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Organoboron catalysis for direct amide/peptide bond formation

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Amides and peptides are ubiquitous functional groups found in several natural and artificial materials, and they are essential for the advancement of life and material sciences. In particular, their relevance in clinical medicine and drug discovery has increased in recent years. Dehydrative condensation of readily available carboxylic acids with amines is the most "direct" method for amide synthesis; however, this methodology generally requires a stoichiometric amount of condensation agent (coupling reagent). Catalytic direct dehydrative amidation has become an "ideal" methodology for synthesizing amides from the perspective of green chemistry, with water as the only byproduct in principle, high atom efficiency, environmentally friendly, energy saving, and safety. Conversely, organoboron compounds, such as boronic acids, which are widely used in various industries as coupling reagents for Suzuki–Miyaura cross-coupling reactions or pharmaceutical structures, are environmentally friendly molecules that have low toxicity and are easy to handle. Based on the chemical properties of organoboron compounds, they have potential Lewis acidity and the ability to form reversible covalent bonds with dehydration, making them attractive as catalysts. This review explores studies on the development of direct dehydrative amide/peptide bond formation reactions from carboxylic acids using organoboron catalysis, classifying them based on chemical bonding and catalysis over approximately 25 years, from the early developmental days to 2023.

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1. Introduction

Amide bond is an essential chemical linkage found in several natural and non-natural materials, such as pharmaceutical, agrochemical, and functional materials.¹ It is particularly useful as a pharmaceutical substructure, with more than 40% of the top-selling 200 small molecule drugs in 2023 containing at least one amide bond.² Peptide bond, which is the amide bond between amino acids, is found in not only biomolecules of the human body but also several pharmaceuticals, functional

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materials, cosmetics, and foods. Recent drug discovery has shifted to medium-molecule drugs with molecular weights of approximately 1000–5000, combining the advantages of small-molecule and antibody drugs. Particularly, peptides have attracted considerable attention for next-generation modalities; more than 260 peptides progressed into human clinical trials in 2018.³ The development of an efficient synthetic methodology for amides is essential because amide bond formation reactions account for 50% of chemical reaction processes in drug discovery and development.⁴ Accordingly, “amide formation avoiding poor atom economy reagents” was voted as the top priority for improvement at the ACS Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) in 2006.⁵ In 2018, ACS GCIPR identified “general methods for catalytic/sustainable (direct) amide or peptide bond formation” as a key green chemistry research area.⁶

Although amide bond formation has been reported using various starting materials, the most straightforward synthesis involves dehydrative amide condensation from readily available carboxylic acids with amines. However, extremely high temperatures (>160 °C) are generally required to obtain amides from carboxylic acids and amines without an activating agent.⁷ This is because ammonium salt formation through acid–base interaction is significantly more favorable than dehydration condensation, particularly for highly acidic carboxylic acids such as aromatic carboxylic acids.⁸ Therefore, to form an amide bond from a carboxylic acid and an amine, it is generally necessary to use a condensation agent (coupling reagent). Although several excellent condensation agents have been developed, there is still room for improvement.⁹ Particularly, the activation of carboxylic acids requires a stoichiometric amount of a condensation agent, which poses several challenges, including low atom efficiency, high cost, a complicated workup and purification process, and frequent racemization. Regarding peptide bond formation, Merrifield¹⁰ established a

solid-phase peptide synthesis (SPPS) method using carbonate-based protecting groups; however, the issue of racemization due to the use of stoichiometric amounts of condensation agents persists.

The “ideal” methodology for synthesizing amides from carboxylic acids and amines involves a direct dehydrative amide condensation reaction using catalysts. Direct dehydrative amide condensation reactions using transition metal complex catalysts such as Ti, Zr, Hf, Nb, and polyoxometalate¹¹ have been reported.¹² A noteworthy recent study is Yamamoto's report,¹³ which presents the use of boron catalysts, namely aromatic boronic acids, and represents a milestone in this field. Boron compounds exhibit Lewis acidity due to the vacant p-orbital and thus induce electrophilic activation through interactions with carbonyl compounds that exhibit Lewis basicity. In addition, boron compounds with a B–OH bond react with the hydroxyl functional groups of alcohols or carboxylic acids to form reversible covalent bonds through dehydration.^{14–16} Both chemical properties exhibited by boron compounds facilitate the catalytic electrophilic activation of carboxylic acids. Furthermore, reactions using carboxylic acids with hydroxyl groups can be applied to substrate-directed molecular transformation.¹⁷

Several excellent reviews have been published focusing on general amide synthesis,¹ catalytic amide bond formations,¹² and organoboron catalysis.¹⁴ In this article, we review studies on organoboron catalysis for direct amide/peptide bond formation using dehydrative condensation.

2. Catalytic direct amide bond formation from carboxylic acids

2.1. Direct amide bond formation using boronic acid catalysis

As a pioneering report on catalytic amidation using organoboron compounds, in 1996, Yamamoto and co-workers¹³ reported the first catalytic amidation using arylboronic acids as a catalyst. Arylboronic acids with electron-withdrawing substituents at the benzene rings are water-, acid-, and base-tolerant Lewis acids. They are also thermally stable and easy to handle in air. Yamamoto¹³ postulated that the strong Lewis acidity of boron enhances the formation of (acyloxy)boron intermediates and their reactivity with amines. In this context, the catalytic activities of a series of electron-deficient aryl boronic acids for amidation reactions were investigated. As a result, the catalytic amount of boronic acids **4–9** promoted the amide condensation reactions of 4-phenylbutyric acid (**1**) and 3,5-dimethylpiperidine (**2**) in toluene under reflux conditions in the presence of molecular sieves (MS) 4A to obtain amide **3** (Scheme 1).

Among them, 3,4,5-trifluorobenzeneboronic acid (**9**) was proven to be an effective catalyst for catalytic amidation. A remarkable feature of this catalysis is that the amide can be obtained with a satisfactory level of purity after only a simple aqueous workup. Yamamoto¹³ proposed a mechanistic insight of amidation reactions using boronic acid catalysts (Fig. 1). First, boronic acid or boroxine **10**, which is a dehydrated trimer

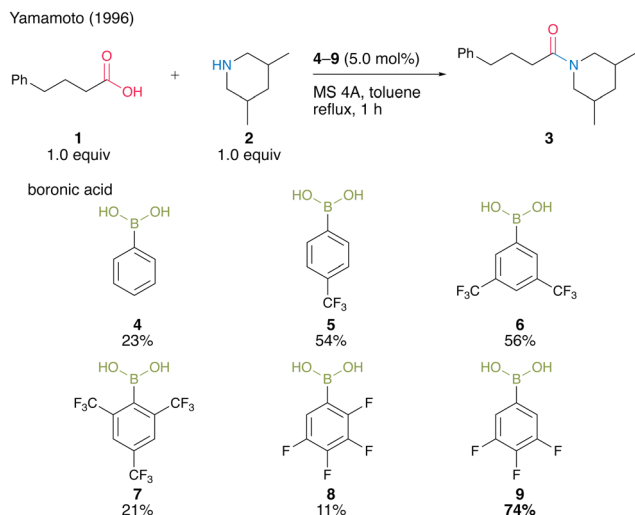


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Scheme 1 Electron-deficient boronic acid-catalyzed amidation reported by Yamamoto.¹³

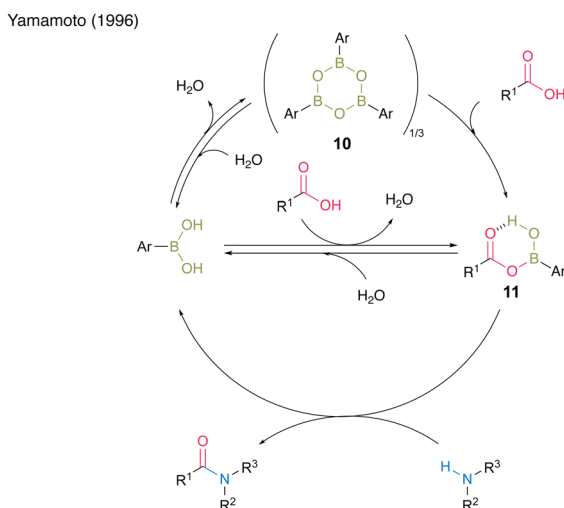
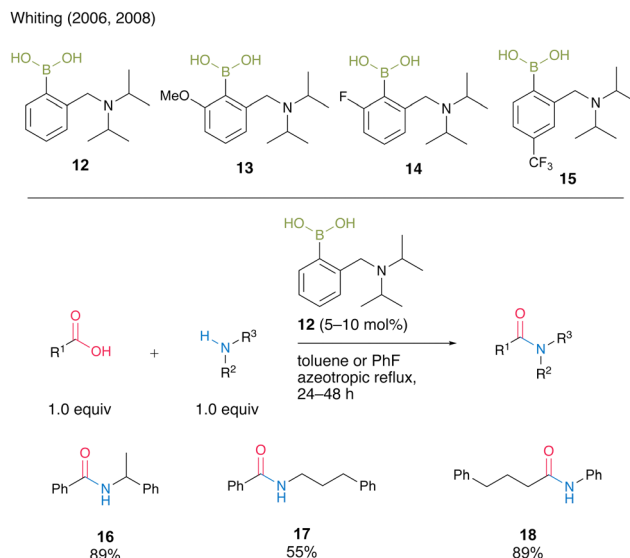


Fig. 1 Proposed amidation mechanism reported by Yamamoto.¹³

of boronic acid, reacts with carboxylic acid to form (acyloxy)-boron intermediate **11**, which is characterized by ¹H NMR and IR analysis. In intermediate **11**, the electrophilic activation of carboxylic acid was doubly induced by the Lewis acidic boron and intramolecular hydrogen bonding. Then, **11** reacts with an amine to yield the corresponding amide with water as a byproduct and regenerates the catalyst.

Because the formation of (acyloxy)boron is an equilibrium reaction, the removal of water is crucial. Following Yamamoto's report,¹³ several scholars subsequently developed their original aromatic boronic acid catalysts to employ in catalytic amidation.

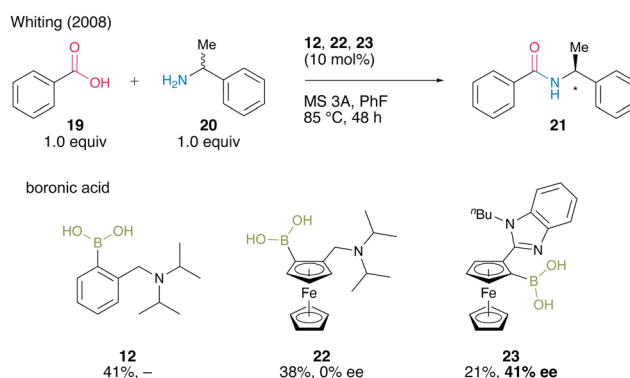
Whiting and co-workers^{8a,b} reported catalytic amidation reactions using *N,N*-diisopropylbenzylaminoboronic acid **12** and its derivatives **13–15** (Scheme 2). They revealed that the electron density of the aromatic rings affected the catalytic activity and amide formation rate *via* kinetic studies. Electron-rich boronic acid **13** exhibited nearly half the catalytic activity of



Scheme 2 *N,N*-Diisopropylbenzylaminoboronic acid-catalyzed amidation reported by Whiting.^{8a,b}

electron-deficient boronic acid **14** for the reaction of 4-phenyl butyric acid and benzylamine. Furthermore, an increase in the reaction rate was observed for the *para*-trifluoromethyl-substituted aromatic boronic acid **15** compared with an unsubstituted boronic acid **12**. Under optimized azeotropic reflux conditions in toluene or fluorobenzene, unsubstituted boronic acid **12** promoted the catalytic amidation of benzoic acid or aniline, which is a difficult substrate for amidation, to produce the corresponding amides **16–18** in good to high yields.

In 2008, Whiting's group¹⁸ reported asymmetric direct amide synthesis by kinetic amine resolution using chiral ferrocene-derived aminoboronic acid. Using chiral ferrocene **22** in the reaction of benzoic acid (**19**) with racemic α -alkylamine **20**, a catalytic activity similar to that of **12**, although by asymmetric induction, was observed. Meanwhile, **23**, in which the amine moiety was replaced by *N*-*n*-butylbenzimidazole, yielded amide **21** with 41% ee (Scheme 3). The relevance of the mild basicity of benzimidazole in asymmetric induction was suggested because catalyst **23** containing benzimidazole may preferentially select



Scheme 3 Asymmetric direct amide synthesis *via* kinetic amine resolution reported by Whiting.¹⁸

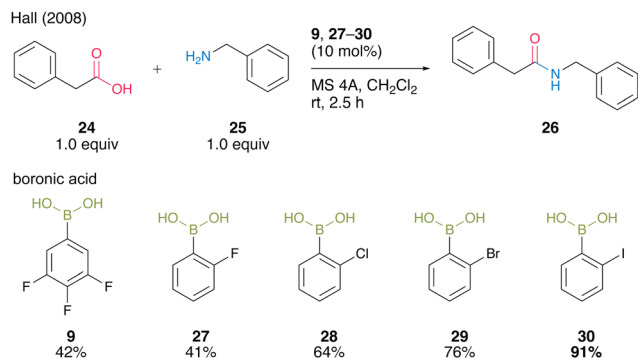


one amine enantiomer that reacts with activated diacyl boronates *via* hydrogen bonding. By contrast, the more basic *N,N*-diisopropylamino group of **22** promotes ammonium formation by deprotonation rather than hydrogen bonding, generating amides without inducing chirality. This Whiting's finding is the first successful boronic acid-catalyzed asymmetric dehydrative amidation. However, little progress has been made in this research field.

