Article

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Substrate-Directed Lewis-Acid Catalysis for Peptide Synthesis

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Tantalum catalysis, Substrate-directed amidation, Solvent-free, Chemical ligation, Peptides, Protecting groups

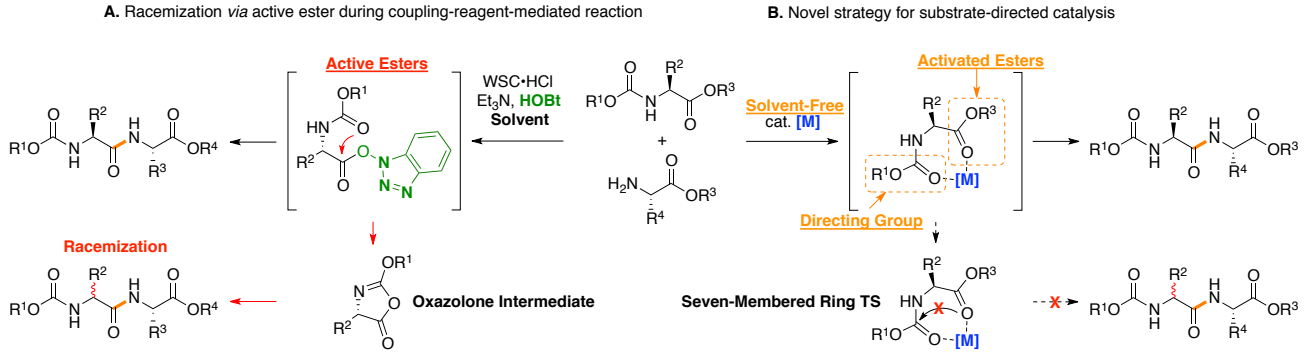
ABSTRACT: A Lewis-acid-catalyzed method for the substrate-directed formation of peptide bonds has been developed, and this powerful approach is utilized for the new "remote" activation of carboxyl groups under solvent-free conditions. The presented method has the following advantages: 1) the high-yielding peptide synthesis uses a tantalum catalyst for any amino acids; 2) the reaction proceeds without any racemization; 3) the new substrate-directed chemical ligation using the titanium catalyst is applicable to convergent peptide synthesis. These advantages overcome some of unresolved problems in classical peptide synthesis.

INTRODUCTION

In the current century, peptides are extensively exploited in the pharmaceutical, agricultural, food, and cosmetic industries.[1,2] Indeed, owing to their range of functionalities, low toxicities, and high specificities towards targeted proteins compared to those of classical small molecules (i.e., <500 Da), the global peptide therapeutics market is increasing in value annually by ~15%,[3] and is currently expected to reach ~ USD 50 billion by 2025.[4] To address the growing worldwide demand for peptides, dramatic technological innovation to current synthetic protocols is required in response to economic and environmental needs.

The classical approach to peptide synthesis constitutes the coupling reaction between amines and carboxylic acids. In the presence of a stoichiometric amount of a sophisticated coupling reagent, peptides are prepared in a stepwise manner by reaction with the amino functional group of the amino acid.[5] Utilizing well established solid-phase peptide synthesis,[6] the peptide is constructed by attaching a terminal amino acid to a resin bead, and adding the subsequent amino acid residues in a sequential manner, with the residual by-products being washed out at each step. With these processes, producing peptide products requires a huge volume of organic solvent and water in addition to substantial quantities of coupling reagent causing significant negative environmental impact.[7–9] Giving these circumstances, investigation of various catalytic routes to peptide bond formation has been stimulated. Indeed, since our initial report of a boron-based catalyst for the amidation between carboxylic acids and amines,[10] a number of catalytic approaches have been reported.[11–13] All of these classical and modern amidation processes are based on activation of the carboxylic acid moiety, which unfortunately leads to issues of racemization of the produced peptides (Scheme 1A).[5] Once racemization occurs, tedious purification becomes unavoidable. In particular, during solid-phase peptide synthesis, the peptide must be cleaved from the resin beads for purification and then linked again with beads for the next reaction, which creates a major expense and other troublesome issues for the synthesis. As an alternative, Kent's native chemical ligation (NCL) allows the coupling of two peptides by the reaction of α-thioester with Cys-peptides.[14,15] This pioneering method facilitates preparation of large peptides by chemical synthesis. Unfortunately, however, the Kent procedure requires specific amino acid termini. If any amino acid terminus could be used, chemical ligation would open an entirely new entry to peptide synthesis. Not only large peptide synthesis, but also smaller peptide synthesis could be simplified by general chemical ligation using a convergent synthesis approach. Thus, considerable room for improvement exists for avoiding environmental degradation, purification involving racemization, and non-convergent linear peptide synthesis. Herein we are pleased to address some of these long-standing issues of peptide synthesis using substrate-directed Lewis acid catalysis.

