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FEATURE ARTICLE

Amide bond formation: beyond the dilemma between activation and racemisation

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The development of methods for amide bond formation without recourse to typical condensation reagents has become an emerging research area and has been actively explored in the past quarter century. Inspired by the structure of vitamin B_{12}, we have developed a metal-templated macrolactamisation that generates a new wave towards classical macrolactam synthesis. Further, distinct from the extensively used methods with condensation reagents or catalysts based on catalyst/reagent control our metal-catalysed methods based on substrate control can effectively address long-standing challenges such as racemisation in the field of peptide chemistry. In addition, the substrate-controlled strategy demonstrates the feasibility of "remote" peptide bond-forming reaction catalysed by a metal–ligand complex. Moreover, an originally designed hydrosilane/aminosilane system can avoid not only racemisation but also unnecessary waste production. This feature article documents our discovery and application of our original approaches in amide bond formation.

1. Introduction

In the realm of chemical and biological synthesis, our ability to form C–N bonds remains an important endeavour with tremendous impact, as relevant as the formation of C–C bonds. In particular, amide bond formation is significantly important to form lactams and peptides in a wide range of fields such as natural product synthesis such as proteins, material development, and drug discovery.[1]

Lactams are among the most important skeletons in drug design and material synthesis. In particular, *β*-lactams such as penicillins and cephalosporins are widely used as representative antibiotics around the world.[2] *ε*-Caprolactams and lacrolactam are well known to be essential raw materials for nylons.[3] In addition, cyclic peptides recently are attracting increasing attention as biologically interesting lactams.[1e,1i,1l] They are usually synthesised by intramolecular dehydrative condensation of an amino group with a carboxyl group under acidic conditions or using condensation reagents in a highly dilute solvent,[4] but other methods such as Beckmann rearrangement[5] and Schmidt reaction[6] also widely used. However, considerable room for innovation exists in macrolactamisation.

Peptides are usually synthesised using classical condensation reagents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and *N*,*N*′-dicyclohexylcarbodiimide (DCC).[7] Since Fischer successfully synthesised an 18-residue peptide composed of Gly and L-Leu in 1906 by classical condensation techniques,[8] numerous condensation reagents that activate carboxylic acids for formation of amide bonds have been designed, including carbodiimides, acylazoles, and phosphonium/aminium/uronium salts.[7] In parallel, a variety of protecting groups for amines have been developed.[9] Especially the appearance of Boc, Cbz, and Fmoc groups has led to dramatic progress enhancing the efficiency of peptide synthesis, leading to the invention of solid-phase peptide synthesis (SPPS) by Merrifield.[10] With growing attention towards biologically active peptides as drug candidates due to their low toxicities and high specificities towards targeted proteins superior to those of classical small molecule drugs (i.e., <500 Da),[11] these condensation reagents are currently indispensable to modern peptide synthesis paradigms. However, racemisation *via* direct enolisation or oxazolone formation has remained a long-standing challenge in peptide synthesis (Figure 1).[7d,12] Further, the use of stoichiometric equivalents of the condensation reagents generates a considerable amount of waste products.[13] To make matters worse, it has recently been revealed that some of the useful condensation reagents can cause severe allergic reactions.[14] To achieve safe and environmentally friendly peptide synthesis,[15] a number of challenges need to be addressed.

This report begins with macrolactamisation using boron reagents as templates and progresses sequentially to catalysis of amide synthesis, and finally describes our efforts towards a game change from catalyst/reagent- to a substrate-controlled

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strategy in peptide synthesis that we have investigated over the last five years.

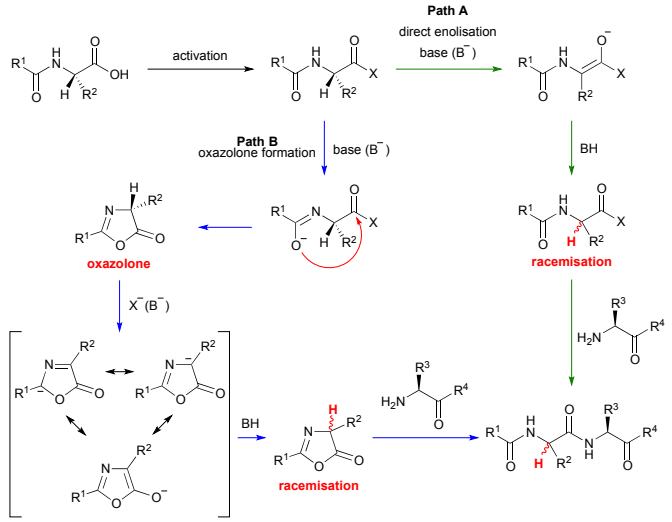


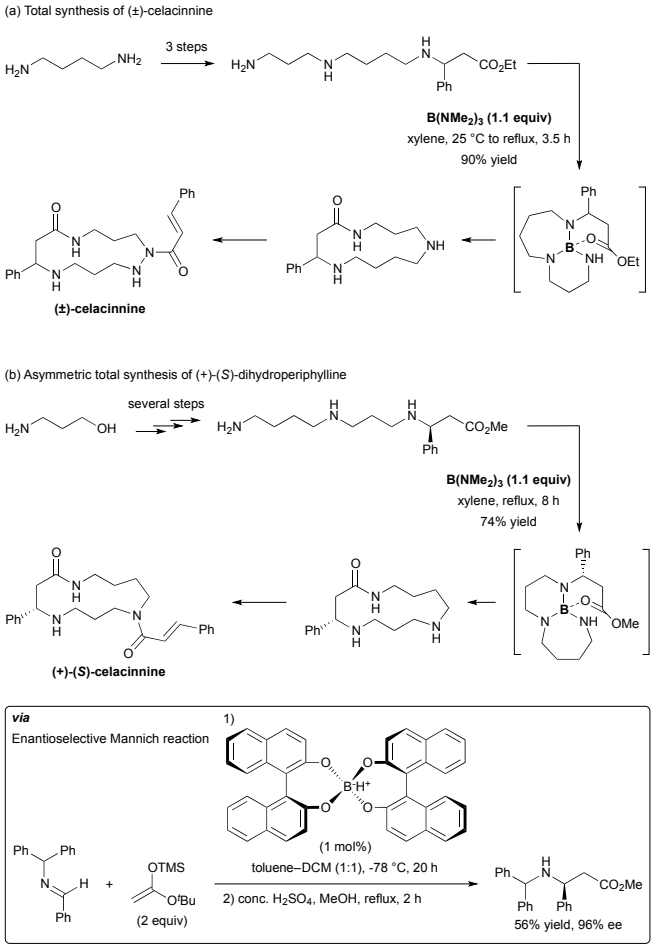
Figure 1 Racemisation mechanism. Path A: direct enolisation (green line). Path B: oxazolone formation (blue line).

2. Amide bond formation using boron-based reagents/catalysts

2.1 Boron-templated macrolactamisation and application for the synthesis of natural products

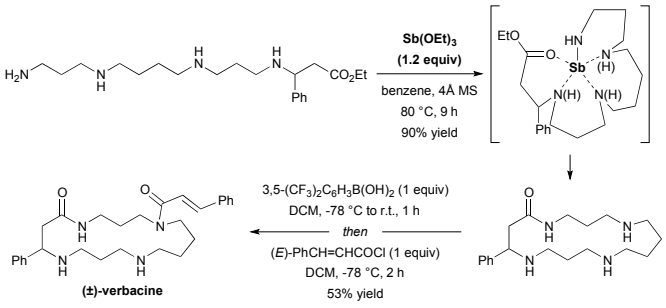
Macrolactams can be ubiquitously found in a broad variety of bioactive natural products[16] and cyclic peptides.[1b] Typical methods for the linkage employ stoichiometric quantities of condensation reagents under high-dilution conditions.[4] Beckmann rearrangement,[5] Schmidt reaction,[6] and iodolactamisation[17] are also highly reliable methodologies and still in the forefront in the construction of lactam skeletons. We have demonstrated elaboration of the 13- and 17-membered ring of spermidine alkaloids *via* boron-templated macrolactamisation inspired by a metal-templated strategy for a direct closure of the macrocyclic rings in Eschenmoser's vitamin B_{12} synthesis.[18]

