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Diboronic Acid Anhydride-Catalyzed Direct Peptide Bond Formation Enabled by Hydroxy-Directed Dehydrative Condensation

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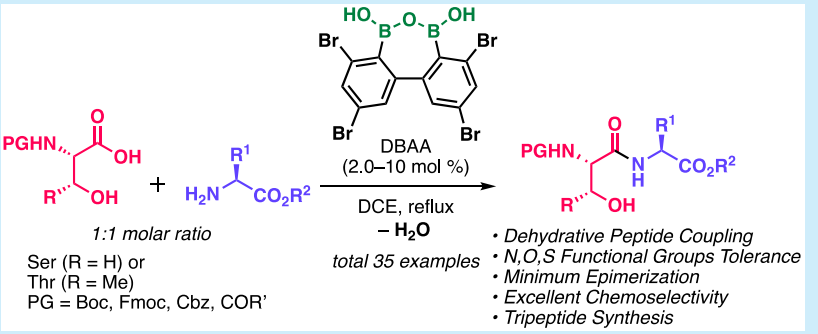

ABSTRACT: We report the catalytic direct peptide bond formations via dehydrative condensation of β-hydroxy-α-amino acids, affording the serine, threonine, or β-hydroxyvaline-derived peptides in high to excellent yields with high functional group tolerance, minimum epimerization, and excellent chemoselectivity. The key to the success of these atom-economical transformations is the use of diboronic acid anhydride catalyst for the hydroxy-directed reactions.

Peptides are extremely valuable species as biomolecules and constituents of pharmaceuticals,[1] functional materials,[2] and catalysts.[3] Several methods[4] for peptide bond formation have been developed relying on carboxylic acid surrogates, including acid halides,[5] thioesters,[6] acyl hydrazides,[7] acyl ureas,[8] esters,[9] selenoesters,[10] amides,[11] thioacids,[12] keto acids,[13] acyl trifluoroborates,[14] and nitro alkanes.[15] Some innovative approaches using isonitriles,[16] azides,[17] thioamides,[18] hydroxy amines,[13] and alkoxyamines[13] as amine surrogates have also been reported. However, these strategies often involve tedious substrate preparation procedures. Thus, the dehydrative condensation of carboxylic acids and amines is one of the most attractive methodologies for peptide bond construction.[19] Although dehydrative condensation using stoichiometric amounts of condensation reagents[20] has been widely utilized in liquid-phase and solid-phase peptide synthesis,[21] its implementation results in low atom economy and partial racemization. The catalytic version of direct dehydrative peptide bond formation provides the means to overcome such drawbacks.[22]

In 1996, Yamamoto[23] reported a pioneering study of catalytic dehydrative condensation of carboxylic acids with amines using electron-deficient arylboronic acids. Subsequently, modified aromatic boronic acid catalysts were developed by Ishihara,[24] Whiting,[25] Hall,[26] and Blanchet.[27,28] By contrast, successful examples of boronic acid-catalyzed peptide bond formation are limited. Although some studies on boronic acid-catalyzed peptide synthesis using common *N*-carbamate-protected α-amino acid derivatives have been reported, room exists for turnover number improvements.[25c,27] The main reason for the observed low catalytic efficiencies may be boronic acid inhibition resulting from the formation of inert species by chelating of amino acids as bidentate substrates.[29] Hall[30] and Ishihara[31] independently found that use of alternative *N*-protecting groups of α-amino acids, like phthaloyl,[30] azido,[30] and trifluoroacetyl[31] groups, increased catalytic efficiencies (Scheme 1a). Over the past three years, breakthroughs in the development of organoboron catalysts other than monoboronic acids have been reported, which afford peptide bond formation using *N*-carbamate-protected amino acids as substrates (Scheme 1a). In 2018, Sheppard[32] demonstrated that a borate ester derived from trifluoroethanol is a highly efficient catalyst for the dehydrative amidation of a range of substrates, including *N*-carbamate-protected α-amino acids[32a,b] and unprotected α-amino acids.[32a] Around the same time, Shibasaki and Kumagai et al. reported the catalytic dehydrative amidation of *N*-carbamate-protected functionalized α-amino acids using catalyst 1,3-dioxa-5-aza-2,4,6-