Scheme 1. Formation of Peptide Bonds

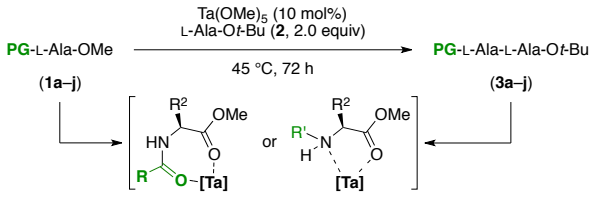


RESULTS AND DISCUSSION

Novel Strategy for Substrate-Directed Lewis-Acid Catalysis for Peptide bonds. Substrate-directed chemical reactions are undoubtedly among the most powerful tools in modern organic chemistry.[16,17] Our early efforts toward peptide bond formation focused on the directing effects of hydroxy[18] and oxime groups[19] in amino acid methyl esters, as such systems resolve the issues of waste production and racemization; however, this approach is unfortunately limited in substrate scope. Therefore, we examined catalytic systems directed by the widely used carbonate protecting groups of simple amino acids.[20] Our envisaged strategy is outlined in Scheme 1B. Initially, the Lewis basic carbonyl oxygen atoms on Boc, Cbz, and Fmoc groups preferentially interact with the Lewis acid catalyst. Subsequently, when a methyl ester moiety is available by proximity to coordinate with the Lewis acid catalyst, the ester is selectively activated. Most importantly, racemization *via* an oxazolone intermediate is blocked by the formation of a seven-membered transition state. Finally, the amino group of the nucleophilic reaction partner site-selectively approaches the activated methyl ester forming the desired peptide bond. We expected the new process to rely on the directing effects of carbonate protecting groups to promote peptide bond formation between the amino moieties and the inactive ester groups of the amino acids while avoiding long-standing stereochemical problems.

Tantalum-Catalyzed Peptide Bond-Forming Reactions. To verify the feasibility of our proposed strategy, we first tested a series of solvents during the peptide-bond-forming reaction of Boc-L-Ala-OMe **1a** with 3.0 equivalents of L-Ala-O*t*-Bu **2** in the presence of 10 mol% $Ta(OEt)_5$ at 50–100 °C for 24 h, according to a previous report on a hydroxy-group-directed reaction involving L-Ser and L-Thr;[18] however no or very trace amount of Boc-L-Ala-L-Ala-O*t*-Bu **3a** was obtained in common solvents, such as toluene, DMF, or Et_2O. When the reaction was repeated in non-polar aliphatic solvents, such as *n*-pentane or *c*-hexane, **3a** was produced in slightly improved yields of ~10%. Surprisingly, the absence of a solvent resulted in a notable improvement with 29% yield of **3a**. We expected that the weak $C{=}O^{+}{-}Ta$ bond formed between the Boc group and $Ta(OEt)_5$ would be disrupted easily, compared to that of the O–Ta bond formed between the OH group and $Ta(OEt)_5$. After identifying a metal catalyst and extensively optimizing the reaction conditions (Tables T1 and 2, see supporting information), we found that the solvent-free catalytic assembly of **1a** and **2**, which was prepared by carefully neutralizing its HCl salt with a weakly basic anion exchange resin, such as Amberlyst™ A21[21] or DIAION™ WA30, proceeded effectively at 45 °C in the presence of 10 mol% $Ta(OMe)_5$ to furnish **3a** in 98% isolated yield with a >99:1 enantiomeric ratio (er) and >99:1 diastereomeric ratio (dr) (entry 1 of Table 1). As expected, the reaction does not proceed in the absence of $Ta(OMe)_5$ (entry 2). In addition, this catalysis facilitates the use of the HCl salts of amino acid esters with Et_3N in the presence of $Ta(OMe)_5$, which is beneficial, as these salts allow overwhelmingly longer storage without racemization or polymerization; they are also significantly easier to handle than their free amines.[22] Hence, the free amine provided by the *in situ* neutralization of L-Ala-O*t*-Bu·HCl with Et_3N coupled smoothly with **1a** to afford **3a** in 92% yield with >99:1 er and >99:1 dr (entry 3). A glove box is not indispensable for preparation of this reaction (96% yield with >99:1 er and >99:1 dr, entry 4). However, since amino acids and $Ta(OMe)_5$ potentially adsorb atmospheric moisture easily, unexpected hydrolysis of the catalyst by ambient moisture may impair the reproducibility of the reaction. The use of microwave irradiation dramatically shortened the time required to form the peptide bond (92% yield with >99:1 er and >99:1 dr, entrie 5). Entries 1, 3, and 4 reveal that the minor diastereomer is not the expected Boc-D-Ala-L-Ala-O*t*-Bu,[5] (from racemization at the *N*-terminal L-Ala residue of **3a**) but surprisingly Boc-L-Ala-D-Ala-O*t*-Bu, in which the *C*-terminal L-Ala residue of **3a** was racemized. In order to further examine this occurrence, **3a** was employed under the same reaction conditions, and racemization was not observed by HPLC. In addition, GC revealed that **2** does not racemize during the neutralization of L-Ala-O*t*-Bu·HCl with the basic anion exchange resins (99.8:0.2 er was obtained after trifluoroacetylation of **2**,[23] see supporting information). In contrast, we clarified by GC that **2** was only slightly racemized by heating (99.5:0.5 er was obtained after trifluoroacetylation of **2**), and the presence of $Ta(OMe)_5$ slightly accelerated its racemization (97.9:2.1 er was obtained after trifluoroacetylation of **2**). Whereas commonly used protecting groups for peptide synthesis, such as Cbz, Troc, and Alloc, were tolerated in this approach to give excellent yields of **3b**–**d** without any loss in stereochemical integrity or additional side-product formation (entries 6–8), replacement of these carbonate protecting groups with Fmoc or Pht led to significantly reduced yields due to the formation of side-products by the unexpected deprotection of **1e** and **1g** (entries 9 and 11). To reduce the reaction time, elevated temperatures (i.e., 100 °C) were investigated, but significantly lower yields of **3b**–**d** were obtained, as compounds **1b**–**d** were converted into their corresponding dipeptides with the concomitant release of phenoxy, trichloroethoxy, and allyloxy anions from **1b**–**d**, respectively; **1c** was particularly sensitive to the reaction temperature, it gave **3c** in only 1% yield at 60 °C. These results indicate that the carbonate protecting groups act as directing groups, as shown in Scheme. 1B. The Bz and Ts groups present in **1f** and **1h** also acted as good directing groups to produce **3f** and **3h** in quantitative yields (entries 10 and 12). Impressively, reactions with **1i** and **1j** provided **3i** and **3j**,[24] respectively, in moderate yields with no racemization under suitable conditions, despite the absence of the carbonyl oxygen atoms of the protecting groups (entries 13 and 14). These results indicate that the nitrogen atoms of **1i** and **1j** can also act as directing groups. However, side reactions were observed when the reaction temperature was raised to 70 °C in an attempt to improve the yields of **3i** and **3j**. In contrast, electrophilic Boc-L-*β*-amino acid methyl esters, such as Boc-L-*β*-Ala-OMe and Boc-L-*β*-HomoAla-OMe, failed to provide the desired peptides in the presence of this catalyst because of the unstable eight-membered ring transition states. As conditions for removing these protecting groups are well-established,[20,25] the Boc, Cbz, Bz, and Bn moieties were smoothly deprotected to provide L-Ala-L–Ala-O*t*-Bu **4** in >90% yields using 4*N* HCl/1,4-dioxane for the cleavage of the Boc group,[26] Pd-catalyzed hydrogenation for the deprotection of the Cbz and Bn groups, and the Meerwein reagent for the removal of the Bz group.[27]