Initially, we focused on the synthesis of (±)-celacinnine containing a 13-membered ring system (Scheme 1a).[19] As a result of accumulating various studies, we found that lactamisation of the triamino ester, provided from the 1,4-diaminobutane in three steps, in the presence of boranetriamine serving as a template under reflux conditions followed by acylation using cinnamoyl chloride gave the desired lactam successfully. After this success, (±)-celallocinnine, (±)-celafutine, and (±)-celabenzine were subsequently synthesised. In addition, the boron-templated protocol can be successfully applied for the asymmetric synthesis of (+)-dihydroperiphylline *via* the preparation of (*S*)-methyl 3-(benzhydrylamino)-3-phenylpropionate from *N*-benzylidenebenzhydrylamine by highly enantioselective Mannich-type reaction with trimethylsilyl ketene acetal using a chiral Brønsted acid assisted chiral Lewis acid (BLA) followed by transesterification (Scheme 1b).[20]



Scheme 1 Boron-templated macrolactamisation for natural product synthesis.

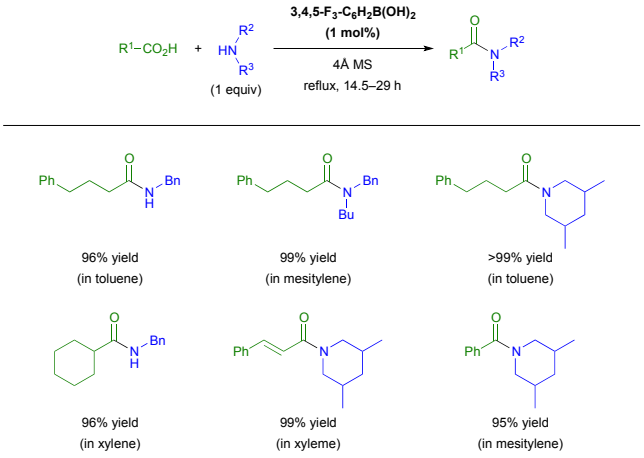
Furthermore, this metalloid-templated strategy for macrocyclisation is unsurprisingly extended to the total synthesis of (±)-buchnerine, (±)-verbacine, (±)-verbaskine, and (±)-verbascenine *via* antimony-templated macrolactamisation (Scheme 2).[21]



Scheme 2 Antimony-templated macrolactamisation for natural product synthesis.

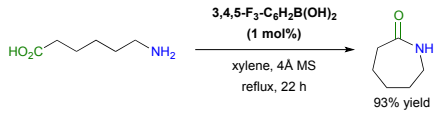
2.2 The beginning of catalysis for amide bond formation

It has been one of the most long-cherished challenges for chemists to develop a catalytic version that would form amide bonds directly from carboxylic acids and amines.[13a] In 1996, we succeeded in the direct condensation reaction between carboxylic acids and amines catalysed by 3,4,5-trifluorophenylboronic acid.[22] This is the first example of a catalytic amide bond formation reaction in synthetic chemistry. This catalytic dehydrative amidation reaction tolerates various structurally diverse carboxylic acids and primary and secondary amines with high yields (Scheme 3).



Scheme 3 Boronic-acid-catalysed dehydrative amidation reaction.

Further, this catalytic system is pleasingly applicable to the dehydrative lactamisation reaction of aminocarboxylic acids (Scheme 4).[22]



Scheme 4 Boronic-acid-catalysed dehydrative lactamisation.

A plausible mechanism proposed for the catalytic dehydrative amidation reaction is depicted in Figure 2. First, 3,4,5-trifluorophenylboronic acid catalyst and its trimeric anhydride species **A**[23,24] react with carboxylic acids to form reactive intermediate **B** *in situ*.[24] Then the intermediate **B** interacts with amines to afford the corresponding amides. Finally, the boronic acid catalyst is regenerated, thus completing the catalytic cycle.

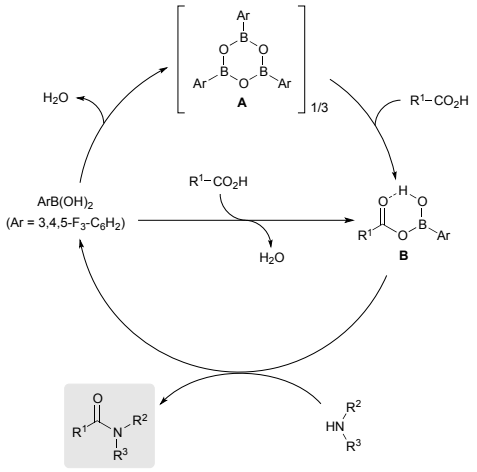


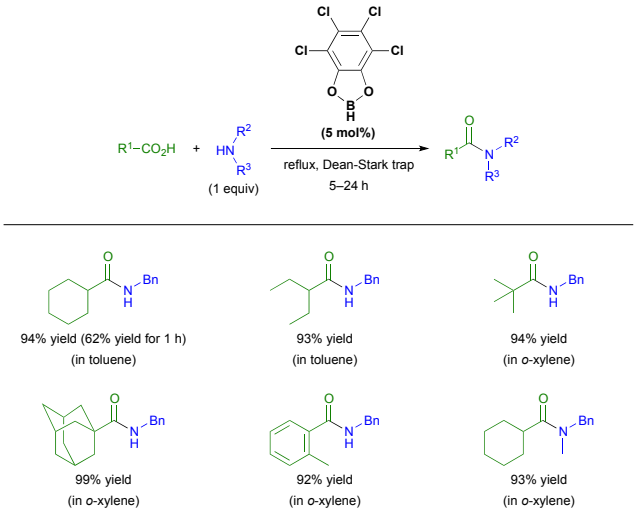
Figure 2 Plausible mechanism.

After our success, catalysts containing various metals and artificial organocatalysts have been designed for amide bond formation of amines with carboxylic acids or inactive esters.[25,26] However, boron-based catalysts modified from our catalyst are still the most utilised catalyst for the formation of amide bonds.[26]

2.3 Design of an efficient amide condensation catalyst

Molecular sieves are widely used to dry solvents. Particularly, the use of 3Å, 4Å, or 5Å molecular sieves is one of the easiest ways to remove water generated by direct condensation reaction such as esterification and amidation.[26a–c,26e,26f,26h,26j,26k,26o,27] On the other hand, a huge amount of molecular sieves would be required on an industrial scale, leading to significant waste production. To solve this challenge, the use of a Dean-Stark trap is clearly one of the most useful approaches.

We designed various amide condensation catalysts based on boronic acid and tested them in the assembly of cyclohexanecarboxylic acid and benzylamine as a model reaction with a Dean-Stark trap. When 5 mol% 2,3,4,5-tetrachlorocatecholborane was employed as a catalyst under azeotropic reflux conditions with a Dean-Stark trap for 1 h, the dehydrative amidation reaction proceeded successfully to afford the desired amide in the best (62%) yield (Scheme 5).[28] The successful use of sterically demanding carboxylic acids has remained a daunting challenge in amidation reaction.[29] The reaction conditions with 2,3,4,5-tetrachlorocatecholborane catalyst tolerate the use of various carboxylic acids and even sterically hindered carboxylic acids.

