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Palladium-Catalyzed Transposition of Allyloxy carbonyl-Protected Amines: Efficient One-Pot Formation of Amides and Dipeptides

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The synthetic utility of the N-(allyloxy carbonyl) (Alloc) substituent in α-amino acid derivatives is substantially extended beyond its well-known function as an amine protecting group. When the palladium-catalyzed deprotection is carried out by using tributyltin hydride as nucleophile (the Guibé method) in the presence of an active acylating agent a new acyl group is introduced on nitrogen. Successful acylating agents include carboxylic acid anhydrides, acid chlorides, and activated esters. A useful example of this methodology is the removal of the Alloc group in the presence of tert-butyl dicarbonate, which in essence amounts to a “transposition” to a Boc-protected α-amino acid derivative. More importantly, the use of activated N-protected α-amino ester derivatives (e.g., pentafluorophenyl esters) leads to dipeptides. This new method for peptide coupling proceeds very fast under mild conditions, in good to excellent yields, and without noticeable racemization.

Introduction

An important feature of synthetic organic chemistry is the choice of a proper protecting group, which allows various synthetic operations while leaving the protected functionality in the molecule intact. Nevertheless, it can be required in certain synthetic sequences to change protecting groups, for reasons of stability and reactivity. Therefore, the availability of methodologies to transform one protecting group into another one in a mild, straightforward, and preferably, one-pot procedure is of high potential interest.

The protecting groups that are probably most frequently used for amino groups are the carbamates. Carbamates utilized in peptide chemistry include the N-(fluorenylmethoxy)carbonyl (Fmoc), N-(benzyloxy carbonyl) (Z), N-(tert-butoxycarbonyl) (Boc), and more recently, the N-(allyloxy carbonyl) (Alloc) groups. A number of papers have appeared describing examples of one-pot transformations of certain carbamates into other carbamates, such as the conversion of a benzyl carbamate into the Boc group and the reverse process (eq 1) and the conversion of Fmoc into Boc (eq 2).4 The scope of these methods is, however, not very wide, as they involve the replacement of the protecting group by a specific other group. A more general method for the conversion of the Z, Boc, or Alloc group into a different carbamate protective group via the corresponding tert-butyldimethylsilyl carbamate was recently published by Sakaitani and Ohfune.5

During the course of our investigations toward synthetic approaches to α-amino acids using C,N-diacyliminium ion chemistry, a study on amine protecting groups was undertaken because the initially chosen groups, the methoxy carbonyl (Meoc) and the Z-group, did, for several reasons, not serve our purposes completely. Our attention was then drawn by the use of the Alloc group. This protecting group has aroused much interest in the last decade, in connection with the development of π-allylpalladium chemistry.6 The allyl carbamate is cleaved in a mild and selective manner using catalytic amounts of palladium.7

The generally accepted reaction pathway for the palladium-catalyzed cleavage of allyl carbamates is given in Scheme 1. Treatment of the protected amine 1 with the palladium(0) catalyst leads to the formation of the π-allylpalladium complex 2. In the presence of a nucleophile (or “allyl acceptor”), this complex is then transformed into the free amine 3, the allylated nucleophile 4, and carbon dioxide. Various types of nucleophiles have been used for this process, including potassium 2-ethyl...
hexanoate,\(^8\) 5,5-dimethyl-1,3-cyclohexanedione (dime-tone),\(^9\) dimethyl malonate,\(^10\) formic acid,\(^11,12\) morpholine,\(^13\) \(n\)-butylamine,\(^12\) diethylamine,\(^7\) and various sulfur nucleophiles.\(^7\) All of these methods are successful not only for Alloc-protected amines but also for alcohols that are protected with this group.