Table 1. Examining Various Protecting Groups as Directing Groups for Peptide Bond Formation.

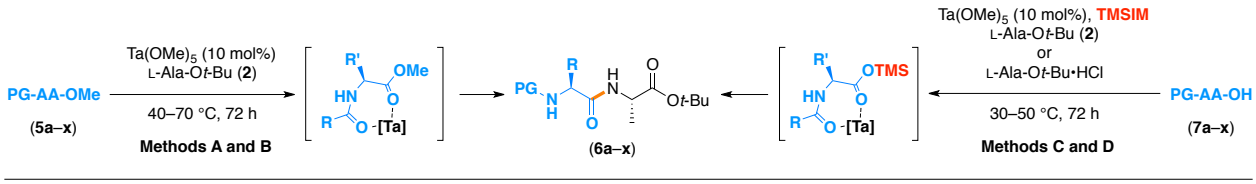


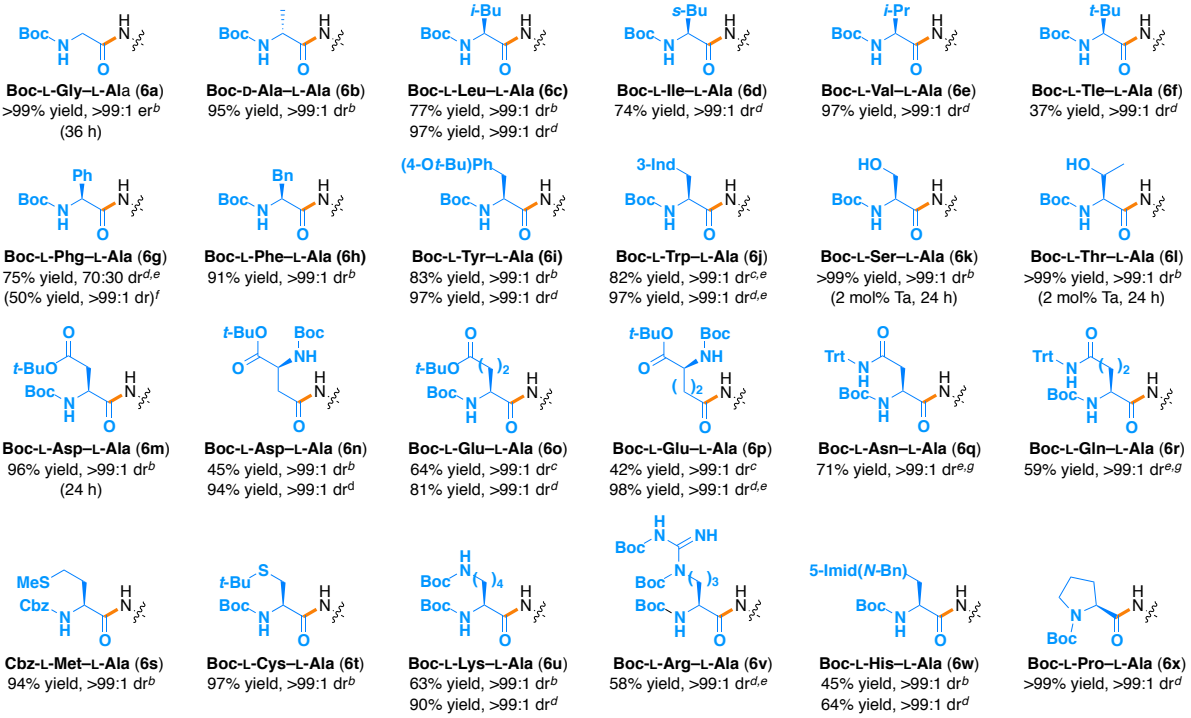
entry	protecting group (PG)	product	yield (%)	dr[a]
1	Boc	**3a**	98	>99:1
2[b]	Boc	**3a**	0	nd
3[c]	Boc	**3a**	92	>99:1
4[d]	Boc	**3a**	96	>99:1
5[e]	Boc	**3a**	92	>99:1
6	Cbz	**3b**	>99	>99:1
7[f]	Troc	**3c**	93	>99:1
8[g]	Aloc	**3d**	98	>99:1
9[h]	Fmoc	**3e**	0 (85)	nd (>99:1)
10	Bz	**3f**	>99	>99:1
11[g]	Pht	**3g**	10	>99:1
12[f]	Ts	**3h**	>99	>99:1
13[g]	Bn	**3i**	60	>99:1
14[g]	$NCCH_2$	**3j**	45	>99:1