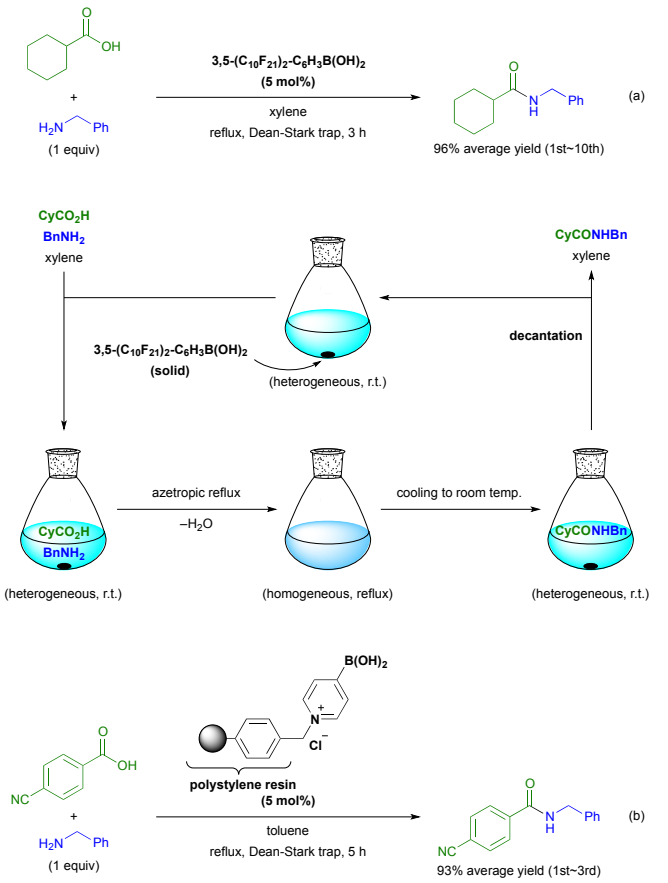


Scheme 5 Catecholborane-catalysed dehydrative amidation reaction.

2.4 Development of reusable boronic acid catalysts

Sustainable resource use is one of the most important challenges in modern chemistry. According to the twelve principles of green chemistry, reuse is an environmentally-friendly way to address negative impacts of growing amounts of waste, along with reduction and recycling.[30] As mentioned earlier, we attained a game change from the classical amidation system which requires excessive amounts of condensation reagents to a catalytic version that leads to a significant reduction in waste production.[22,25,26,28] Therefore, we next tried to develop reusable catalysts for the formation of amide bonds (Scheme 6).

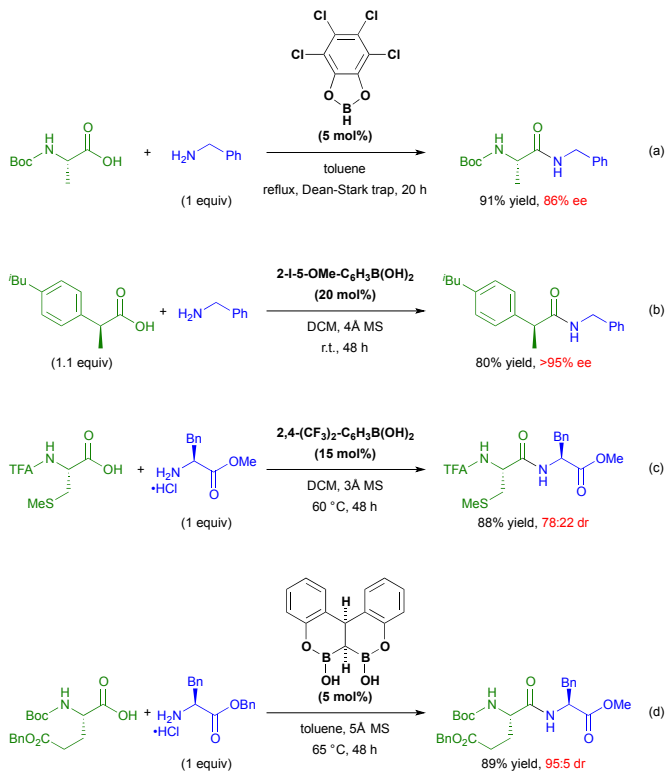
3,5-Bis(perfluorodecyl)phenylboronic acid catalyst is a green catalyst for the direct condensation reaction between carboxylic acids and amines due to the virtue of the strong electron-withdrawing effect and its notable features of the immobility in the fluorous recyclable phase of the perfluorodecyl group. Namely, after the reaction is completed, the residual catalyst can be easily reused by decantation of the reaction mixture without isolation by normal silica-gel chromatography, and the catalyst has been reused 10 times without any significant loss of activity (Scheme 6a).[31] Furthermore, *N*-polystyrene resin-bound 4-boronopyridinium salts as heterogeneous catalysts are also reusable for the amide condensation reaction and all of the reactions between 4-cyanobenzoic acid and benzylamine give excellent yields of the desired amide without any catalyst deactivation (Scheme 6b).[32]



Scheme 6 Dehydrative amidation reaction using reusable catalysts.

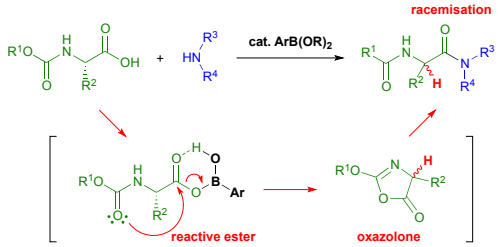
2.5 The dilemma between activation and racemisation (epimerisation)

As mentioned earlier, boronic acids and their derivatives are recognised as the most powerful catalysts for the formation of amide bonds.[22,26,31,32] However, several groups including us have occasionally observed racemisation during the amidation reactions using boron-based catalysts (Scheme 7a and 7b).[26b,32b,] To make matters worse, epimerisation problems have been frequently reported in peptide synthesis (Scheme 7c and 7d).[26j,26o]



Scheme 7 Racemisation (epimerisation) in dehydrative amidation reaction using boron-based catalysts.

This unexpected racemisation (epimerisation) can be explained as follows (Scheme 8). First, carboxyl groups of *N*-protected amino acids are activated by boronic acid or its derivative catalysts to form the corresponding reactive esters *in situ*. Then, the reactive esters are intramolecularly cyclised to form racemised oxazolone intermediates. Finally, ring-opening reaction of the intermediates affords the peptides with loss of stereochemical integrity. Namely, this racemisation (epimerisation) is thought to follow a similar process in a manner as that observed in classical peptide synthesis using condensation reagents such as EDC, DCC, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) and so on as shown Figure 1.[7d,12]

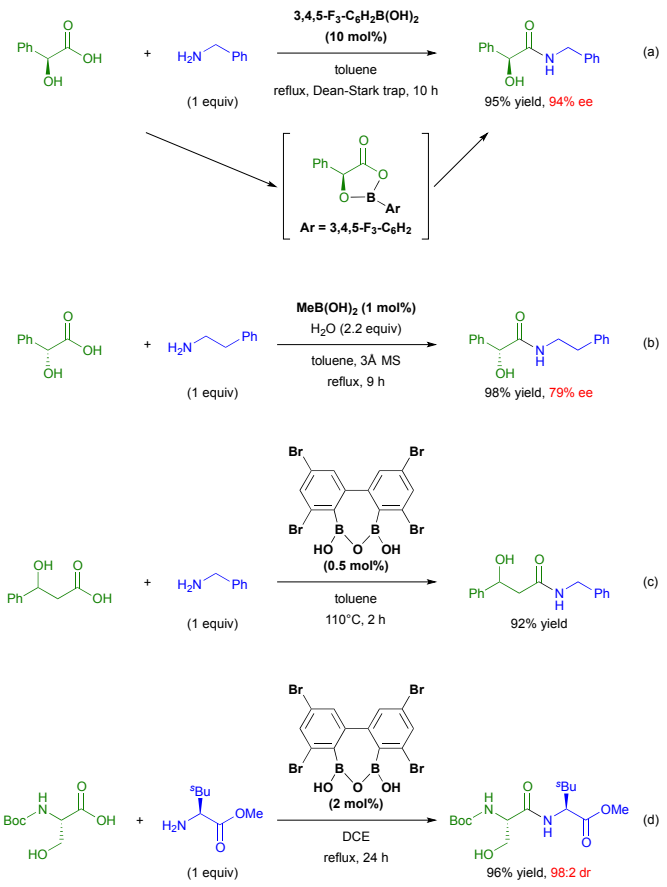


Scheme 8 Racemisation *via* oxazolene intermediates.