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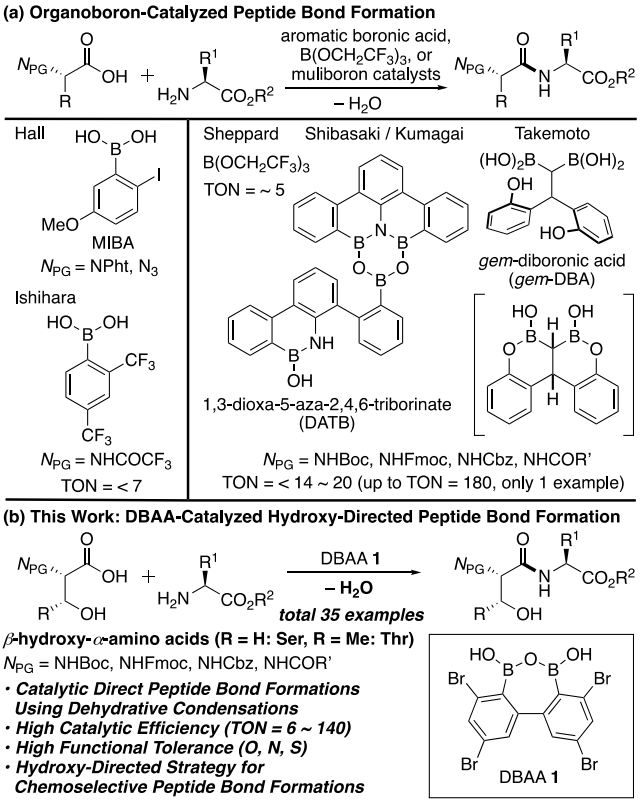
Scheme 1. Catalytic Peptide Bond Formations

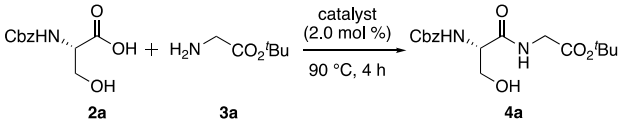


triborinate (DATB).[33] The exceptional power of this catalysis was demonstrated by application to the syntheses of an oligopeptide and various dipeptides.[34] Most recently, Takemoto[35] designed a *gem*-diboronic acid (*gem*-DBA) catalyst for dehydrative peptide synthesis based on a revised mechanism of boronic acid-catalyzed amidation via a dimeric anhydride intermediate with a B−O−B skeleton described by Whiting and Sheppard.[36]

We recently disclosed that diboronic acid anhydride (DBAA) with a preorganized B−O−B motif is an effective catalyst for the hydroxy-directed dehydrative amidation carboxylic acids.[37,38] Herein, we report the DBAA-catalyzed dehydrative peptide bond formations of α-amino acids having a free hydroxy group on the β-position (Scheme 1b). This hydroxy-directed reaction using low catalyst loading enabled the direct formation of serine- or threonine-derived dipeptides with high functional group tolerance, minimum epimerization, and excellent chemoselectivity.