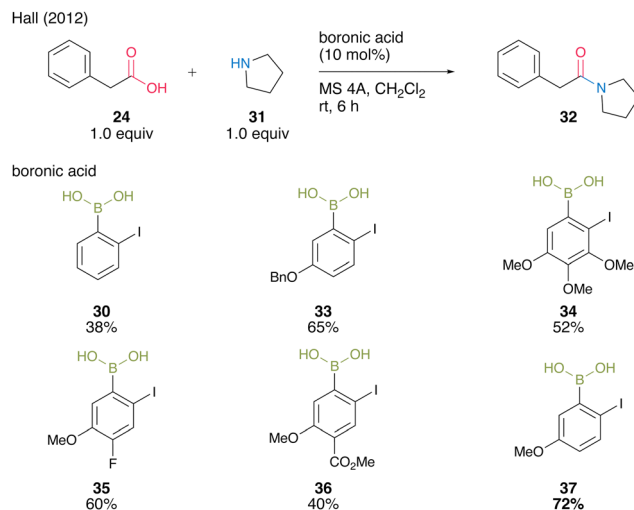
In the same year, Hall and co-workers¹⁹ reported that the halogen atom at the *ortho*-position drastically enhances the catalytic activity of aromatic boronic acids in dehydrative amidation. The catalytic activities of functionalized arylboronic acids, including **9**, **27–30**, in the reaction of phenylacetic acid (**24**) with benzylamine (**25**) in the presence of activated MS 4A were surveyed (Scheme 4). As a result, 2-iodophenylboronic acid (**30**) served as the best catalyst to produce the corresponding amide **26** in the highest yield, although *para* isomers or *o,o'*-dihaloarylboronic acids did not exhibit sufficient catalytic activity. These results indicate that an *ortho*-mono substituent is necessary for boronic acids to achieve satisfactory levels of catalytic activity. This catalysis is advantageous because the reaction proceeded even at room temperature.

In 2012, the same group developed 5-methoxy-4-iodophenylboronic acid (MIBA, **37**), which was designed based on 2-iodophenylboronic acid (**30**), and revealed that an electron-donating group introduction at the *para* position of the iodide enhanced the catalytic activity for dehydrative amidation at room temperature (Scheme 5).²⁰ The methoxy group enhanced the electron density of *para*-iodine, resulting in high catalytic activity. These results indicate that the catalytic activity of aromatic boronic acids is influenced not only by the inductive effect but also by other effects. The proposed catalytic cycle based on density functional theory (DFT) calculations by Marcelli²¹ is shown in Fig. 2. First, intermediate **39** was formed by the nucleophilic addition of amine to acyl boronate intermediate **38**, which was formed by boronic and carboxylic acid reactions. Intermediate **39** exhibits the transition state shown in **40**, which promotes the dehydration step of amide bond formation *via* hydrogen bonding between the electron-rich iodine atom and water molecules and is highly catalytically active.

The catalytic activity was assumed to be high by accelerating the dehydration step in amide bond formation *via* hydrogen



Scheme 4 *ortho*-Halophenylboronic acid-catalyzed amidation reported by Hall.¹⁹



Scheme 5 MIBA-catalyzed amidation reported by Hall.²⁰

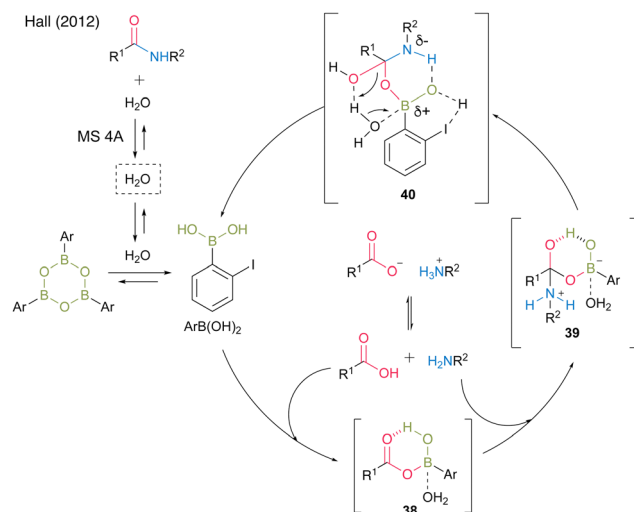
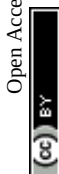


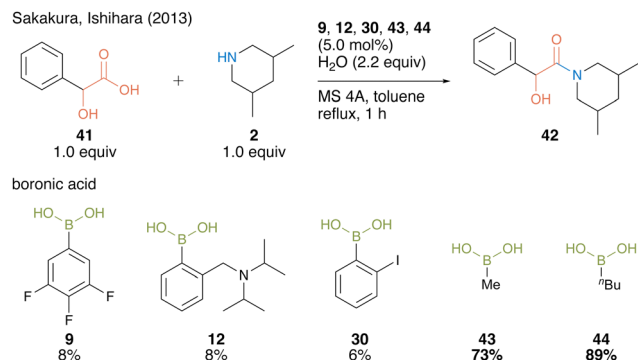
Fig. 2 Proposed amidation mechanism reported by Hall.²⁰

bonds between electron-rich iodine atoms and water molecules. As an alternative reaction mechanism, Hall proposed a plausible mechanism *via* a transition state in which a water molecule in a transition state **40** is replaced by a carboxylic acid. In this reaction, the use of powdered MS 4A dried at 250 °C under high vacuum (<2 mbar) with a Kugelrohr instrument is crucial for obtaining high product yields and reproducibility. MS is thought to play a role in both taking in water and releasing it again as a water reservoir. In addition, a premix of a boronic acid catalyst and carboxylic acid in the presence of MS is extremely effective.

In 2013, Sakakura, Ishihara, and co-workers²² found that alkylboronic acids such as methylboronic acid (**43**) and *n*-butylboronic acid (**44**) are more active catalysts for amidation using α -hydroxycarboxylic acids than arylboronic acid catalysts **9**, **12**, and **30** (Scheme 6).

In this catalysis, 2.2 equivalent of water was necessary to obtain a high amide yield because water promotes triboroxine

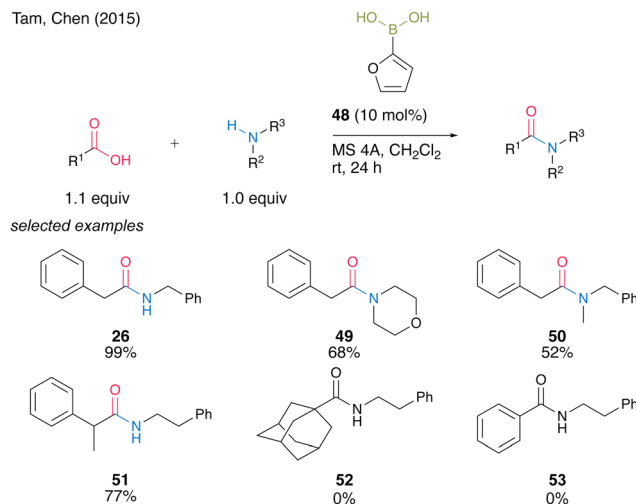




Scheme 6 Alkylboronic acid-catalyzed amidation reported by Sakakura and Ishihara.²²

hydrolysis. Based on the X-ray structure of a complex of methylboronic acid, phenylpruvic acid, and 1,2,3,4-tetrahydroquinoline, a cyclic active intermediate was proposed (Fig. 3). Alkylboronic acid and α -hydroxycarboxylic acids formed cyclic acyl boronate **45**. Subsequent dehydration led to equilibrium between active species **46** and **47**. Although the desired product was obtained by the addition of an amine to **46** or **47**, it was assumed that the equilibrium was biased toward **47** rather than toward the more reactive active species **46** while using electron-deficient aromatic boronic acid catalysts. This result indicated that electron-rich alkylboronic acids were prevented from forming inactive **47**, providing better amidation results than electron-deficient arylboronic acids. Furthermore, in some cases, the addition of a catalytic amount of benzoic acid improved the product yield by promoting ligand exchange between the product or substrate on the catalyst and benzoic acid.

In 2015, Tam, Chen and co-workers²³ screened a wide range of commercially available aryl boronic acids, including *meta*-substituted benzenboronic acid or heteroarylboronic acid and found that 2-furanylboronic acid (**48**) is an active catalyst for the dehydrative amidation of aliphatic carboxylic acids and primary or secondary amines (Scheme 7). Although bulky or aromatic carboxylic acids were not applicable, amides **26**, **49–51** were obtained in high yields even at room temperature in the presence of MS 4A in dichloromethane.



Scheme 7 2-Furanylboronic acid-catalyzed amidation reported by Tam and Chen.²³

In the same year, Blanchet and co-workers²⁴ developed a bench-stable 2-(thiophen-2-ylmethyl)phenylboronic acid (**54**). They expected that sulfur atoms would promote active intermediate formation and dehydration after forming amides. Boronic acid **54** was effective for the direct dehydrative amidation of aliphatic and heteroaromatic carboxylic acids at room temperature in the presence of MS 5A in dichloromethane to afford the corresponding amides **55–57** in good to excellent yields (Scheme 8). Although moderate heating at 45 °C was required, acyclic secondary amine was also applicable to obtain tertiary amides **55** in excellent yield.

In 2016, Ishihara and co-workers²⁵ discovered the electron-deficient 3,5-bis(trifluoromethyl)phenylboronic acid (**6**) and DMAPO (**63**) cooperative catalysis for dehydrative amidation. **63** exhibited significantly more effectiveness as an additive than other bases **60–62** and **64** (Scheme 9).

This cooperative catalysis was useful for the chemoselective amidation of β -substituted acrylic acid **65** with aniline derivative **66** to obtain the desired amide **67**. When boronic acid **6** was used without DMAPO (**63**), the yield and selectivity of **67** were moderate (Scheme 10).

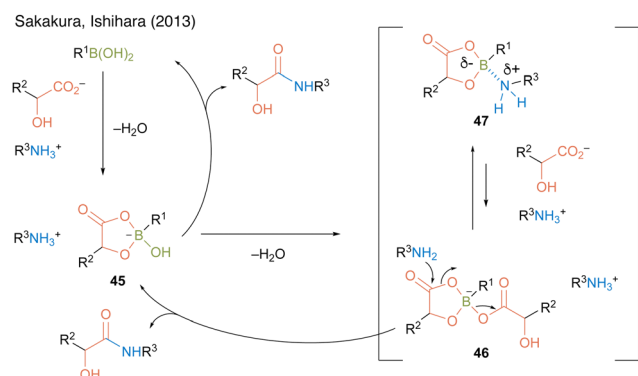
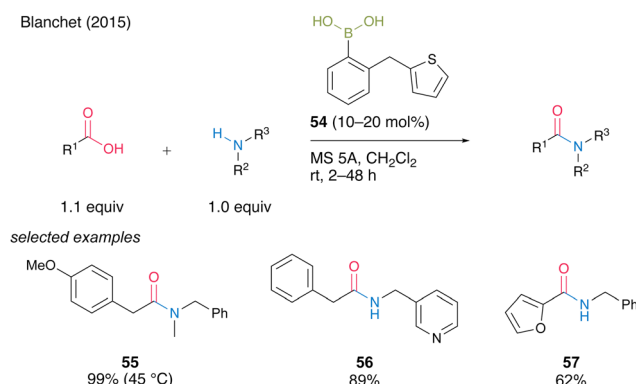
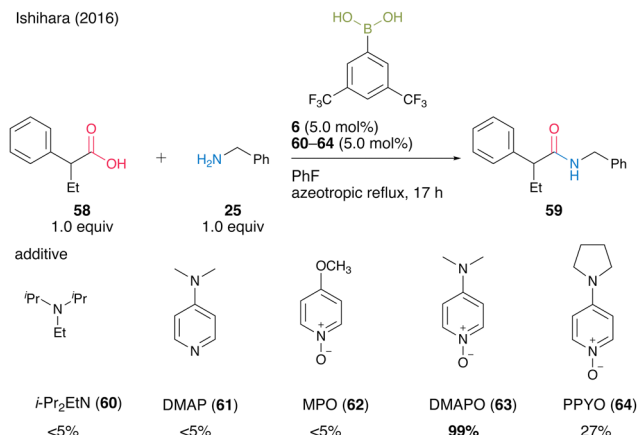


Fig. 3 Proposed amidation mechanism reported by Sakakura and Ishihara.²²

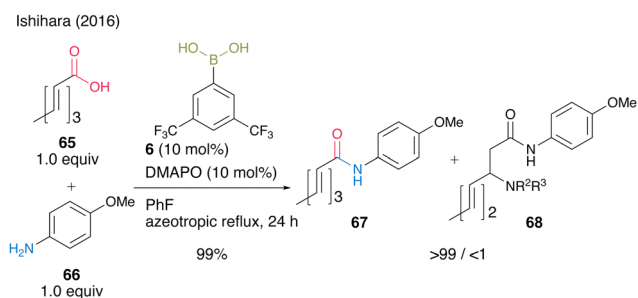


Scheme 8 2-(Thiophen-2-ylmethyl)phenylboronic acid-catalyzed amidation reported by Blanchet.²⁴





Scheme 9 Boronic acid-DMAPO cooperatively catalyzed amidation reported by Ishihara.²⁵



Scheme 10 Boronic acid-DMAPO cooperatively catalyzed chemoselective amidation reported by Ishihara.²⁵

In the presence of a nucleophilic catalyst (Nu) as an additive, the reaction proceeded through a more active intermediate **71** via tetrahedral intermediate **70**, accelerating amidation. However, when the additive reacted with the boron of the boronic acid catalyst as a Lewis base, inactive intermediate **69** was formed, which might have inhibited amide formation; thus, the choice of additive was crucial in this cooperative catalysis (Fig. 4).

Since Yamamoto's pioneering work,¹³ there have been several reports on improved reaction mechanisms of boronic acid-catalyzed

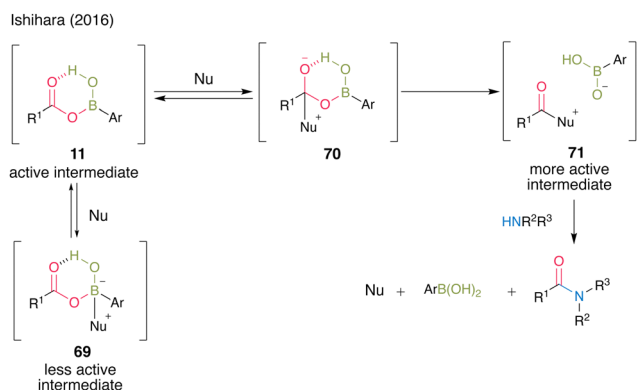


Fig. 4 Proposed amidation mechanism reported by Ishihara.²⁵

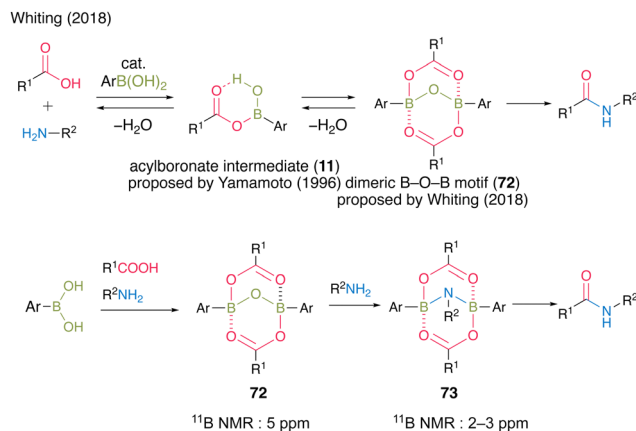


Fig. 5 Proposed amidation mechanism reported by Whiting.²⁷

amidation via a monoacyl boronate intermediate **11**.^{20,21,26} In 2018, Whiting *et al.*²⁷ reported a completely novel reaction mechanism for boronic acid-catalyzed amidation (Fig. 5). They proposed B-O-B motif **72** as a certain active intermediate, which has a unique structure of a dimer of monoacyl boronate intermediate **11** based on the X-ray analysis of intermediates, theoretical studies, and experimental results on the reaction mechanism. In this report, a more reactive B-N-B structure of **73** was also proposed and detected using the ^{11}B NMR spectra derived from a dimeric B-O-B compound with an internal amine. This report marked a turning point in the field of boronic acid-catalyzed dehydrative amidation.

