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Communication

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Tantalum-Catalyzed Amidation of Amino Acid Homologs

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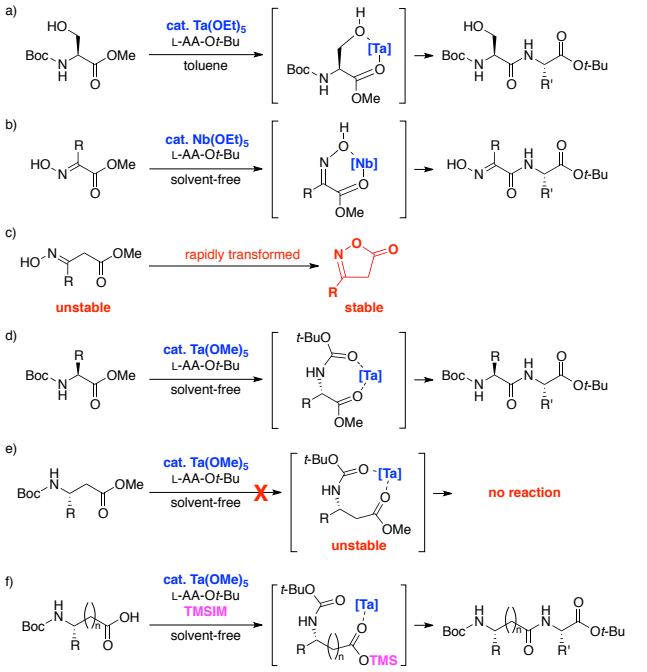
Supporting Information Placeholder

ABSTRACT: A tantalum-catalyzed solvent-free approach for the construction of amide bonds with 1-(trimethylsilyl)imidazole is developed, and the mild reaction conditions are applicable to a wide variety of electrophilic amino acid homologs. This approach delivers a new class of peptides in high yields without any epimerization.

Amide bond formation using carboxylic acids and amines is a classical reaction encountered widely in organic synthesis and bioorganic chemistry.[1] The typical approaches for this transformation involve the use of coupling-reagent-mediated strategies which proceed *via* formation of an active ester and have been extensively used in pharmaceutical, agrochemical, cosmetic, and polymer material syntheses.[2] For many years, considerable efforts have been devoted to the development of powerful and useful coupling reagents.[3] However, the coupling-reagent-mediated CO–NH bond formation methodologies usually require large amounts of reaction solvents[4] and typically suffer from racemization problems[3b] in addition to the production of chemical waste related to the coupling reagents.[5] A catalytic version of the amide bond formation between carboxylic acids and amines has attracted considerable attention in the last quarter century, and several metal catalyses have been developed for this transformation.[1b,6] However, most of these metal-catalyzed amidations requir high temperatures and use of a Dean-Stark trap[6c] and/or molecular sieves[6a–b] for promoting the conversion of the hydroxy group into an active leaving group by removal of water. Furthermore, these approaches can sometimes cause racemization challenges during peptide synthesis. Arguably, considerable room for improvement and innovation exists in this area of amide bond formation.

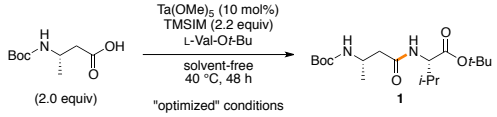
We recently developed three original strategies based on a substrate-directed approach[7] to solve racemization problems in CO–NH bond formations and to significantly reduce the associated environmental challenges[8] due to chemical waste generation. We initially introduced a hydroxy-group-directed Lewis acid catalysis approach to amide bond formation (Scheme 1a), that affords moderate to high yields of the desired dipeptides without any epimerization.[9] However, the substrate scope of this methodology is limited to Ser, Thr, and their derivatives only. We subsequently extended the hydroxy-group-directed strategy to a solvent-free amidation of *N*-hydroxy-*α*-imino esters (Scheme 1b).[10] The obtained *N*-hydroxy-*α*-imino amides could be diastereoselectively hydrogenated under palladium catalysis to prepare the corresponding L,L-dipeptides. Unfortunately, the *N*-hydroxy-*β*-imino esters were unstable and immediately transformed to the stable isoxazolones (Scheme 1c).[11] More recently, we reported a solvent-free peptide bond-forming methodology for most natural *α*-amino acids which proceed under protecting-group-directed Lewis acid catalysis (Scheme 1d).[12] However, the *N*-protected *β*-homoamino acid methyl esters were not suitable substrates for peptide synthesis using this methodology (Scheme 1e) as the transition state of the 8-membered ring generated by the coordination of the Lewis acid catalyst to the *N*-protected *β*-homoamino acid methyl esters is generally less stable than the 7-membered ring transition state generated using the *N*-protected *α*-amino acid methyl esters. Because *β*-amino acids and *β*-peptides possess unique properties in biological and structural aspects,[13] potentially game-changing strategies to address their synthesis problems are clearly required. We present herein, a powerful Lewis acid catalysis approach for preparation of NH–CO linkages using electrophilic amino acid homologs with high generality and broad functional group tolerance (Scheme 1f).

