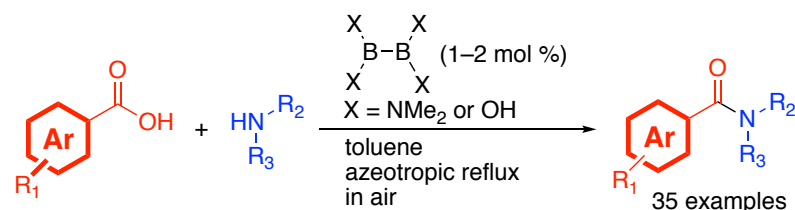# Diboron-catalyzed dehydrative amidation of aromatic carboxylic acids with amines

Dinesh N. Sawant,†[2] Dattatraya B. Bagal,[2] Saeko Ogawa,[1] Selvam Kaliyamoorthy,[1] Susumu Saito*[1]

Graduate School of Science[1] and Research Center for Materials Science,[2] Nagoya University, Chikusa, Nagoya 464-8602, Japan

Supporting Information

ABSTRACT: Tetrakis(dimethylamido)diboron and tetrahydroxydiboron are herein reported as new catalysts for the synthesis of aryl amides by catalytic condensation of aromatic carboxylic acids with amines. The developed protocol is both simple and highly efficient over a broad range of substrates. This method thus represents an attractive approach for the use of diboron catalysts in the synthesis of amides without having to resort to stoichiometric or additional dehydrating agents.

Amide moieties are ubiquitous in, e.g., pharmacologically active compounds, agrochemicals, as well as synthetic and natural polymers.[1] To construct amide C–N bonds, several methods have been developed, which include carbonylative amidations,[2] transamidations,[3] the hydrolysis of nitriles,[4] and the condensation of carboxylic acids with amines.[5] Among these, the direct condensation of carboxylic acids with amines is one of the simplest ways to prepare amides, and several homogeneous and heterogeneous transition-metal-based catalysts have been reported to promote the formation of the amide bond.[6,7] Subsequently, the use of Lewis-acidic boron catalysts for the direct amidation between carboxylic acids and amines has been discovered as a promising greener alternative. In 1996, Yamamoto *et al.* reported the first example of the dehydrative amide condensation catalyzed by substituted phenylboronic acids under azeotropic conditions and an atmosphere of inert gas.[8a] Since then, much progress has been accomplished on such organoboron compounds via, e.g., tuning the electronic nature of boron by modulating their substituents, which may result in the formation of hydrogen-acceptor bonds. Seminal studies by Ishihara,[8] Whiting,[9] Blanchet,[10] and Hall[11] have shown that bespoke boronic/borinic acids can serve as more effective catalysts. It should be noted, however, that most of the reported boronic/borinic-acid-catalyzed amidation protocols aim at the synthesis of *aliphatic* amide derivatives. In contrast, examples for aromatic carboxylic acids such as benzoic acid derivatives remain scarce. Very recently, Kumagai and Shibasaki *et al.* have disclosed that a B_3NO_2 ring system based on 1,3-dioxa-5-aza-2,4,6-triborinane (DATB) efficiently promotes this

reaction at low temperature (50 °C–reflux in toluene).[12] However, in this study, molecular sieves (4 Å) were used as a dehydrating agent, and systematic studies on a viable catalyst system that exhibits increased compatibility with various combinations of aromatic carboxylic acids and amines are still elusive. A practical alternative that is widely encountered in industry is the use of coupling reagents for the amidation of aromatic carboxylic acids.[7] However, the use of coupling reagents has its own limitations, as, e.g., the formation of stoichiometric amounts of waste is inevitable, which decreases the atom economy.[13]
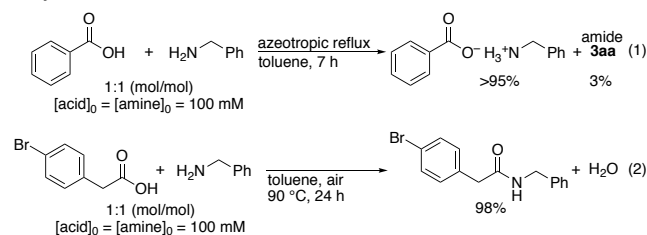
A major reason for the lower number of examples reported on the ideal one-step condensation of aromatic carboxylic acids with amines is their higher acidity relative to that of the aliphatic analogues. In reality, this reaction ends with the formation of an ammonium salt of the aryl carboxylate, which renders the synthesis of the amide kinetically less favorable.[7,9e,14] Likewise, this synthetic obstacle can be easily demonstrated by simple comparison experiments, i.e., catalyst-free thermal reactions of the same amine with an aliphatic or aromatic carboxylic acid, which affords different products (eqs 1