Initially, we explored the dehydrative coupling of an equimolar mixture of Cbz-Ser-OH (**2a**) and H-Gly-O^{t}Bu (**3a**) in the presence of 2.0 mol % of DBAA **1** in toluene (Table 1). The reaction proceeded at 90 °C within 4 h without the need for dehydration protocols, affording the desired dipeptide Cbz-Ser-Gly-O^{t}Bu (**4a**) in 72% yield with minimum racemization at the α-position of the carbonyl group (entry 1). Although no product yield improvements were observed using C_6H_5Cl or cyclopentyl methyl ether as solvents (entries 2, 3), use of 1,2-dichloroethane afforded **4a** in 89% yield (entry 4). A survey of solvent concentrations indicated 0.05 M to be optimal for product yield and racemization, increasing dipeptide **4a** yield to 95% without loss of optical purity (entry 5 vs entries 4, 6). To compare the catalytic efficiency, we examined the reaction using some organoboron catalysts,

Table 1. Optimization of Catalytic Dehydrative Peptide Bond Formation[a]



entry	catalyst	solvent	conc (M)	yield (%)	% ee[b]
1	DBAA **1**	toluene	0.10	72	97
2	DBAA **1**	C_6H_5Cl	0.10	31	98
3	DBAA **1**	CPME	0.10	11	96
4	DBAA **1**	DCE	0.10	89	99
5	DBAA **1**	DCE	0.05	95	>99
6	DBAA **1**	DCE	0.20	81	98
7	$B(OCH_2CF_3)_3$	DCE	0.05	trace	nd
8	DATB	DCE	0.05	47	98
9	*gem*-DBA	DCE	0.05	9	99
10[c]	DBAA **1**	DCE	0.05	90	>99
11[d]		DCE	0.05	trace	nd

[a]The reactions were carried out in the presence of Cbz-Ser-OH (**2a**) (0.10 mmol, 1.0 equiv), H-Gly-O^{t}Bu (**3a**) (0.10 mmol, 1.0 equiv), and catalyst **1** (2.0 μmol, 2.0 mol %) at 90 °C (bath temp). [b]Ee was determined by chiral HPLC analysis. [c]Performed with HCl salt of H-Gly-O^{t}Bu (**3a·HCl**) (1.0 equiv) in the presence of 4 Å molecular sieves (100 mg/0.10 mmol). [d]In the absence of catalyst **1**. CPME: cyclopentyl methyl ether; DCE: 1,2-dichloroethane.

showing higher catalytic activity of **1** (entry 5 vs entries 7−9).[39] In this catalytic system, commercially available HCl salts of amino esters could be used as substrates: the HCl salt of H-Gly-O^{t}Bu (**3a·HCl**), in the presence of 4 Å molecular sieves, afforded a product yield (90%) comparable with that of free amine **3** (entry 5 vs entry 10). This protocol is experimentally advantageous as it does not require advance free amine. No peptide bond formation occurred without **1** (entry 11). These results indicate the suitability of **1** as the catalyst for the dehydrative coupling of β-hydroxy-α-amino acid.[39]

With the optimal conditions in hand, we explored the substrate scope of the catalytic dipeptide synthesis (Scheme 2). Besides Cbz, Boc and Fmoc could be used as serine *N*-protecting groups, affording Boc-Ser-Gly-OBn (**4b**) and Fmoc-Ser-Gly-OEt (**4c**) in 88 and 81% yield, respectively. We then evaluated the reactivities of a range of α-amino esters. All reactions involving H-Ala-O^{t}Bu (**3d**), H-Leu-OMe (**3e**), H-Ile-OMe (**3f**), and H-Val-OMe (**3g**) possessing an alkyl side-chain at the α-position proceeded smoothly within 24 h with dipeptides **4d**−**4j** obtained in high to excellent yields (74−>99%). Notably, all dipeptide bonds were formed without substantial epimerization (dr 98/2−>99/1). In the case of **4i**, catalyst loading could be reduced to 0.5 mol %, and the turn over number recorded 142 (71% yield). The present protocol could be performed in 1.0 mmol scale, affording **4j** in 88% yield without epimerization. Bulky *tert*-leucine derivative H-Tle-OMe (**3h**) could also be used as an α-amino ester substrate, affording Boc-Ser-Tle-OMe (**4k**) in excellent yield (97%) in the presence of 5.0 mol % of **1**. In the case of α,α-disubstituted amino ester-derived dipeptide **4l**, the coupling reaction progressed at elevated temperature in toluene with high racemization at the carbonyl α-position. By contrast, use of sarcosine derivative H-Sar-OBn (**3j**) as secondary amine substrate afforded dipeptide Boc-Ser-Sar-OBn (**4m**) in moderate yield and minimal racemization. Subsequently, we

