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Catalytic Peptide Synthesis: Amidation of *N*-Hydroxyimino Esters

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ABSTRACT: A catalytic method for the formation of amide bonds has been developed, in which the amidation of *N*-hydroxyimino esters with a broad range of amino acid *tert*-butyl esters is promoted by a niobium catalyst in the absence of solvent. Contrary to the predominant protocol based on reagent control commonly applied to amidation reactions, this study provides insight into an approach based on substrate control. This system affords the corresponding amides in high yields in addition to both high atom-efficiency and racemization-free. An advantage of this system is shown in that the Lewis acid catalysis proceeds chemoselectively in the presence of non-activated esters. Furthermore, the resulting amides are easily transformed into their corresponding di- and tripeptides with high diastereoselectivities under simple hydrogenation conditions.

KEYWORDS: amidation, peptides, niobium catalysis, solvent-free reactions, hydrogenation

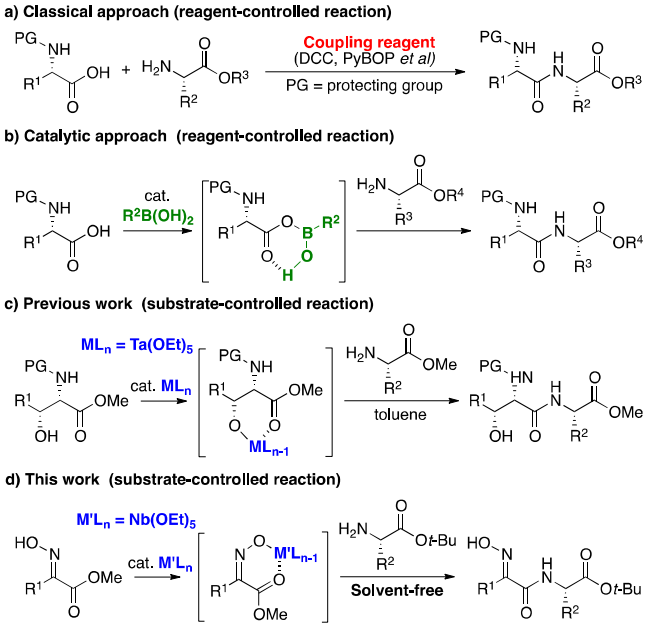
■ INTRODUCTION

Peptides have attracted increased interest as pharmaceuticals because of their high specificity compared to small molecule drugs.[1] Cosmetic and health food industries are also interested in peptidic products. Their industrial rise has prompted industrial and academic chemists to seek atom efficient manufacturing processes for peptide-based products to reduce the environmental impact and production cost.

In organic synthesis of peptides, one of the key routes involves the condensation reaction between amines and either esters or carboxylic acids.[2] Thus, peptides are synthesized stepwise by coupling the amino functional group of one amino acid to an activated carboxylic acid group, which is generated *in situ* from carboxylic acids and stoichiometric amounts of a coupling reagent, such as *N*,*N*′-dicyclohexylcarbodimide (DCC) and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) (Scheme 1a).[2d] In solid-phase synthesis, which is now the most common industrial approach to peptide synthesis, the peptide backbone is assembled one amino acid at a time while attached to resin beads, which require washing away residual reagents at each step.[3] From these processes, producing 1 kg of peptide typically requires several metric tons of solvent and thousands of liters of water in addition to the large quantities of chemicals, creating a significant environmental footprint.[4] As such, studies carried out in the past few decades have focused on the search for a catalytic route to amide bond formation. Indeed, since our initial report of a highly active catalytic method for the amidation reaction between carboxylic acids and amines,[5] a variety of prominent catalytic approaches have been reported (Scheme 1b).[6] The most recently reported catalysts employed for this transformation are boronic acid derivatives, with Shibasaki most recently reporting the catalytic amidation reaction using a 1,3-dioxa-5-aza-2,4,6-triborinane derivative.[7] However, these

aforementioned methods are aimed at the conversion of the hydroxy group to an active leaving group based on reagent control, whereas they sometimes lead to non-trivial issues regarding racemization.[8] As such, considerable room for improvement exists in the context of both waste production and racemization during amide bond formation. To address this issue, our group recently developed a powerful catalytic protocol in which $Ta(OEt)_5$ promotes the amidation of a wide range of β-hydroxy esters in good yields using a diverse array of amine nucleophiles (Scheme 1c).[9] This catalytic approach is based on substrate control, with a hydroxy group located at the β-position of the carbonyl group playing a key role as a directing group in initiating the site-selective activation of the carbonyl group by the tantalum catalyst, to ultimately promote amide bond formation. However, this method is limited in its applicability to esters of specific amino acids such as threonine (Thr) and serine (Ser) for the preparation of peptides. Herein, we present a novel and highly atom-efficient approach for the catalytic amidation of *N*-hydroxyimino esters[10] with a broad range of amino acid *tert*-butyl esters to achieve the desired C–N bond formation without any racemization (Scheme 1d). Furthermore, we aim to demonstrate that the resulting amides can be readily transformed into di- and tripeptides in high diastereoselectivities.

