Catalytic Dehydrative Peptide Synthesis with *gem*-Diboronic Acids

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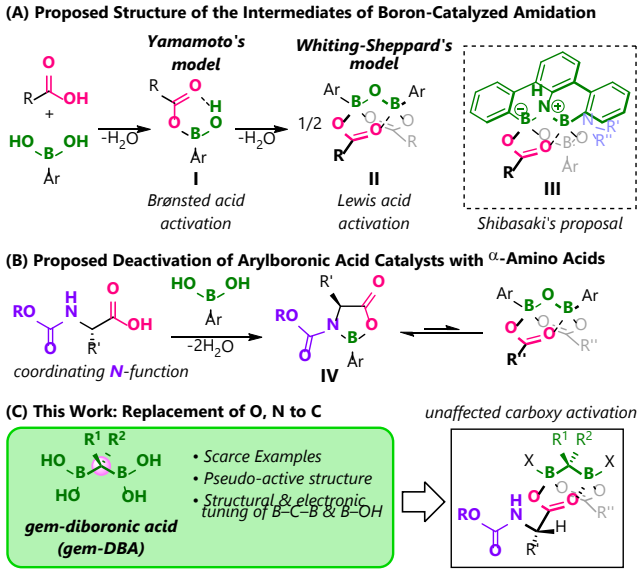
Supporting Information Placeholder

ABSTRACT: Alkane-*gem*-diboronic acids have emerged as versatile organoboron catalysts for dehydrative amidation of *α*-amino acids. A phenol-substituted multi-boron catalyst with a B–C–B structure outperformed simple arylboronic acids in the condensation of *α*-amino acids with suppressed epimerization of electrophiles. *gem*-diboronic acid catalysis were compatible with various *O*, *N*, and *S*-functionalized *α*-amino acids bearing *N*-protecting groups including common carbamates used in peptide synthesis (Boc, Cbz, Fmoc). *N*-trifluoroacetyl protection enabled an unprecedented catalytic dehydrative peptide synthesis at room temperature. Preliminary mechanistic studies revealed carboxylate-binding nature of *gem*-diboronic acids, orthogonal to the activation of carboxylic acids by arylboronic acids. The distinctive reactivity of the *gem*-diboronic acids would open prospects for mild catalytic peptide condensation.

keywords: organoboron catalyst, gem-diboronic acid, dehydrative amidation, peptide synthesis, oligopeptide, carboxylate activation

In the last half century, the practical synthesis using low-electrophilic carboxylic acids has been broadened by virtue of condensation reagents.[1] In particular, reagent-driven dehydrative amidation has largely contributed to the mass production of amide-containing entities, including artificial pharmaceuticals, bioactive peptides, and functional polymers.[2] Therefore, this highly reliable methodology is still in the forefront of organic synthesis, notwithstanding the stoichiometric generation of chemical wastes. In contrast, the recent high demand for environment-friendly alternatives has led to the exploitation of catalytic amide C–N bond construction.[3,4] In 1996, Yamamoto reported catalytic amide condensation using arylboronic acids, which release only water as the side product.[5] This innovative discovery triggered off the research to establish highly active organoboron catalysts.[6] Yet, severe limitations have confronted arylboronic acids in catalytic peptide synthesis: the reactions still suffer from insufficient catalyst performance and restrictions in the protecting and functional groups. The development of new catalysts for peptide condensation is thus still in its nascent stage, because, to date, only a few catalysts are capable of coupling carbamate-protected, heteroatom-functionalized *α*-amino acids.[6,7]

To tackle these issues, we focused on the structure of the intermediates in organoboron-catalyzed amidation. Since Yamamoto's original mechanistic proposal,[5] Brønsted acid-activation of the carbonyl group in a "monomeric" mixed anhydride **I** has been widely accepted.[8a,b] In sharp contrast, Whiting and Sheppard demonstrated a more feasible intermediate based on spectroscopic observations and isolation of the mixed anhydride **II**.[8c] The structure of **II** features "diboroxane", a bridged B–O–B motif, which can be formed by dehydrative dimerization of **I**. This tetragonal boron species suggested bidentate Lewis acid-activation of the carboxy groups. The pathway involving **II** was further supported by a more detailed spectroscopic analysis by Ishihara.[6l] The analogous intermediate **III** with a B–N–B unit within B_3NO_2 heterocycles has also been proposed by Shibasaki as a crucial structure for carboxy activation (Scheme 1A).[6k,6n,8d] However, *α*-amino acids would give the low-reactive, five-membered complex **IV** through the coordination of both the acid and a proximal nitrogen toward arylboronic acids.[7b] The formation of the dimerized "active" species might thereby be hampered, preventing further development of simple arylboronic acids as catalysts for peptide synthesis (Scheme 1B). To circumvent this dilemma, we envisaged the efficient bidentate carboxy activation of *α*-amino acids with a B–C–B structure, leading to the design of *gem*-diboronic acid (denoted here as "*gem*-DBA") (Scheme 1C).[9] Because *gem*-DBAs possess "pseudo-active" B–C–B moiety in advance, the more efficient acid activation could be expected in the presence of *N*-protecting groups of the *α*-amino acids. The structural and electronic tuning of the catalyst, in respect to the central carbon, as well as the B–OH, would disclose unknown reactivity of *gem*-DBAs towards amidation.[10]