[a]The drs of **3a**–**j** were determined by ^{1}H NMR. [b]In the absence of $Ta(OMe)_5$. [c]**2**·HCl and Et_3N (2.0 equiv) were used instead of **2**. [d]Without glove box. [e]Through the use of microwave irradiation for 24 h. [f]The reactions were carried out at room temperature. [g]The reactions were carried out at 60 °C. [h]The numbers in brackets are yield and dr obtained under the following reaction conditions: Fmoc-L-Ala-OH (2.0 equiv), **2**·HCl (1.0 mmol), $Ta(OMe)_5$ (10 mol%), TMSIM (2.0 equiv), 40 °C, 72 h.

We explored the versatility of our method under the optimized conditions using a wide array of amino acids as electrophilic coupling partners (Scheme 2). Most of the amino acids were successfully coupled, including *S*-functionalized amino acids **5s** and **5t**, which produced **6a**–**c**, **6h**–**p**, and **6s**–**u** in moderate to excellent yields. In particular, **6k**–**m** were obtained quantitatively at lower catalyst loadings (2.0 mol%) and/or over a shorter reaction time (24 h) because the secondary directing effect of the hydroxy group on Ser and Thr (**5k** and **5l**),[18] or the *tert*-butyl ester group at the *β*-position of Asp (**5m**), strongly supports these reactions by facilitating the formation of a six- or seven-membered transition state. In contrast, the presence of bulky side chains at the *α*-positions of amino acids, especially secondary alkyl groups, such as *s*-Bu in Ile, *i*-Pr in Val, and tertiary groups such as *t*-Bu in Tle, detrimentally affected the yields of these reactions (0–2% yields of **6d**–**f**). It is reasonable to assume that the inertness of **5d**–**f** under the $Ta(OMe)_5$-catalyzed conditions is due to steric hindrance between the bulky side chains of **5d**–**f** and the bulky Boc group, which hinders formation of the seven-membered transition state as outlined in Scheme 1B. Hence, silyl esters, namely Boc-L-Ile-OTMS, Boc-L-Val-OTMS, and Boc-L-Tle-OTMS, possessing potential leaving groups with lower pKa values (TMSOH: 11, MeOH: 16),[27] generated *in situ* from the corresponding carboxylic acids **7d**–**f** with 1-(trimethylsilyl)imidazole (TMSIM), at 50 °C were found to be exquisitely effective in the $Ta(OMe)_5$-catalyzed reaction, to give **6d**–**f** in yields of 37–97%, without loss in stereochemical integrity; **6d**–**f** did not form in the absence of $Ta(OMe)_5$ due to the immobility of the substrate-directed activation of the silyl esters. Silylating agents are known to activate amines[29] or carboxylic acids[30] in several amidation reactions; however, our method operates in a completely different manner to these processes. Our one-pot catalytic protocol with TMSIM was used to further improve the yields of **6g**, **6i**, **6j**, **6o**, and **6u**–**x**. In addition, this system satisfactorily enabled coordination with the carbonyl oxygen atoms on ester groups located at the *β*- and *γ*-positions, as well as those located at the *α*-positions of Asp and Glu, respectively, to afford **6n** and **6p** in moderate to high yields. As mentioned above, HCl salts of amino acids are preferable to the corresponding free amines because they are easier to handle and can be stored for long periods without polymerization and/or racemization. This one-pot protocol involving silyl esters is superior to the use of HCl salts of amino acids as nucleophilic counterparts, giving the desired dipeptides **6q** and **6r** in 71 and 59% yields, respectively, because the HCl salts of amino acids are neutralized in situ in the presence of imidazole. Fortunately, this one-pot protocol involving TMSIM and the HCl salts of amino acids dramatically improved the unresolved amidation of amino acids bearing Fmoc groups; Fmoc is the most used base-labile protecting group (85% yield and >99:1 dr, entry 9 of Table 1). The success of our novel method in LPPS leads to its prospective application in SPPS. In addition to the advantages of our method, most of the dipeptides obtained by the one-pot protocol could be isolated in high purity with only simple washing and extraction without column chromatography, since the reactions via silyl esters do not provide any side-reaction products. These advantages were used in the triply convergent synthesis depicted in Scheme 4B.