and 2). At 90 °C in air, the aliphatic acid was fully converted into the corresponding amide within 24 h.

Given our continuous interest in developing new methods for the catalytic addition of H–H and O–H bonds to the C=O bonds of amides[15] and carboxylic acids,[16] as well as the removal of OH groups from alcohols in the form of H_2O by S_N reactions in N-alkylations,[17] we report herein the use of commercially available tetrakis(dimethylamido)diboron (DB-**1**) and tetrahydroxydiboron (DB-**3**) as efficient dehydrative catalysts for the formation of C–N bonds (N–H addition to the C=O bond of HOC=O and subsequent removal of the OH group) between aromatic carboxylic acids and amines (Figure 1). Considering that these diboron reagents are inexpensive and easy to handle, it is very surprising that they have not yet been used for such dehydrative amidations.
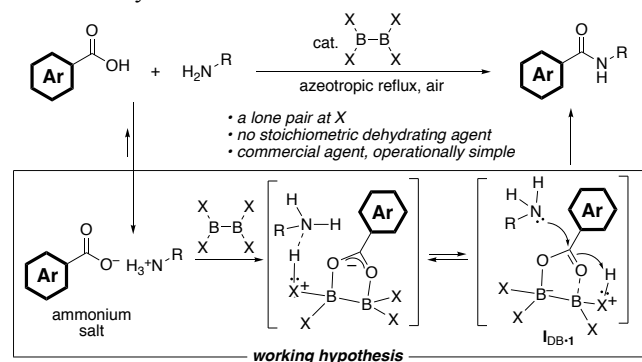

Figure 1. Working hypothesis for this study: commercially available diboron reagents of the type (X₂B–BX₂) (DB-**1**: X = NMe₂; DB-**3**: X = OH) as potential catalysts for the amidation of aromatic carboxylic acids.

Prior to starting this project, our working hypothesis (Figure 1) was based on two critical aspects: (i) retrieving the free amine from the corresponding ammonium salt, and (ii) selectively activating the carboxylate by a bidentate coordination to the B–B moiety. Steps (i) and (ii) should be facilitated by the cooperative role of the two boron centers and a secondary coordination (ligand) sphere. Since the molecular framework of $I_{DB\cdot 1}$ contains four X groups that are electronically equivalent, the liberated proton should be distributed with equal probability over the four X groups, which would enhance the charge separation, where the free amine and H⁺ would get spatially separated under a potentially smooth concomitant protonation of the C=O group.

The dehydrative amidation was initially examined by using benzoic acid (**1a**) and benzylamine (**2a**) as the representative substrates in the presence of 5 mol % of DB-**1** (X = NMe₂ in Figure 1) in anhydrous toluene under N₂ and azeotropic reflux conditions (Scheme 1). Within 6 h, amide **3aa** was formed in 81% yield. Gratifyingly, the azeotropic reflux *in air* afforded **3aa** more efficiently. For example, when the reaction was carried out in air for 6 h with a decreased catalyst loading of DB-**1** (1–2 mol %) or at higher concentration ($[1a]_0$ = 100 mM; $[DB\text{-}1]_0$ = 5 mM), **3aa** was obtained in 86–88% and 98% yield, respectively. Upon decreasing the temperature to 80 °C, only a negligible amount of **3aa** was produced. In contrast, the use of bis(pinacolato)diboron (DB-**2**, X = O; 5 mol %, Scheme 1) resulted in a substantial decline of the reaction rate (**3aa**: 32–34%).