Scheme 1. Our Strategies for Lewis-Acid-Catalyzed Amidation Reactions



We began our studies by screening a large number of Lewis acid catalysts and commonly available silylating agents for peptide bond construction between Boc-L-*β*-HoAla-OH and L-Val-O*t*-Bu. The reaction conditions evaluated for the optimization and several varied conditions are shown in Table 1. When L-Val-O*t*-Bu was treated with 2.0 equiv. of Boc-L-*β*-HoAla-OH in the presence of 10 mol% $Ta(OMe)_5$ and 2.2 equiv. of 1-(trimethylsilyl)imidazole (TMSIM), the catalytic $Ta(OMe)_5$ activated the carbonyl group of the silyl ester, which is generated *in situ* by the reaction of Boc-L-*β*-HoAla-OH with TMSIM, toward nucleophilic attack by L-Val-O*t*-Bu, smoothly providing the desired dipeptide **1** in the best yield (97% yield) without any epimerization (entry 1). The gram-scale synthesis of **1** was also successful under the optimized conditions (94 and 95% yields, entries 1 and 2). Amino acid *tert*-butyl esters are usually commercially available as their HCl salts due to their overwhelmingly longer storage stability without racemization and/or polymerization.[14] To exploit their use for amide bond formation, the availability of general methods for amidation using HCl salts of the amines, in addition to free amines is necessary. In this context, our method allows for the use of a more diverse set of nucleophilic counterparts that are HCl salts without any loss in yield (97% yield, entry 2). This trial revealed that the imidazole, generated by the silylation of Boc-L-*β*-HoAla-OH with TMSIM, had a significant role as a base for neutralization of L-Val-O*t*-Bu·HCl in the reaction. Both $Ta(OMe)_5$ and TMSIM are essential for this peptide bond-forming reaction (entries 3, 4). A series of tantalum alkoxides and other metal alkoxides were evaluated as a Lewis acid catalyst for this reaction, and most of them gave comparable results with 86–96% yields, while a more suitable silylating agent was not found for improving yield (entries 5–15).

Table 1. Tantalum Catalysis for Solvent-Free Amidation of Boc-L-β-HoAla-OH with L-Val-O*t*-Bu



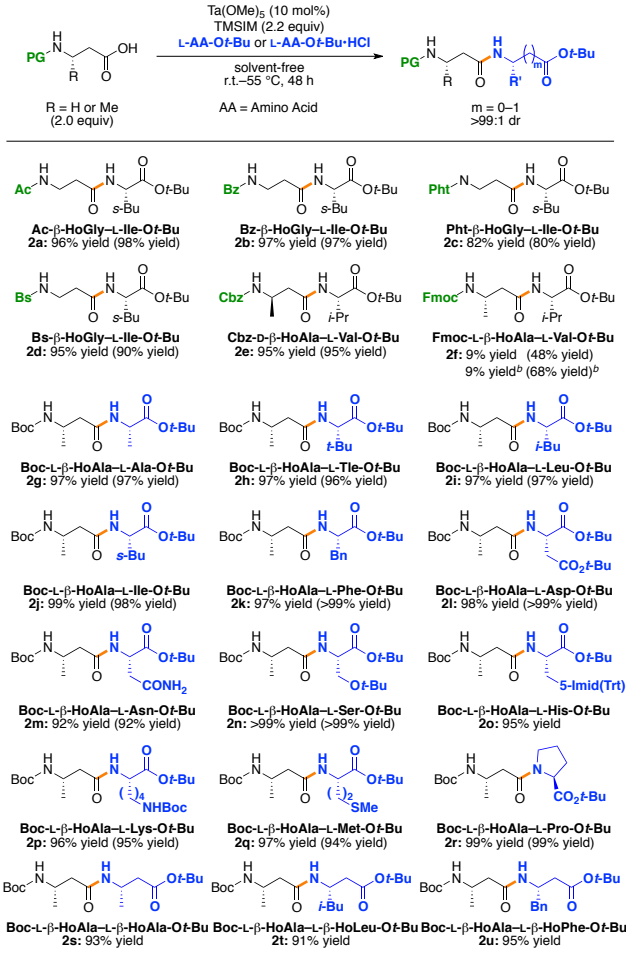
entry	variation from the "optimized" conditions	yield of **1** (%)[a]	dr[b]
1	none	97 (94)[c]	>99:1
2	L-Val-O*t*-Bu·HCl	97 (95)[c]	>99:1
3	no $Ta(OMe)_5$	0	nd
4	no TMSIM	0	nd
5	$Ta(OEt)_5$	96	>99:1
6	$Ta(OBu)_5$	93	>99:1
7	Ta_2O_5	2	nd
8	$TaCl_5$	10	>99:1
9	$Nb(OEt)_5$	96	>99:1
10	$Ti(Oi\text{-}Pr)_4$	86	>99:1
11	BSTFA	5	nd
12	BSA	4	nd
13	TBSIM	40	>99:1
14	HMDS	24	>99:1
15[d]	TMSI-H	0	nd