Scheme 2. Reaction Scope: Protected Amino Acid Methyl Esters (Highlighted in Blue)[a]

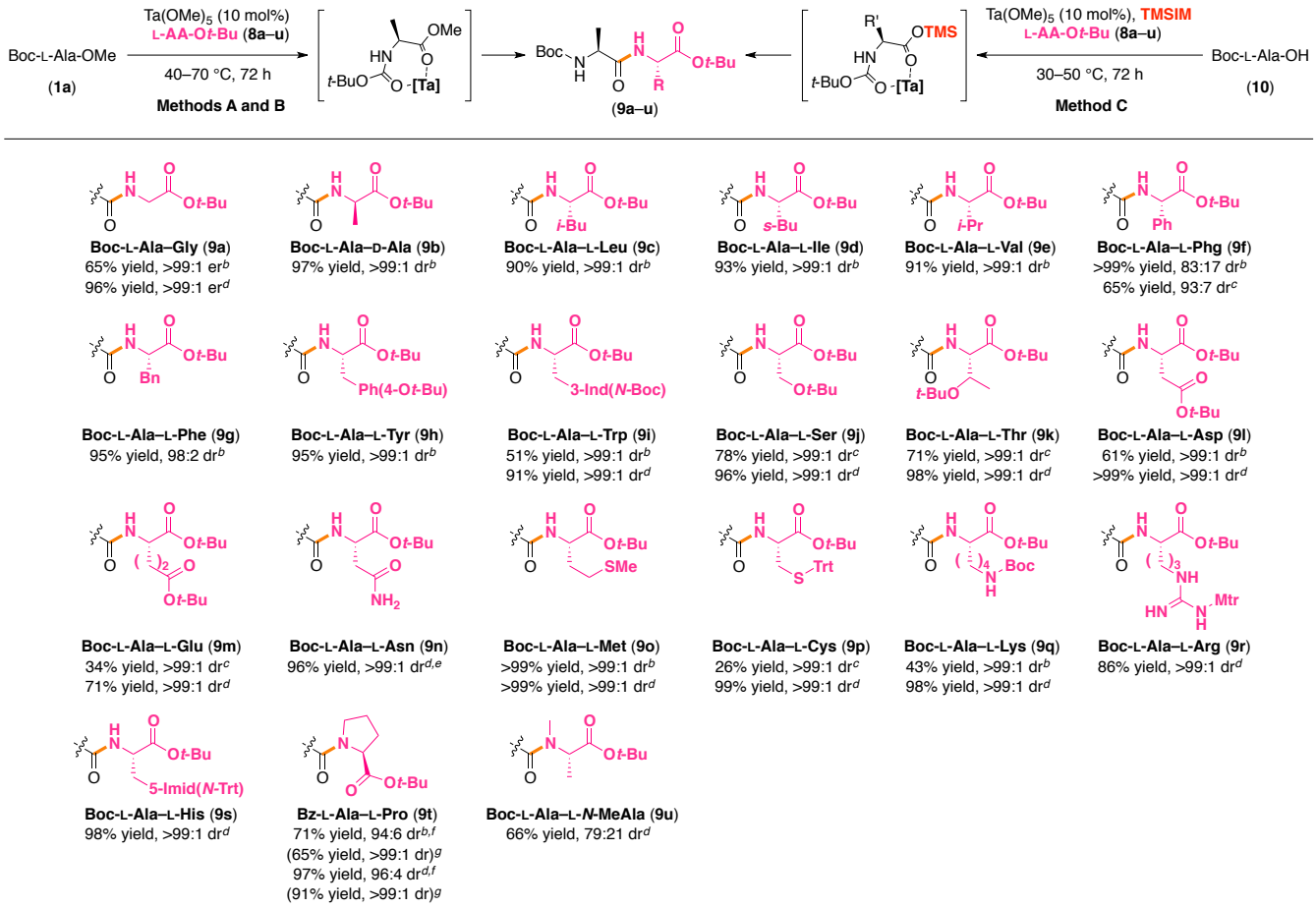




[a]The er of **6a** was determined by HPLC. The ers and drs of **6g** and **6h** were determined by HPLC and ^{1}H NMR. The drs of **6b**–**f** and **6i**–**x** were determined by ^{1}H NMR. [b]Method A: **5** (1.0 mmol), **2** (2.0–3.0 equiv), and $Ta(OMe)_5$ (10 mol%) were used. [c]Method B: **5** (2.0–2.5 equiv), **2** (1.0 mmol), and $Ta(OMe)_5$ (10 mol%) were used. [d]Method C: **7** (2.0 equiv), **2** (1.0 mmol), TMSIM (2.0–2.2 equiv), and $Ta(OMe)_5$ (10 mol%) were used. [e]These reactions were carried out in solvent ($CHCl_3$ or DMSO). [f]After separation of both diastereomers by normal-phase silica-gel chromatography. [g]Method D: **7** (2.0 equiv), **2**·HCl (1.0 mmol), TMSIM (2.2 equiv), and $Ta(OMe)_5$ (10 mol%) were used.

Similarly, these methods tolerated numerous functional groups, such as ethers, esters, amides, and sulfides, in the electrophilic amino acid species, as well as nucleophilic species, during the preparation of dipeptides **9a**–**e** and **9h**–**s**; these reactions proceeded without any racemization (Scheme 3). Unnatural amino acid, phenylglycine (Phg), is known to racemize more easily than other amino acids,[31] and this was unfortunately observed using our substrate-directed method implemented for **6g** (>99:1 er and 70:30 dr) and **9f** (>99:1 er and 93:7 dr). The racemization of **6g** and **9f** is not due to oxazolone formation but rather to enolization through direct deprotonation of the acidic benzylic proton on **5g** (or **6g**) or **8f** (or **9f**), respectively. However, **6g** and its diastereomer could be separated by silica-gel chromatography. In addition, **9f** and its diastereomer can be separated by recrystalization after cleavage of the Boc protecting group.[19] An abundance of side-products was observed when this catalysis was applied to **8p** at 70 °C, which is ascribable to the instability of the S–C bond of the Trt group under the reaction conditions. On the other hand, an excellent yield of **9p** was obtained using the TMSIM protocol at 50 °C. Although partial racemization was observed for **9t** (94:6 dr) and **9u** (79:21 dr), **9t** was fortunately isolated from the mixture of diastereomeric products in 91% yield (92:8 ratio of rotational isomers) by silica-gel chromatography.