Scheme 1. Approaches in Peptide Synthesis

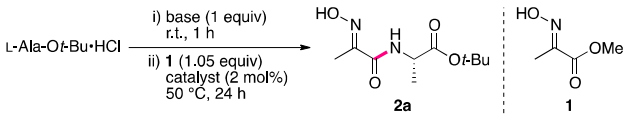


■ RESULTS AND DISCUSSION

Initially we examined the reaction between *E*-*N*-hydroxy-α-imino ester **1**[11] and amino acid *tert*-butyl ester HCl salts using a range of different bases and catalysts (Table 1). **1** was quantitatively prepared from methyl pyruvate and $NH_2OH{\cdot}HCl$.[10b] As the HCl salts of amino acid esters are generally more stable than the free amines, this allows their long-term storage and use without polymerization or racemization, and the salts tend to be easy to handle.[12] In addition, *tert*-butyl esters are advantageous for peptide synthesis, as side reactions such as the self-intermolecular condensation or intramolecular cyclization of peptides can be avoided due to steric hindrance from the *tert*-butyl moiety.[13] Based on the route outlined in Scheme 1c, $Ta(OEt)_5$ was first selected as a catalyst for this transformation. Following optimization of the reaction conditions using this catalyst, we found that **1** smoothly engaged with L-Ala-O*t*-Bu·HCl to afford the desired amide **2a** with no observation of racemization in the presence of 2 mol% of $Ta(OEt)_5$ and

1 equiv of Et_3N at 50 °C under solvent-free conditions (low *e*-value, entry 1, 95% yield). However, in the absence of Et_3N, the reaction was unsuccessful, indicating that a base is required to neutralize the HCl salt (entry 2). Although the free amine, L-Ala-O*t*-Bu, can be used instead of its HCl salt, the one-pot procedure described herein is technically and practically more convenient, and the ammonium chloride generated during neutralization has no effect on the catalyst activity. Although a modicum of the product **2a** was produced in the absence of the catalyst (entry 3), its yield was not improved dramatically at higher temperatures or under microwave irradiation (entries 4 and 5). We subsequently examined the effect of different types of bases on the reaction, and found that the obtained yields were significantly lower than those obtained for Et_3N (entries 6–9, <1–71% yields). In addition, upon repeating the reaction using a series of tantalum catalysts, a range of yields of **2a** were observed, including a number of unsatisfactory results (entries 10–15, 28–98% yields). Furthermore, the investigation of various metal alkoxide catalysts (entries 16–22) indicated that the $Nb(OEt)_5$-catalyzed amidation of **1** with L-Ala-O*t*-Bu·HCl produced **2a** in the best yield (entry 22, >99% yield). Moreover, these optimized conditions were applicable to the gram-scale synthesis of **2a** (entry 22 in the bracket, >99% yield). We also demonstrated that the reaction time could be significantly shortened (i.e., from 24 to 3 h) using microwave irradiation with petroleum ether as the solvent, as only a small decrease in yield was observed. (entry 23, 95% yield).[14] When methyl pyruvate was employed instead of **1**, only imine formation reaction between amino group of L-Ala-O*t*-Bu and carbonyl group of methyl pyruvate proceeded instead of amidation reaction to give the corresponding amide compound (entry 24).[15]

Table 1. Solvent-Free Catalytic Amidation of 1 with L-Ala-O*t*-Bu·HCl Salt[a]