Although the Alloc group is usually cleaved satisfactorily by one of the above-mentioned methods, the deprotection can in some cases be accompanied by the formation of significant quantities of allylamines \(^5\) (Scheme 1), due to attack of the deprotected amine, instead of the external nucleophile, on the intermediate \(\pi\)-allylpalladium complex. Several research groups have studied the use of more efficient nucleophiles, in order to suppress this undesired competitive side reaction.\(^14\) A particularly interesting method, reported by Guibe and co-workers, involves the use of tributyltin hydride (Bu\(_3\)SnH) as the allyl acceptor.\(^15\) The mechanism proposed for this palladium-catalyzed hydrostannolytic cleavage of allyl carbanates is shown in Scheme 2. The first step in this process is the formation of the \(\pi\)-allylpalladium complex 2 from the starting Alloc-protected amine 1. In a subsequent step, Bu\(_3\)SnH transfers a hydride ion to this complex, leading to the tributyltin carbatate 7 with concomitant evolution of propene. The hydride transfer is extremely rapid and therefore suppresses the formation of allylamine 6 from the intermediate 2. The reason for this fast hydride transfer from Bu\(_3\)SnH, a reagent which is normally used for the transfer of hydrogen radicals, is not explained in this paper, although it is suggested that palladium(0) plays a role in this process. The tributyltin carbatate 7 is relatively stable and can, in principle, be isolated and characterized.\(^15\) However, the reaction is usually performed in the presence of a protic acid such as acetic acid, which causes the cleavage of 7 to yield the free amine 8, carbon dioxide, and the tributyltin ester.

In this paper we wish to report a variation of the above-mentioned Guibe conditions, which will be referred to as the “transprotection” or “transacylation” reaction. The discovery of this reaction led to the development of a mild and efficient one-pot conversion of Alloc-protected amines into Boc-protected amines and to a variety of amides. A mechanistic rationale accounting for these results will be presented. Furthermore, the application of this new methodology to the one-pot synthesis of dipeptides will be outlined in detail.\(^16\)

**Results and Discussion**

**Attempted Deprotections of 9.** During the course of our protective group studies, several literature methods\(^8\)\(^\text{-}\)\(^15\) were applied to the Alloc-protected allylglycine derivative 9. In the early experiments, the conditions of Noyori and co-workers were employed,\(^12\) using Pd(PPh\(_3\))\(_4\) in the presence of triphenylphosphate and formic acid. However, despite extensive experimentation with various conditions and workup procedures, the desired free amine could not be isolated after the reaction. Although there are several possible explanations, the exact cause of the problems was not clarified. Our attention was then caught by the Bu\(_3\)SnH method of Guibe.\(^15\) Thus, 9 was reacted with Pd(PPh\(_3\))\(_4\) and Bu\(_3\)SnH in CH\(_2\)Cl\(_2\) in the presence of acetic acid as the proton donor. Although the starting material had completely disappeared by TLC after 15 min, the product could not easily be isolated. An improvement was realized when the reaction was initiated in the absence of protic acid. When the reaction mixture was then treated with gaseous HCl the free amine was indeed formed, as could be inferred from the \(^1\)H NMR spectrum of the crude product. However, purification of the product present as the hydrochloride salt appeared difficult.

In a related study a suitable protecting group was sought for hydrazine derivatives such as 10. When this doubly (Alloc-) protected compound was reacted under Guibe’s conditions, but in the presence of an excess of acetic anhydride instead of acetic acid, a clean, quantita-

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The formation of product 12 is the net result of a one-pot replacement of the allyloxy carbonyl group by the acetyl group, so that this reaction can be called a transacylation or transprotection reaction.

As acetic anhydride can be regarded as an activated carbonyl compound, it was anticipated that other molecules containing activated carbonyl functionalities would, under these conditions, react in the same manner with Alloc-protected compounds, thus giving rise to the formation of various different amides. The results of such experiments are collected in Table 1.