In 2018, Ishihara and co-workers²⁸ reported catalytic dehydrative amidation using 2,4-bis(trifluoromethyl)boronic acid (**74**). In this reaction, the bulky *ortho*-trifluoromethyl group played a vital role in suppressing the coordination of amines to boron atoms in the active intermediate **78**, thereby preventing the loss of Lewis acidity, which is crucial for catalytic activity (Fig. 6).

A dimeric intermediate of acyl boronate was detected by *in situ* IR analysis and ESI-MS. Furthermore, similar to the findings of Hall,²⁰ a premix of boronic acid and carboxylic acid was effective, ascribed to the initiation step for the formation of an active intermediate containing the B-O-B bond proposed by Whiting.²⁷ This catalyst can be used for reactions at low temperature (25 °C) and bulky substrates to provide the corresponding amides **75** and **76** in high yields. Moreover, racemization was not observed even when α -amino acid derivatives were

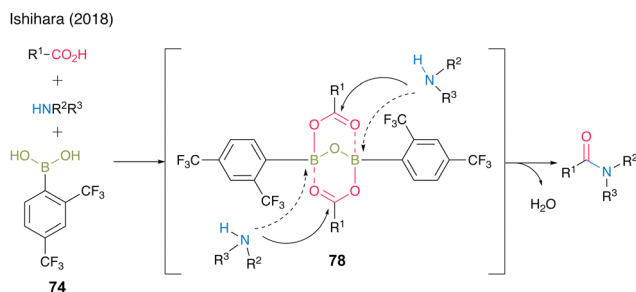
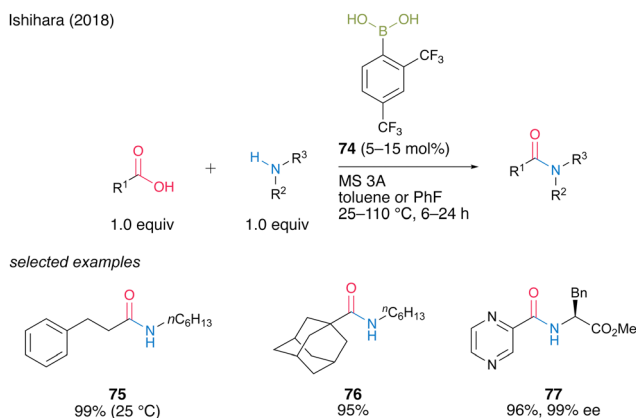


Fig. 6 Effect on the *ortho*-substituent group reported by Ishihara.²⁸



Ishihara (2018)



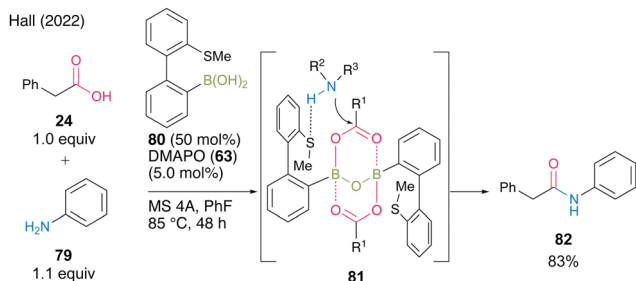
Scheme 11 2,4-Bis(trifluoromethyl)phenylboronic acid-catalyzed amidation reported by Ishihara.²⁸

used as amine substrates to produce amide **77** in 96% yield. (Scheme 11).

In 2022, Hall and co-workers²⁹ reported thioether-substituted biphenylboronic acid **80** as an effective amidation catalyst for poorly nucleophilic amines such as aniline derivatives. Most boronic acids for catalytic amidation have been reported to be highly reactive when combined with aliphatic amines; however, few studies have focused on the amidation of aromatic amines. Furthermore, these studies often required very high-temperature conditions. They suggested that **80** could serve as a bifunctional catalyst because the boron atom activated the carboxylic acid and sulfur could serve as a hydrogen-bond acceptor for amine, thereby producing reaction intermediate **81**. In the presence of 50 mol% of **80** and 5.0 mol% of DMAPO (**63**), the amidation of aniline (**79**) at 85 °C with MS 4A in fluorobenzene was very effective (Scheme 12). This catalysis can be applied to highly electron-deficient aromatic amines, such as 3-cyanoaniline.

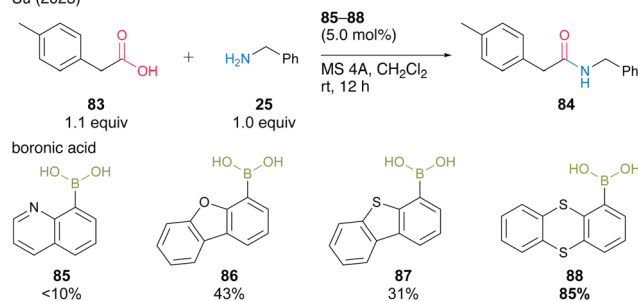
In 2023, Su and co-workers³⁰ screened aromatic boronic acids with heterocyclic structures, including **85–88**, and found that 1-thianthrenylboronic acid (**88**) was an effective catalyst for dehydrative amidation at room temperature in the presence of MS 4A in dichloromethane (Scheme 13). In this catalysis, the sulfur atom of thianthrene was assumed to contribute to the activation of amines *via* hydrogen bonding or the electrophilic activation of carboxylic acids *via* the formation of sulfonium ions. Boronic acid **88** is commercially available, easy to handle, and has pharmaceutical benefits.

Hall (2022)



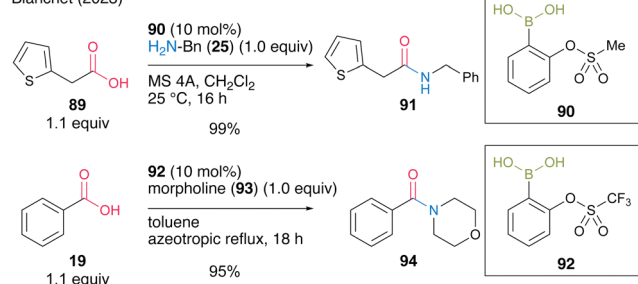
Scheme 12 Thioether-substituted biphenylboronic acid-catalyzed amidation reported by Hall.²⁹

Su (2023)



Scheme 13 1-Thianthrenylboronic acid-catalyzed amidation reported by Su.³⁰

Blanchet (2023)



Scheme 14 2-Sulfonatobenzenboronic acid-catalyzed amidation reported by Blanchet.³¹

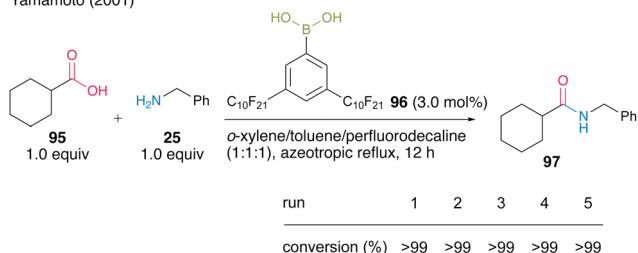
In the same year, Blanchet and co-workers³¹ found that *ortho*-(sulfonyloxy)benzeneboronic acids, which are aromatic boronic acids containing strong electron-withdrawing groups, were effective for dehydrative amidation at low temperatures in the presence of MS 5A in dichloromethane or under azeotropic reflux conditions in toluene. Based on their original studies using electron-deficient (aryloxybenzene)boronic acid catalysts and the estimated Lewis acidity of boron calculated using DFT, highly electron-deficient *ortho*-(sulfonyloxy)benzeneboronic acids, such as 2-(methanesulfonyloxy)phenylboronic acid (**90**) and 2-(trifluoromethanesulfonyloxy)phenylboronic acid (**92**), were proposed and synthesized (Scheme 14). These catalysts were stable and showed high catalytic activities to produce amides **91** and **94** in excellent yields.

2.2. Direct amide bond formation using recoverable and reusable boronic acid catalysis

From the perspective of improving the practicality of amide synthesis, a recoverable and reusable boronic acid catalyst for the direct dehydrative amidation of carboxylic acids is desired. In this section, we present some successful examples. In 2001, Yamamoto and co-workers³² developed 3,5-bis(perfluorodecyl)phenylboronic acid (**96**), which has a fluororous alkyl side chain exhibiting properties of electron-deficient and fluororous-layer-supporting functional groups. They successfully developed two different protocols for catalyst recovery and reuse. Catalyst **96** (3.0 mol%) promoted dehydrative amidation under azeotropic reflux conditions in a homogeneous system of a mixed solvent



Yamamoto (2001)



Scheme 15 3,5-Bis(perfluorodecyl)phenylboronic acid-catalyzed amidation reported by Yamamoto.³²

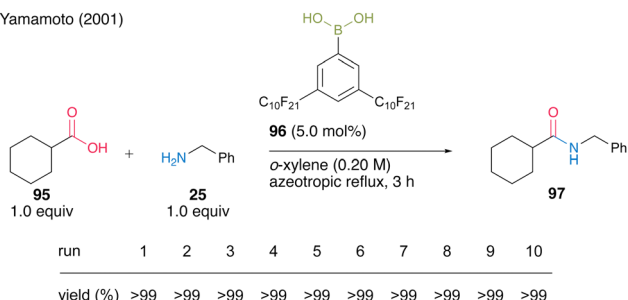
of *o*-xylene, toluene, and perfluorodecalin (1 : 1 : 1) (Scheme 15). When the homogeneous mixture was cooled to room temperature, it separated into a heterogeneous organic solvent layer and a catalyst-supported fluorine layer, allowing liquid-liquid separation by decantation. In the reaction to obtain amide **97** from cyclohexanecarboxylic acid (**95**) and benzylamine (**25**), the fluorine solvent containing the fluorine catalyst was recovered and reused five times.

Another protocol exploited the property that catalyst **96** is soluble in nonfluorous *o*-xylene under high-temperature conditions of azeotropic reflux but is insoluble under low-temperature conditions. It was reported that 5.0 mol% of catalyst **96** could be recoverable and reusable 10 times in the same dehydrative amidation of **95** and **25** (Scheme 16).

In the same year, Wang and co-workers³³ developed an electron-deficient polymer-supported pyridinium boronic acid. A polystyrene-based pyridinium catalyst **98** (no more than 1.0 mol%) prepared from 1,3-propanediol cyclic ester of pyridine-3-boronic acid and Merrifield's resin promoted dehydrative amidation between benzoic acid (**19**) and benzylamine (**25**) under reflux conditions using a Soxhlet extractor in toluene (Scheme 17). The solid-phase catalyst **98** exhibited catalytic activity comparable to liquid-phase synthesis using pyridine-3-boronic acid as a catalyst and could be recovered and reused three times. This report is the first successful example of a solid-phase supported aromatic boronic acid catalyst.

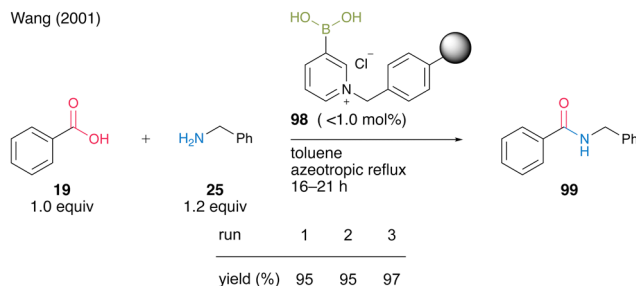
In 2005, Yamamoto and Ishihara's group³⁴ found that 4-pyridineboronic acid is more stable to heat than 3-pyridineboronic acid and 2-pyridineboronic acid, and developed a polystyrene polymer-supported 4-pyridinium boronic acid catalyst. The

Yamamoto (2001)



Scheme 16 3,5-Bis(perfluorodecyl)phenylboronic acid-catalyzed amidation in nonfluorous solvent reported by Yamamoto.³²

Wang (2001)



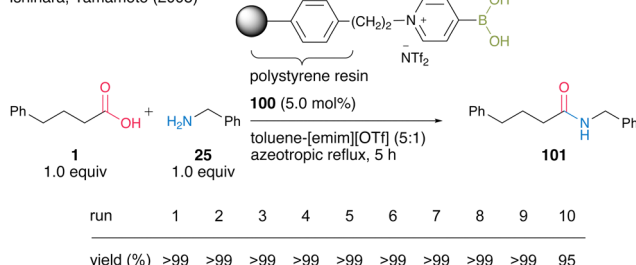
Scheme 17 Polymer-supported 3-pyridinium boronic acid-catalyzed amidation reported by Wang.³³

pyridinium salt-type catalyst exhibits much higher catalytic activity when using a mixed biphasic solvent (5:1) of toluene and 1-ethyl-3-methylimidazolium trifluoromethanesulfonate [emim][OTf] than when using only toluene as the solvent. Unlike Wang's polystyrene polymer-supported 3-pyridinium salt-based boronic acid catalyst, which partially decomposes during the catalyst recovery and reuse process, polystyrene polymer-supported 4-pyridinium salt-based boronic acid catalyst **100** shows high recovery and reusability. Polymer-supported catalyst **100** could be recovered and reused ten times in the dehydrative amidation of an equal mixture of phenylbutanoic acid (**1**) and benzylamine (**25**) under azeotropic reflux conditions (Scheme 18). The polymer-supported catalyst can be recovered simply by filtration without any extraction after the reaction was completed.