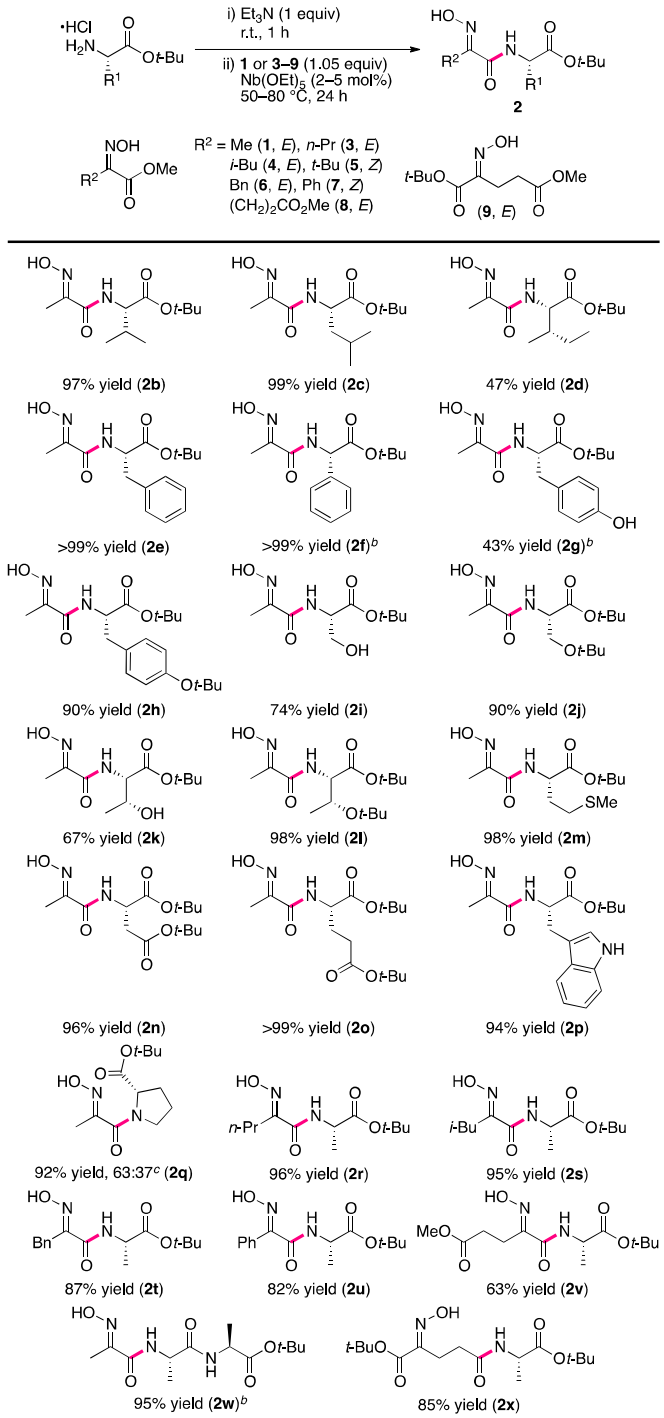
Entry	Base	Catalyst	Yield of **2a** (%)[b]
1	Et_3N	$Ta(OEt)_5$	95
2	–	$Ta(OEt)_5$	<1
3	Et_3N	–	29
4[c]	Et_3N	–	35
5[d]	Et_3N	–	3
6	DABCO	$Ta(OEt)_5$	6
7	*i*-Pr_2NH	$Ta(OEt)_5$	71
8	pyridine	$Ta(OEt)_5$	<1
9	K_2CO_3	$Ta(OEt)_5$	2
10	Et_3N	$Ta(OMe)_5$	98
11	Et_3N	$Ta(OBu)_5$	93
12	Et_3N	$Ta(NMe_2)_5$	81
13	Et_3N	$Ta(acac)(OEt)_4$	55
14	Et_3N	$TaCl_5$	28
15	Et_3N	$TaBr_5$	77
16	Et_3N	$VO(OEt)_3$	37
17	Et_3N	$Cu(OEt)_2$	57
18	Et_3N	$Hf(OEt)_4$	62
19	Et_3N	$W(OEt)_6$	39
20	Et_3N	$Pd(OAc)_2$	85
21	Et_3N	$Fe(OTf)_3$	35
22	Et_3N	$Nb(OEt)_5$	>99 (>99)[e]
23[d]	Et_3N	$Nb(OEt)_5$	95
24[f]	Et_3N	$Nb(OEt)_5$	0[g]

[a]Conducted on a 1.0 mmol scale of L-Ala-O*t*-Bu·HCl. [b]Determined by GC analysis with the aid of dodecane as a calibrated internal standard. [c]100 °C. [d]Through the use of microwave irradiation in petroleum ether for 3 h. [e]Isolated yield of the reaction with 10 mmol of L-Ala-O*t*-Bu·HCl. [f]Methyl pyruvate was employed instead of **1**. [g]Isolated yield of the corresponding amide.

To highlight the wide applicability of this method, we applied the most successful catalyst, $Nb(OEt)_5$, and conditions (entry 22 of Table 1) to the amidation of several *N*-hydroxyimino esters[10] with a range of amino acid *tert*-butyl ester HCl salts (Scheme 2). As indicated in the scheme, the amidation of L-Val-O*t*-Bu·HCl, L-Leu-O*t*-Bu·HCl, and L-Phe-O*t*-Bu·HCl with **1** proceeded smoothly to afford the corresponding amides **2b**, **2c**, and **2e** in excellent yields. Unexpectedly, L-Ile-O*t*-Bu·HCl showed low reactivity and reacted with **1** to give the amide **2d** in only moderate yield without formation of any side products including a diastereomer of **2d**.[16]