The allylglycine derivative 9, the cyclopentenyl derivative 13, and Alloc-protected L-alanine methyl ester (Alloc-L-Ala-OMe) 14 were selected as Alloc protected a-amino acid derivatives serving as starting materials. The reactions described in entries 2–6 of Table 1 were carried out as follows: the Alloc compound and the activated carbonyl or sulfonyl compound (1.05 equiv) were dissolved at rt in dry CH₂Cl₂ under an atmosphere of dry nitrogen. Pd(PPh₃)₃ (0.02 equiv) was then added, and immediately after that Bu₃SnH (1.1 equiv) was added to the reaction mixture in one portion to exclude possible allylamination formation. The reaction was monitored by TLC and in most cases shown to be complete within 5 min. The solvent was then removed in vacuo, and the residue was chromatographed using flash chromatography.

Table 1 shows that the transprotection reaction has broad applicability. Various types of activated carbonyl moieties were reactive in this process, such as acyclic and cyclic anhydrides, carbonates, and acyl chlorides, all leading to a fast and mild one-pot conversion of the Alloc-compound into the newly protected amine in good to excellent yields. In the case of a succinic anhydride (entry 3), the initial product was directly converted to the methyl ester 21. Entry 6 illustrates that not only electrophilic carbonyl compounds but also tosyl chloride was successfully used in this process. However, when less reactive electrophiles such as esters, halides, tosylates, enones, and epoxides used, the desired transprotected product was not obtained.

As already reported previously, 10 the transprotection reaction turned out to be an excellent solution for our earlier encountered deprotection problems. γ,δ-Unsaturated Alloc-protected a-amino amides such as 9 and 13 could now be converted into the corresponding Boc derivatives 20 and 22 using this transprotection process. Subsequently, the Boc group could be cleaved in a facile way using formic acid to give the formate salt of the desired a-amino amide in high overall yield.

Mechanistic Discussion. A mechanism accounting for the results on the Alloc deprotection process obtained so far is outlined in Scheme 3. It can be regarded as a revision, or extension, of the mechanism postulated by Guibé and co-workers for the palladium-catalyzed hydrostannolytic deprotection of Alloc-protected amines (see Scheme 2). 15 The mechanism proposed here is corroborated by several observations that were made during our investigations.

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18 The latter compound was synthesized from L-Ala by using standard protective group chemistry. See, e.g.: Muller, E., Ed. *Methoden der Organischen Chemie (Houben-Weyl); Georg Thieme Verlag: Stuttgart, 1974; Band XV/1 + 2 (Synthese von Peptiden).
Evolution of gas from the reaction mixture was observed immediately after the addition of Bu₃SnH. However, in some of the reactions a second gas evolution was noticed after a reaction time of 10–30 min, sometimes spontaneous, sometimes after opening of the reaction flask. These observations substantiate the proposal that propene is evolved from the reaction mixture immediately after hydride addition to give the intermediate tributyltin carbamate (29, see Scheme 3). The occurrence of the second part of the reaction, which probably involves the liberation of CO₂, seems to depend on variables that are not yet fully understood.

The course of the reactions appeared to be highly dependent on the purity of the Bu₃SnH used. When a fresh or sufficiently purified batch of this reagent was used, the reactions proceeded as described above. However, when lower quality Bu₃SnH was used, the desired reaction was not observed. Apparently, the presence of certain contaminants in this reagent dramatically influences the outcome of the reaction.

As mentioned previously, the Bu₃SnH is thought to act as a very fast hydride donor in this process. There are only a few cases known in which this reagent, usually being a typical free-radical reducing agent, exhibits hydride donor properties. One of these cases is the palladium(0)-catalyzed reduction of activated double bonds, e.g., the conjugate reduction of α,β-unsaturated carbonyl compounds. It has been shown that this reaction occurs via addition of the tin hydride across the double bond, followed by hydrolytic removal of the tin by aqueous acid. Although there is evidence that the initial step, the so-called hydrosyntilation of the double bond, occurs through an ionic rather than a radical mechanism, the role of the palladium in this process has not been fully clarified. However, it is suggested that palladium activates the Sn–H bond, probably via an oxidative addition process to form an intermediate palladium hydride species.