Scheme 3. Reaction Scope: Amino Acid *tert*-Butyl Esters (Highlighted in Pink)[a]

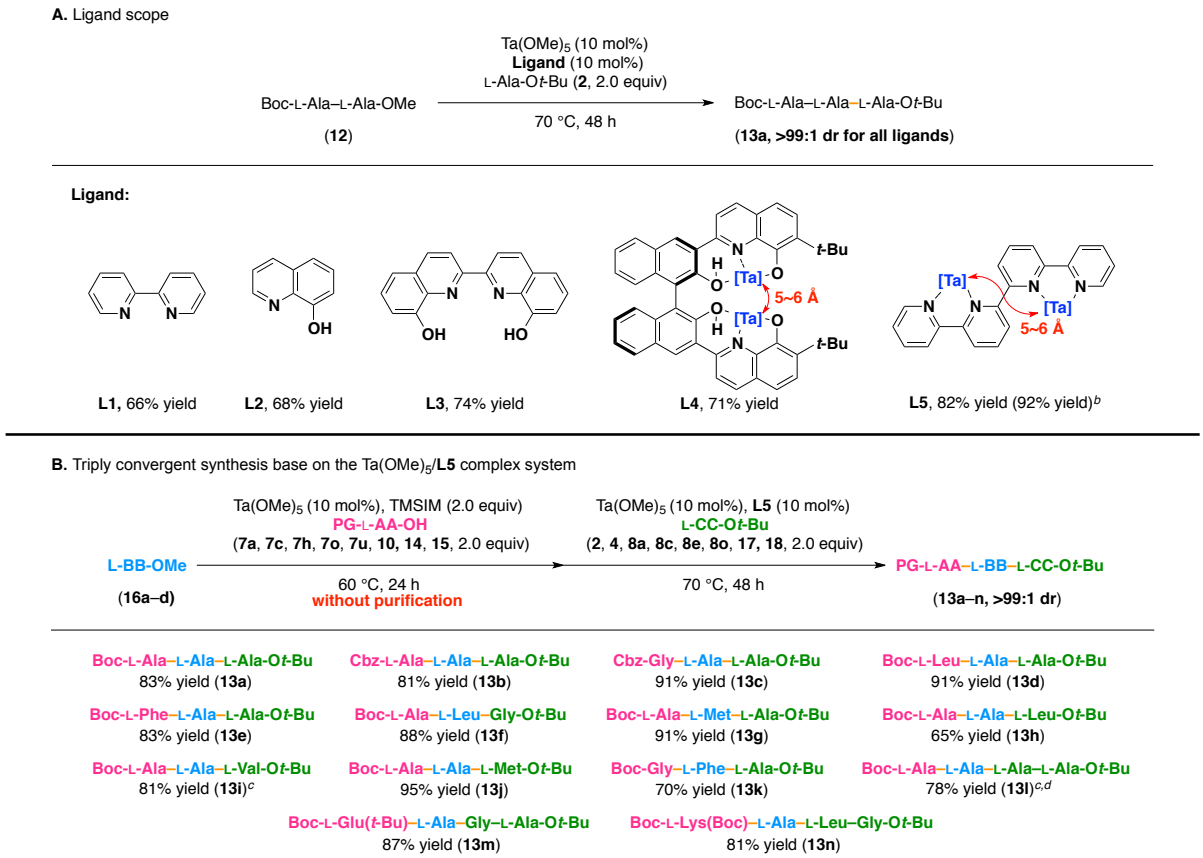


[a]The er of **9a** was determined by HPLC. The ers and drs of **9f** and **9g** were determined by HPLC and ^{1}H NMR. The drs of **9b**–**e** and **9h**–**u** were determined by ^{1}H NMR. [b]Method A: **1a** (1.0 mmol), **8** (2.0–3.0 equiv), and $Ta(OMe)_5$ (10 mol%) were used. [c]Method B: **1a** (2.0–2.5 equiv), **8** (1.0 mmol), and $Ta(OMe)_5$ (10 mol%) were used. [d]Method C: Boc-L-Ala-OH **10** (2.0 equiv), **8** (1.0 mmol), TMSIM (2.0–2.2 equiv), and $Ta(OMe)_5$ (10 mol%) were used. [e]The reaction was carried out in $CHCl_3$. [f]**1f** or Bz-L-Ala-OH **11** was used instead of **1a** or **10**, respectively. [g]After separation of both diastereomers by normal-phase silica-gel chromatography.

Applications to the Substrate-Directed "Remote" Peptide Bond-Forming Reactions. Tantalum catalysts are known to activate the carbonyl oxygen of an amino acid ester at least six atoms away from directing groups as electrophilic coupling partners.[18,19] Hence, we envisaged that our catalytic system might be suitable for substrate-directed 'remote' amidations with dipeptide methyl esters as electrophilic coupling partners, facilitated by ligands (Scheme 4A). To explore this concept, we examined the solvent-free reaction of Boc-L-Ala–L-Ala-OMe **12** and 2.0 equivalents of L-Ala-O*t*-Bu **2** with a 10 mol% $Ta(OMe)_5$, which gave the desired tripeptide **13a** in 41% yield with >99:1 dr. Upon screening several bidentate and tetradentate ligands for the tantalum catalysis, the use of **L1**–**3** gave improved yields (additional screening data were listed in Scheme S1 and Table T3, see supporting information). Since the methyl ester group is located about 5–6Å away from the Boc directing group, we designed the bitantalum catalyst using ligands **L4**[32] and **L5**.[33] Gratifyingly, when **L5** was employed with $Ta(OMe)_5$, **13a** was obtained in 92% yield. Thus, one tantalum coordinates to the Boc group, and the other tantalum activates the terminal methyl ester.