Although L-Phg-O*t*-Bu cannot be effectively incorporated using classical amidation methods of Scheme 1a due to its high tendency to racemize,[17] our substrate-controlled method dramatically provided a quantitative yield of **2f** with no observation of racemization.[18] When amino acids bearing free hydroxy groups were treated in the presence of $Nb(OEt)_5$, slightly lower yields of **2g**, **2i**, and **2k** (43%, 74%, and 67% yields, respectively) were obtained compared to those of the corresponding protected amides **2h**, **2j**, and **2l** (90%, 90%, and 98% yields, respectively). Interestingly, the reaction tolerated amino acids bearing not only hydroxy, carbonyl, and *S*-alkyl groups, but also those bearing the indole moiety, providing **2m**–**2p** in 94 to >99% yields. These results therefore indicate that nucleophilic amines bearing a variety of functional groups can take part in this amide bond formation reaction to produce high yields of the desired amides. Furthermore, even the secondary amine, L-Pro-O*t*-Bu·HCl, reacted to furnish **2q** in 92% yield with a rotamer ratio of 63:37. Not only β-substituted *E*-*N*-hydroxy-α-imino esters **3**, **4**, and **6**[11] but also *Z*-*N*-hydroxy-α-imino ester **7**[11] was subject to the amidation to give the corresponding amides **2r**–**2u** in 82 to 96% yields.[19] *E*-*N*-hydroxyimino ester **8**, which bears two methyl ester groups at α- and γ-positions, reacted with L-Ala-O*t*-Bu·HCl to produce **2v** as a major product. Moreover, this protocol could be extended to the amidation using the dipeptide **11a** as well as *N*-hydroxy-γ-imino methyl ester **9**,[20] giving the corresponding oligopeptide precursors **2w** and **2x** in 95% and 85% yields, respectively.

Scheme 2. Solvent-Free $Nb(OEt)_5$-Catalyzed Amidation[a]



[a]Conducted on a 1.0 mmol scale of L-amino acid *tert*-butyl ester·HCl. [b]Commercially available free amines, L-Phg-O*t*-Bu and L-Tyr-O*t*-Bu, and L-Ala-L-Ala-O*t*-Bu (**11a**) provided by hydrogenation of **2a** in Scheme 4 were used instead of their corresponding HCl salts with Et_3N. [c]The ratio of rotational isomers was determined by ^1H NMR analysis.

Unexpectedly, *Z*-*N*-hydroxy-α-imino ester **5**[11] containing *tert*-butyl group at β-position was not reacted with L-Ala-O*t*-Bu, prepared by neutralization of L-Ala-O*t*-Bu·HCl, in the presence of 2–10 mol% of $Nb(OEt)_5$ or $Ta(OEt)_5$ at 50–100 °C. Because steric repulsion between the *tert*-butyl group and methoxy group prevents the interconversion of the geometric isomer ***s-trans*-5** to ***s-cis*-5**, the carbonyl moiety of **5** may not be activated by niobium catalyst (Fig 1a). To reveal the reactivity pattern of Lewis acid (Nb)–imino ester **5** complexes, the most stable structures and relative free energy levels of **TS1** and **TS2** were calculated at MP2/(6-31G(d), LANL2DZ) level. This confirmed that the complex **TS2** is 2.07 kcal/mol higher in relative energy than **TS1** (Fig 1b).

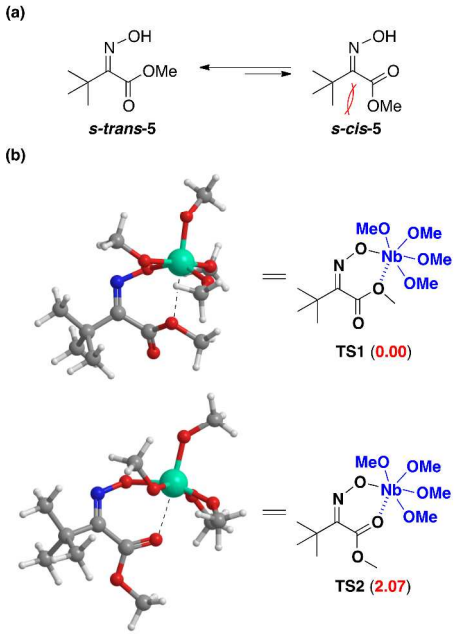
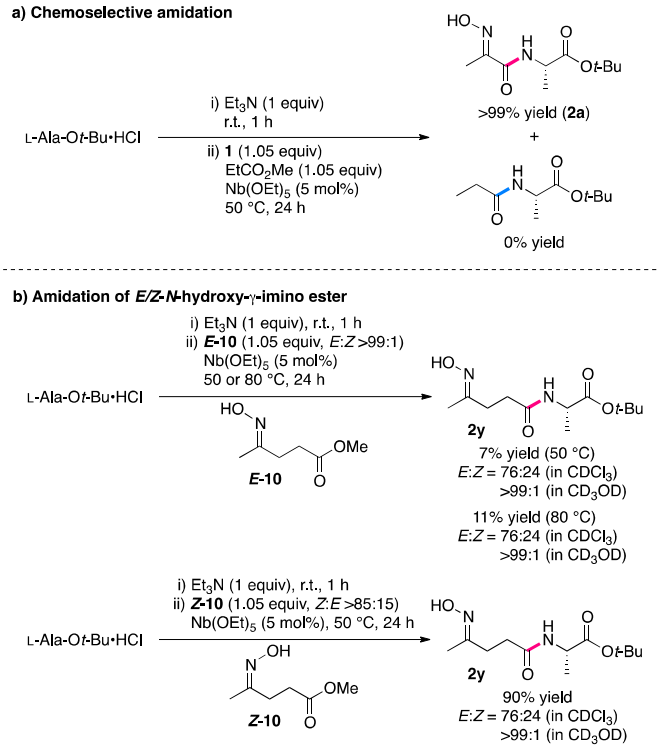