In 2013, Hall³⁵ successfully developed solid-phase-supported 5-alkoxy-2-phenylboronic acid, which is a highly active solid-phase-supported MIBA catalyst.²⁰ Solid-phase-supported catalyst **102**, which has a structure in which a polystyrene resin and an aminopropyl ether linker at the 5-position of an aromatic boronic acid are connected by an amide bond, can undergo dehydrative amidation in the presence of MS 4A in dichloromethane even at room temperature, similar to MIBA. It accelerates the reaction and can be recovered by filtration with a polypropylene filter. Polymer catalyst **102** can be recovered by filtration using a polypropylene filter. Amide **26** or **103** can be obtained in high yields using the recovered catalyst (Scheme 19).

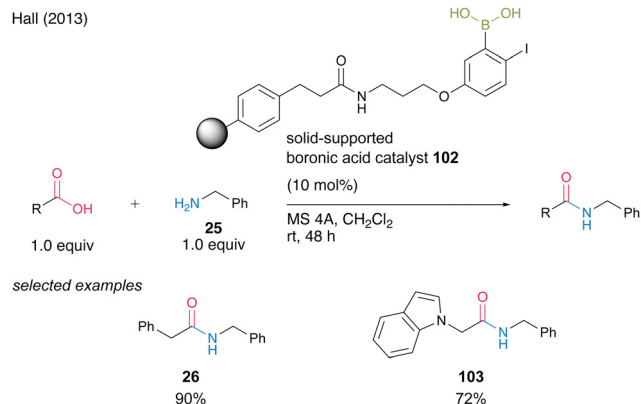
In 2014, Gu and Lee's group³⁶ developed a silica-supported boronic acid catalyst using mesocellular siliceous foam (MCF) as a solid support. They found that capping silanol groups on the silica gel surface with fluoroalkyl groups was effective in

Ishihara, Yamamoto (2005)

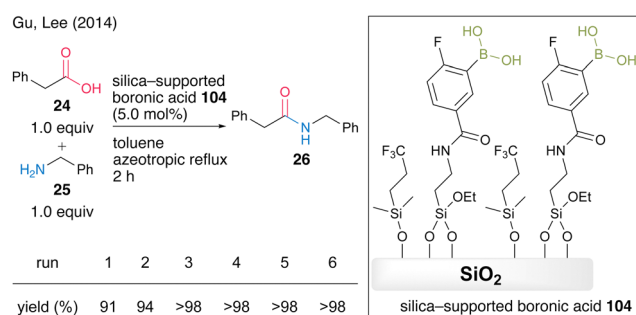


Scheme 18 Polymer-supported 4-pyridinium boronic acid-catalyzed amidation reported by Ishihara and Yamamoto.³⁴





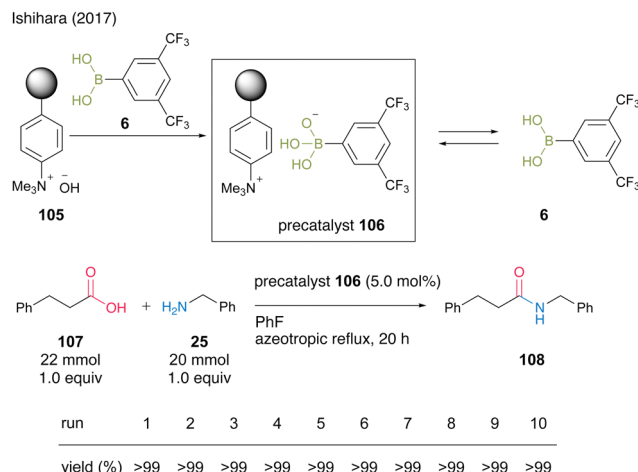
Scheme 19 Polymer-supported MIBA-catalyzed amidation reported by Hall.³⁵



Scheme 20 Silica-supported boronic acid-catalyzed amidation reported by Gu and Lee.³⁶

improving the catalytic activity and silica-supported catalyst **104** with a trifluoroalkyl capping group showed high catalytic activity for the dehydrative amidation of several aliphatic and aromatic carboxylic acids. In the presence of 5.0 mol% of catalyst, the reaction between phenylacetic acid (**24**) and benzylamine (**25**) proceeded to produce amide **26** in high yield under azeotropic reflux conditions in toluene, and the silica-supported boronic acid **104** was recoverable and reusable six times by a simple filtration operation (Scheme 20).

In 2017, Ishihara and colleagues³⁷ reported two protocols for recoverable and reusable catalytic dehydrative amidation based on the development of homogeneous boronic acid precatalysts by the complexations between a boronic acid and a base. The first protocol uses the formation of an acid–base complex between an electron-deficient aromatic boronic acid and a strongly basic anion-exchange resin. In this reaction, the complex serves as a precatalyst, and the free boronic acid is released into the reaction mixture and exhibits high catalytic activity. As a result of examining various boronic acids, the complex with 3,5-bis(trifluoromethyl)phenylboronic acid (**6**) produced the best results, and the reaction with phenylpropanoic acid (**107**) and benzylamine (**25**) proceeded under azeotropic reflux conditions in fluorobenzene in the presence of precatalyst **106** to produce amide **108** in excellent yield (Scheme 21). After the reaction was completed, the resin-supported boronate **106** was recovered by decantation, and

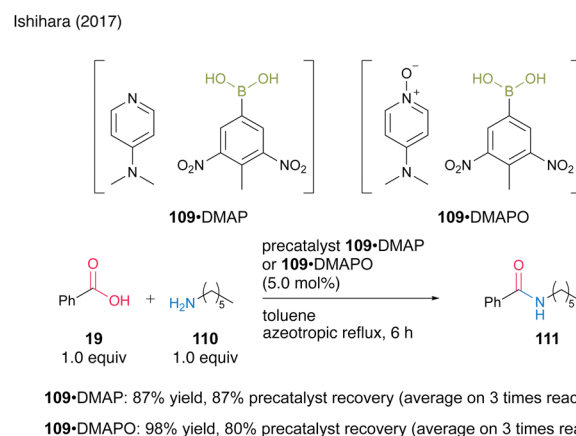


Scheme 21 Boronic acid–DOWEX™ complex-catalyzed amidation reported by Ishihara.³⁷

no decrease in catalyst activity was observed even after 10 reuses. Notably, this reaction system is highly practical, as it can be scaled up to 200 mmol in the presence of 1 mmol of precatalyst.

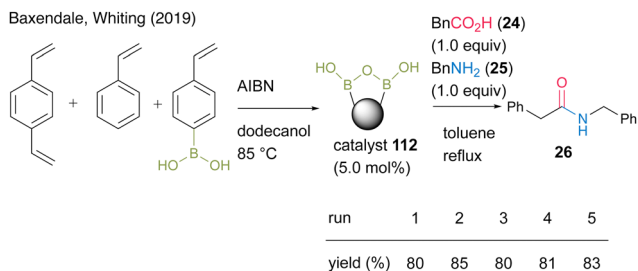
The second approach uses the formation of acid–base complexes between electron-deficient aromatic boronic acids and DMAP or DMAPO. In this catalysis, the complex serves as a precatalyst, and the boronic acid is liberated during the reaction. Using a complex derived from 3,5-dinitro-4-toluenboronic acid (**109**), a precipitated solid suitable for recovery and reuse was generated. Amines DMAP (**61**) and DMAPO (**63**) formed complexes with boronic acid **109**, which were recoverable and reusable three times in the amidation reaction of benzoic acid (**19**) and hexylamine (**110**) (Scheme 22). The complex with DMAPO showed higher activity as a precatalyst, whereas the complex with DMAP showed better recovery efficiency. Notably, the amidation catalytic activity of boronic acid **109** itself was reported to be extremely low.

In 2019, Whiting and Baxendale's group³⁸ developed solid-supported boronic acids *via* copolymerization. Polystyrene-supported boronic acid catalyst **112** was prepared by the copolymerization

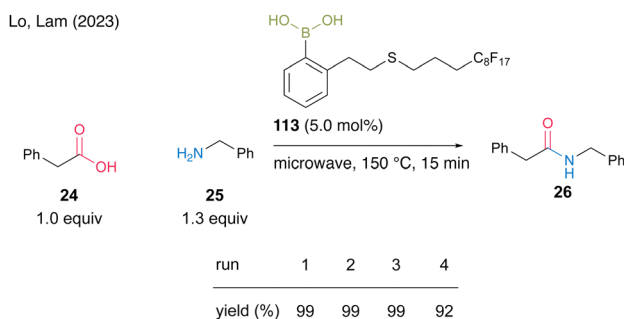


Scheme 22 Boronic acid–DMAP(O) complex-catalyzed amidation reported by Ishihara.³⁷





Scheme 23 Polymer-supported boronic acid-catalyzed amidation reported by Baxendale and Whiting.³⁸



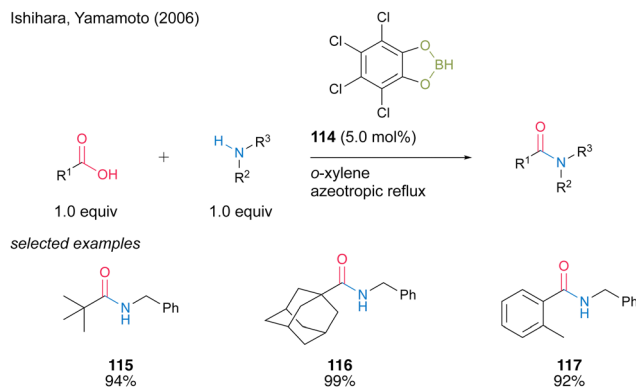
Scheme 24 Fluorous boronic acid-catalyzed amidation reported by Lam.³⁹

of 4-vinylphenylboronic acid, divinylbenzene, and styrene in the presence of AIBN. In the reaction between phenylacetic acid (**24**) and benzylamine (**25**), catalyst **112** was recoverable and reusable (Scheme 23). Solid-state ¹¹B-NMR and *in situ* IR (ReactIR) observations suggested the formation of a dicarboxylate active intermediate containing a B–O–B bond, similar to that previously reported in homogeneous catalysis.²⁷ Furthermore, a preliminary application to the flow reaction using a heat column packed with the catalyst was considered.

Most recently, Lo and Lam's group³⁹ developed catalyst **113** by incorporating a perfluoroalkyl group (C₈F₁₇) at the end of the side chain of aromatic boronic acid at the *ortho*-position and reported a catalytic dehydrative amidation of carboxylic acids with microwave irradiation under neat conditions. The product and catalyst can be easily separated from the crude product *via* fluororous solid-phase extraction (SPE). For the reaction between phenylacetic acid (**24**) and benzylamine (**25**), catalyst **113** could be recovered and reused four times (Scheme 24).

2.3. Direct amide bond formation using other monoboron catalysis

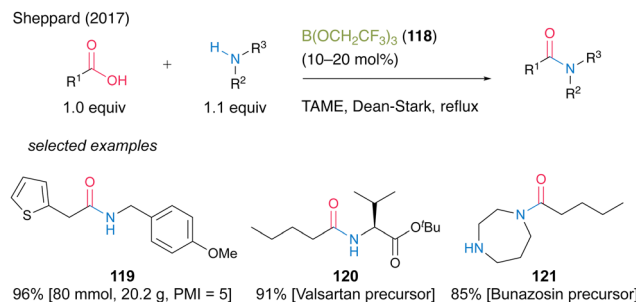
In 2006, Ishihara and Yamamoto⁴⁰ reported catalytic amidation with 4,5,6,7-tetrachlorobenzo[d][1,3,2]dioxaborole (**114**) prepared using tetrachlorocatechol and BH₃·SMe₂. **114** showed superior catalytic activity to 3,5-bis-(trifluoromethyl) phenylboronic acid (**6**) for the amidation of sterically hindered aliphatic and aromatic carboxylic acids, although **114** presented slightly lower catalytic activity than **6** for the amidation of less hindered carboxylic acid substrates (Scheme 25). Catalysis using **114** proceeds in toluene or *o*-xylene under azeotropic reflux conditions.



Scheme 25 4,5,6,7-Tetrachlorobenzo[d][1,3,2]dioxaborole-catalysed amidation reported by Ishihara.⁴⁰

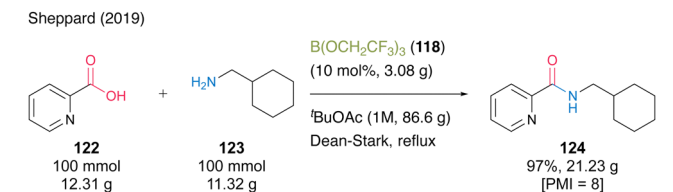
In 2017, Sheppard and co-workers⁴¹ found that B(OCH₂CF₃)₃ (**118**) was an effective catalyst for dehydrative amidation reaction under azeotropic reflux conditions in *tert*-amyl methyl ether (TAME) (Scheme 26).⁴² In this reaction, unreacted carboxylic acids, amines, and catalysts can be easily removed by simple filtration using three mixed resin scavengers, *i.e.*, poly hydroxylated Amberlite IRA743 as a boron scavenger, acidic Amberlyst 15 as an amine scavenger, and basic Amberlyst A-26(OH form) as an acid scavenger, to produce the corresponding amides. The catalytic protocol using B(OCH₂CF₃)₃ (**118**) offers significant improvements in terms of a large reduction of overall waste during amide bond formation and shows a low process mass intensity (PMI)⁴³ value of 5 for **119**. Furthermore, this reaction is suitable for manufacturing active pharmaceutical ingredient precursors such as **120** and **121**.

In 2019, the same group reported that *tert*-butyl acetate (*t*-BuOAc) was more suitable for B(OCH₂CF₃)₃ (**118**)-catalyzed dehydrative amidation than TAME.⁴⁴ This catalysis demonstrated a wide substrate scope, and the corresponding amides were obtained using a solid-phase workup procedure. The catalytic efficiency was demonstrated using a 100-mmol scale reaction of the synthesis of 2-picolinic acid (**122**) and cyclohexanemethylamine (**123**) in the presence of 10 mol% of **118** in *t*-BuOAc under Dean–Stark reflux conditions (Scheme 27). The desired amide **124** was obtained in 97% yield (21.23 g) with a PMI of 8. This is one of the few successful examples of large-scale synthesis using organoboron-catalyzed amidation.