Scheme 1. Initial screening of different diboron (DB) or boron (B) catalysts for the amidation of 1a with 2a.[a,b]
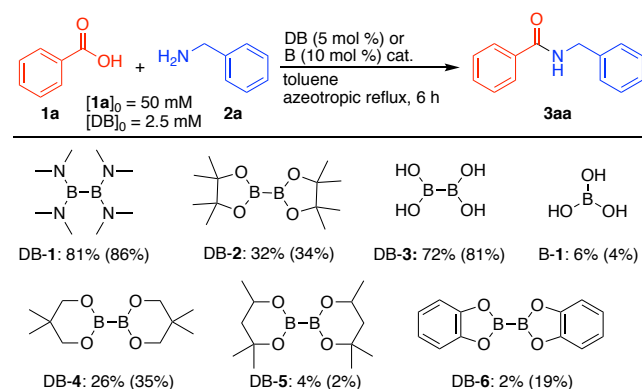
[a]Reaction conditions: **1a** (0.5 mmol) and **2a** (0.5 mmol) in toluene (10 mL). [b]GC-MS yield of **3aa** under N₂ or in air (in parentheses) using chlorobenzene as the internal standard.
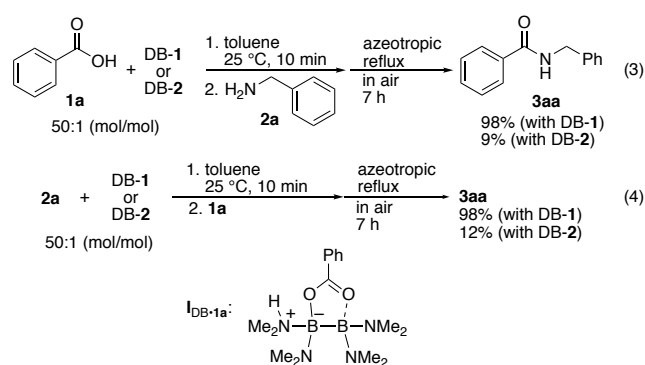
Figure 2. Control experiments: effects of the addition order of DB (2 mol %) and substrates on the yield of **3aa** (eqs 3 and 4; $[1a]_0$ = $[2a]_0$ = 100 mM) and proposed structure for $I_{DB\cdot 1a}$, which was detected by ESI-HRMS.

Encouraged by these initial studies, we conducted a series of control experiments to examine potential further advantages of using a reduced amount of DB-**1** (2 mol %) compared to DB-**2** (2 mol %) under azeotropic reflux conditions in air (Figure 2). The addition order of **1a**, **2a**, and DB-**1** did not affect the final yield of **3aa** (eqs 3 and 4), while the reaction with DB-**2** was consistently slow. The initial interaction of **1a** with DB-**1** afforded **3aa** quantitatively (eq 3), which supports our working hypothesis (Figure 1). The formation of catalyst intermediate $I_{DB\cdot 1}$ (Figure 1), which contains a B–B structure, was confirmed by ESI-HRMS analysis (Figure 2 and S19 in the Supporting Information). A chemical entity, presumably $I_{DB\cdot 1a}$ (m/z = 320.2555; calcd: 320.2555), in which DB-**1** and **1a** interact datively and/or ionically, was detected. Such tetra-coordinated boron center(s), obtained from the more preferable interaction of the B–B moiety with the carboxylate than the amine was confirmed by a ¹¹B NMR spectroscopic analysis (external standard: BF₃·OEt₂ at 0 ppm) of a 1:1:1 molar mixture of DB-**1** (δ 35.0, bs), **1a**, and pyrrolidine (**2f**), which showed ¹¹B signals (δ 21.1, bs and 2.7, s) similar to those of a 1:1 mixture of DB-**1** and **1a** (δ 20.7, bs and 2.7, s) (Figure S2). In any events, selective "**1a**–DB-**1** interaction" that initially occurs is primarily important at the early stage during the course of amidation. Simple reflux conditions (where a reflux condenser without a

water trap was used) gave higher yields of **3aa** when using DB-**1** (68%) than when using DB-**2** (<5%). These results highlight practical advantages over previous methods that frequently use molecular sieves as a dehydrating agent and/or azeotropic reflux conditions, which require cooling water and inert gas.