Figure 1. (a) Equilibrium between the geometric isomer ***s-trans*-5** and ***s-cis*-5**. (b) The most stable structures and relative free energy levels of the $Nb(OMe)_5$–imino ester **5** complexes. Red characters indicate relative free energy levels in kcal/mol.

Our success opened new insight to evaluate the application of this niobium-catalyzed amidation. When the $Nb(OEt)_5$-catalyed amidation of **1** was carried out in the presence of 1.05

equiv of methyl propionate, **2a** was chemoselectively obtained in >99% yield (Scheme 3a). In addition, this catalysis could proceed *via* a specific geometric conformer. Since the isomerization between *E*- and *Z*-*N*-hydroxy-γ-imino esters such as **10** is much slower than that between *E*-and *Z*-*N*-hydroxy-α-imino esters such as **1**, both geometric isomers ***E*-10** and ***Z*-10** could be prepared from methyl levulinate and $NH_2OH{\cdot}HCl$.[10b] Interestingly, while ***Z*-10** was smoothly converted to the amide **2y** with an *E*/*Z* ratio of 76:24[21] in the presence of 5 mol% of $Nb(OEt)_5$, the amide **2y** was hardly obtained from ***E*-10** (Scheme 3b). Thus, these results clearly indicate that the geometric conformation of *N*-hydroxyimino esters is related to the progress of this amidation reaction.

Scheme 3. Chemoselective Amidation and Effect of the Geometry of 10[a]

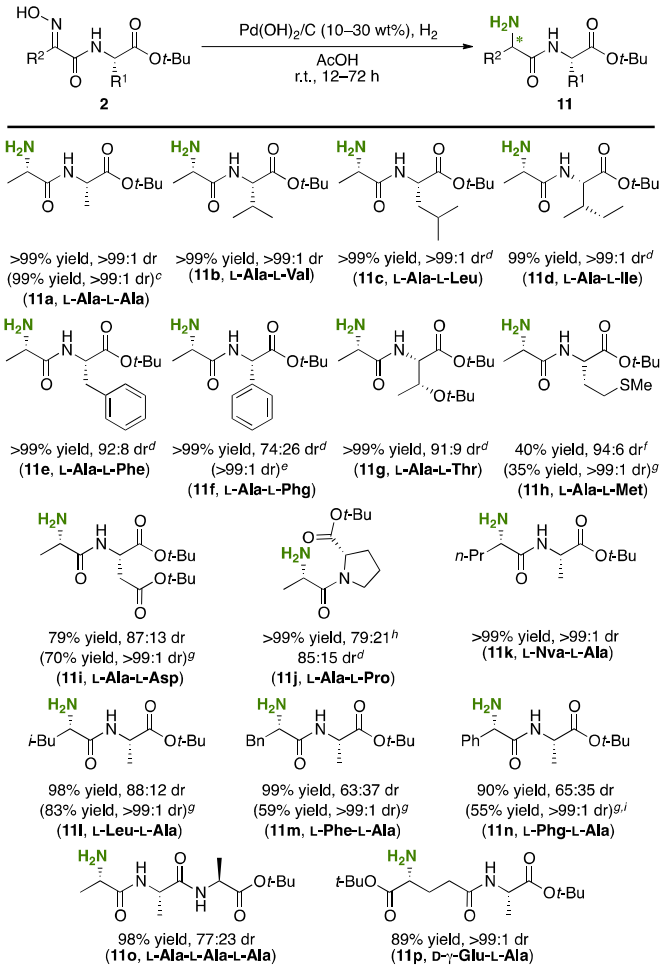


[a]Conducted on a 1.0 mmol scale of L-Ala-O*t*-Bu·HCl.