Scheme 26 B(OCH₂CF₃)₃-catalyzed amidation reported by Sheppard.⁴¹





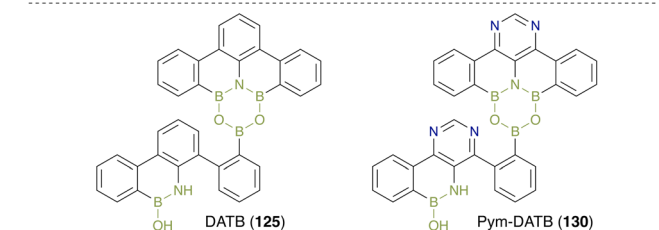
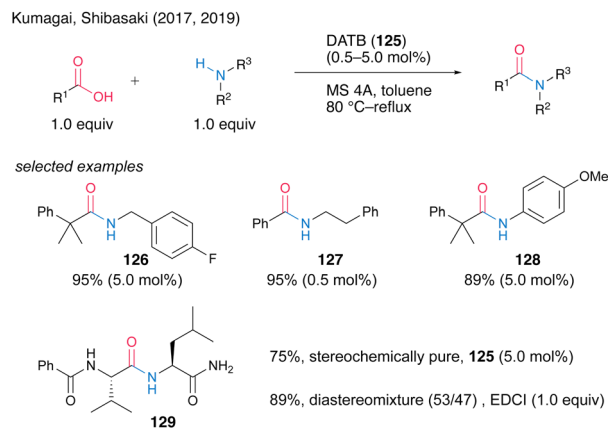
Scheme 27 B(OCH₂CF₃)₃-catalyzed large-scale amidation reported by Sheppard.⁴⁴

2.4. Direct amide bond formation using multiboron catalysis

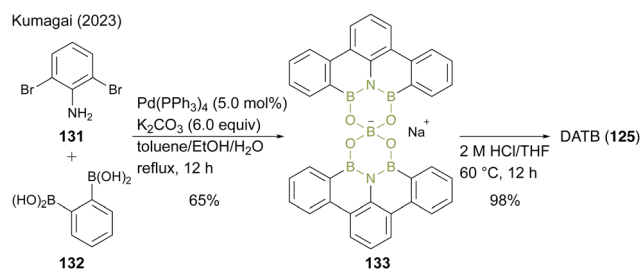
In 2017, Shibasaki, Kumagai and co-workers⁴⁵ developed multi-boron containing six-membered heterocycles, 1,3-dioxo-5-aza-2,4,6-triborinane (DATB) ring systems. DATB derivatives are unique compounds with a stable *m*-terphenyl scaffold, and their boron atoms exhibit peculiar Lewis acidity. The catalytic performance of DATB was investigated, and its catalytic activity was superior to that of commercially available boronic acid or metal catalysts, especially in the reaction of bulky carboxylic acids to produce **126** in excellent yield. DATB (**125**) maintained excellent catalytic activity even in the amidation of aromatic carboxylic acids, which have low reactivity, and the corresponding amide **127** can be obtained in high yield even in the presence of only 0.5 mol% of the catalyst. Furthermore, aniline derivatives are applicable as amine substrates, affording **128** in high yield. It is also shown that pharmaceuticals that were previously synthesized using stoichiometric amounts of activating reagents can now be synthesized by catalytic amidation using **125**. DATB demonstrated not only a wide range of substrate scope but also its great level of functional group tolerance. DATB catalysis was promoted under mild conditions; thus, the degradation of optical purity of α -chiral carboxylic acid or α -chiral amines did not occur for **129**.

In 2019, the same group also developed a novel DATB derivative containing a pyrimidine ring.⁴⁶ They found a reliable and rapid synthetic route to install boron atoms into the 4,6-diarylpyrimidine scaffold using a pyrimidine ring as a directing group (Scheme 28). The previous synthetic protocol of DATB required stepwise synthesis of the *m*-terphenyl scaffold to introduce two boron atoms properly and it caused difficulty in functionalizing or introducing arbitrary substituents into the skeletons. By contrast, the pyrimidine ring introduction allows the effective and sufficient synthesis of the derivatives without chromatographic purification. Although the catalytic performance of functionalized Pym-DATB (**130**) derivatives slightly decreased, the most accessible unsubstituted one exhibited sufficient catalytic activity for the amidation of a wide range of substrates.

Recently, Kumagai⁴⁷ reported an improved two-step synthetic route for DATB containing a *m*-terphenyl scaffold without chromatographic purification. In this protocol, 2,6-dibromoaniline (**131**) and 1,2-phenylenediboronic acid (**132**) were converted to a dimeric spiroborate salt (**133**) as a thermodynamically stable intermediate under Suzuki–Miyaura coupling conditions (Scheme 29). The intermediate (**133**) was converted to DATB (**125**) derivatives with acidic hydrolysis under high-temperature conditions. Although this



Scheme 28 DATB-catalyzed amidation reported by Kumagai, Shibasaki.^{45,46}



Scheme 29 Improved synthesis of DATB reported by Kumagai.⁴⁷

method requires slight modifications of the reaction conditions for each substrate, it enables the gram-scale synthesis of various DATB derivatives.

The plausible catalytic cycle for DATB-catalyzed direct amidation was proposed based on NMR (Fig. 7).⁴⁵ First, a kinetically and thermodynamically favored complex (**134**) was produced by the reaction of DATB with an amine substrate. Next, intermediate **135** was formed by harnessing two B–O bonds, thereby electrophilically activating the carboxylic acid functional group *via* the interaction of two boron Lewis acidic atoms. Amine was then attached to the carboxylic acid carbonyl group to form intermediate **136**. Subsequently, intermediate **136** collapsed, simultaneously forming the corresponding amide product and water as a clean byproduct and then regenerating the DATB catalyst.

Recently, Kumagai, Noda, and co-workers⁴⁸ developed a novel diboron **139** with the N(BOH)₂ structure and found its usefulness as an amidation catalyst (Scheme 30). This is the first isolable N(BOH)₂ compound, and it showed superior catalytic activity to DATB (**125**) in terms of turnover frequency for dehydrative amidation. In fact, for the reaction between acid



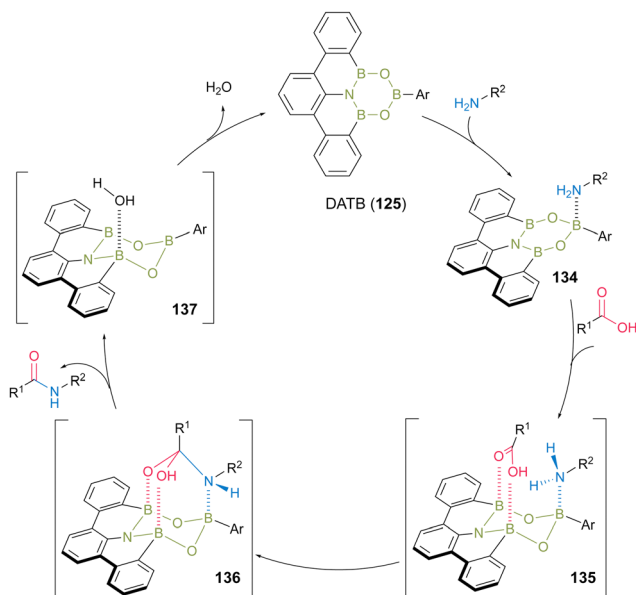
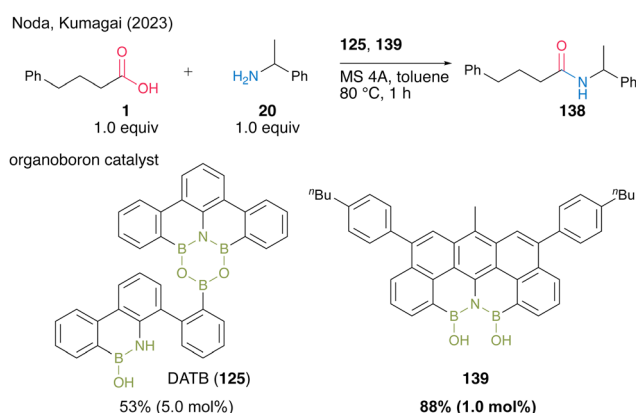


Fig. 7 Proposed amidation mechanism reported by Kumagai and Shibasaki.⁴⁵



Scheme 30 $N(\text{BOH})_2$ -containing diboron-catalyzed amidation reported by Noda and Kumagai.⁴⁸

1 and amine **20** in toluene, the use of 1.0 mol% of **139** resulted in a higher product yield than using 5.0 mol% DATB (**125**).

In 2018, the Saito group⁴⁹ reported a successful catalytic amidation of aromatic carboxylic acids using catalysts of the $\text{X}_2\text{B}-\text{BX}_2$ structure. In general, aromatic carboxylic acids are inert because they form stable salts with amines. They hypothesized that **140**, which undergoes protonation, promotes the generation of free amines and carboxylates and that the B-B moiety electrophilically activates carboxylate derived from aromatic carboxylic acids, thereby accelerating the amidation reaction through intermediate **141**. Based on the screening of catalysts with diboron structures (**142–144**), commercially available catalysts—tetrakis(dimethylamido)diboron (**142**) and tetrahydroxydiboron (**143**)—demonstrated catalytic efficiency in the direct amidation of aromatic carboxylic acids, affording amide **99** in high yield (Fig. 8).

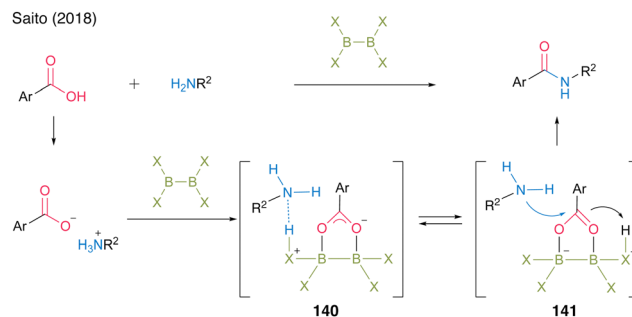
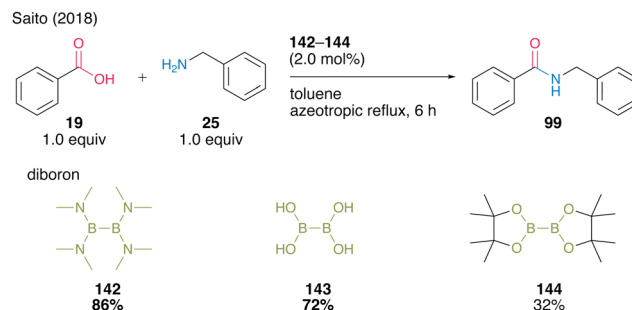


Fig. 8 Proposed amidation mechanism reported by Saito.⁴⁹

In most cases, using aromatic carboxylic acids as substrates, catalysts **142** and **143** demonstrate far superior catalytic activity compared with boric acid ($\text{B}(\text{OH})_3$)^{15a,b} (Scheme 31).

In 2019, Shimada and co-workers⁵⁰ designed a hydroxy-directed catalytic amidation of α - or β -hydroxycarboxylic acids using a catalyst containing preorganized B-O-B motif **145** based on the structure of an active intermediate in the revised amidation mechanism reported by Whiting.²⁷ They hypothesized that the B-OH moiety of **145** recognizes the hydroxyl group to form intermediate **146** via covalent B-O bonds and then the two boron atoms in the B-O-B motif promotes the electrophilic activation of carboxylic acid in a bidentate manner to form reactive cyclic intermediate **147**, thereby accelerating the reaction to produce α - or β -hydroxy amides (Fig. 9).



Scheme 31 Diboron-catalyzed amidation reported by Saito.⁴⁹

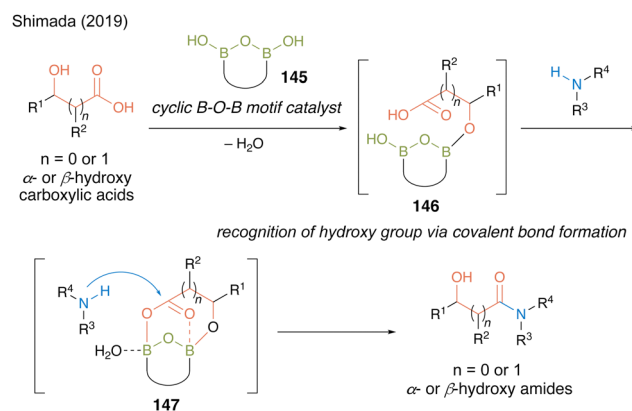
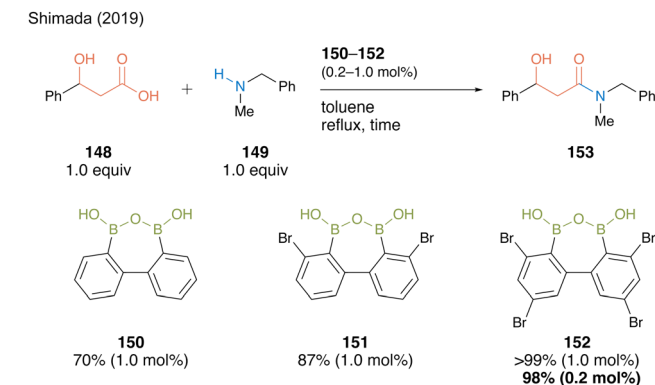


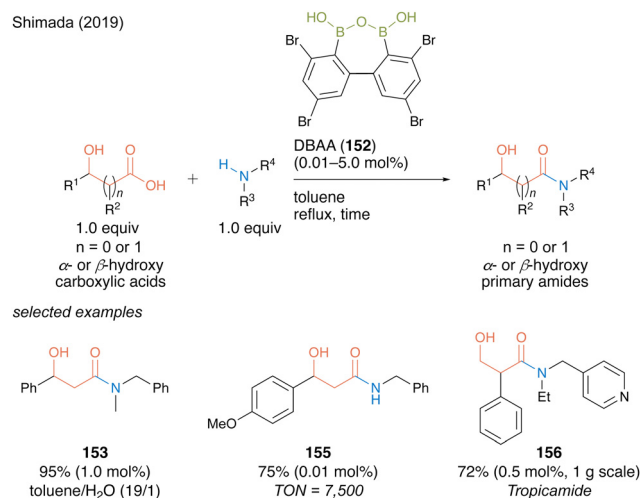
Fig. 9 Design of hydroxy-directed catalytic amidation reported by Shimada.⁵⁰

Scheme 32 DBAA-catalyzed amidation reported by Shimada.⁵⁰

The reaction of 3-hydroxy-3-phenylpropanoic acid (**148**) with *N*-benzyl-*N*-methylamine (**149**) in the presence of 1.0 mol% of biphenyl-based diboronic acid anhydride **150** proceeded smoothly in toluene at 110 °C within 4 h without any azeotropic dehydration protocol or a dehydrating agent, producing β-hydroxyamide **153** in 70% yield (Scheme 32). The yield improved to 87% when 1.0 mol% of catalyst **151**, which has two bromine atoms at both *ortho*-positions of the boron atom based on Hall^{19,20} reports, was used. Furthermore, amide **153** was obtained in quantitative yields when **152** namely DBAA (diboronic acid anhydride), which has additional bromine substituents at the *para* position, was used, and a high yield of 98% was maintained even when the catalytic amount was reduced to only 0.2 mol%. The *ortho*-bromine atom contributed to not only the electron-withdrawing effect but also the stabilization effect of the catalyst B–O–B motif and inactivity suppression due to amine coordination.