We suggest that in the reaction described here the palladium plays a similar role in the process of hydride transfer from Bu₃SnH to the allyl moiety (Scheme 3). This is envisaged to occur by reaction of the initially formed π-allylpalladium complex (in which the carbamate portion is bound as a ligand to palladium rather than present as a free counterion, as was suggested by Guibé) with the tin hydride to give the tin carbamate and an intermediate palladium hydride species. The hydride is then transferred to the metal to the allyl cation to release propene. That the use of unpurified Bu₃SnH prevents the reaction can be explained by assuming that the palladium species, which is employed in only catalytic amounts, is poisoned by certain contaminants present in this reagent.

We have shown in this paper that the use of a highly electrophilic carbonyl species (EX, Scheme 3) as a replacement for a protic acid (HX, Scheme 2) leads to transacylation instead of deprotection. Although the details of this process remain to be clarified, we suggest that the presence of the tin significantly enhances the nucleophilicity of the nitrogen in the intermediate tin carbamate. Hence, this intermediate can undergo a facile reaction with the active carbonyl compound via a six-membered ring transition state (eq 5), with the evolution of CO₂ as a possible additional driving force, to furnish the transprotection product.

Although the interaction of palladium with the Sn–H (and the Sn–Sn) bond is not a well-documented process, it has been reported that metals such as palladium(0) can insert in Si–H and Si–Si bonds. Furthermore, the successful conversion of allyl carbamates into silyl carbamates by using palladium as the catalyst and Et₃SiH or silylated amines as the nucleophile is known. Therefore, Bu₃SnH was replaced by Et₃SiH as the hydride donor in an attempted transprotection reaction. However, when using standard conditions no formation of transprotection product was observed, indicating that the presence of tin in the intermediate tin carbamate is essential for the successful conversion into the transprotection product. Further work is necessary, however, to comprehend the lack of desired reactivity of Et₃SiH in this process, particularly because the use of this hydride donor instead of Bu₃SnH would be preferable.

The Transprotection: Synthesis of Dipeptides.

Generally speaking, the coupling of two peptide fragments requires three separate reaction steps, namely: (i) deprotection of the amino nitrogen of the first fragment, (ii) activation of the carboxylic moiety of the second fragment; and (iii) coupling of the two fragments that result from these operations. In some cases, the

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reagents such as dicyclohexylcarbodiimide (DCC).

transacylation, without necessitating the transprotection process described above to the synthesis furnish peptides in a clean, mild and rapid way. Most importantly, however, these peptide structures would be obtained from Alloc-protected fragments using a direct transacylation, without necessitating the removal of the amine-protective group in an initial, separate step.

Obtained from Alloc-protected fragments using a direct esterification, no acid derivatives and a number of active α-amino esters. The Alloc-protected fragments used included tfluorophenyl (OPFP) and the N-hydroxysuccinimide activating the carboxylic moiety of dipeptides, starting from various Alloc-protected α-amino esters, as well as two different activating groups that are well-known in peptide chemistry, namely the pentfluorophenyl (OPFP) and the N-hydroxysuccinimide (OSu) ester. These fragments were easily prepared following standard procedures.15

An example of the coupling reactions performed with the latter being prepared by standard procedures.15

When the standard transprotection procedure was used, racemic Alloc-All-O-Me (31) was reacted with 1.05 equiv of Fmoc-Gly-OPFP (33) in the presence of a catalytic amount of Pd(PPh₃)₄ and 1.1 equiv of Bu₄SnH. The reaction was finished within a few minutes at rt and gave, after concentrating the mixture in vacuo and purification by flash chromatography, the dipeptide Fmoc-Gly-All-O-Me (37) in high yield (94%).