[a]Isolated yields. [b]drs were determined by ^{1}H NMR. [c]Conducted at 50 °C on a gram scale synthesis of **1**. [d]TMSI-H = HMDS (2) : TMSCl (1) : pyridine (10).

Having optimized the reaction conditions, we investigated the tunability of this solvent-free tantalum catalysis with respect to both protecting groups and nucleophilic amino acid esters. As summarized in Scheme 2, a range of *N*-protecting groups from acyl (Ac, Bz, and Pht) to sulfonyl (Bs) and carbonate (Cbz) groups were compatible with the $Ta(OMe)_5$/TMSIM system and furnished the amides **2a**–**e** in up to 97% yield. Unfortunately, the Fmoc group was found to be largely sensitive in the presence of the free amines such as L-Val-O*t*-Bu or imidazole, and afforded a lower yield of **2f** (up to 68% yield) due to the cleavage of the group from Fmoc-L-*β*-HoAla-OH and/or the produced **2f**.[15] Nucleophilic α-amino acid esters and their HCl salts bearing hydrophobic side chains were amenable to the peptide bond-forming reaction with Boc-L-*β*-HoAla-OH, used as a model electrophilic counterpart, and formed the desired dipeptides **2g**–**k** in excellent yields without loss of stereochemical integrity. Furthermore, a broad variety of functional groups, including the ester group in Asp, amide group in Asn, hydroxy group in Ser, amino groups in His and Lys, and the sulfide group in Met were well tolerated under reaction conditions, and successfully delivered the corresponding dipeptides **2l**–**r** in high yields without any formation of side products. Peptide bond formation between *β*-amino acids was also evaluated

under the optimal conditions, affording the coupling products **2s**–**u** in 91–95% yields.

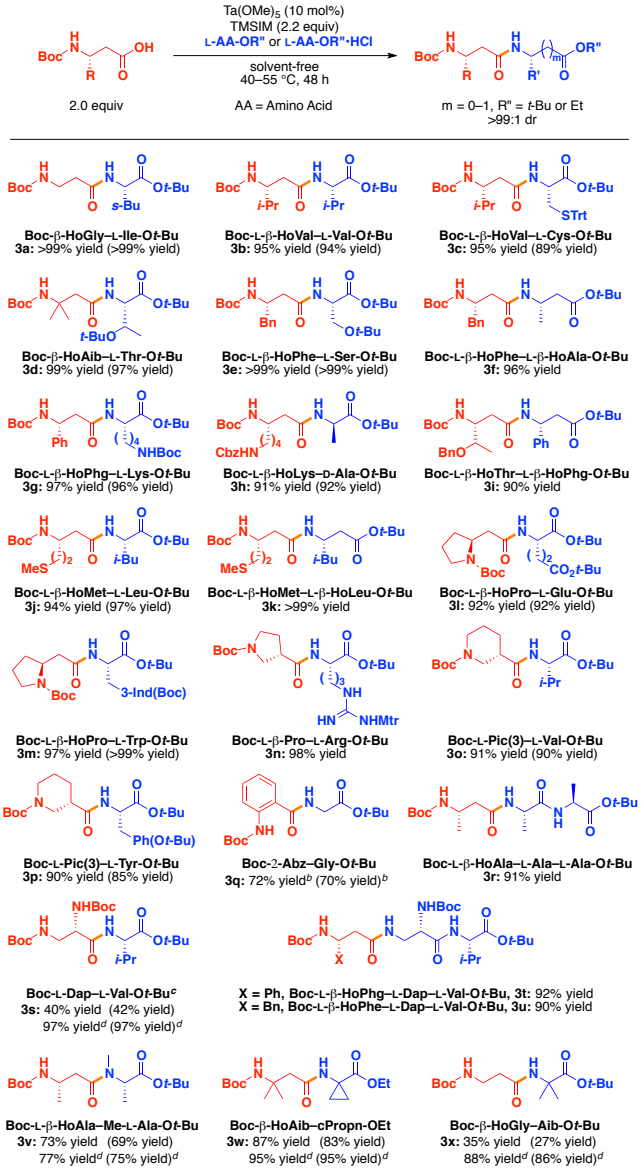
Scheme 2. Scope of Protecting Groups and Nucleophilic Amino Acids[a]