This substrate-directed catalytic dehydrative amidation proceeded through an effective electrophilic activation of carboxylate by the multiboron B–O–B motif of the acyl boronate intermediate **154** via covalent bond formation of hydroxy groups of carboxylic acid substrates with the catalyst. The proposed mechanism was supported by the detection of intermediates by ESI-MS and ¹¹B-NMR analyses (Fig. 10).

DBAA (**152**) showed exceptionally high catalytic activity for dehydrative amidation of α- or β-carboxylic acids and amines. Notably, DBAA catalysis does not require strict dehydration operations, such as adding a drying agent or azeotropic reflux conditions. Indeed, high catalytic performance is maintained even in a mixed solvent of toluene/water (19:1), providing a corresponding β-hydroxy amide **153** in excellent yield with

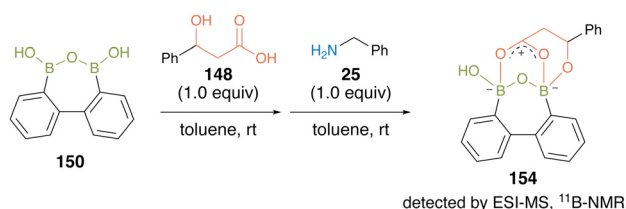
Scheme 33 DBAA-catalyzed amidation reported by Shimada.⁵⁰

1.0 mol% of the catalyst (Scheme 33). For amide **155**, the catalytic amount of DBAA (**152**) could decrease to 0.01 mol% and turnover number (TON) recorded 7500, which is noteworthy for an organoboron catalysis. The synthetic efficiency of DBAA catalysis was demonstrated by one-step gram-scale synthesis of tropicamide (**156**), a known a mydriatic drug, from readily available tropic acid with 4-(ethylaminomethyl)pyridine at a Lewis basic site with 0.5 mol% of the catalyst.

In 2020, the same group applied dehydrative amidation using DBAA (**152**) for the catalytic synthesis of Weinreb amides.⁵¹ The *N*-methyl-*N*-methoxy amine (**157**) has poor nucleophilicity compared to ordinarily secondary amines due to the electron-withdrawing oxygen substituted in the amino group, thereby posing challenges for dehydrative amidation. Nevertheless, in the presence of a catalytic amount of DBAA (**152**), the reaction of carboxylic acid with 3.0 equivalents of **157** proceeded smoothly to produce the corresponding Weinreb amide in high to excellent yields. This was the first successful catalytic direct synthesis of useful Weinreb amide from carboxylic acid. Because the only byproduct of this reaction was water, the resulting Weinreb amide could be used in the next reaction step without purification. Indeed, by exploiting the convenience of this operation, the concise synthesis of various bioactive α-hydroxy ketone natural products (acyloin natural products) **158–161** was achieved using a one-pot two-step sequence including DBAA-catalyzed Weinreb amide synthesis followed by a reaction of a Grignard reagent addition after switching the solvent (Scheme 34).

In 2021, a facile synthetic protocol of Garner's aldehyde (**164**), which is useful as a chiral building block, was achieved using a three-step sequence on a gram scale based on a similar DBAA-catalyzed Weinreb amide synthesis from *N*-Boc protected serine **162** as the chiral starting material.⁵² The optical purity of Weinreb amide **163** was high and the α-position of the carbonyl group was not racemized (Scheme 35). Notably, no racemization was observed at the α-position of the carbonyl group, yielding Garner's aldehyde with high optical purity.

In 2023, the same group⁵³ reported catalytic primary amide synthesis using an aqueous ammonia solution (**167**) as an

Fig. 10 Mechanistic insights reported by Shimada.⁵⁰

Shimada (2023)

Reaction scheme for the synthesis of (±)-aegeline (173) and (±)-tembamide (174) from substituted benzyl alcohols.

Starting materials:

- 165** (R = Bn)
- 166** (R = Me)

Reaction 1: 165 or 166 + aq. NH_3 + DBAA (**152**) (10 mol%) + $\text{C}_6\text{H}_5\text{Cl}$ (reflux, 24 h) → **168** (R = Bn) (80%) or **169** (R = Me) (88%)

Reaction 2: **168** or **169** + LiAlH_4 (3.4 equiv) in THF (70 °C, 4 h) → **170** or **172** (without purification)

Reaction 3: **170** or **172** + Cl-C(=O)-R (1.1 equiv) in $\text{CH}_2\text{Cl}_2/\text{pyridine}$ (0 °C, 2 h) → **(±)-octopamine (171)** (74% over 2 steps) or **(±)-aegeline (173)** (83%)

Reaction 4: **170** or **172** + Cl-C(=O)-R (1.1 equiv) in $\text{CH}_2\text{Cl}_2/\text{pyridine}$ (0 °C, 2 h) → **(±)-tembamide (174)** (72%)

Structures:

- 165**: $\text{RO-C}_6\text{H}_4\text{-CH}_2\text{-CH(OH)-COOH}$
- 166**: $\text{RO-C}_6\text{H}_4\text{-CH}_2\text{-CH(OH)-COOH}$ (R = Me)
- 168**: $\text{RO-C}_6\text{H}_4\text{-CH}_2\text{-CH(OH)-CONH}_2$
- 169**: $\text{RO-C}_6\text{H}_4\text{-CH}_2\text{-CH(OH)-CONH}_2$ (R = Me)
- 170**: $\text{BnO-C}_6\text{H}_4\text{-CH}_2\text{-CH(OH)-CH}_2\text{-NH}_2$
- 172**: $\text{MeO-C}_6\text{H}_4\text{-CH}_2\text{-CH(OH)-CH}_2\text{-NH}_2$
- (±)-octopamine (171)**: $\text{HO-C}_6\text{H}_4\text{-CH}_2\text{-CH(OH)-CH}_2\text{-NH}_2$
- (±)-aegeline (173)**: $\text{MeO-C}_6\text{H}_4\text{-CH}_2\text{-CH(OH)-CH}_2\text{-NH-C(=O)-CH=CH-C}_6\text{H}_5$
- (±)-tembamide (174)**: $\text{MeO-C}_6\text{H}_4\text{-CH}_2\text{-CH(OH)-CH}_2\text{-NH-C(=O)-C}_6\text{H}_5$

Shimada (2021)

DBAA (152)
(2.0 mol%)
HNMeOMe (157)
(3.0 equiv)

DCE (0.2 M)
reflux, 24 h

1.0 equiv
N-Boc-Serine (162)

163
Without purification

2 steps

Garner's aldehyde (164)
89% over 3 steps
75% over 3 steps [1 a scale]

amine substrate. Although the primary amide is a key structure for several bioactive compounds, no successful synthesis using carboxylic acid as a substrate was observed. The fact that DBAA promotes catalytic amidation without any dehydrative reagent or azeotropic reflux conditions facilitated the expansion of the catalytic synthesis using an aqueous ammonia solution. Using 10 mol% DBAA, the reaction between α -hydroxycarboxylic acid and aqueous ammonia solution (**167**) proceeded smoothly under reflux conditions in chlorobenzene and the corresponding primary amides **168** and **169** were obtained in high yields (Scheme 36). The synthetic efficiency of the protocol was demonstrated by the derivatization of bioactive molecules, such as octopamine (**171**), aegeline (**173**), and tembamide (**174**), by β -aminoalcohol **170** or **172** prepared by reducing the synthetic primary amides.

3. Catalytic direct peptide bond formation from α -amino acids

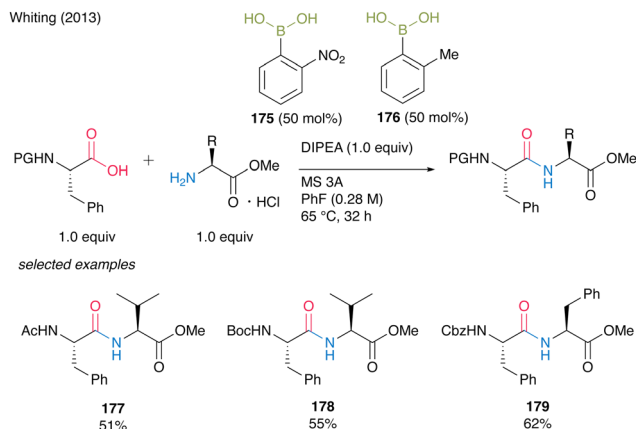
3.1. Direct peptide bond formation using boronic acid catalysis

The development of catalytic amidation has been well studied. However, there was little example to establish catalytic peptides synthesis using α -amino acids as carboxylic acid substrates. In 2013, Whiting and co-workers⁵⁴ reported the first example of direct amidation using α -amino acids as both carboxylic acids and amines, respectively. First, they found that the electron-

deficient *o*-nitrophenylboronic acid (**175**) was an effective catalyst for amidation using α -amino acids as carboxylic acids, and the resulting amides retained the optical purity at the α -position of carbonyl groups. Nonpolar solvents such as fluorobenzene were suitable for this reaction and the reaction proceeded smoothly in the presence of MS 3A. However, the steric hindrance of amines had a negative impact on the product yields. Next, they found that α -amino acid hydrogen chloride salts could be used for dipeptide synthesis as amine substrates in the presence of Hünig's base by *in situ* generation of free amine functional groups. Thus, electron-deficient arylboronic acids were effective in the presence of MS 3A in an electron-deficient and non-polar solvent for amidation using amino acids as carboxylic acids or amines. However, it has been difficult to apply a simple catalyst system using a single boronic acid for the direct access of dipeptide derivatives. As a result of continuing challenges, they found that the use of the mixture of two catalysts, *o*-nitrophenylboronic acid (**175**), and *o*-methylphenylboronic acid (**176**), which have different electronic factors, was effective for the direct dipeptide synthesis. Although this binary arylboronic acid catalyst systems required 50 mol% each of them to obtain dipeptides, the corresponding dipeptides **177–179** were afforded in moderate yields (Scheme 37).

Certainly, these results indicate that boronic acids have room for improvement in catalytic efficiency; however, they showed that peptide bonds can be formed by boronic acid catalysis without using stoichiometric amounts of condensation reagents. Whiting's report became the milestone of peptide synthesis using boronic acids.

Thereafter, during the optimization study for catalytic amide synthesis using boronic acids with sulfur atoms, Blanchet and co-workers²⁴ found that (2-(thiophen-2-ylmethyl)phenyl)boronic acid (**54**) was effective in generating catalytic peptide bond

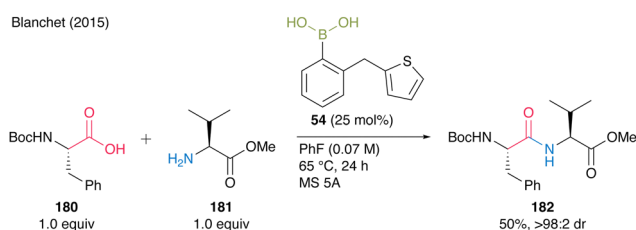


Scheme 37 Peptide bond formation using arylboronic acids reported by Whiting.⁵⁴

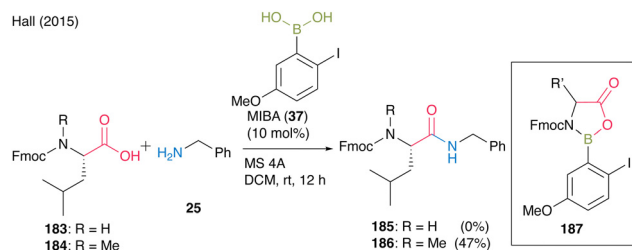
formation. The boronic acid catalyzed the coupling of each equimolar amount of Boc-Phe-OH (**180**) and free H-Val-OMe (**181**) in the presence of MS 5A in fluorobenzene at 65 °C (Scheme 38). Although there is room for improvement in catalytic efficiency (TON = 2) in only one preliminary case, the catalysis can achieve dipeptide synthesis with minimal epimerization. Thus, improving catalytic activity remains a major issue in applying aromatic boronic acids to catalyze peptide bond formation.

In 2015, Hall⁵⁵ found that free, relatively acidic NH functional groups in carboxylic acids had a significant negative impact on catalytic direct peptide bond formation using their proprietary MIBA catalyst. They suggested that the inhibition of the reaction occurred because boronic acids could form 5-membered complexes with monoprotected α -amino acids derivatives through covalent bond formation with NH. The amidation of Fmoc-Leu-OH (**183**) and benzylamine (**25**) did not proceed; however, the amidation of *N*-methylated Fmoc-Leu-OH (**184**) and benzylamine (**25**) did (Scheme 39). Therefore, doubly protected α -amino acids such as *N*-phthaloyl α -amino acids or amine surrogates like α -azido and α -amino acid substrates were designed to avoid the formation of inactive complex **187**, leading to inhibition during boronic acid catalysis.

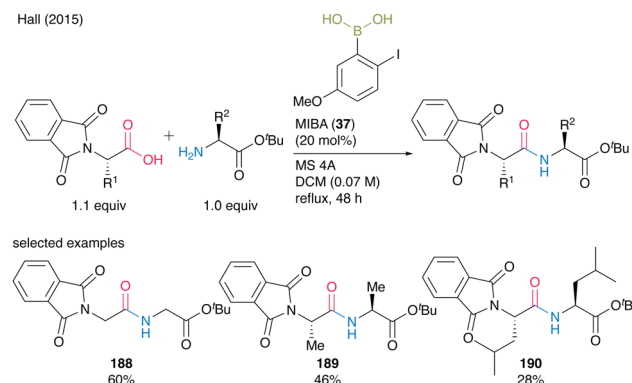
Indeed, a catalytic amount of MIBA (**37**) accelerated dipeptide **188–190** formation in moderate to good yields (28–60%) when *N*-phthaloyl α -amino acids were used as the carboxylic acid substrate, although steric bulkiness still negatively influenced the yield (Scheme 40).