2.6 The first step towards racemisation-free catalytic peptide synthesis

Development of the catalytic method faced racemisation, which is one of the main challenges in peptide synthesis. In order to solve this racemisation challenge, we began to investigate an innovative conceptual methodology and hence developed a new hydroxy-group-directed peptide bond-forming reaction relying on boronic acid catalysis.

In 1996, we firstly reported a catalytic hydroxy-group-directed approach using 3,4,5-trifluorophenylboronic acid that acts as a highly efficient catalyst in the dehydrative amidation reaction between α-hydroxycarboxylic acids and benzylamine (Scheme 9a).[22] After our success, Ishihara and Shimada groups demonstrated catalytic dehydrative amidation reaction of α- and β-hydroxycarboxylic acids, respectively (Scheme 9b and 9c).[26d,26g,26l,26n,32b] However, these methods led to serious racemisation during the amidation of sensitive substrates such as α-aryl carboxylic acids. Recently, Shimada and co-workers demonstrated a catalytic hydroxy-group-directed peptide synthesis to expand their approach (Scheme 9d),[26m] however there still remains not only substrate limitations (Ser and Thr) but also potential risk of racemisation *via* oxazolone intermediates.



Scheme 9 Hydroxy-group-directed dehydrative amidation reaction using boronic acid catalysts.

Our new strategy for racemisation-free catalytic hydroxy-group-directed formation of peptide bonds is illustrated in Figure 3. First, boronic acid catalyst and its trimeric anhydride species **A**[23,24] react with *N*-Bn-*N*-OH-amino acid methyl esters to form reactive cyclic intermediate **B** *in situ*.[24] Amino acid methyl esters involving Bn and OH groups on amino groups can be prepared from readily available amino acid methyl esters.[33] Then the intermediate **B** interacts with amino acid esters serving as nucleophilic components to afford the corresponding peptides. Finally, the boronic acid catalyst is regenerated, thus completing the catalytic cycle. Advantageous features of the proposed strategy are the reactivity of intermediate **B** and high substrate tolerance of *N*-Bn-*N*-OH-amino acid methyl esters. The use of a Bn group instead of a carbamate essentially prevents the formation of oxazolones that lead to peptides with loss of stereochemical integrity. Furthermore, substrate limitation as shown in Scheme 9d can be avoided by placing the OH group as directing group on the nitrogen atom.

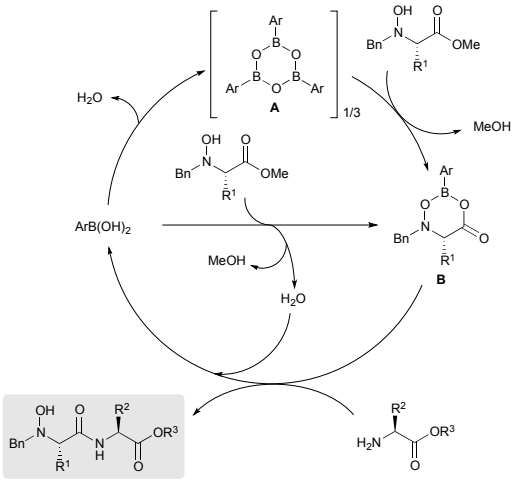
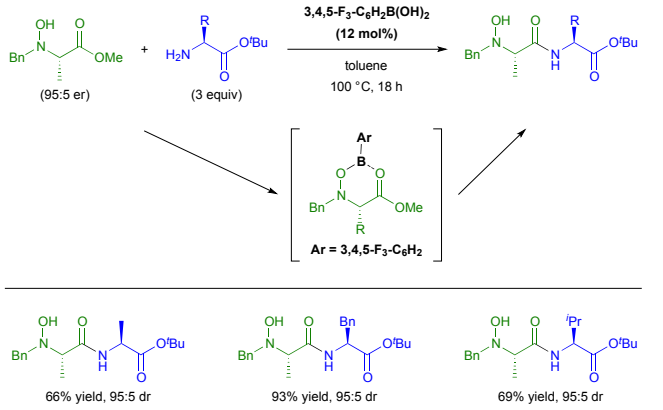


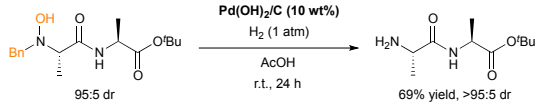
Figure 3 Non-racemisation strategy for boronic-acid-catalysed peptide synthesis.

With this working hypothesis, we screened various boronic acids and observed that the use of 3,4,5-trifluorophenylboronic acid effectively promotes the formation of a peptide bond between *N*-Bn-*N*-OH-L-Ala-OMe and H-L-Ala-O^{t}Bu[34] without any epimerisation problems in this catalytic cycle (Scheme 10).[35] Having identified conditions for the epimerisation-free conversion from the amino acid methyl esters serving as electrophilic components to the corresponding dipeptides, the effectiveness of our strategy was proved. This type of catalytic reaction is categorised as a substrate-controlled reaction and it is controlled by the inherent nature of the substrate.[36] In contrast to the substrate-controlled reactions, amidation reactions using condensation reagents and boronic acid catalysts shown in Figure 1 and Schemes 3–8, respectively, are called catalyst/reagent-controlled reactions and are controlled by the inherent nature of the catalyst/reagent.[37]



Scheme 10 Hydroxy-group-directed peptide bond-forming reaction using boronic acid catalyst.

Simultaneous cleavage of the hydroxy directing group and Bn protecting group were quantitatively facilitated by general palladium-catalysed hydrogenation under acidic conditions (Scheme 11).

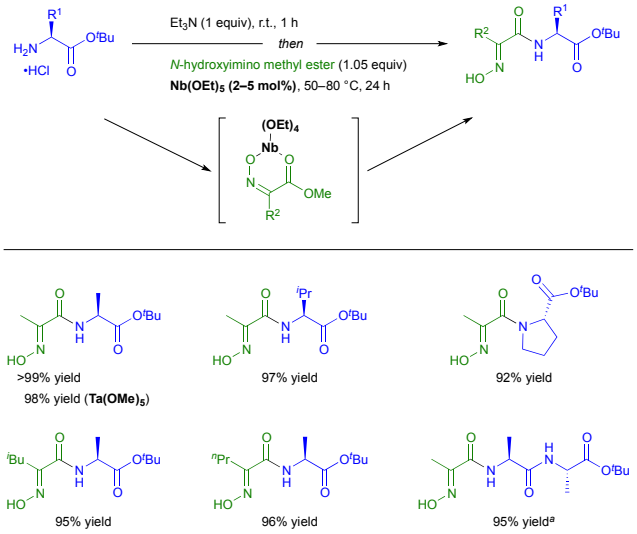


Scheme 11 Palladium-catalysed hydrogenation under acidic conditions.

3. Amide bond formation using a niobium catalyst

Another idea for peptide synthesis based on the substrate control concept is the use of *N*-hydroxy-*α*-imino esters serving as electrophilic components. The desired *N*-hydroxy-*α*-imino amides provided by the hydroxy-group-directed amidation reaction of *N*-hydroxyimino methyl esters with a series of amino acid *tert*-butyl esters,[34] generated by the *in situ* neutralisation of their HCl salts,[38] can be envisaged as an ideal precursor of peptides (Scheme 12).[39] An advantage of this strategy is easier preparation of electrophilic components compared with that in Scheme 10 because *N*-hydroxy-*α*-imino esters can be quantitatively synthesised by condensation reaction between readily available *α*-keto esters and hydroxylamine hydrochloride.[40] Thus, it is completely free from substrate limitations resulting from inconvenient preparation. In fact, when niobium ethoxide was chosen as a catalyst, *N*-hydroxy-*α*-imino amides bearing a broad variety of functional groups, such as hydroxy, ether, ester, amino, amide, and sulfide groups, were mostly obtained in >90% yields without formation of any by-products. Surprisingly, the

catalysis smoothly proceeded under solvent-free conditions which could also be valuable to reduce waste production.