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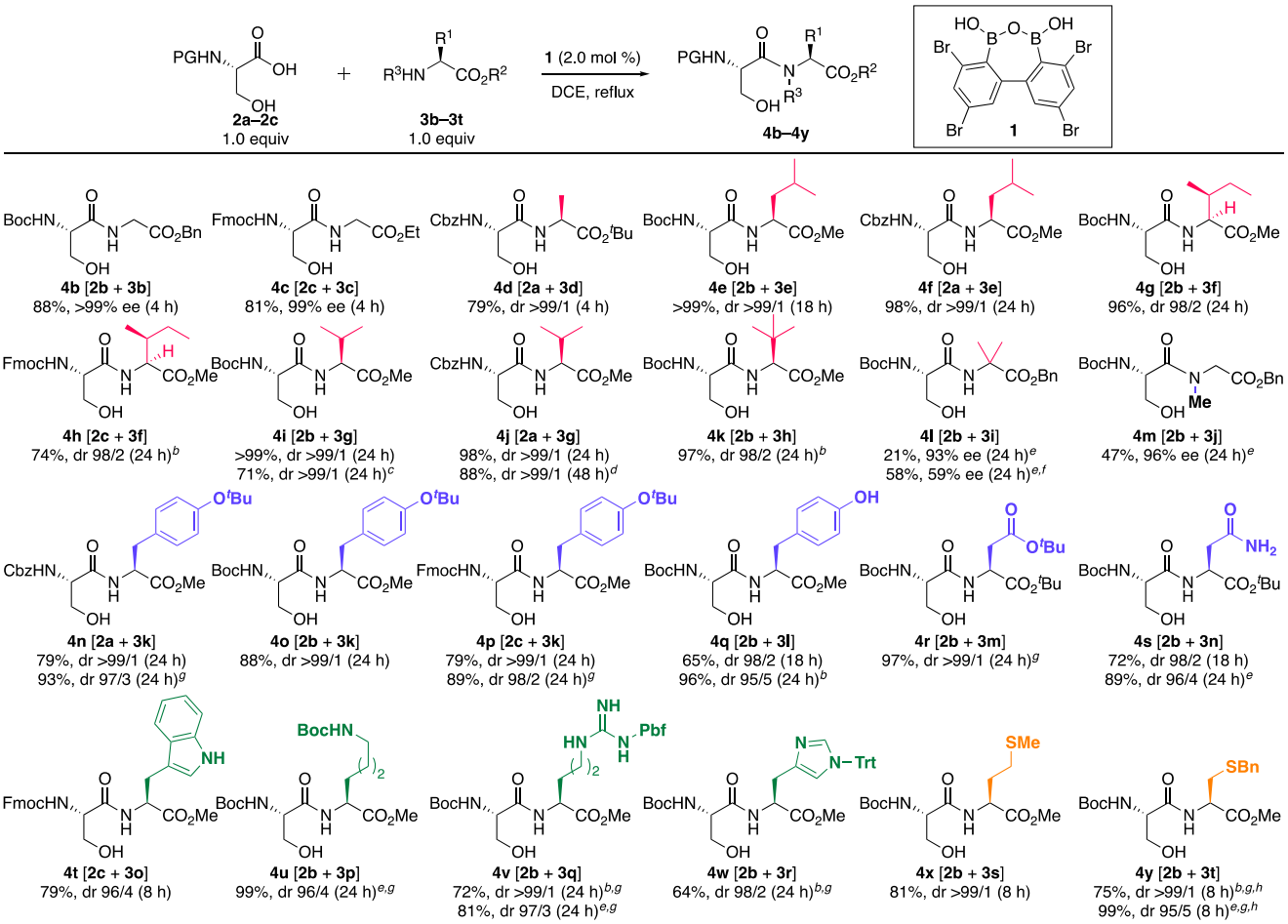
Scheme 2. Substrate Scope for Diboronic Acid Anhydride-Catalyzed Serine-Derived Peptide Bond Formation[a]