Scheme 38 2-(Thiophen-2-ylmethyl)phenylboronic acid-catalyzed peptide bond formation reported by Blanchet.²⁴



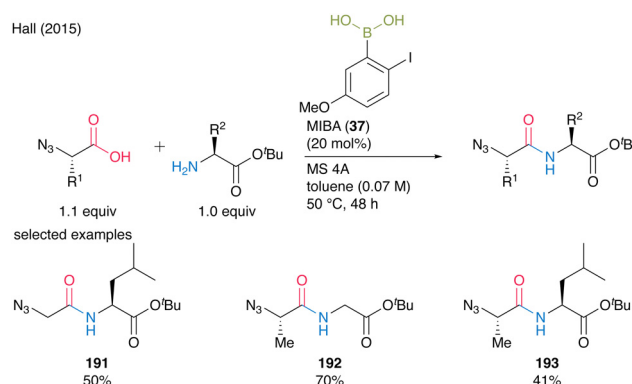
Scheme 39 MIBA-catalyzed peptide bond formation reported by Hall.⁵⁵



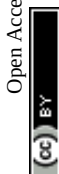
Scheme 40 MIBA-catalyzed peptide bond formation of *N*-phthaloyl amino acids reported by Hall.⁵⁵

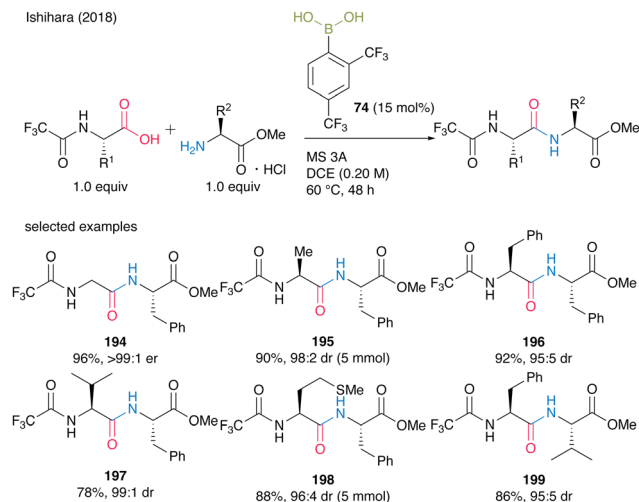
When α -azido acids were used as carboxylic substrates, toluene was a more suitable solvent than dichloromethane, and dipeptides **191–193** were obtained in good yields. MIBA (**37**) was also applicable to the multigram-scale synthesis of *N*-Boc β -alanine-derived dipeptides with carbamate-protecting groups (Scheme 41).

In 2018, Ishihara and co-workers²⁸ expanded the 2,4-bis(trifluoromethyl)phenylboronic acid (**74**)-catalyzed amidation reaction of carboxylic acids to α -peptide synthesis. Based on the idea that the electron-deficient *N*-protecting group weakens the nucleophilicity of the amino moiety of α -amino acids and prevents the construction of an inert five-membered complex derived from an arylboronic acid and an α -amino acid,

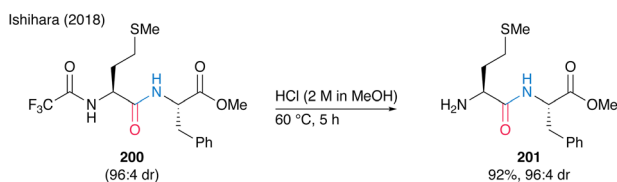


Scheme 41 MIBA-catalyzed peptide bond formation of α -azido acids reported by Hall.⁵⁵





Scheme 42 2,4-Bis(trifluoromethyl)phenylboronic acid-catalyzed peptide bond formation reported by Ishihara.²⁸



Scheme 43 Selective deprotection of N -trifluoroacetamide reported by Ishihara.²⁸

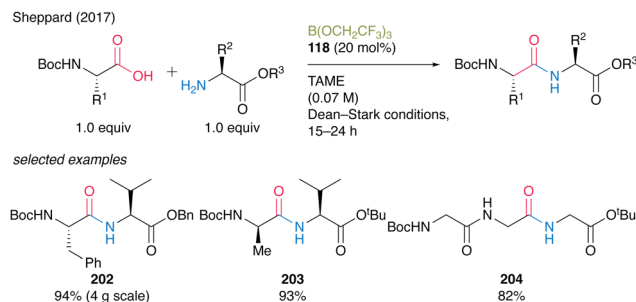
N -trifluoroacetyl-protected α -amino acids were designed. Direct peptide bond formation catalyzed by 15 mol% of 2,4-bis(trifluoromethyl)phenylboronic acid (**74**) produced dipeptides **194**–**199** with minimum epimerization (Scheme 42).

Notably, N -trifluoromethyl-masked dipeptides **200** can be chemoselectively deprotected to produce **201** using methanolic hydrogen chloride (Scheme 43).

As described above, several scholars have reported organoboronic acid catalyzed direct dipeptide syntheses derived from α -amino acids with devised protecting groups on the nitrogen. However, the difficulty of applying frequently used carbamate-protecting groups to catalytic peptide synthesis using organoboronic acids still remains a severe issue. Recently, the application of catalytic peptide synthesis using a mono organoboron catalyst has been reported for limited examples,^{30,39,56} but the catalytic activity still needs to be improved.

3.2. Direct peptide bond formation using borate ester catalysis

In 2017, Sheppard's group⁴¹ reported a peptide synthesis of α -amino acids bearing a carbamate group that exhibits efficient catalytic turnover. They confirmed that a commercially available borate ester $B(OCH_2CF_3)_3$ (**118**) was the most effective catalyst for the reaction under azeotropic reflux conditions with Dean–Stark apparatus in *tert*-amyl methyl ether (TAME). The reaction produced dipeptides or tripeptides in high to excellent



Scheme 44 $B(OCH_2CF_3)_3$ -catalyzed peptide bond formation reported by Sheppard.⁴¹

yields (82–96%) with a catalytic amount of $B(OCH_2CF_3)_3$ (**118**, 10–20 mol%) without epimerization (Scheme 44).

A practical advantage of this protocol is the simple purification procedure of the target peptides **202**–**204** by filtration using scavenger resins to remove unreacted α -amino acid substrates and catalysts. Surprisingly, this environmentally benign catalysis can be applicable to the chemoselective amidation of unprotected α -amino acids with amine, although its application to peptide bond formation is limited.⁵⁷

3.3. Direct peptide bond formation using multiboron catalysis

Recently, a series of successful reports of peptide synthesis using multinuclear organoboron catalysts have been published. In 2018, Kumagai and Shibasaki group⁵⁸ reported DATB (**125**)-catalyzed peptide bond formation reactions. For this catalysis, commercially available α -amino acid hydrogen chloride salts could be directly used in the presence of MS 4A. Although dipeptides often construct oxazolones and promote epimerization during peptide bond formation, electrophilic activation with DATB (**125**) is not stringent, thereby making amidation of dipeptides as carboxylic substrates to produce tripeptides **206**–**208** in high yields without epimerization (Scheme 45).

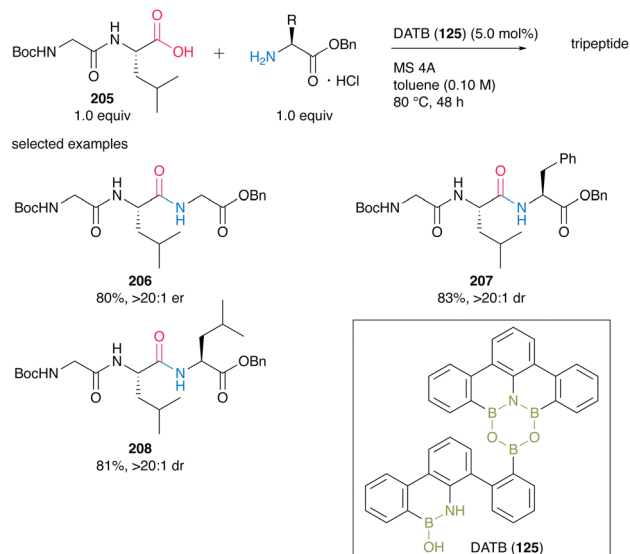
They also demonstrated catalytic peptide synthesis using Fmoc-protected α -amino acids as carboxylic acid substrates, suggesting future application for solid phase peptide synthesis (SPPS). Indeed, the reaction catalyzed by DATB (**125**) proceeded smoothly to convert both nonfunctionalized and functionalized natural α -amino acids, affording the corresponding peptides **209**–**214** without epimerization in most cases (Scheme 46).

Although the highly reactive carboxylic acid substrates exhibited partial epimerization at 80 °C, the corresponding dipeptides **215**–**217** were obtained without notable stereochemical erosion *via* coupling reaction at a lower temperature of 50 °C (Scheme 47).

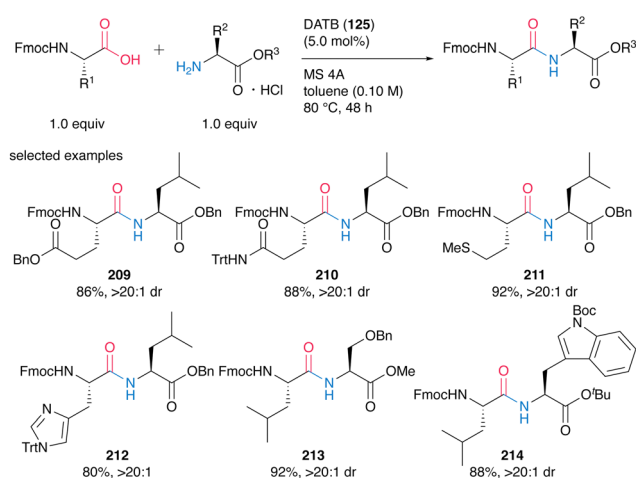
The synthetic efficiency of DATB (**125**)-catalyzed peptide bond formation was highlighted by the convergent chemical synthesis of biologically active pentapeptides OGP(10–14) and H-Tyr-Gly-Phe-Gly-Gly-OH (Scheme 48). They achieved an efficient synthesis of the target peptide by repeating the catalytic protocol four times, including dipeptide and tripeptide fragment synthesis processes. Notably, 0.5 mol% DATB (**125**) in dipeptide synthesis of Fmoc-Gly-Gly-O^tBu (**220**) by the coupling



Kumagai, Shibasaki (2018)

Scheme 45 DATB-catalyzed peptide bond formation reported by Kumagai and Shibasaki.⁵⁸

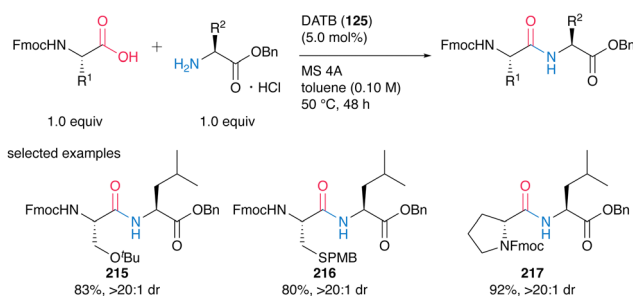
Kumagai, Shibasaki (2018)

Scheme 46 DATB-catalyzed peptide bond formation of Fmoc-protected amino acids reported by Kumagai and Shibasaki.⁵⁸

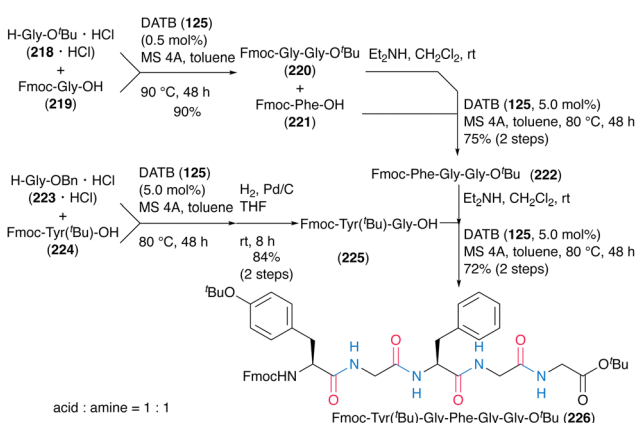
of Fmoc-Gly-OH (219) with H-Gly-O^tBu·HCl (218·HCl) recorded a TON of 180. The deprotection of Fmoc-Tyr(^tBu)-Gly-Phe-Gly-O^tBu (226) formed by DATB-catalyzed coupling of tripeptide and dipeptide led to the synthesis of OGP(10–14).

In 2020, Takemoto and co-workers⁵⁹ developed a catalytic direct peptide bond formation reaction using a multiboron catalyst possessing pseudo-active B–C–B moieties. Based on the structure of the active intermediate reported by Whiting *et al.*,²⁷ they assumed that a catalyst possessing *gem*-diboronate (*gem*-DBA) structure would be more effective in amidation of amino acids with lower reactivity than simple carboxylic acids. Initially, catalytic amidation of α -amino acid **180** with simple amine **25** was investigated using **228** or **229** as a catalyst,

Kumagai, Shibasaki (2018)

Scheme 47 DATB-catalyzed peptide bond formation at lower temperatures reported by Kumagai and Shibasaki.⁵⁸

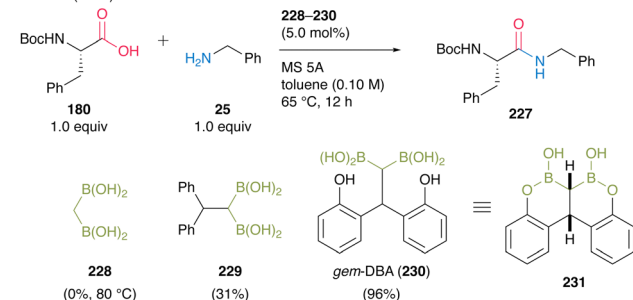
Kumagai, Shibasaki (2018)

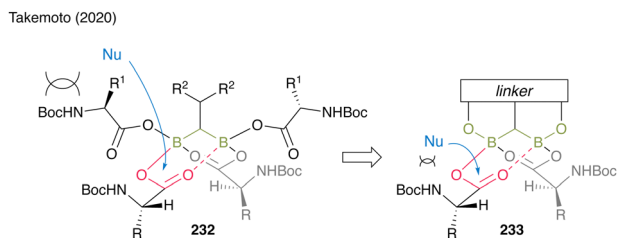
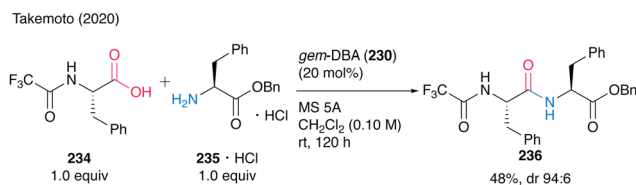
Scheme 48 DATB-catalyzed oligopeptide synthesis reported by Kumagai and Shibasaki.⁵⁸

demonstrating that the bulkiness of both the substrate and center atom of the catalyst significantly influenced product yields (Scheme 49).