Scheme 12 Solvent-free hydroxy-group-directed amidation reaction using niobium catalyst. [a]Neutralisation using Et_3N was omitted because H-L-Ala-L-Ala-O^{t}Bu was employed.

Despite these successes, reaction of *Z*-*N*-hydroxy-*α*-imino ester **A** containing a ^{t}Bu substituent at the *β*-position did not proceed in the presence of $Nb(OEt)_5$ or $Ta(OEt)_5$ catalyst due to steric hindrance between the ^{t}Bu and methoxy group, which inhibits transformation of the ***s-trans*-A** geometric isomer to ***s-cis*-A** orientation, necessary for efficient activation of the carbonyl group of **A** by these catalysts. To elucidate the reactivity patterns of the Nb–**A** complexes, calculations of the most stable conformations and relative free energy levels of complex **TS-1** and **TS-2** were performed at MP2/(6-31G(d), LANL2DZ) level confirming that **TS-2** is 2.07 kcal/mol higher in relative energy than **TS-1** (Figure 4).

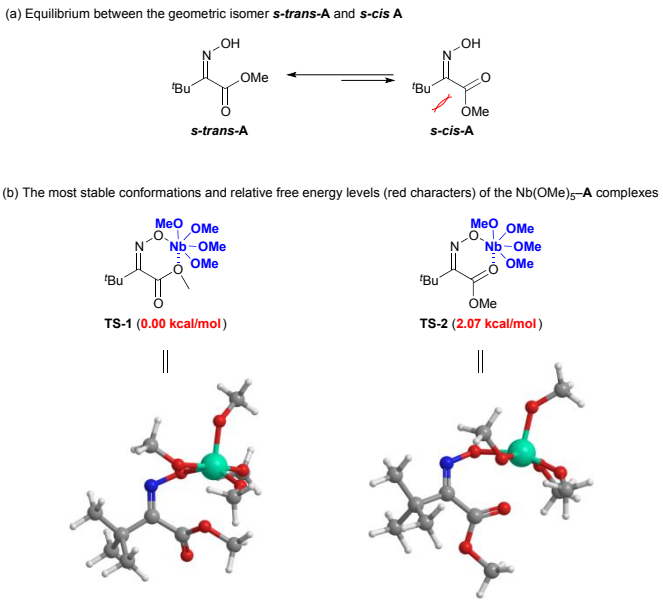
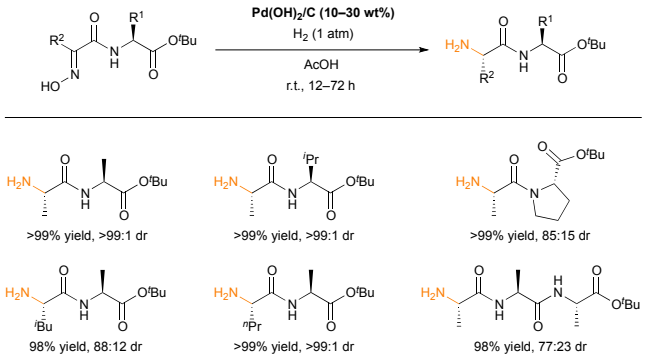


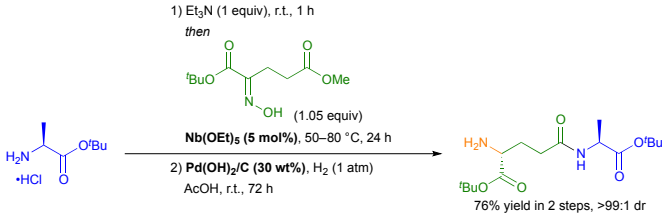
Figure 4 Computational studies.

To the best of our knowledge, only three papers and a patent have been published on catalytic enantioselective hydrogenation of *N*-hydroxy-*α*-imino esters to afford the corresponding chiral amino acid esters.[41] Unfortunately, we were not able to apply these hydrogenation systems for the transformation of *N*-hydroxy-*α*-imino amides into the corresponding peptides because they need to be carried out under high-pressure conditions. Therefore, we tested several known methods for the transformation of *N*-hydroxyimines into amines under mild conditions. When a general protocol in palladium-catalysed hydrogenation was conducted in acetic acid, di- and tripeptides with (*S*)-configuration at the new carbon centre were preferentially obtained in remarkably high yields and diastereoselectivities (Scheme 13).[39] Although we continued the evaluation of several acids instead of acetic acid and ligands to induce a new carbon centre with (*R*)-configuration in targeted di- and tripeptides, unfortunately this endeavor has yet to be successful.



Scheme 13 Diastereoselective hydrogenation using palladium catalyst under acidic conditions.

The application of this hydroxy-group-directed niobium catalysis can be extended to the formation of amide bonds using *N*-hydroxy-*β*- and *γ*-imino esters *via* 7- and 8-membered ring intermediates, respectively. Thus, palladium catalyst was also capable of enabling the corresponding *N*-hydroxy-*β*- and *γ*-imino amides to undergo diastereoselective hydrogenation under acidic conditions (Scheme 14).[39]



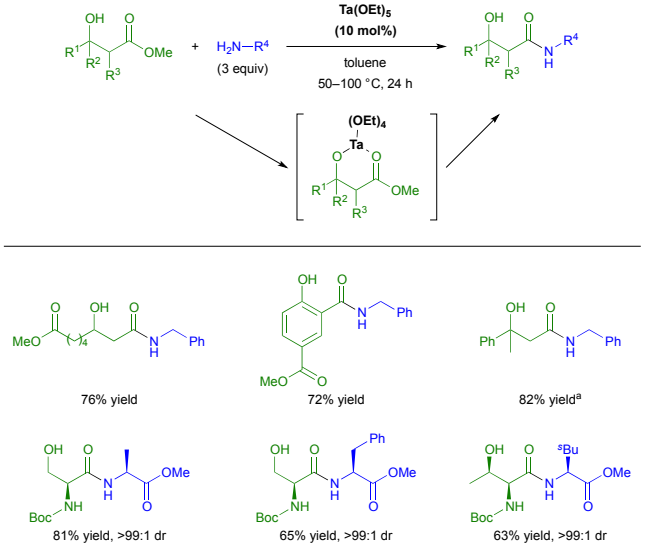
Scheme 14 Hydroxy-group-directed amide bond formation of *N*-hydroxy-*γ*-imino methyl ester using niobium catalyst.

4. Tantalum-catalysed peptide bond-forming reactions

4.1 Hydroxy-group-directed amidation by tantalum catalysis

Catalytic amidation reactions have recently become a valuable platform for the facile construction of peptide bonds. However, not only a protocol without risk of racemization but also even its methodology has never been established. In 2018, we made a significant advancement with hydroxy-group-directed techniques based on substrate control catalysed by 3,4,5-trifluorophenylboronic acid and niobium ethoxide to solve the challenges of racemisation resulting from formation of oxazolone intermediates as introduced in sections 2.6 and chapter 3, respectively.[35,39] But some challenges remain unresolved, e.g., inconvenience of the synthesis of *N*-Bn-*N*-OH-protected amino acid methyl esters and insufficient optical purities of them in the former approach, and diastereoselective hydrogenation of *N*-hydroxyimino amides in the latter approach. Furthermore, because the former protocol requires harsh reaction conditions, there is a concern that some of the amino acids may undergo racemisation *via* direct enolisation by 3,4,5-trifluorophenylboronic acid catalyst which is characterised by strong electron-withdrawing characteristics. Thus, we commenced development of a new catalytic reaction for peptide synthesis based on substrate control that not only completely suppresses the two racemisation pathways (oxazolone formation and direct enolisation)[7d,12] but also has both high substrate generality and practicality.