We then moved on to demonstrate the diastereoselective reduction of a selection of dipeptide precursors **2**, where we expected that any chirality incorporated into **2** may bias the stereoselectivity of the reduction (Scheme 4). After testing several known methods for the transformation of *N*-hydroxyimines into amines,[22] we found that the Pd-catalyzed hydrogenation[22a,b] of **2a** in acetic acid was particularly effective, preferentially furnishing dipeptide **11a** with (*S*)-configuration at the new chiral carbon center in remarkably high yield and diastereoselectivity. Similarly, upon hydrogenation of **2b**, dipeptide **11b** was yielded with (*S*)-configuration at the new chiral carbon center in >99% yield with >99:1 dr. Indeed, the reaction tolerates amino acids bearing a variety of functional groups, providing dipeptides **11c**–**11j** and tripeptide **11o** in good to excellent yields and diastereoselectivities. Unfortunately, the hydrogenation of **2m**, **2n**, and **2x** gave incomplete conversion to **11h** (40% yield, 94:6 dr), **11i** (79% yield, 87:13 dr), and **11p** (89% yield, >99:1 dr). Indeed, Kise previously reported that the reduction of methyl esters of **2c** and **2e** with 10 equiv of a reducing agent (i.e., Zn/methanesulfonic acid, Zn/trifluoroacetic acid, Zn/$TiCl_4$, or $NaBH_4$/$CoCl_2 \cdot 6H_2O$), afforded the corresponding dipeptides with 53:47 to 60:40 dr.[22e] Moreover, although the diastereoselective reduction of **2q** was reported by Mukaiyama, he employed excess quantities of SmI_2 as a reducing agent to obtain an ***epi*-11j**, D-Ala-L-Pro-O*t*-Bu, in 67% yield with 89:11 dr.[22d] However, our method is more practical and provided the other diastereomer **11j** in >99% yield and 85:15 dr. This Pd-catalyzed approach for the hydrogenation of *N*-hydroxy-α-imino moiety tolerates the amides **2** bearing different types of sterically hindering R^2 groups, giving dipeptides **11k**–**11n** and **11p** in excellent yields with diastereoselectivities ranging from 63:37 dr of **11m** for Bn group to >99:1 dr of **11k** for *n*-Pr group. In the case of **2u** with catalytic amount of $Pd(OH)_2$/C, only 21% of **11n** was isolated with >99:1 dr. Even though the reaction was carried out at 1.0

MPa pressure of hydrogen, the yield was not improved. Pd/C (K type)[23] showed excellent reactivity (>99% yield), but the diastereoselectivity of **11n** was 50:50 dr. When Pt/charcoal was employed instead of $Pd(OH)_2/C$, **2u** was completely consumed. However, reduction of both Ph and *N*-hydroxyimino groups to cyclohexyl and methylene groups was observed, respectively. After optimization studies using several non-chiral hydrogenation catalysts[24], we found that the hydrogenation using $Pd(OH)_2/C$ in 0.4*N* HCl in CPME/AcOH (1:9) proceeded smoothly to afford **11n** in 90% yield with 65:35 dr. When diastereoselectivity is not sufficiently high, separation of these diastereomers is usually carried out by recrystallization including chiral resolution, chiral derivatization, or the use of HPLC technology,[25] and we accomplished the separation of these diastereomers to obtain highly pure **11f**, **11h**, **11i**, and **11l**–**11n** by practical techniques of recrystallization and/or normal phase silica-gel column chromatography without any chiral sources.[26] All spectroscopic data pertaining to the produced di- and tripeptides **11a**–**11q** were accorded with those of the authentic samples prepared via a common synthetic method using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl) and 1-hydroxybenzotriazole (HOBt).[2d]

Scheme 4. Diastereoselective Hydrogenation[a,b]



[a]Conducted on a 1.0 mmol scale of **2a**. [b]Diastereomeric ratio was determined by ^{1}H NMR analysis (see Supporting Information). [c]Conducted on a 10 mmol scale of **2a**. [d]The dipeptides were isolated as their acetic acid salts. [e]After recrystallization with Et_2O. [f]In AcOH/MeOH (2:1) at 1.0 MPa pressure. [g]After separation of both diastereomers by normal phase silica-gel column chromatography. [h]The ratio of rotational isomers was determined by ^{1}H NMR analysis. [i]0.4*N* HCl in CPME/AcOH (1:9) was used as a solvent.