Moreover, *gem*-DBA (**230**), which has a phenolic hydroxyl group, exhibits high catalytic activity. The *in situ* cyclocondensation of **230** to **231** reduces the bulkiness around the carbonyl group of the electrophile, enhancing attack by nucleophiles to promote catalytic efficiency. Owing to the covalent bond formation between the linker and boron atoms, *gem*-DBA effectively causes electrophilic activation of two carboxylic acid moieties (Fig. 11).

Takemoto (2020)

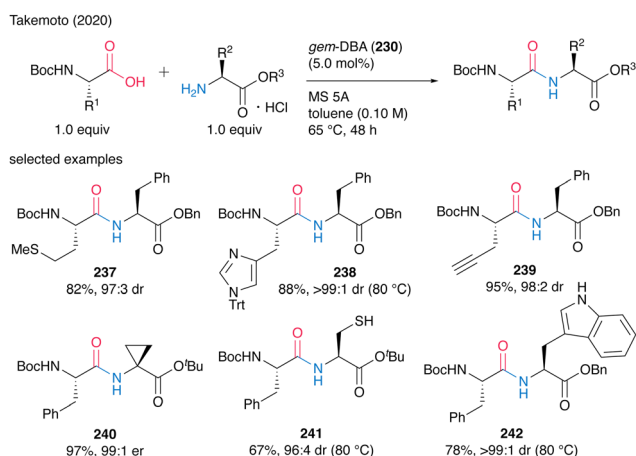
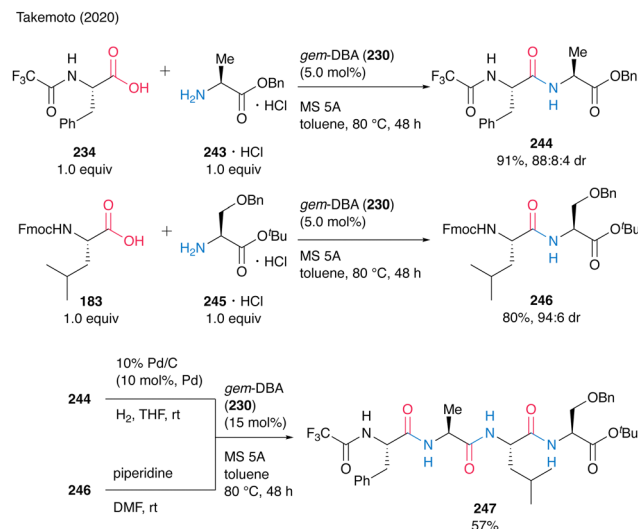
Scheme 49 *gem*-DBA-catalyzed peptide bond formation reported by Takemoto.⁵⁹

Fig. 11 Design of the *gem*-DBA catalyst reported by Takemoto.⁵⁹Scheme 50 *gem*-DBA-catalyzed peptide bond formation at room temperature reported by Takemoto.⁵⁹

Notably, the reaction of *N*-trifluoroacetyl-protected α-amino acid **234** with **235**·HCl proceeded to produce dipeptide **236** at room temperature (Scheme 50). This is the first successful unprecedented catalytic peptide synthesis at room temperature.

This catalysis tolerated a wide range of functionalized α-amino acids incorporating α-side chains, such as alkynes, sulfur atoms, and amide moieties, to produce dipeptides **237**–**242** in moderate to high yields with minimum epimerization (Scheme 51). Cyclopropane, unprotected thiol, and NH-free indole functional groups also survived during the catalysis. Commercially available amine hydrogen chloride salts could be used as amine substrates without coexisting bases in the presence of MS 5A, but the hydrogen bromide and tosylate salts of amines could not be used.

The *gem*-DBA (**230**)-catalyzed peptide bond formation could be applied to the synthesis of oligopeptide **247** (Scheme 52). Dipeptides **244** and **246** were prepared by catalytic peptide synthesis using *gem*-DBA. To avoid cyclization during

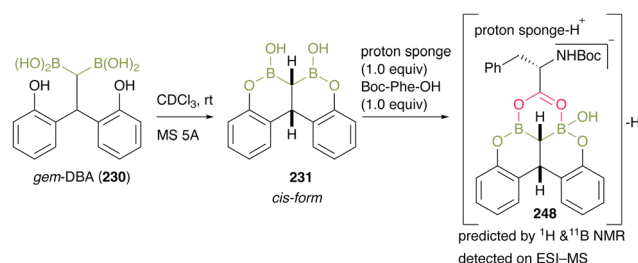
Scheme 51 *gem*-DBA-catalyzed dipeptide synthesis reported by Takemoto.⁵⁹Scheme 52 *gem*-DBA-catalyzed oligopeptide synthesis reported by Takemoto.⁵⁹

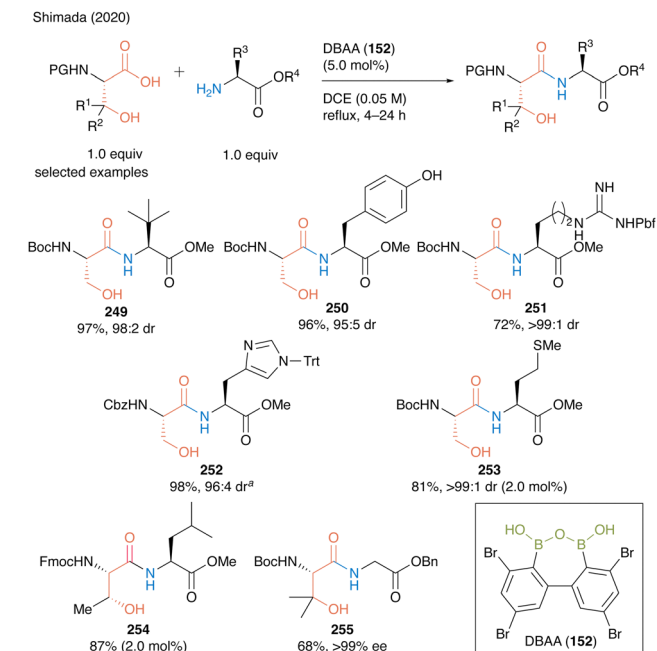
deprotection, the *tert*-butyl ester protecting group was suitable for dipeptide C-terminus. The deprotection of **244** and **246** was followed by *gem*-DBA (**230**)-catalyzed coupling to produce the corresponding tetrapeptide **247** in 57%. This Fmoc-based *gem*-DBA catalytic method is thought to be suitable for application in SPPS.

To gain mechanistic insight, they treated *gem*-DBA (**230**) in CDCl₃ with MS 5A and obtained **231**, and the bearing *cis*-configuration structure was determined by X-ray crystallography (Scheme 53). When intermediate **248** was treated with an equimolar amount of Boc-Phe-OH and proton sponge, the negative ESI-MS value of the mixture represented a corresponding structure of a dehydrative complex **231** that was assumed to be caused by a unique bidentate carboxylate activation by *gem*-DBA. This result indicated that *gem*-DBA (**230**) forms anion-binding with carboxylate anions, unlike the usual arylboronic acids.

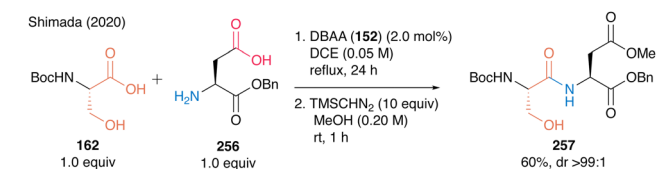
In the same year, Shimada and co-workers⁶⁰ reported DBAA (**152**) as an effective catalyst for the hydroxy-directed dehydrative peptide bond formation of β-hydroxy-α-amino acids such as serine, threonine, and β-hydroxy valine as carboxylic acid substrates, and various amino acid esters were suitable for this reaction as amine substrates, affording the corresponding dipeptides **249**–**255** in high to excellent yields (Scheme 54).

Notably, this DBAA catalysis proceeded smoothly without azeotropic reflux using Dean–Stark apparatus or dehydrative

Scheme 53 Mechanistic insights reported by Takemoto.⁵⁹



Scheme 54 DBAA-catalyzed peptide bond formation reported by Shimada: ^aPerformed with HCl salt of amino ester (1.0 equiv.) in the presence of MS 4A.⁶⁰



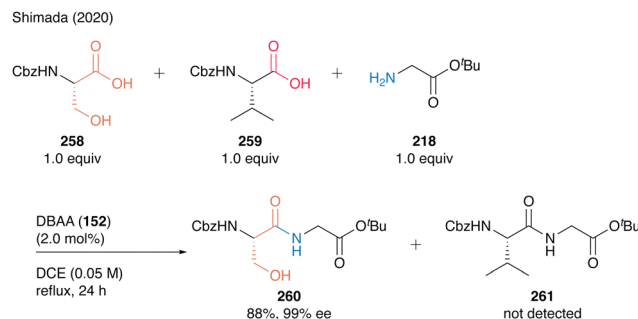
Scheme 55 DBAA-catalyzed dipeptide synthesis reported by Shimada.⁶⁰

reagents, and the desired dipeptides were obtained with minimal epimerization. DBAA (**152**) can selectively activate α -amino acids containing hydroxy group at the β -position. Indeed, dehydrative condensation between serine derivative **162** and aspartic acid derivative **256** containing a free carboxyl group occurred with only a hydroxycarboxylic acid moiety, selectively producing the serine-derived dipeptide **257** (Scheme 55).

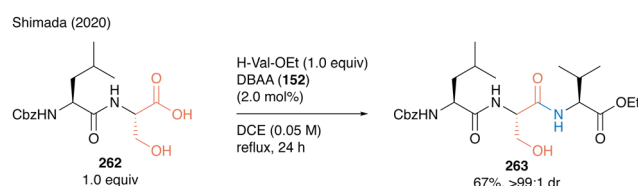
This chemoselectivity in DBAA catalysis was highlighted by the competition reaction of Cbz-Ser-OH (**258**) and Cbz-Val-OH (**259**) with H-Gly-O^tBu (**218**), generating dipeptide Cbz-Ser-Gly-O^tBu (**260**) as a sole product in high yield (Scheme 56). These results show that DBAA (**152**)-catalyzed hydroxy-directed peptide bond formation enables selective peptide coupling of β -hydroxy- α -amino acid residue at its C-terminus.

Tripeptide **263** was synthesized using DBAA-catalyzed peptide bond formation of **262** as a carboxylic substrate without any epimerization at the α -position of serine moieties (Scheme 57).

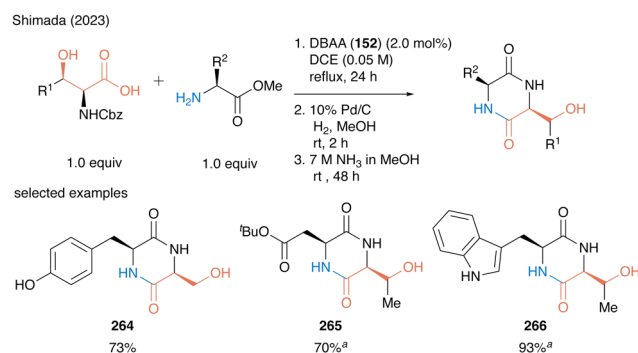
In 2023, Shimada and co-workers also reported a concise synthesis of serine- or threonine-derived 2,5-diketopiperazines (2,5-DKPs) (Scheme 58).⁶¹ In catalytic peptide synthesis using DBAA, water is the only byproduct so that the crude product can be used for the next reaction without any purification. A three-step



Scheme 56 DBAA-catalyzed chemoselective peptide bond formation reported by Shimada.⁶⁰



Scheme 57 DBAA-catalyzed tripeptide synthesis reported by Shimada.⁶⁰

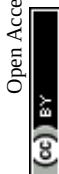


Scheme 58 Concise synthesis of 2,5-diketopiperazines using DBAA-catalyzed peptide bond formation reported by Shimada.⁶¹ ^aPerformed with HCl salt of amino ester (1.0 equiv.) in the presence of MS 4A.

sequential reaction comprising catalytic peptide synthesis, deprotection of the nitrogen-protecting group, and subsequent intramolecular condensation reaction, affording 2,5-diketopiperazines **264–266** in high to excellent yields without the purification of each synthetic intermediate. The synthetic efficiency of the protocol was demonstrated by the synthesis of bioactive molecules.

4. Conclusions

In this article, we review boron-catalyzed direct dehydrative amide bond and peptide bond formation reactions of carboxylic acids. Boron compounds are attractive as catalysts because of their ability to form reversible covalent bonds *via* dehydration and their potential Lewis acid properties. Dehydrative amide condensation using boron compounds as catalysts, which have low toxicity and are easy to handle, can become a practical and



environmentally friendly method to replace conventional condensation reactions using stoichiometric amounts of reagents.

Historically, this research field began with the development of dehydrative amidation using electron-deficient aromatic boronic acids. After the discovery of the effect of substituents at the *ortho*-position of aromatic boronic acids, several boronic acid catalysts have been developed. In parallel with these efforts, the development of recoverable and reusable boronic acid catalysts has been investigated and reusable catalysts supported on polystyrene, MCF, fluororous, and ion-exchange resins have been discovered. The direct dehydrative amide bond formation reaction of carboxylic acids with amines was expected to be applied to direct peptide bond formation reactions between amino acids. However, it was not easy to develop a practical boronic acid catalysis. The report of an improved mechanism for aromatic boronic acid-catalyzed dehydrative amidation that supports the existence of an active intermediate with a B–O–B bond was the turning point in this research field. In the past five years, several excellent multiorganoboron catalysts have been developed and research on direct dehydrative peptide bond formation reactions has rapidly progressed.

Recent developments in this field have been remarkable; however, some issues still need to be addressed in terms of catalytic activity (reducing the amount of the catalyst), energy saving (lowering reaction temperature), substrate limitations (wide range of substrate application), ease of operation (no dehydration operation), ease of catalyst availability, and catalyst reusability. To overcome the current situation and realize truly practical catalytic amide and peptide bond formation that can be used in several industries, researchers are required to continue creating novel catalysts.

Author contributions

M. K. and N. T. wrote the initial draft. N. S. proofread and revised the manuscript. M. K. and N. T. contributed equally to this work.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare no competing financial interest.

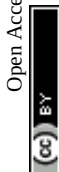
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