[a]Percentages are the isolated yields when L-AA-O*t*-Bu were used. Percentages in parentheses are the isolated yields when L-AA-O*t*-Bu·HCl were used. [b]Performed in $CHCl_3$.

Having evaluated protecting group compatibility, we studied the reaction system with a multitude of amino acid combinations (Scheme 3). The amidation of amino acids bearing hydrophobic side chains afforded **3a** and **3b** in >99% and 95% yields, respectively. Substrates carrying sulfur atoms often impair the performance of metal catalysts due to their stronger binding affinities.[16] Such limitations were not observed in our system, and L-Cys(Trt)-O*t*-Bu and its HCl salt were compatible with the reaction conditions and afforded **3c** in favorable yields comparable to those of **3a** and **3b**. Irrespective of the nature of the functional group variations on amino acids, the reactions proceeded to furnish all of the desired dipeptides **3d**–**q** and tripeptide **3r** in high yields. *α*-Substituted-*β*-amino acids were also converted smoothly into the corresponding dipeptides **3o**–**q** and **3s** without any epimerization. The steric effect of the *N*-Me group was evident from the loss of yield[17] when L-Ala-O*t*-Bu (97% yield of **2g**) was replaced with Me-L-Ala-O*t*-Bu (73% yield of **3v**). We have solved such a steric issue by switching the use of silylating agents,[18] and were pleased to find that the less sterically hindered silylating agent 1-(dimethylsilyl)imidazole (DMSIM), generated *in situ* from chlorodimethylsilane and imidazole, significantly increased the yields of **3s** and **3v**–**x**.

Scheme 3. Scope of Electrophilic/Nucleophilic Amino Acids[a]



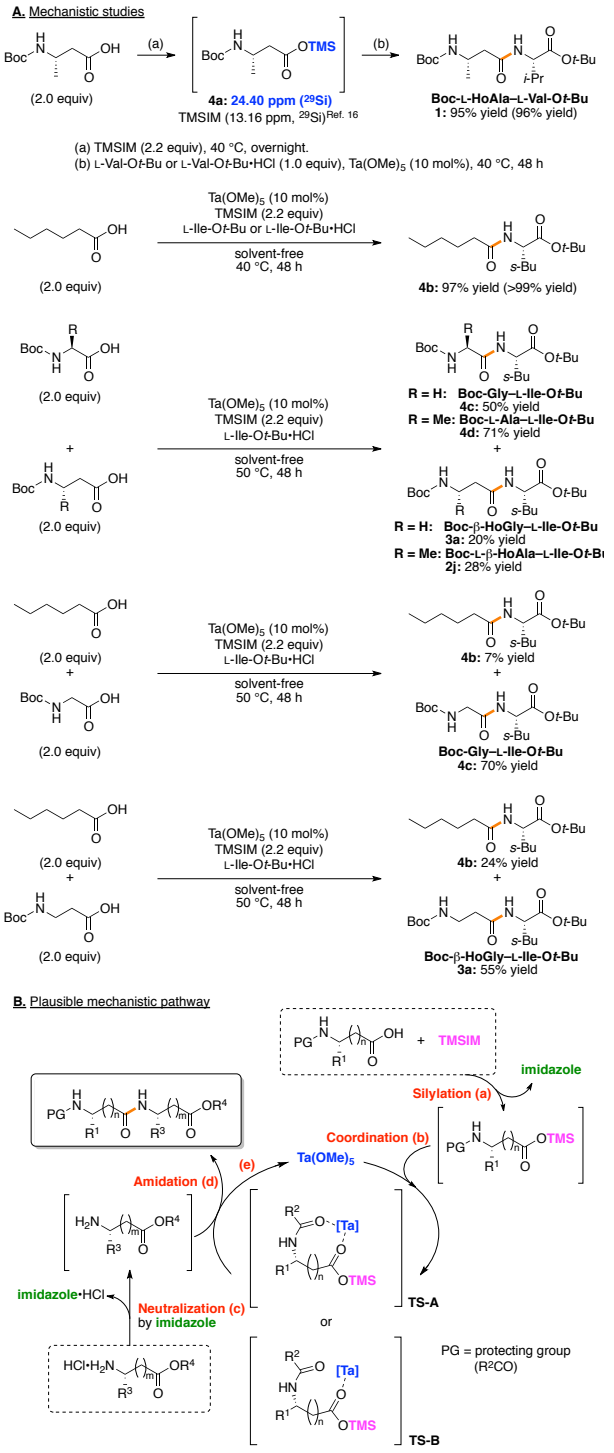
[a]Percentages are the isolated yields when L-AA-OR" were used. Percentages in parentheses are the isolated yields when L-AA-OR"·HCl were used. [b]Performed at 70 °C for 72 h. [c]Boc-L-Dap(Boc)-OH · DCHA was used. [d]Chlorodimethylsilane (2.2 equiv) and imidazole (4.4 equiv) were used instead of TMSIM. The reactions were performed in $CHCl_3$.