[a]The reactions were carried out in the presence of serine derivative **2** (0.10 mmol, 1.0 equiv), amino ester **3** (0.10 mmol, 1.0 equiv), and catalyst **1** (2.0 μmol, 2.0 mol %) in 1,2-dichloroethane (DCE, 0.05 M) under reflux (bath temp, 90 °C). Ee and dr were determined by chiral HPLC analysis. [b]Performed with 5.0 mol % of **1**. [c]Performed with 0.5 mol % of **1**. [d]Performed in 1.0 mmol scale. [e]Performed with 10 mol % of **1**. [f]Performed in toluene (0.05 M) under reflux (bath temp, 110 °C). [g]Performed with HCl salt of amino ester **3** (1.0 equiv) in the presence of 4 Å molecular sieves (100 mg/0.10 mmol). [h]Performed at 80 °C (bath temp).

explored the use of functionalized α-amino esters incorporating heteroatoms as substrates. Reaction of H-Tyr(^{t}Bu)-OMe (**3k**), whereby a hydroxy group is protected by a *tert*-butyl group, gave dipeptides **4n**–**4p** in high yields (79–88%). Moreover, unprotected H-Tyr-OMe (**3l**) afforded dipeptide Boc-Ser-Tyr-OMe (**4q**) in high yield. Evidence thus indicates that an unprotected phenolic hydroxy group does not suppress the present catalysis. Aspartic acid derivative H-Asp(^{t}Bu)-O^{t}Bu (**3m**) gave dipeptide **4r** in 97% yield. **1** was also effective for the dipeptide coupling between serine and asparagine to produce dipeptide Boc-Ser-Asn-O^{t}Bu (**4s**) with a primary amide functional group. We then examined the tolerance of the present protocol for *N*-functional groups: not only was *N*-H free indole tolerated, but so were acid-labile *N*-*tert*-butoxycarbonyl-protected amine, *N*-2,2,4,6,7-pentamethyldihydrobenzofuran-5-surfonyl-protected guanidine, and *N*-trytyl-protected imidazole. H-Trp-OMe (**3o**), H-Lys(Boc)-OMe (**3p**), H-Arg(Pbf)-OMe (**3q**), and H-His(Trt)-OMe (**3r**) afforded dipeptides **4t**–**4w** in acceptable yields (64–99%). Significantly, stereochemical integrity was almost completely preserved in most cases (dr 96/4–>99/1). The reaction between **2b** and H-Met-OMe (**3s**) proceeded smoothly within 8 h, affording dipeptide Boc-Ser-Met-OMe (**4x**) in 81% yield. This result indicates the tolerance of our DBAA-based catalysis for the Lewis-basic sulfide group. The *S*-functionalized α-amino ester H-Cys(Bn)-OMe (**3t**) produced Boc-Ser-Cys(Bn)-OMe (**4y**) in high yield in 1,2-dichloroethane, although the reaction temperature had to be lowered to 80 °C to avoid a noticeable drop in stereochemical integrity. The wide functional group tolerance of the catalysis was thus demonstrated.

To expand the scope of this DBAA-catalyzed peptide bond formation, we investigated threonine derivatives bearing β-hydroxy-α-amino acid motifs similar to serine. As detailed in Scheme 3, Boc-Thr-OH (**5a**), Fmoc-Thr-OH (**5b**), and Cbz-Thr-OH (**5c**) afforded dipeptides **6a**–**6f** in high to excellent yields (72–98%). No major negative impact was associated with the steric hindrance of the additional β-methyl substituent group. Notably, high functional tolerance and no detectable epimerization were observed in all cases.