As a beginning, we sought relatively mild Lewis acid catalysts as an alternative to the boronic acid for hydroxy-group-directed amidation reaction. As a result of finding several candidates as Lewis acid catalysts among commercially available metal and metalloid reagents followed by optimisation of the reaction conditions using these catalysts, we found that tantalum ethoxide activates site-selectively and chemoselectively the carbonyl groups located at the appropriate distance from the hydroxy groups to smoothly convert *β*-hydroxy esters to the corresponding amides in moderate to high yields due to its strong affinity with the hydroxy groups. Moreover, the catalytic system can be applied to the peptide bond formation between Ser (Thr) and various structurally diverse amines (Scheme 15).[42]



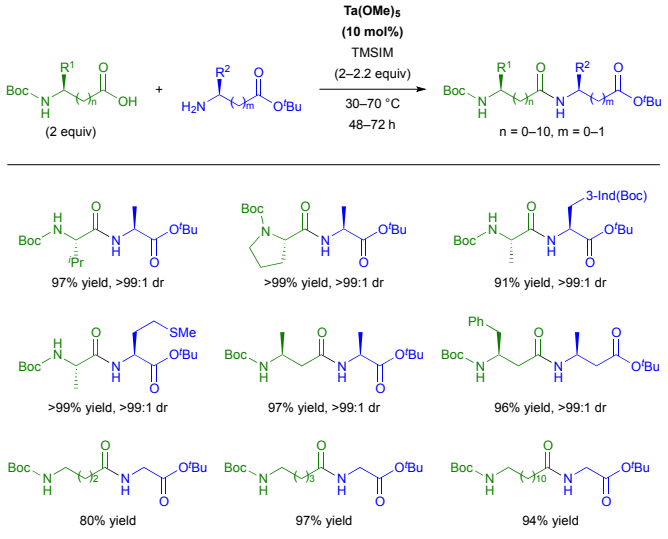
Scheme 15 Hydroxy-group-directed peptide bond-forming reaction using tantalum catalyst. [a]In the presence of methyl butyrate (1 equiv).

4.2 Carbonyl-group-directed peptide bond-forming reaction by tantalum catalysis

In anticipation of the strong affinity between Lewis acid catalysts, such as niobium, tantalum, and boronic acid catalysts, and the oxygen atoms of hydroxy groups, we next envisaged that a directing effect between Lewis acid catalysts and the carbonyl oxygen atoms on protecting groups such as Boc, Cbz, and Fmoc would enable a substrate controlled formation of peptide bonds between the amino group of one amino acid and the carboxyl group of another amino acid. This would be highly valuable because of high generality and practicality.

We first tested a series of solvents during the peptide-bond forming reaction of Boc-L-Ala-OMe with 3 equiv of H-L-Ala-O^{t}Bu[34] in the presence of 10 mol % $Ta(OEt)_5$ at 50–100 °C for 24 h, according to a previous study on a hydroxy-group-directed reaction shown in Scheme 15; however, only ~10% yield of Boc-L-Ala-L-Ala-O^{t}Bu was produced in less polar solvents such as toluene, *n*-hexane, *i*-Pr_2O, and $CHCl_3$. The use of highly polar solvents, such as DMF, DMA, and DMSO, completely shut down the formation of peptide bond between Boc-L-Ala-OMe and H-L-Ala-O^{t}Bu. This is probably due to the high affinity of $Ta(OEt)_5$ to these polar solvents. Surprisingly,

solvent-free conditions resulted in a notable improvement with 29% yield of Boc-L-Ala-L-Ala-O^{t}Bu. This indicates that the bond strength of the C=O–Ta bond formed between the Boc group and $Ta(OEt)_5$ is weaker than that of the O–Ta bond formed between the OH group in Ser (or Thr) and $Ta(OEt)_5$ as shown Scheme 15. Upon surveying a wide array of Lewis acid catalysts and extensively optimising the reaction conditions, we found that 10 mol% $Ta(OMe)_5$ enabled formation of a peptide bond between Boc-L-Ala-OMe with 2 equiv of H-L-Ala-O^{t}Bu without any solvents to furnish Boc-L-Ala-L-Ala-O^{t}Bu in 98% yields with >99:1 dr. Unfortunately, the protocol gave unsatisfied yields when *N*-protected amino acids bearing sterically hindered side chains were employed as electrophilic or nucleophilic components. To solve the substrate limitation, we chose trimethylsilyl (TMS) esters of *N*-protected amino acids serving as electrophilic counterpart because they possess potential leaving groups with lower pK_a values (TMSOH: 11, MeOH: 16)[43] and are easily prepared *in situ* by silylation of *N*-protected amino acids with *N*-(trimethylsilyl)imidazole (TMSIM). In fact, the yield of Boc-L-Leu-L-Ala-O^{t}Bu is increased from 77% to 97%. In addition, this protocol is more operationally beneficial because imidazole generated during the silylation can neutralise the amino acid ester HCl salts *in situ*.[38] With the optimised reaction conditions in hand, a range of dipeptides was obtained as expected in excellent yields without any problems.[44] Furthermore, the electrophilic component can be expanded to a variety of amino acid homologues (Scheme 16).[45]



Scheme 16 Solvent-free carbonyl-group-directed peptide bond-forming reaction using tantalum catalyst.

As shown in Figure 5a, a plausible mechanism is proposed that is initiated by the silylation of protected amino acids with TMSIM, and simultaneously the generated imidazole neutralises amino acid ester HCl salts (mostly; X = O^{t}Bu) serving as nucleophilic counterparts. Next, carbonyl oxygen atoms on the protecting groups, which are more Lewis basic oxygen atoms,[46] preferentially interact with $Ta(OMe)_5$ catalyst. Concurrently, a cyclic transition state is formed to selectively activate the silyl ester moieties when they are available by proximity to coordinate with $Ta(OMe)_5$ catalyst. The resulting cyclic intermediates facilitate formation of peptide bonds with amino acid esters serving as nucleophilic counterpart. Of most importance is an oxazolone intermediate, which is a major cause of racemisation, is effectively blocked by the formation of a cyclic transition state.

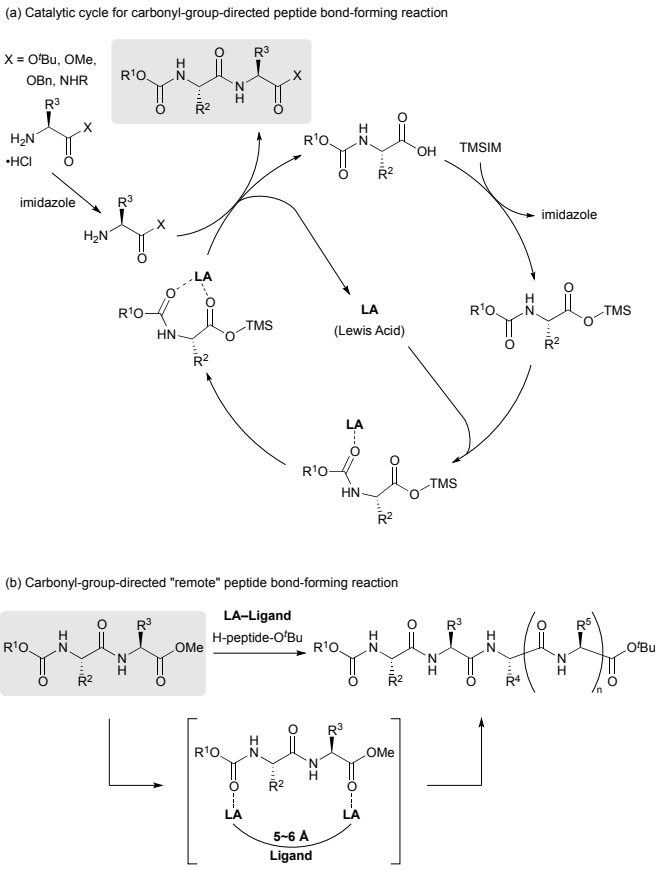
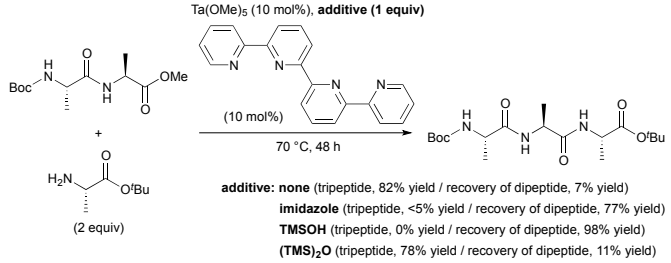


Figure 5 Strategies for carbonyl-group-directed peptide bond formation.

