13ac**. We anticipated that the coordination of **3a** to **6ab** increases its



Scheme 5 *In situ* IR analyses

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stability and lowers its reactivity, thus suppressing amidation.[2q] To obtain more mechanistic insights, we conducted the initial rate kinetic experiments to determine rate orders in **1c**-catalyzed amidation between **2a** and **3a**.[17] Although the formation of ammonium carboxylate salt slightly complicated this system, we obtained approximate first orders for **1c** and **3a**, and a zero order for **2a**.

Moreover, as Hall's previous report,[3d] we also found the pre-mixing of **1c** and **2a** in the presence of molecular sieves for several minutes is indispensable. Control reactions with a simultaneous addition of both substrates with the catalyst provided less than 5% yield of amide product after several hours. A coherent explanation for this initiation step asserts **6** as the actual catalytic species (Scheme 1).[12] Once formed, **6** can react with the added amine to give active intermediate **7**, which gives amide **5** quickly. The formation of **7** should be the rate-determining step according to the kinetics studies. Moreover, steric effect of **1c** helped to suppress the formation of inactive complexes **8** and **9**.

In summary, 2,4-bis(trifluoromethyl)phenylboronic acid **1c** serves as a highly effective catalyst for direct amidation under mild conditions. A variety of amides including α-dipeptides can be successfully constructed through this catalysis. Moreover, the *in situ* IR experiments proved that the *ortho*-substituent of boronic acid **1** plays a key role in preventing the coordination of amines to the boron atom of 2:2 mixed anhydride **6**, thus accelerating the amidation.

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Conflicts of interest

There are no conflicts to declare.

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9 According to ref. 3d, it is noted that the catalytic activity of **1m** with MS 3Å is much lower than with MS 4Å. In sharp contrast, MS 3Å was much more effective than MS 4Å for the **1c**-catalyzed synthesis of α-peptides.

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17 See details of IRKE in ESI.