A plausible pathway of the process is outlined in Fig 2. As **1** can easily convert between two geometric conformers due to low free-energy barriers, two possible reaction pathways through geometric conformers **I** and **II** are proposed to account for the amidation of **1** with amino acid esters *via* substrate-control models. Initially **1** is transformed into either conformer **I** or **II** by overcoming the appropriate free-energy barrier (2.0 or 3.4 kcal/mol, respectively).[27]

Subsequently, the imino-*N* moiety of conformer **I** or the hydroxy-*O* moiety of conformer **II** may coordinate with the metal center (M) of the catalyst to form 5-membered intermediate **III** or 6-membered intermediate **IV**. According to the results of Scheme 3, the second proposal is more reasonable. Finally, the amine species, supplied by the *in situ* neutralization of the amino acid ester HCL salts using Et_3N, undergoes nucleophilic substitution at the activated carbonyl group of intermediate **III** or **IV** to form the desired amide products, such as **2a** (Fig 2a). In the classical amidation reaction, two pathways for racemization have been recognized. One is direct enolization after activation of the carbonyl group by coupling reagents. The other is the enolization of the oxazolones generated by deprotonation at N–H moieties of activated amino acid esters (Fig 2b).[2d] Our catalytic approach, however, can perfectly avoid the racemization because neither of these two events are possible in our new process. That is because the enolization in Fig 2b does not proceed due to the absence of an α-proton in **1**. Additonally, as the amidation reaction proceeds, coordination of the metal ion to the oxygen atom of *tert*-butyl ester is not allowed because of the instability of the nine-member ring intermediate as well as steric hindrance from the bulky *tert*-butyl group. Furthermore, the amide oxygen is not able to react with the bulky and non-activated *tert*-butyl ester to generate oxazolone intermediate (Fig 2c).

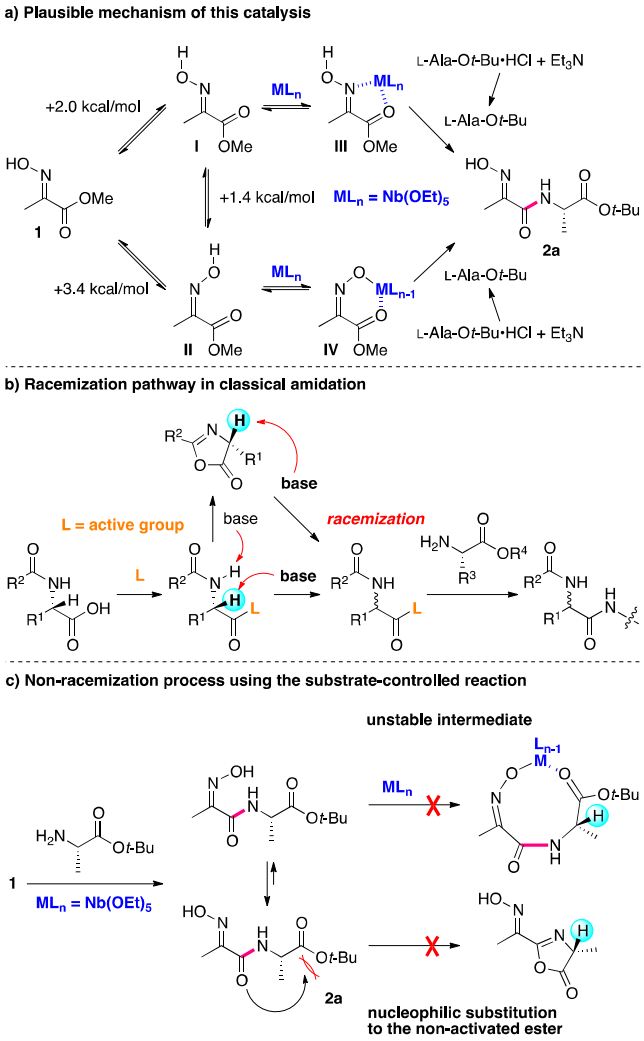


Figure 2. Plausible catalytic pathway.

■ CONCLUSION

We have explored a novel and powerful catalytic route for peptide synthesis based on substrate control. The use of a niobium catalyst to promote amide bond formation between *N*-hydroxyimino esters and amino acid *tert*-butyl esters bearing a range of functional groups produced high yields of the corresponding amides. Since the starting *N*-hydroxyimino esters are known to be prepared quantitatively in one step from the corresponding keto esters with $NH_2OH \cdot HCl$,[10b] from the corresponding esters with nitroso reagents,[10e] or by other

methods,[10a,c,d,f,g] the various artificial amino acids can be easily incorporated by this new catalytic method. The resulting amides were readily converted into their corresponding di- and tripeptides in excellent yields and excellent to good diastereoselectivities. Our developed protocol has several advantages compared to the conventional amidation techniques in liquid-phase peptide synthesis: 1) solvent-free, 2) catalytic, 3) high atom-efficiency, 4) no racemization, 5) the use of amino acid ester HCl salts, 6) chemoselective, 7) scalable, 8) applicable to unnatural amino acids. We expect that this novel substrate-controlled reaction will express the clear advantages over current peptide synthetic methods, associated with waste production, racemization, and limited applicability.