In a similar fashion, a number of other dipeptides were prepared. The results of these reactions (Table 2) show that the transprotection process can be successfully applied to the synthesis of dipeptides, providing products in an extremely facile one-pot reaction in good to excellent (unoptimized) yields. The stereochemical integrity of the peptide coupling procedure, already reported for the deprotection by Guibe and co-workers,16 was confirmed by synthesizing Boc-i-Ala-i-Ala-O-Me (46) from Boc-L-Ala-OPFP (32) and Alloc-L-Ala-O-Me (14, entry 9). The specific rotation of 46, which was obtained as the sole product in high yield, was found to be identical to the literature value.26

The method described here could be even further simplified as shown in entry 10. Instead of preparing the active ester beforehand it was also found possible to activate the free acid (Boc-i-Ala-OH) in situ by mixing it with DCC (1 equiv) and HOBT (1 equiv), resulting in the HOBT ester. This mixture 38 was then used as the active ester fragment in the coupling reaction. This gave the desired dipeptide 46 in a very high yield. In this way, the three separate reaction steps that were mentioned above as being the required steps for achieving peptide bond formation, were combined into a single, easy, and effective procedure.

**Experimental Section**

**General Information.** Experimental techniques and analytical measurements were applied as previously described.18 Tetrakis(triphenylphosphine) palladium (Pd(PPh₃)₄) was purchased from Aldrich and stored at 4 °C under exclusion of light. The preparation of 2-[(allyloxy carbonylamino)-N-methoxy-4-pentenamide (Alloc-All-NHOMe; 9), 2-[(allyloxy carbonylamino)-2-(3-cyclopentenyl)-N-methoxycacetamide (13), 2-[(tert-butyloxy carbonyl)amino]-N-methoxy-4-pentenamide (20) and 2-[(tert-butyloxy carbonylamino)-2-(3-cyclopentenyl)-N-methoxycacetamide (22) were described previously.19 Fmoc-Gly-...
OPFP (33) and Fmoc-1-Ala-OPFP (34) were provided by Organon B. V. (Oss, The Netherlands). Boc-L-Leu-OSu (35) and Boc-L-Phe-OSu (36) were purchased from Fluka.

**Alloc-1-Ala-OME (14).** A vigorously stirred solution of L-alanine (10 g, 0.11 mol) in a 2 N aqueous solution of NaOH (56 mL, 0.11 mol) was cooled to 0 °C. Allyl chloroformate (12.5 mL, 0.12 mol) and 2 N aqueous NaOH (60 mL, 0.12 mol) were added in a few portions over a period of 30 min. After being stirred at 0 °C for 1 h, the reaction mixture was acidified with concentrated HCl and extracted with EtOAc (3 x 250 mL). The combined organic fractions were washed with 2 N aqueous HCl and water, dried (Na2SO4), and concentrated in vacuo to give Alloc-L-Ala-OMe (5.88 g, 34 mmol, 30%) as a colorless oil. 1H NMR: 10.6 (s, 1 H), 6.85 (brs, 1 H), 5.98-5.79 (m, 1 H), 5.53 (d, J = 7.4 Hz, 1 H), 5.33-5.17 (m, 2 H), 4.55 (d, J = 5.4 Hz, 2 H), 4.41-4.28 (m, 1 H), 1.44 (d, J = 7.2 Hz, 3 H). One g of this compound was dissolved in MeOH (12 mL), and concentrated sulfuric acid was added. The reaction mixture was stirred at rt for 4 h. It was then poured into ice-cold aqueous NaHCO3 and extracted with CHCl3 (5 x) as a colorless oil. 1H NMR: 5.92-5.78 (m, 1 H), 5.49 (d, J = 5.7 Hz, 1 H), 5.28-5.12 (m, 2 H), 4.51 (d, J = 5.1 Hz, 2 H), 4.35-4.28 (m, 1 H), 3.79 (s, 3 H), 1.35 (d, J = 7.2 Hz, 3 H).

**General Procedure A for the Pd(0)-Catalyzed Coupling Reactions of 9, 13, and 14 with Activated Carbonyl Compounds.** The activated carbonyl compound (1.05-2.5 equiv) was added to a 0.05 M solution of the N-Alloc-α-amino acid derivative (9, 13, or 14) in THF or CH2Cl2. To this mixture a solution of Pd(PPh3)4 (0.02 equiv) in the same solvent was added, immediately followed by the addition of Bu3SnH (1.1 equiv) in one portion. The mixture was stirred at rt and monitored by TLC, which generally showed the reaction to be complete after 2 minutes. After another 20-30 min the reaction mixture was concentrated in vacuo and the residue was chromatographed.