To confirm the importance of the β-hydroxy group in the substrate-directed reaction, we conducted some additional experiments (Scheme 4).[40] First, we performed a catalytic dipeptide synthesis using β-hydroxyvaline derivative **7** as a challenging β,β-disubstituted substrate (Scheme 4a). In the presence of 5.0 mol % of **1**, the corresponding dipeptide **8** was

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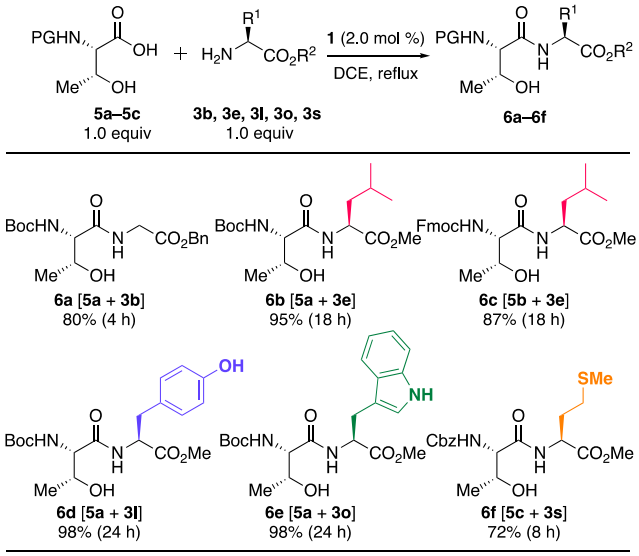
Scheme 3. Diboronic Acid Anhydride-Catalyzed Threonine-Derived Peptide Bond Formation[a]



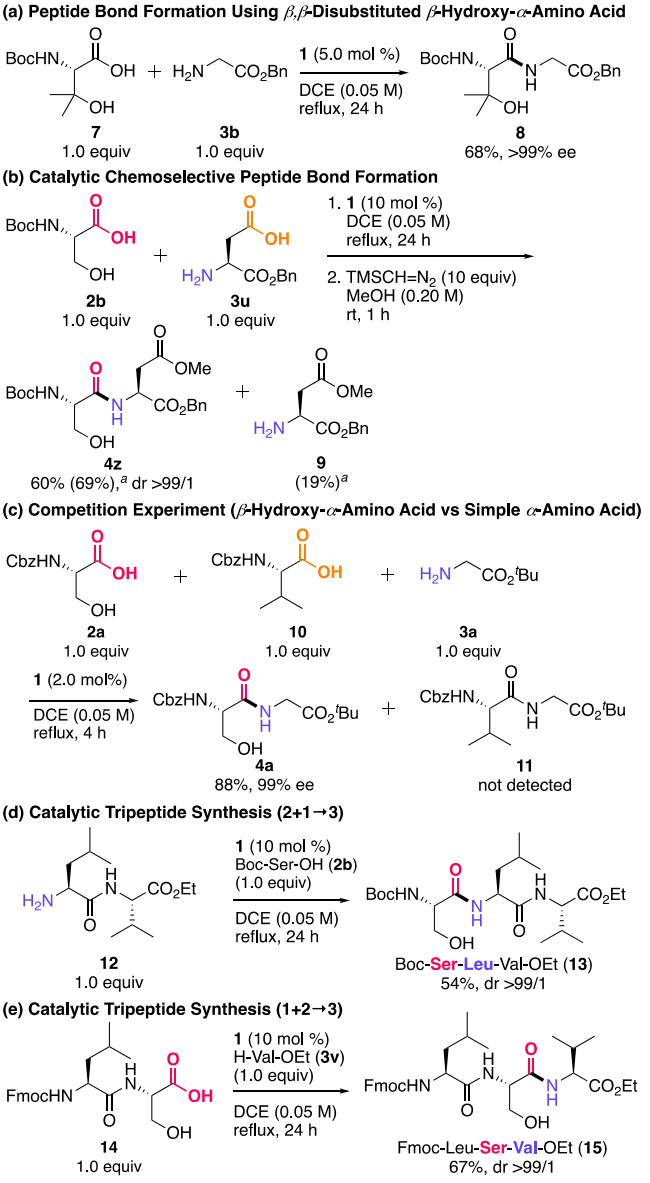
[a]The reactions were carried out in the presence of threonine derivative **5** (0.10 mmol, 1.0 equiv), amino ester **3** (0.10 mmol, 1.0 equiv), and catalyst **1** (2.0 μmol, 2.0 mol %) in 1,2-dichloroethane (DCE, 0.05 M) under reflux (bath temp, 90 °C). Diastereomers were not detected by ^{13}C NMR analysis.