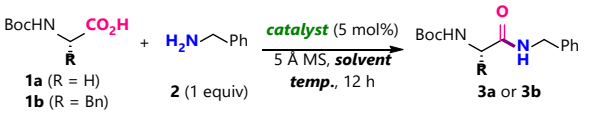


Scheme 1. Structure of the Intermediates and Catalyst Design

On the basis of the catalyst design described above, we initiated our studies by evaluating the reactivity of methylenediboronic acid (**A**), the simplest *gem*-DBA,[10c] as a catalyst. Extensive reagent screening revealed that a 5 mol% of catalyst **A** coupled *N*-Boc-Gly (**1a**) with benzylamine (**2**) to afford amide **3a** in 99% yield in the presence of molecular sieves 5 Å (5 Å MS) in toluene at 80 ºC (Table 1, entry 1). Nonetheless, *N*-Boc-L-Phe (**1b**) was completely inert

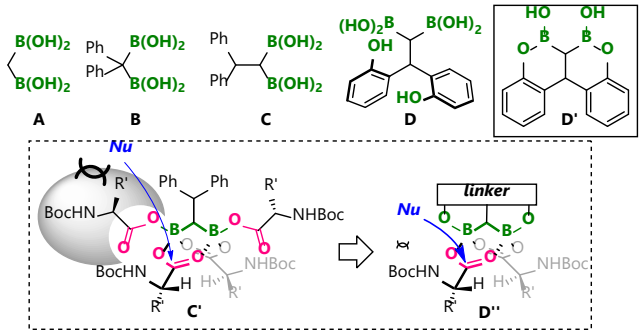
under the same conditions (entry 2), which prompted us to investigate the substituent effects on the central carbon atom of *gem*-DBA. Examination of several *gem*-DBAs illustrated the strong influence of steric effects around the central carbon atom: no reaction occurred with bulky catalyst **B** (entry 3), while relatively small monoalkyl-substituted catalyst **C** furnished **3b** in 82% yield (entry 4). However, a considerable drop in the yield was observed at 65 ºC (entry 5). We assumed this lack of efficiency arose from the overbinding of amino acids to form **C'**: bidentate activation of only two carboxy groups left two residues that would merely encumber the nucleophilic attack. Hence, we expected that the use of the *ortho*-hydroxyphenyl-substituted catalyst **D** would reduce the bulkiness around the activated carbonyls by *in situ* cyclocondensation to produce **D'**. The putative less hindered complex **D''** might thus exhibit higher reactivity towards the addition of amines (below Table 1).[11] The catalytic performance of **D** was much greater than that of **C**, affording **3b** in 96% yield without racemization (entry 6). Investigation of other parameters uncovered that low-polarity solvents gave better results (entries 7–10) and lowering temperature diminished the yield (entry 11). No amidation occurred in the absence of either the catalyst or molecular sieves, indicating that the carboxy activation and the removal of water were both indispensable (entries 12 and 13).[12]

Table 1. Optimization of the Reaction Conditions.



entry	substrate	catalyst	solvent	temp. (ºC)	**3b** (%)[a]
1	**1a**	**A**	toluene	80	99
2	**1b**	**A**	toluene	80	0
3	**1b**	**B**	toluene	80	0
4	**1b**	**C**	toluene	80	82
5	**1b**	**C**	toluene	65	31
6	**1b**	**D**	**toluene**	**65**	**96**[b]
7	**1b**	**D**	PhF	65	78
8	**1b**	**D**	$(CH_2Cl)_2$	65	68
9	**1b**	**D**	CPME	65	85
10	**1b**	**D**	DMF	65	0
11	**1b**	**D**	toluene	50	77
12	**1b**	none	toluene	65	0
13[c]	**1b**	**D**	toluene	65	0

Reaction conditions: **1** (0.20 mmol, 1.0 equiv), **2** (0.20 mmol, 1.0 equiv), catalyst (10 μmol, 5 mol%), 5 Å MS (200 mg), solvent (2.0 mL), 12 h. [a]Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b]The er was estimated by chiral HPLC analysis as >99:1. [c]The reaction was performed without 5 Å MS.