Based on this observation, we were encouraged to apply the $Ta(OMe)_5$/**L5** complex system in triply convergent syntheses of tri- and tetrapeptides (Scheme 4B). Although Boc-L-Ala-OMe **1a** was initially selected as the electrophilic coupling partner, the reaction of **1a** with L-Ala-OMe **16a** in the presence of catalytic $Ta(OMe)_5$ unexpectedly furnished cyclic L-Ala–L-Ala as the major product, rather than the desired Boc-L-Ala–L-Ala-OMe **12**. To make matters worse, the one-pot process for the three-component peptide-forming reaction of Boc-L-Ala-OTMS generated *in situ* from Boc-L-Ala-OH **10** and TMSIM, with **16a** as the second component and **2** as the third component, gave only trace amounts of **13a** due to the unexpected effect of the imidazole generated in the second peptide-forming reaction. Accordingly, after the first peptide-forming reaction using **10** and **16a** was carried out in the presence of $Ta(OMe)_5$ and TMSIM, the imidazole was removed by simply washing with water prior to treatment of the crude **12** with **2** in the presence of the $Ta(OMe)_5$/**L5** complex to give **13a** in 83% yield without any stereochemical problems. The protocol was also extended to the preparation of tri- and tetrapeptides **13a**–**n** that contain a variety of amino acid residues as well as other functional groups

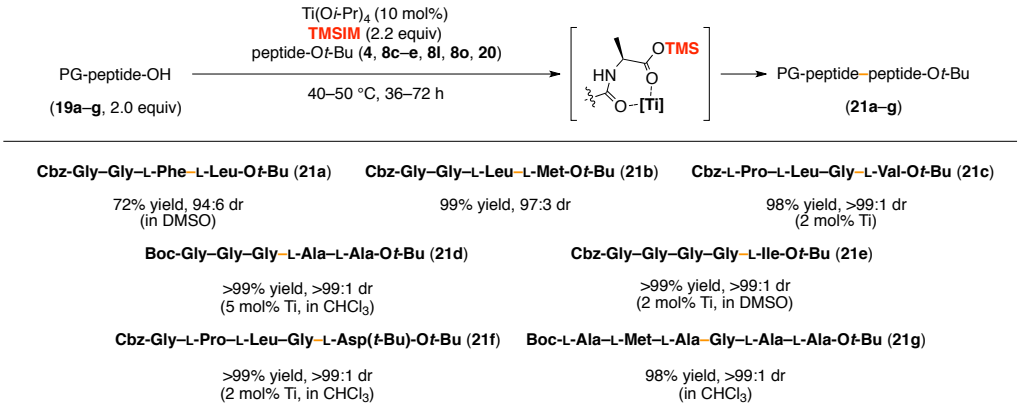
Scheme 4. Substrate-Directed "Remote" Peptide Bond-Forming Reactions[a]



[a]The drs of **13a**–**n** were determined by ^{1}H NMR. [b]The reaction was carried out for 72 h. [c]L-Val-O*t*-Bu **8e** and L-Ala-L-Ala-O*t*-Bu **4** (3.0 equiv) were used. [d]The reaction was carried out at 80 °C.

Applications to the Substrate-Directed Catalytic Chemical Ligation Using Amino Acid Terminus without Any Prefunctionalization.[34] The chemical ligation between two different peptides is one of the most important and unsolved processes for the generation of longer peptides.[35–40] NCL was pioneered by Kent,[14,15] and more recently, Bode invented a novel *α*-ketoacid/hydroxylamine ligation system.[41] The great contribution of these chemical ligations by Kent and Bode is noteworthy as the milestone of modern peptide chemistry. Although these reactions proceed efficiently in diluted aqueous conditions in the presence of many functional groups, the former process is still problematic with respect to generality, as thioester groups and unprotected-Cys residues are required at the *C*-terminal and *N*-termini of the corresponding peptides, respectively. Similarly, in the latter case, the advance preparations of *α*-ketoacid residues at the *C*-terminal and hydroxylamine residues at the *N*-terminal are essential. Clearly, a more general chemical ligation system for direct peptide bond formation between the amino group of one peptide and the carboxyl group of another peptide is much valuable. Herein, we investigated Lewis acid-catalyzed chemical ligation between peptides to demonstrate the robustness of our concept in terms of generality, utility, significance, and originality (Scheme 5). Our approach eliminates the inconvenience of laborious prefunctionalization at the mutually ligation junctions of peptides. This success of our simple approach in catalytic chemical ligation leads to its application to the "all catalytic convergent peptide synthesis" which solves the problems of multistep processes of linier SPPS and LPPS. Additionally, it will be helpful for prospective development of chemical ligation between polypeptides and/or proteins without any limitation and the use of prefunctionalized polypeptides as well as proteins. After a series of optimization studies (Table T4, see supporting information), we found that Cbz-Gly–Gly–L-Phe-OH **19a** underwent peptide bond formation with **8c** and TMSIM in the presence of a Ti(O*i*-Pr)$_4$ catalyst to give **21a** in 72% yield and with 94:6 dr. The tetrapeptide **21a** is a common building block for the synthesis of Met- and Leu-enkephalins,[42] and the physical and spectroscopic data for **21a** are in good agreement with those for the known data.[43] Gratifyingly, we achieved catalytic coupling reaction with 2–10 mol% Ti(O*i*-Pr)$_4$ as the catalyst to give oligopeptides **21a**–**g** bearing a series of functional groups in yields of up to >99% and with high diastereomeric ratios. We believe that this is an elegant solution for the long-standing problem of general chemical ligation of peptides.