To probe the mechanism of these amide bond-forming reactions, we tested a series of reaction conditions (Scheme 4-A). Initially, Boc-L-*β*-HoAla-OH was reacted with TMSIM alone, and the formation of the silyl ester

4a was confirmed by ^{1}H and ^{29}Si NMR spectra (**4a**: 24.40 ppm, TMSIM: 13.16 ppm).[18] The crude **4a** was successfully converted to **1** in the presence of L-Val-O*t*-Bu or L-Val-O*t*-Bu·HCl. Next, a model experiment using hexanoic acid was conducted to verify whether these amidation reactions with electrophilic *β*-amino acids proceeded *via* cyclic transition state **TS-B** as shown in Scheme 4-B, which is assembled by directing effects of the *N*-protecting groups as well as with *α*-amino acids reported in the previous study. Remarkably, the reaction of hexanoic acid with L-Ile-O*t*-Bu or L-Ile-O*t*-Bu·HCl under the reaction conditions led to the formation of **4b** in 97% or >99% yield. This result clearly points to the broad applicability of the developed methodology for peptide synthesis employing a wide range of amines and carboxylic acids (Scheme 5-C). Subsequently, several competitive reactions were tested. In a tantalum-catalyzed competitive reaction using *α*- and *β*-amino acids, the *α*-amino acids Boc-Gly-OH and Boc-L-Ala-OH preferentially reacted with L-Ile-O*t*-Bu to afford **4c** and **4d**, respectively. Further, the competitive amide bond-forming reactions of hexanoic acid with Boc-Gly-OH or Boc-*β*-HoGly-OH (Boc-*β*-Ala-OH) afforded **4c** or **3a** as the major products, respectively.

On the basis of these results, a plausible mechanistic pathway of the process is depicted in Scheme 4-B. Initially, PG-L-amino acid homologs react with TMSIM to generate the corresponding silyl esters and imidazole *in situ* (step a). Subsequently, the more Lewis basic carbonyl oxygen atoms of PG (PG = Boc, Cbz, etc.) preferentially coordinate with the tantalum catalyst followed by the possible secondary coordination of carbonyl oxygen atoms of silyl ester moieties that may assist the assembly of **TS-A**. Although the **TS-A** seems to be relatively unstable, as seen in the unsuccessfully attempted transformation shown in Scheme 1e, the activated silyl ester moieties could react with amines to form amide bonds because the lower p*K*a values of silyl esters (TMSOH: 11, MeOH: 16) potentially render them as better leaving groups.[19] According to the magnitude of strain energy, stable **TS-A** could be formed. Otherwise, a tantalum-migration may occur to form **TS-B** from **TS-A**. Next, the free amine, formed by the *in situ* neutralization of the amino acid *tert*-butyl ester HCl salt with imidazole (step c), approaches the activated silyl ester moiety, and the ensuing peptide bond-forming reaction forges the smooth production of the corresponding dipeptides (step d). Finally, the tantalum catalyst is regenerated, thus completing the catalytic cycle (step e).