With the optimal conditions in hand, the applicability of the dehydrative amidation of **1b** with catalyst **D** in peptide synthesis was evaluated. To our delight, the amino ester hydrochloride **4a** was a promising nucleophile, giving dipeptide **5ba** in 88% yield at 80 ºC.[6l,7c] The other *N*-protecting groups, including carbamates (**1c**, **1d**), amides (**1e**, **1f**[6l]) and a sulfonamide (**1g**), also afforded the corresponding dipeptides in good yields, although epimerization occurred in all cases (*vide infra*). The *N*-phthaloyl group (**1h**) was not a suitable protecting group for this system (Figure 1), in contrast to the results with arylboronic acids.[7b] Remarkably, in case of **1f**, unprecedented catalytic dehydrative peptide synthesis at room temperature was achieved. The turnover frequency was still very low, the result suggested the feasibility of peptide condensation under mild conditions by further modification of the *gem*-DBA catalysts.

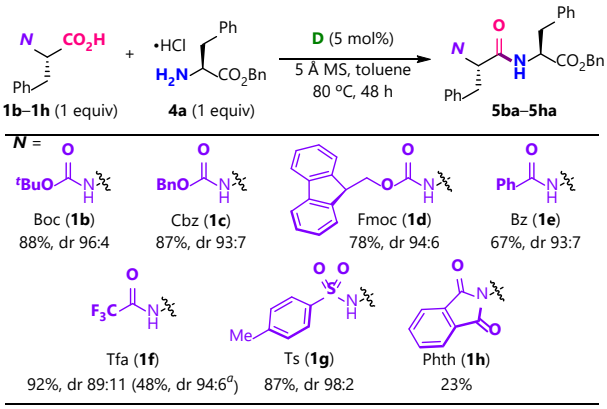


Figure 1. Variation of *N*-Protecting Groups of Electrophile. Isolated yields are shown. Drs were estimated by Chiral HPLC analysis. [a]The reaction was carried out using 20 mol% catalyst **D** in CH_2Cl_2 at rt for 120 h.

The potent activity of catalyst **D** toward dehydrative peptide synthesis motivated us to explore the scope of α-amino acids endowed with various functionalized side chains (Figure 2). The coupling of *N*-Boc-protected amino acids and **4a** unveiled that **1b** underwent the amidation at 65 ºC to give **5ba** in better yield than the reaction at 80 ºC. Notably, a terminal alkyne (**1i**), a sulfide (**1j**), an ester (**1k**), and an amide (**1l**) were compatible, providing the corresponding dipeptides **5ia**–**5la** in good yields. In addition, the presence of imidazole nitrogen did not affect the formation of **5ma**. Furthermore, though a prolonged reaction time was necessary, *N*-Boc-L-proline provided the corresponding dipeptide **5na** in 73% yield. The versatility of *gem*-DBA towards the amino ester counterparts was next probed using **1b**. Importantly, a range of alkyl-substituted nucleophiles could be applied, giving the leucine derivative **5bb**, as well as the bulky valine- and *tert*-leucine-derived dipeptides **5bc** and **5bd** in good yields. The cyclopropane ring in **5be** survived, and protected tyrosine (**5bf**) and lysine (**5bg**) were also tolerated. Moreover, the nucleophiles bearing unprotected thiol (**5bh**) and indole (**5bi**) groups also underwent the amidation, which could offer further direct transformations of the side chains. Markedly, the temperature could be lowered to 65 ºC for **5bb** and **5be**. For all reactions of dipeptide synthesis, the commercial amine·HCl salts could be directly engaged in the catalytic amidation, enabling a simple protocol free from pre-treatments and external bases. Meanwhile, significant counteranion effects were realized that **5bb** was obtained in high yield with HCl salt **4b**, whereas the efficiency was drastically deteriorated with the different counteranion analogues of **4b** (e.g. HBr or HOTs salts).[13,14]