Scheme 5. Lewis Acidic Metal-Catalyzed Peptide Coupling Reaction[a]



[a]The drs of **21a**–**g** were determined by ^{1}H NMR.

CONCLUSION

Over the past century, a number of technological advances in peptide synthesis have been made. However, despite remarkable progress in catalytic and stoichiometric peptide bond-forming reactions, the amide bond formation for peptides still remains one of the top challenges.[44] In this article, we introduced a substrate-directed strategy that makes a seminal contribution to the field of peptide synthesis and demonstrated the dramatic potential of this novel Lewis acid-catalyzed approach. The new method addresses some of the critical issues associated with classical SPPS and LPPS routes, including racemization, waste production, complicated operation, tedious purification steps,[45,46] limited applicability, and generality of peptide chemical ligation. In particular, our tantalum-catalyzed method completely blocks the generation of an oxazolone intermediate, which causes numerous purification steps for racemization. In addition, this approach can be exploited in the triply convergent synthesis of tri- and tetrapeptides. Thus, since our method does not cause any racemization, it will be able to significantly simplify the process without some of the tedious purification steps in classical peptide synthesis. Furthermore, our new chemical ligation method using non-prefunctionalized peptides opens efficient and straightforward all catalytic convergent synthetic approach for oligopeptide synthesis, and it will be able to generate a variety of (3 x 2^n)-residue peptides (n = 1, 2, 3 ···) in very few steps. We therefore expect that the presented Lewis acid method constitutes an important new protocol for future peptide synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, ^{1}H- and ^{13}C NMR spectra, HPLC data, and GC data (PDF)

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Notes

The authors declare no competing interests.

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(34) With regard to chemical ligation, it seems that there are several interpretations such as that it must be proceed in the presence of most unprotected functional groups, tolerate aqueous conditions, and/or work for longer peptide chains et al. Indeed, a majority of chemical ligations seem to tolerate aqueous conditions and work for longer peptide chains such as polypeptides and proteins. On the other hand, we have not found a precise definition for chemical ligation. Our presented investigation of chemical ligation herein is focused on the chemical peptide synthesis without any limitation and prefunctionalization of the ligation sites through "all catalytic convergent process" which solves the problems of multistep processes of linier SPPS and LPPS. Thus, we decide to use the term "chemical ligation" for our all catalytic convergent peptide synthesis strategy.
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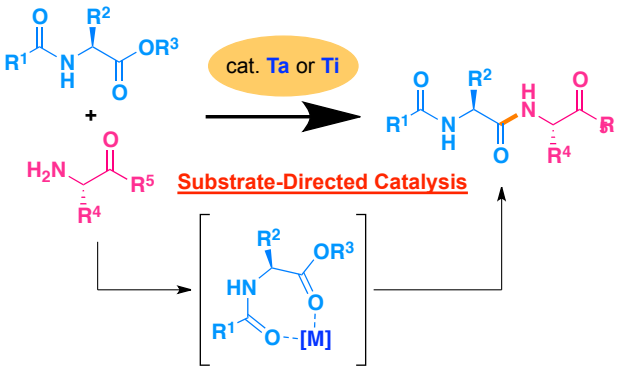

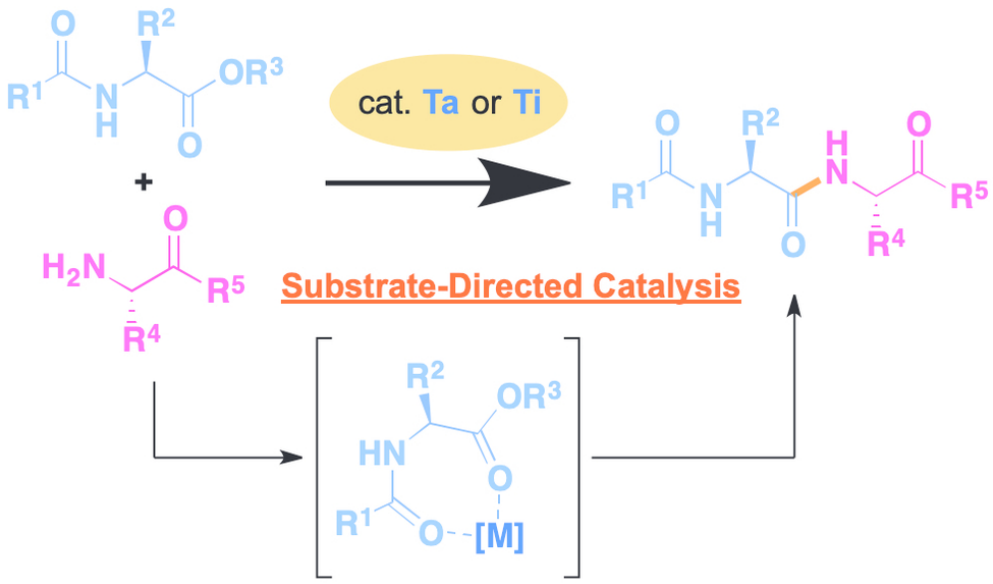

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