Although step-by-step approaches for peptide synthesis may be suitable for some peptides, the synthesis of long peptides and proteins would most often benefit from a one-pot approach.[47] As mentioned in Scheme 16, we are now able to obtain the desired dipeptides without racemisation by the successful development of carbonyl-group-directed catalysis based on substrate control.[44,45] We next envisaged that the carbonyl-group-directed strategy might be suitable for oligopeptide synthesis in one-pot. Hence, we tried a one-pot synthesis of tri- and tetrapeptides by carbonyl-group-directed "remote" peptide bond-forming reaction using tantalum–ligand catalysts.

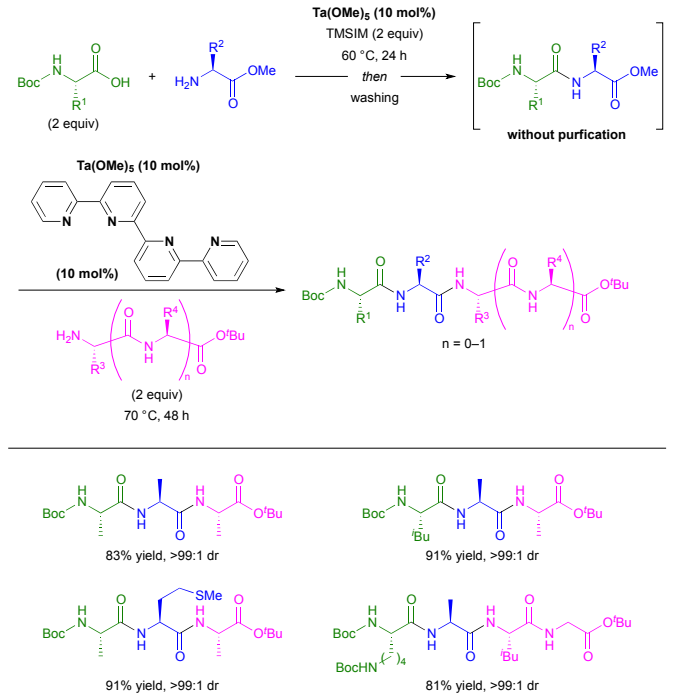
The key to success of this research is a catalyst that can activate esters located relatively far from the carbonyl group in *N*-protecting

groups such as Boc, Cbz, and Fmoc. Namely, the development of a suitable ligand that can bridge the two carbonyl groups is highly desirable (Figure 5b). Upon screening of several bidentate and tetradentate ligands with $Ta(OMe)_5$ for the coupling reaction of Boc-L-Ala-L-Ala-OMe with H-L-Ala-O^{t}Bu, we found that tetrapyridyl ligand[48] gave the best yield (82%) of the desired tripeptide without epimerisation. This may be because the distance between the two carbonyl oxygen atoms (5~6 Å) coincides with that between the two tantalum atoms coordinated to the ligand. With these optimised reaction conditions in hand, catalytic one-pot synthesis of tri- to tetrapeptides was demonstrated. Unfortunately, this one-pot approach did not succeed because some by-products (probably imidazole or TMSOH) generated in the first catalytic peptide bond-forming reaction seemed to interfere with the second catalytic peptide bond formation. This hypothesis was partially supported by some investigations (Scheme 17).



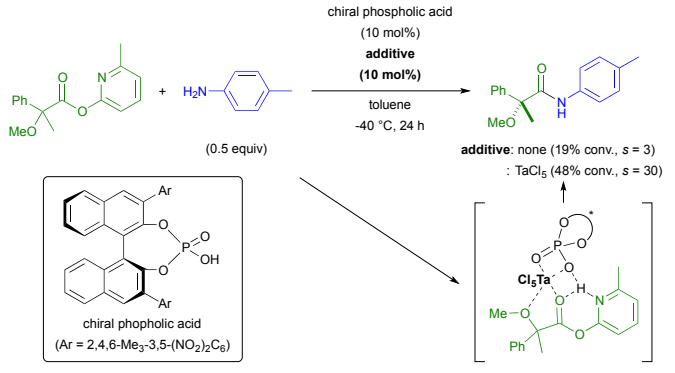
Scheme 17 Investigation for deactivation of tantalum catalysis.

Therefore, we gave up on the one-pot approach and decided to add a washing operation. In fact, when washing with water was performed after the first reaction, the subsequent reaction proceeded smoothly and gave the desired oligopeptides in high yields without any trouble (Scheme 18).[44]



Scheme 18 Solvent-free carbonyl-group-directed "remote" peptide bond-forming reaction by tantalum–ligand catalysis.

Surprisingly, the outstanding directing effect of the tantalum catalysts on oxygen-containing functional groups was also found to contribute to the remarkable improvement of the *s* factor in the chiral phosphoric-acid-catalysed kinetic resolution *via* amide bond formation and this synergistic catalysis using Lewis and Brønsted acids gave the desired amide having a chiral quaternary carbon centre at the *α*-position with 48% conversion yield and a selective factor of 30 (Scheme 19).[49]

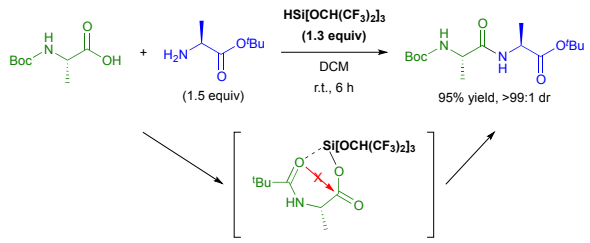


Scheme 19 Effect of tantalum catalysts in the chiral phosphoric-acid-catalysed kinetic resolution.

5. Aminosilane-catalysed peptide bond-forming reactions

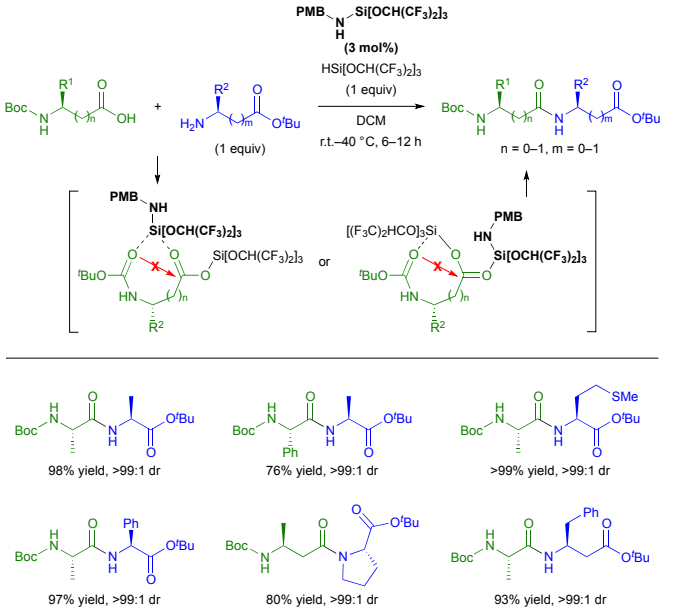
From the outset, we recognised that economical use of raw materials would be necessary to not only realise a sustainable resource use but also to build an eco-friendly society. In the process of our energetic exploration of substrate-controlled peptide synthesis, we have successfully demonstrated that the metal catalysts such as niobium and tantalum catalysts promote efficiently peptide bond formation without racemisation. However, these metals are not only rare metals but also expensive. Likewise, most emerging catalyses for formation of peptide bonds also depend on rare metals.[25] On the other hand, silicon is the second most abundant element in the Earth's crust after oxygen.[50] Therefore, there is no doubt that the effective use of inexpensive and abundant silicon resources is advantageous from the perspective of sustainable chemistry.[13] Thus, we began our studies by developing new silicon-based condensation reagents and catalysts for peptide bond formation.