obtained in 68% yield without any racemization, indicating the steric tolerance of this coupling reaction.

Next, a dehydrative condensation between serine derivative **2b** and aspartic acid derivative H-Asp-OBn (**3u**) having a free carboxyl group was performed (Scheme 4b). To facilitate purification, the free carboxylic functional groups were converted to methyl esters by treating the crude product with excess trimethylsilyl diazomethane. After two-step sequences, the expected dipeptide **4z** was obtained in 69% yield (60% isolated yield) alongside the methyl ester **9** (19% yield), resulting from the esterification of unreacted aspartic acid moiety. Analysis of stereochemical integrity of **4z** revealed no epimerization at the carbonyl α-position, indicating the high chemoselectivity for β-hydroxycarboxylic acid over simple carboxylic acid of the DBAA-catalyzed dehydrative coupling. This tendency was confirmed by the results of the competition experiment involving β-hydroxy-α-amino acid and simple α-amino acid (Scheme 4c). The reaction of 1.0 equiv each of Cbz-Ser-OH (**2a**) and Cbz-Val-OH (**10**) with H-Gly-O^{t}Bu (**3a**) afforded dipeptide Cbz-Ser-Gly-O^{t}Bu (**4a**) as sole product in 88% yield (99% ee). Valine-derived dipeptide **11** was not observed, confirming the extremely high chemoselectivity for β-hydroxycarboxylic acid.

We then focused on tripeptide synthesis. Although a higher catalyst loading of 10 mol % was required, the tripeptide Boc-Ser-Leu-Val-OEt (**13**) was obtained in 54% yield via coupling of **2b** with dipeptide H-Leu-Val-OEt (**12**) as amine substrate (Scheme 4d). Moreover, dipeptide Fmoc-Leu-Ser-OH (**14**) comprising an amide linkage on the nitrogen atom of serine was utilized to afford the tripeptide Fmoc-Leu-Ser-Val-OEt (**15**) in 67% yield (Scheme 4e). Notably, **15** was obtained without any loss of stereochemical integrity at the α-position of serine's carbonyl, despite epimerization often becoming a problem in dehydrative condensation of peptides.[20] These results suggest that our DBAA-based catalysis might be

Scheme 4. Diboronic Acid Anhydride-Catalyzed Dehydrative Peptide Bond Formation[a]



[a]Determined by ^{1}H NMR analysis of the crude product mixture using 1,1,2,2-tetrachloroethane as internal standard.

applicable to a selective peptide coupling using a N-terminal peptide fragment having a β-hydroxy-α-amino acid residue at its C-terminus.

In summary, we demonstrated that DBAA is an effective catalyst for the hydroxy-directed amidation of β-hydroxy-α-amino acids with a wide range of α-amino esters. This catalysis shows high functional group tolerance in peptide bond formations using serine, threonine, and hydroxyvaline derivatives as α-amino acid substrates, producing di- and tripeptides in high to excellent yields and minimum epimerization. The present protocol affords excellent chemoselectivity for α-amino acids having the β-hydroxycarboxylic acid unit. Further applications of DBAA-based catalysis are underway in our laboratories.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, analytical data, supplemental data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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