Different catalytic activities among various diboron reagents and a boric acid (B-**1**)[18] were also compared in the dehydrative amidation of **1a** with **2a** (Scheme 1; for detailed optimization studies, see Table S1). Notably, tetrahydroxydiboron (DB-**3**), in which characteristic multiple OH groups similar to that of B-**1** are incorporated, afforded an appreciable yield of **3aa** (81%). Since B-**1** (10 mol %) barely promoted the reaction, the possibility of the formation of B-**1** from DB-**1** and DB-**3**, followed by an *in-situ* generation of boron (tri)carboxylate as the catalytic species could be ruled out. Bis(neopentylglycolato)diboron (DB-**4**), bis(hexyleneglycolato)diboron (DB-**5**), and bis(catecholato)diboron (DB-**6**) consistently furnished much poorer yields of **3aa**. The low yield of **3aa** using DB-**6** may be due to the lower basicity of the substituents on boron (in this case a lone pair on oxygen) that are delocalized over the Ph groups of the catecholates.

Under the optimized conditions (azeotropic reflux in air), the substrate scope of the amidation of several aromatic carboxylic acids with **2a** using a catalytic amount of DB-**1** (2 mol %) was explored, and the results were compared with the amidation using DB-**3**, B-**1**, and that without using any catalysts (Scheme 2). Both electron-donating and electron-withdrawing groups at the *para*-, *meta*-, and *ortho*-position of **1a** were mostly compatible, furnishing the corresponding amidation products (**3aa–3ha** and **3ka–3oa**). Functional thioether, aryl iodide, (benzo)furan, thiophene, and pyridine groups were also tolerated (**3ea**, **3ga** and **3pa–3sa**). While employing 4-nitrobenzoic acid (**1i**) and 4-(dimethylamino)benzoic acid (**1j**), the corresponding carboxylates of **2a** were considerably less soluble in toluene. Hence, the reactions were carried out in chlorobenzene at higher temperature, which resulted in the formation of **3ia** in 98% yield (for a solvent screening, see: Table S2). The amidation of **1j** proceeded sluggishly to furnish **3ja** in low yield, as the solubility of the corresponding amine salt of **1j** remains low. Acid **1a** was also tested in the reaction with different amines (**2a–2g**) (Scheme 2), where primary (1°, **2b** and **2c**) and secondary (2°, **2e–2g**) aliphatic amines underwent effective amidations using catalytic DB-**1** or DB-**3**. The less basic aniline **2d** showed a lower reactivity (**3ad**: 37%), although DB-**1** still proved to be the best catalyst among those tested. Sterically bulky ArCO$_2$H (**1t** and **1u**) and 2° amines (**2h** and **2i**) are also compatible with reaction conditions, giving **3ta**, **3ua**, **3ah**, and **3ai**. The interior 1° amine of **2j** underwent faster amidation over the interior 2° amine, giving **3aj**. Amidation of **1a** or other carboxylic acids with chiral amines such as C-protected α-amino acids with different functionalized side chains (Scheme 2, **3ak–3ao** and Table S3), were amenable to the catalyst system, although H$_2$N-Thr-OMe underwent poor amidation under azeotropic reflux of toluene. Slight to moderate racemization was observed, giving scalemic **3ak** and **3al** (S13–S14) derived from **1a**. In contrast, epimerization at the stereogenic carbon center of the amidation products Boc-Gly-Val-OBn and Boc-Gly-Phe-NHBn was negligible (S16–S17). Scaling up the amidation of **1a** with **2a** to 40 mmol worked as well (S6).