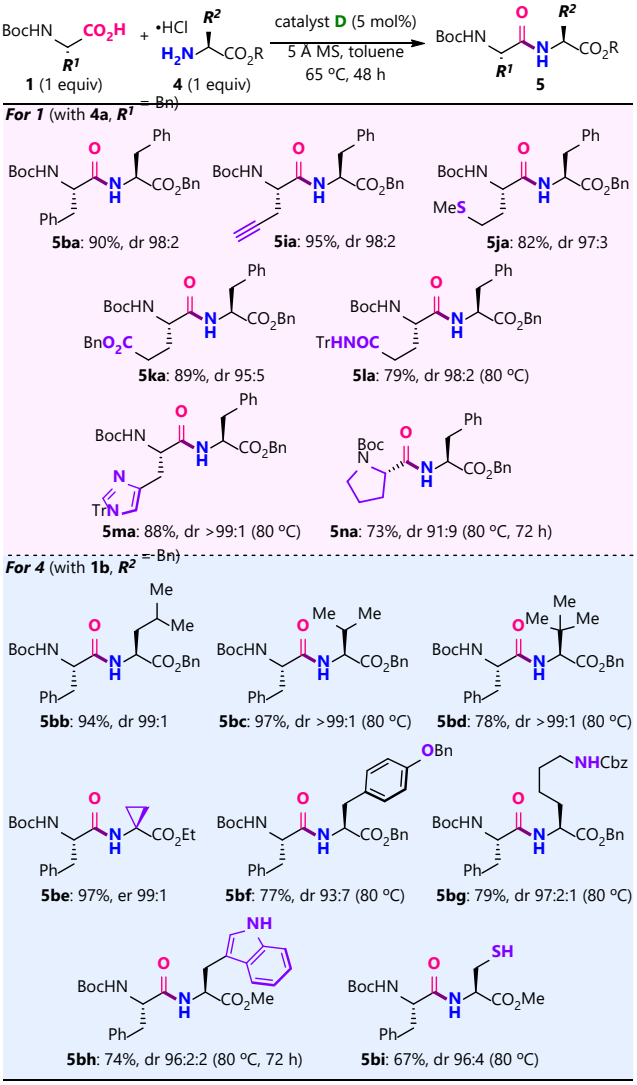
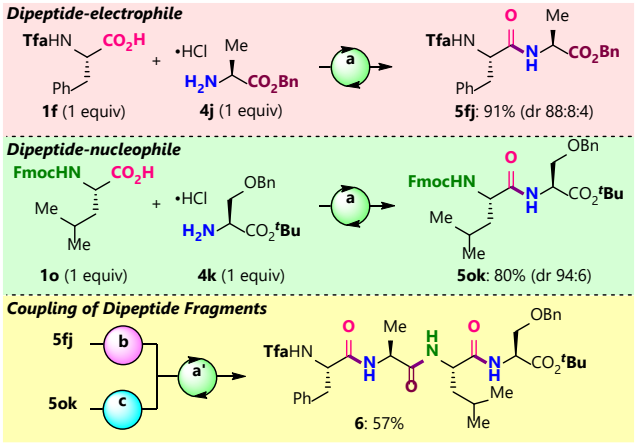


Figure 2. Scope of *N*-Boc Amino Acids **1** in Dipeptide Synthesis with **4a**. Isolated yields are shown. Drs were estimated by chiral HPLC analysis.