Scheme 4. Mechanistic Studies and Plausible Mechanistic Pathway[a]

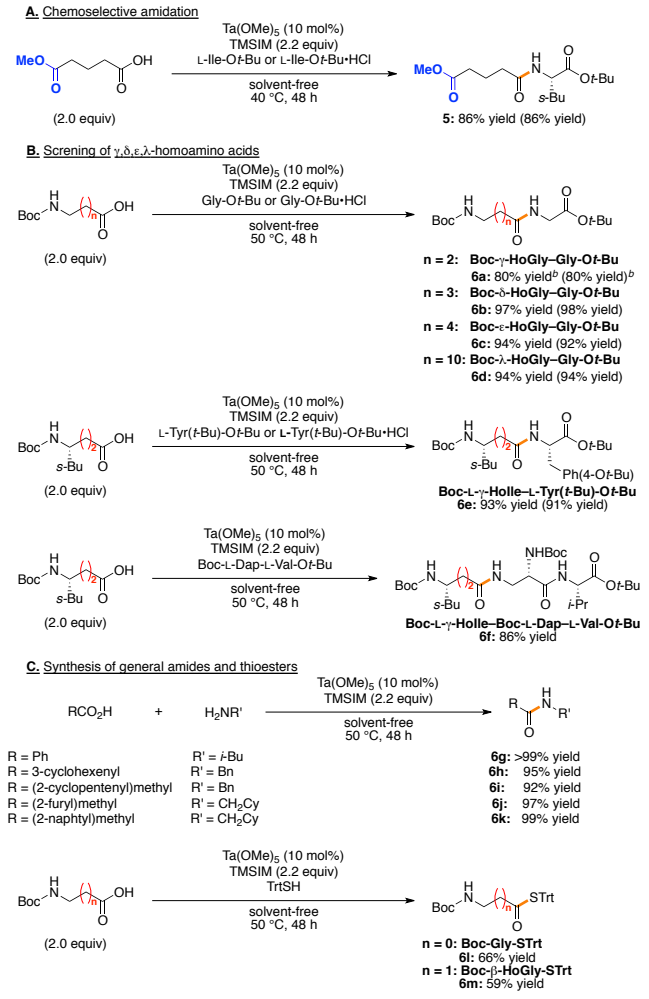


[a]Percentages are the isolated yields when L-AA-O*t*-Bu were used. Percentages in parentheses are the isolated yields when L-AA-O*t*-Bu·HCl were used.

Finally, the Ta(OMe)$_5$/TMSIM system was extended to the chemoselective amidation reaction (Scheme 5-A), application to the amidation of a series of electrophilic *γ*- to *λ*-homoamino acids (Scheme 5-B), and the synthesis of typical amides and thioesters (Scheme 5-C). The chemoselective reaction of mono-methyl glutarate with L-Ile-O*t*-Bu or L-Ile-O*t*-Bu·HCl led to the formation of **5** in 86% yield without any observation of side products

(silyl ester vs. methyl ester as an electrophile). The reaction of Boc-γ-HoGly-OH with Gly-O*t*-Bu or its HCl salt gave **6a** in 80% yield. Additionally, **6b**–**d** were obtained in higher yields when Boc-γ-HoGly-OH was replaced with Boc-δ-HoGly-OH, Boc-ε-HoGly-OH, Boc-λ-HoGly-OH, and their HCl salts. Furthermore, the dipeptide **6e** and tripeptide **6f** were successfully obtained from Boc-L-γ-HoIle-OH in 86–93% yields without any epimerization. The protocol is also applicable to the synthesis of typical amides without any observation of side reactions and it may be significantly helpful for the preparation of thioacid precursors for the emerging chemical ligation.[1a,20]

Scheme 5. Chemoselective Amidation, Scope of Electrophilic Amino Acid Homologs, and Application to the Typical Reactions[a]



[a]Percentages are the isolated yields when L-AA-O*t*-Bu were used. Percentages in parentheses are the isolated yields when L-AA-O*t*-Bu·HCl were used. [b]70 °C.

In conclusion, we found that $Ta(OMe)_5$ is a highly efficient catalyst for amide bond formation between a wide range of carboxylic acids and amines, and proceeds without any epimerization in the presence of silylating agents. The reaction proceeded with broad functional group tolerance under solvent-free conditions. Notably, the present catalytic system offers an expedient solution for chemoselective amidation (e.g., silyl ester vs. methyl ester). Overall, this approach will open a general path to CO–NH bond formation. Further studies on the applications of tantalum catalysis and reaction mechanism are currently under investigation in our laboratory.

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 financial interests.

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