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Notes

The authors declare no competing financial interests.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and copies of spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures (PDF)

^{1}H-, ^{13}C-NMR spectral, and HPLC data (PDF)

Computational details (PDF)

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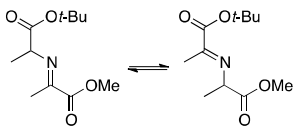
(14) The use of other solvents (*n*-pentane, *n*-hexane, *c*-pentane, *c*-hexane, diethyl ether, diisopropyl ether, THF, CPME, ethyl acetate, and toluene) also affected the obtained yields (67–95% yields).

(15) Only a mixture of equilibrium imines was produced.



(16) If the amidation proceeds with racemization at α-position of amino acids, diastereomers of **2d**, **2k**, **2l**, and **2w** should be produced. However, any diastereomers were not isolated in the formation of **2d**, **2k**, **2l**, and **2w**.

(17) Smith, G. G.; Sivakua, T. *J. Org. Chem.* **1983**, *48*, 627–634.

(18) HPLC data of **2f** was shown in Supporting Information.

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(20) We previously reported the catalytic amidation of esters containing a hydroxyl group as directing group at α-, β-, γ-, or δ-position, see ref. 9.

(21) ***E*-2y** can be isolated by normal phase silica-gel column chromatography. However, a portion of ***E*-2y** is rapidly isomerized to ***Z*-2y** in $CDCl_3$, so that **2y** was observed as an equilibrium mixture of 76:24 (*E*/*Z*) by ^1H NMR analysis. In contrast, isomerization of ***E*-2y** was not observed because of the stability of ***E*-2y** in CD_3OD.

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(23) Pd/C (K type) is commercially available from Wako Pure Chemical Ind., Ltd.

(24) To the best of our knowledge in regards to the methods for catalytic enantioselective hydrogenation of *N*-hydroxyimino esters, only three papers and a patent have been reported. However, these methods require high pressure of H_2 gas, and obtained yield and/or stereoselectivity are not satisfactory. See, (a) Krasik, P.; Alper, H. *Tetrahedron Asymm.* **1992**, *3*, 1283–1288. (b) Chan, A. S. C.; Chen, C.-C.; Lin, C.-W.; Lin, Y.-C.; Cheng, M.-C.; Peng, S.-M. *J. Chem. Soc., Chem. Commun.* **1995**, 1767–1768. (c) Xie, Y.; Mi, A.; Jiang, Y.; Liu, H. *Synth. Commun.* **2001**, *31*, 2767–2771. (d) Ryberg, P.; Berg, R. *PCT Int. Appl.* 2015178847, November 26, 2015.

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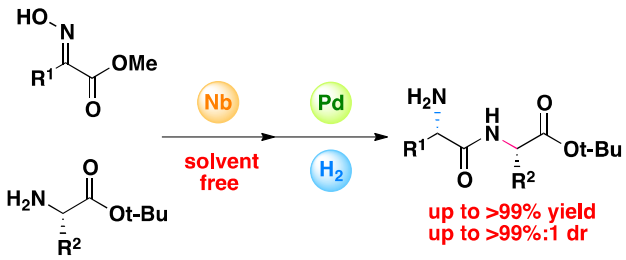
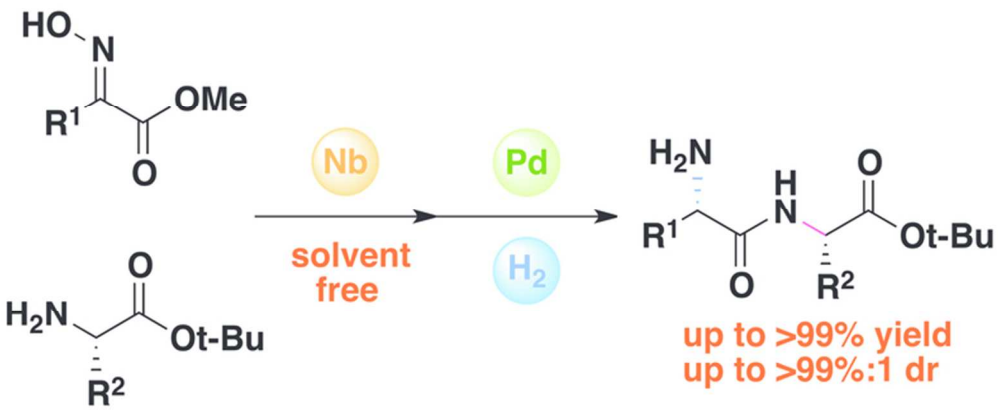

HO
N
R1
OMe
O
H2N
O
Ot-Bu
R2
Nb
Pd
H2
solvent
free
H2N
R1
H
N
O
O
Ot-Bu
R2
up to >99% yield
up to >99%:1 dr



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