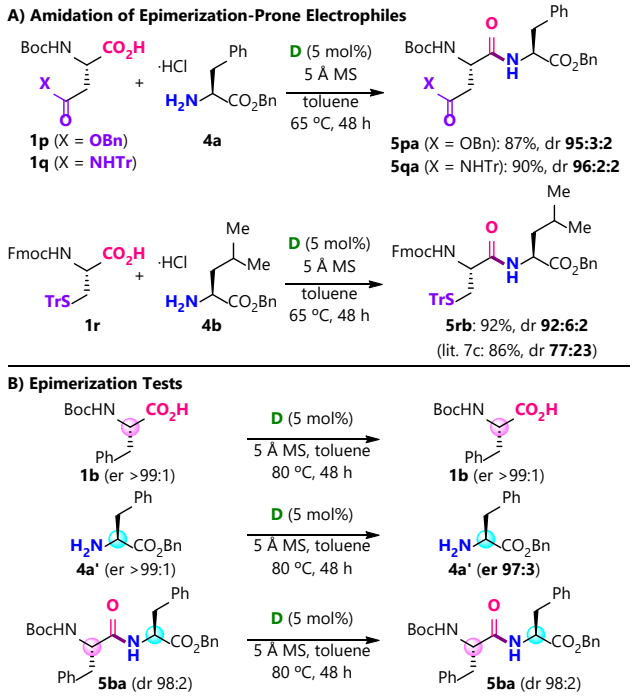
The remarkable performance of *gem*-DBAs towards activation of *α*-amino acids provided the opportunity for catalytic oligopeptide synthesis (Scheme 2).[7c] Several studies revealed the crucial effect of the protecting groups for both the *N*- and *C*-termini.[4c,4e,6m,7b] Since the electron-rich *N*-Boc protection hampered the amidation of dipeptide carboxylic acids, we prepared the electron-withdrawing *N*-trifluoroacetyl-protected **5fj** by coupling **1f** and **4j**.[6l] For the *C*-terminus of the dipeptide nucleophile, a *tert*-butyl ester protection was suitable to avoid intramolecular cyclization.[15] The dipeptide **5ok** was thus prepared, and after deprotection, catalytic interconnection of dipeptide segments successfully provided tetrapeptide **6** in moderate yield with a high catalyst loading. In particular, this Fmoc-based method would be expedient for the application of the *gem*-DBA catalysis in solid-phase peptide synthesis.[16,17]



Scheme 2. Catalytic Coupling of the Dipeptide-Derived Electrophile and Nucleophile

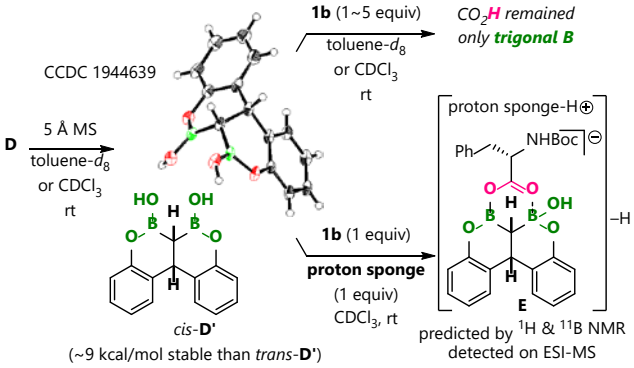
Reaction conditions: **a**) catalyst **D** (5 mol%), 5 Å MS, toluene, 80 ºC, 48 h; **a'**) catalyst **D** (15 mol%), 5 Å MS, toluene, 80 ºC, 48 h; **b**) 10% Pd/C (10 mol% Pd), THF, rt, H_2 (1 atm); **c**) piperidine, DMF, rt.

Generally, reagent-driven and boron-catalyzed peptide synthesis frequently induce considerable epimerization of the electrophiles.[18,19] Indeed, the epimerization-prone cysteine and aspartic acid-derived electrophiles underwent approximately 20% of enantiopurity loss by strong carboxy activation with the electron-deficient boron catalysts[6l,7d] and the B_3NO_2 heterocycle.[7c] In marked contrast, the *gem*-DBA catalysis significantly suppressed the stereochemical erosion of aspartic acid derivatives **1p** and **1q** as well as the cysteine electrophile **1r** (Scheme 3A). Meanwhile, enantiopurity of the nucleophiles was eroded, which was supported by the independent exposure of electrophile **1b** or neutralized nucleophile **4a'** or amide **5ba** to the optimal conditions, leading to a slight racemization of only **4a'** (Scheme 3B).[20] The reagent sensitivity trend toward epimerization was inverted under the *gem*-DBA catalysis, offering a complementary alternative to the known boron catalysts that promote epimerization of the electrophiles.



Scheme 3. Sensitivity of the Electrophiles and Nucleophiles toward Epimerization Under the *gem*-DBA Catalysis