When exploring some commercially available as well as our originally developed hydrosilane reagents as silicon-based condensation reagents in the reaction of Boc-L-Ala-OH with 1.3 equiv of H-L-Ala-O^{t}Bu,[34] the use of HSi[OCH(CF$_3$)$_2$]$_3$ inspired by Mukaiyama's investigations[51] furnished Boc-L-Ala-L-Ala-O^{t}Bu in the best yield without by-products (Scheme 20).[52] The reaction completely suppressed unwanted racemisation resulting from formation of oxazolones because it is preferably passed through a relatively stable 7-membered ring transition state.



Scheme 20 HSi[OCH(CF$_3$)$_2$]$_3$-mediated peptide bond-forming reaction.

Furthermore, we found that 3 mol% PMBNHSi[OCH(CF$_3$)$_2$]$_3$ catalyst enabled efficient formation of an amide bond without loss of stereochemical integrity while minimising the use of substrates (Boc-L-Ala-OH/H-L-Ala-O^{t}Bu/HSi[OCH(CF$_3$)$_2$]$_3$ = 1:1:1). To our delight, the optimised reaction conditions tolerated a number of amine and carboxylic acids bearing a broad variety of functional groups (Scheme 21).[52]



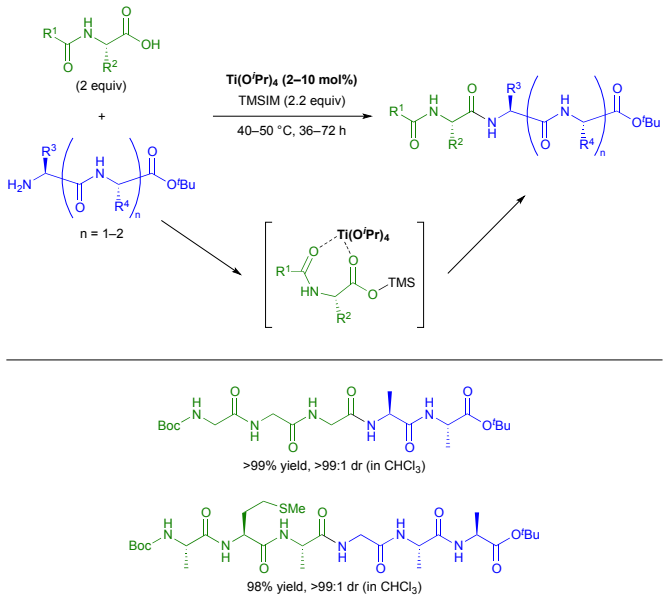
Scheme 21 Peptide bond-forming reaction using aminosilane catalyst.

6. Titanium-catalysed peptide–peptide segment coupling reactions

It is generally recognised that the classical liquid-phase peptide synthesis (LPPS) technologies are suitable for oligopeptides involving up to 10 amino acid residues.[13d,53] On the other hand, if a convergent method to chemically combine two peptides is developed, it will be possible to efficiently synthesise a variety of polypeptides and proteins by coupling between small peptides prepared in advance by the LPPS. Based on the background, several chemical ligations have been developed as a set of techniques for constructing polypeptides and proteins.[54] The most practical and robust method is native chemical ligation (NCL) pioneered by Kent and co-workers.[55] More recently, Bode and co-workers invented a notable chemical ligation system.[56] However, both strategies are still problematic with respect to generality because they require specific functional groups at the reaction site. Namely, the NCL requires unprotected Cys residues at the *N*-termini and thioesters or other highly active ester derivatives at the *C*-termini of the reacting peptides.[54] The Bode ligation requires the advance preparation of *α*-ketoacid residues and hydroxyamine residues at the *C*- and *N*-terminals of the corresponding peptides, respectively. Clearly, a method with high substrate generality allowing formation of a peptide bond between the amino group of one peptide and the carboxyl group of the other peptide without any prior chemical modification is more valuable. As mentioned above, we have showcased an innovative strategy based on substrate control for formation of peptide bonds, and tantalum alkoxides were found to be significantly effective for the racemisation-free synthesis of peptides involving a broad variety of amino acid residues *via* carbonyl-group-directed peptide bond formation. Therefore, we expected that the carbonyl-group-directed

system may ultimately provide opportunities for achieving peptide–peptide coupling.

As a typical example, we initially attempted a segment coupling reaction between Boc-Gly-Gly-Gly-OH with H-L-Ala-L-Ala-O^{t}Bu in the presence of TMSIM and catalytic amount of Ta(OMe)$_5$; consequently, the desired reaction was not demonstrated to work under the reaction conditions. To realise our expectations, a number of metal catalysts serving as a Lewis acid were evaluated, and we finally found that Ti(O^{i}Pr)$_5$ shows great adaptability in the coupling reaction, providing Boc-Gly-Gly-Gly-L-Ala-L-Ala-O^{t}Bu in quantitative yield without epimerisation. Besides this example, the reaction system also gave tetra- to hexapeptides in high yields with excellent diastereoselectivities (Scheme 22).[44] The success of our novel method in peptide–peptide segment coupling reaction leads to its prospective application in chemical ligation under SPPS as well as LPPS systems.



Scheme 22 Carbonyl-group-directed peptide–peptide segment coupling reaction using titanium catalyst.

Conclusions

The development and application of Lewis acid catalysts and condensation reagents for not only facilitating amide bond formation but also suppressing racemisation has been the major goal of our research in the synthesis of natural products and peptides. Boronic acid acceleration *via* formation of the reactive cyclic intermediates has enabled the development of many new boronic-acid-catalysed peptide bond-forming reactions. Tantalum and niobium catalysts have been instrumental in the development of racemisation-free peptide bond formation based on substrate control. Aminosilane catalyst has enabled not only the acceleration in silylation of carboxylic acids using HSi[OCH(CF$_3$)$_2$]$_3$ but also peptide synthesis with minimal substrate use (electrophile/nucleophile/silylating reagent = 1:1:1) and waste production (hydrogen gas and a siloxane). These methods have been applied in a number of peptide syntheses, proving their high practicality and functional group compatibility. Furthermore, we have investigated tantalum/tetrapyridyl-ligand-catalysed "remote" reaction and titanium-catalysed segment coupling reaction for peptide synthesis to demonstrate the robustness of our concept in terms of generality, utility, significance, and originality. These approaches for convergent peptide synthesis have successfully eliminated the inconvenience of purification operation and laborious prefunctionalisation at the mutual ligation junctions of peptides, respectively, which addresses the problems of step-by step processes of linear SPPS and LPPS.

We believe that the game change from catalyst/reagent- to substrate-controlled strategies would enable the discovery of many new and useful Lewis-acid-catalysed peptide bond-forming reactions. In fact, we have already started investigations on application of the presented substrate-controlled SPPS here to flow synthesis and LPPS, as well as several other new challenges, and interesting results are being obtained for each challenge. Although the discovery of boronic acid, niobium, tantalum, aminosilane, and titanium catalysts and the development of tetrapyridyl ligand for peptide synthesis is just a small step towards not only realizing the untapped potential of substrate-controlled peptide synthesis but also highlighting new challenges and issues as a synthetic strategy, this report provides an extensive guide to methods that can be used in the design of any amide and peptide synthesis for the foreseeable future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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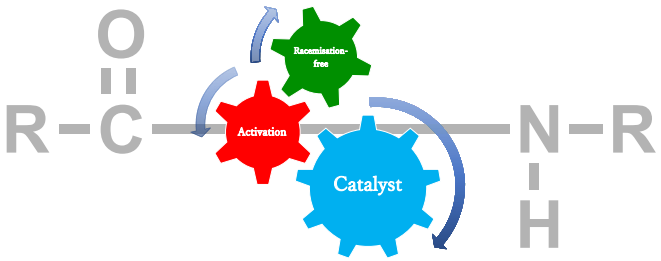
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