In summary, we have demonstrated that the diboron compounds can serve as viable catalyst alternatives for the

Scheme 2. Various combinations in the amidation between 1 and 2 to give 3.[a,b]
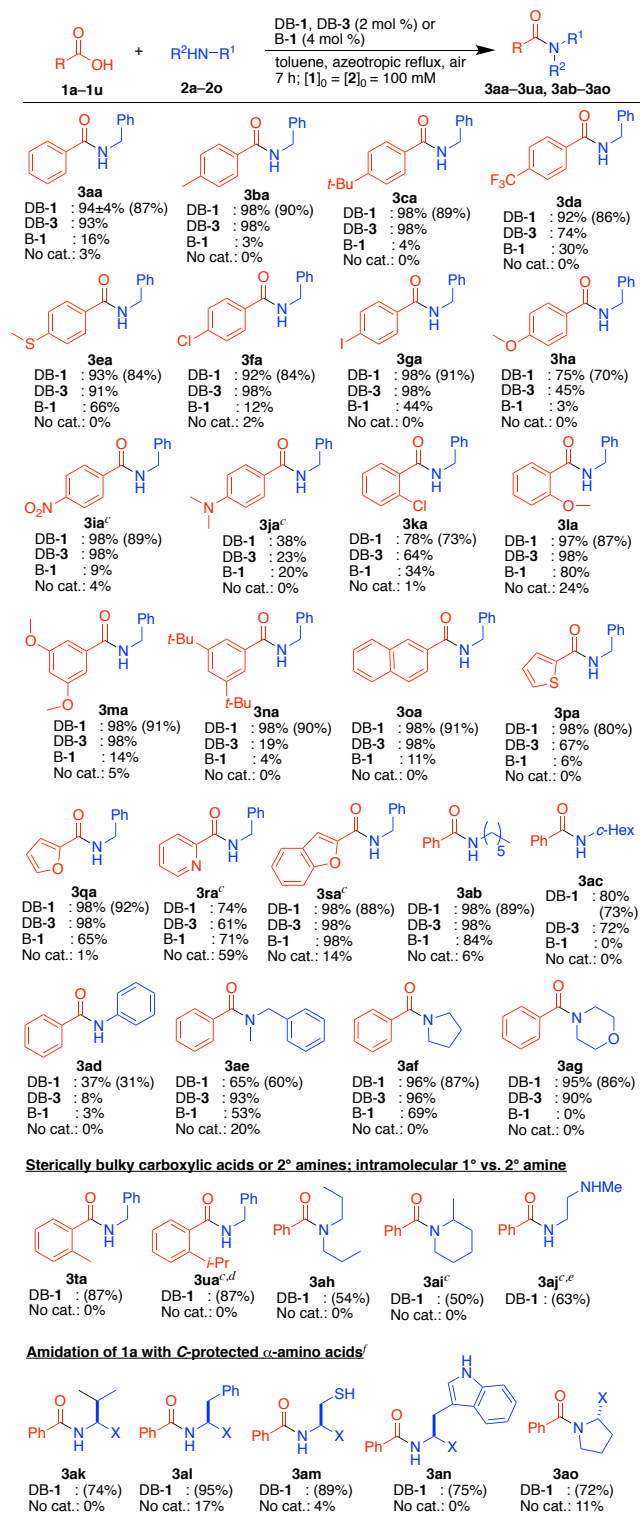
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol) and DB-**1** (2 mol %), DB-**3** (2 mol %) or B-**1** (4 mol %) in anhydrous toluene (5 mL). [b]NMR yield based on 1,1,2,2-tetrachloroethane as the internal standard with isolated yields in parentheses. [c]In refluxing chlorobenzene instead of toluene. [d]DB-**1** (10 mol %) was used. [e]PhCO(NMe)(CH$_2$)$_2$NHCOPh (5%) was by-produced. [f]X = CO$_2$R (**3ak**: R = PhCH$_2$; **3al–3ao**: R = Me).

promotion of one of the most difficult amidation reactions involving aromatic carboxylic acids. Further extensions of this method to amidation that involve a series of other N- and C-protected amino acids with chiral centers are currently in progress.

ASSOCIATED CONTENT

Supporting Information

AUTHOR INFORMATION

Corresponding Author

*E-mail: saito.susumu@f.mbox.nagoya-u.ac.jp

Present Addresses

†Leibniz Institute for Catalysis (LIKAT Rostock), Albert-Einstein-Str. 29 a, 18059 Rostock, Germany.

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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