The above unusual behavior of *gem*-DBA led us to attempt to observe the intermediates to gain mechanistic insights into the reaction. First, the phenolic protons were quickly disappeared upon the treatment of **D** with 5 Å MS in toluene-d_8 to give *cis*-**D'**, and the structure was unambiguously determined by X-ray crystallography.[21,22] *cis*-**D'** possesses a bent HO–BCB–OH unit, which was theoretically more stable than *trans*-**D'** by *ca*. 9 kcal/mol, consistent with the obtained structure.[23] Remarkably, no dehydration of *cis*-**D'** and **1b** occurred even in the presence of 5 Å MS and excess **1b** (1~5 equiv). Both the two boron atoms of *cis*-**D'** remained trigonal in ^{11}B NMR analysis. The inertness of *cis*-**D'** toward **1b** would be attributed to the lower Lewis acidity of *gem*-diborylalkane moiety relative to the arylboronic acids that easily form mixed anhydrides with carboxylic acids.[6l,7c] Instead, equimolar amount of *cis*-**D'**, **1b**, and proton sponge in toluene-d_8 produced new species. The observed negative chemical shift of B–C*H*–B proton was consistent with the proximity of boronate anions.[24] The ^{11}B NMR analysis revealed that both the two boron atoms became tetragonal. However, switching the solvent to $CDCl_3$ gave a different species with unsymmetrical aromatic protons of *cis*-**D'**, and ^{11}B NMR showed the existence of both trigonal and tetragonal boron atoms.[21] Moreover, the negative ESI-MS spectroscopy of the mixture represented a *m*/*z* peak at 512.2032, implying the existence of a dehydrated complex **E** consisting of *cis*-**D'** and **1b** in 1:1 ratio ([M]$^-$: calcd *m*/*z* = 512.2057) (Scheme 4).[6o] Although the structure of **E** is still unclear, the spectroscopic aspects would indicate a unique bidentate "carboxylate-activation" nature of *gem*-DBAs, orthogonal to arylboronic acids and B_3NO_2 heterocycles activating carboxylic acids.[6g,6o,7d] The anion-binding property would give rise to suppress epimerization of the electrophiles, while the epimerization of nucleophiles might be induced by the coordination of amines to the boron atoms. Besides analytically, catalytic amidation of **1b**/**4b**' salt proceeded, whereas a proton source was necessary for the reaction of the quaternary ammonium salt (Schemes S1 and S4). Thus, *gem*-DBAs involve the acid/base "salt form" into the catalytic cycle, where the proton source might play a crucial role for the reaction progress. The distinctive reactivity of *gem*-DBAs would open prospects for catalyst modifications based on unconventional approaches in respect to their propensity as anion acceptors.



Scheme 4. Preliminary Attempts to Gain Mechanistic Insights

In summary, we have developed *gem*-DBAs as peptide condensation catalysts, which successfully connected a variety of functionalized *α*-amino acids with suppressed epimerization of electrophiles. The first example of catalytic dehydrative peptide synthesis at room temperature is also described. The catalytic coupling of peptide segments with appropriate protecting groups manifested the feasibility of solid-phase peptide synthesis under the *gem*-DBA catalysis. In addition, preliminary spectroscopic studies indicated an "anion-binding" nature of *gem*-DBA, which clearly differs from arylboronic acid catalysis. Further research to improve the catalytic activity of *gem*-DBAs, including catalyst modification and mechanistic studies, is actively ongoing in our laboratory, and the results will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

X-ray data file (CIF)

Experimental procedures and analytical data for all new compounds.

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Notes

The authors declare no competing financial interests.

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(12) 5 Å MS provided the better result than 4 Å and 3 Å MS, see Table S2.

(13) For a detailed investigation of counteranion effects, see Table S3, Scheme S1 and Scheme S2.

(14) The HCl salts were fully neutralized upon treatment with 5 Å MS (without catalyst), while no conversion from the other salts (e.g. HBr, HNO_3, HOTs). See also ref. 6l, 7c, 19, and Scheme S3.

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(20) **4a** (HCl salt) also underwent a slight racemization under the same conditions with full neutralization. For a detailed investigation, see Scheme S3.

(21) For detailed NMR and ESI-MS studies, see the Supporting Information.

(22) The crystal twinning occurred with *cis*-**D'** likely due to the axial chirality. For the details of X-ray structure, see the Supporting Information.

(23) All levels of DFT calculation performed gave 8.5~9.3 kcal/mol lower energy values for *cis*-**D'** than for *trans*-**D'**. For the details of calculations, see the Supporting Information.

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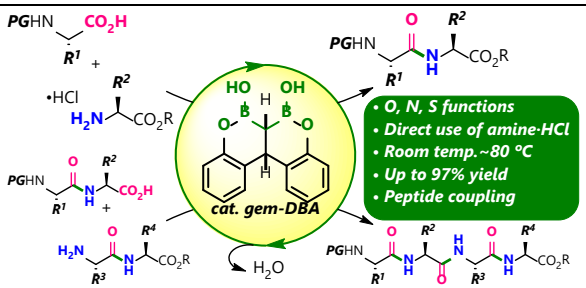

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