**2-(Acetylamino)-N-methoxy-4-pentanamide (12).** According to the general procedure A, starting from 53 mg (0.23 mmol) of 9, 54 μL (58 mg, 0.57 mmol) of acetic anhydride (15), 6 mg (5.2 μmol) of Pd(PPh3)4, 68 μL (74 mg, 0.25 mmol) of Bu3SnH, and 5.0 mL of CH2Cl2, there was obtained 25 mg (0.13 mmol, 58%) of 12, as a solid, after flash chromatography, Rf 0.37 (CH2Cl2/acetone 2:1).

**General Procedure B for the Pd(0) Catalyzed Coupling Reactions of Alloc-Protected α-Amino Acids with Activated α-Amino Esters.** The activated
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α-amino ester (1.05 equiv) was added to a 0.05 M solution of the N-Alloc-α-amino acid derivative in THF or CH₂Cl₂. To this mixture was added Pd(PPh₃)₄ (0.02 equiv) (as such or as a 4 mM solution of the same solvent), immediately followed by the addition of Bu₃SnH (1.1 equiv) in one portion. The mixture was stirred at rt and monitored by TLC, which generally showed the reaction to be complete after 2 min. The reaction mixture was then concentrated in vacuo, and the residue was chromatographed.

Fmoc-Gly-All-OME (37). According to the general procedure B, starting from 49 mg (0.23 mmol) of 31, 110 mg (0.24 mmol) of 33, 5.4 mg (4.6 μmol) of Pd(PPh₃)₄, 69 μL (74 mg, 0.26 mmol) of Bu₃SnH, and 4.6 mL of CH₂Cl₂, there was obtained 89 mg (0.22 mmol, 94%) of Fmoc-Gly-All-OMe, as a colorless oil which solidified upon standing, after flash chromatography (EtOAc/hexane 3:1), as a mixture of diastereomers (50:50).

IR (CHCl₃): 3420, 1730, 1710, 1675, 1495. ¹H NMR (300 MHz): 10.36 and 10.30 (s, 1 H), 5.77–5.62 (m, 2 H), 5.60 (d, J = 6.9 Hz, 1 H) and 5.36 (d, J = 6.2 Hz, 1 H), 5.14–5.04 (m, 2 H), 4.58–4.42 (m, 1 H), 4.11–4.05 (m, 1 H), 3.71 and 3.70 (s, 3 H), 2.95–2.47, 1.64–1.31 (m, 12 H), 0.69 (s, 6 H). ¹C NMR (50 MHz, most carbons show two peaks because of diastereomers): 173.2 and 173.1, 168.1, 156.4, 143.4 and 140.9, 132.1 and 132.0, 127.3, 126.7, 124.5 and 119.5, 118.2, 66.6, 63.4, 50.3 and 50.0, 46.7, 35.8, 17.4.

Boc-L-Leu-All-NHOMe (43). According to the general procedure B, starting from 31 mg (0.14 mmol) of 9, 47 mg (0.14 mmol) of 35, 3.2 mg (2.7 μmol) of Pd(PPh₃)₄, 40 μL (43 mg, 0.15 mmol) of Bu₃SnH, and 2.7 mL of CH₂Cl₂, there was obtained 38 mg (0.11 mmol, 79%) of 43, as a colorless oil, after flash chromatography, Rf = 0.34 (EtOAc/hexane 2:1), as a mixture of diastereomers (50:50).

IR (CHCl₃): 3460, 3300, 1750, 1640, 1510. ¹H NMR (300 MHz): 10.38 and 10.30 (s, 1 H), 5.68–5.54 (m, 1 H), 5.48 (d, J = 6.9 Hz, 1 H) and 5.36 (d, J = 6.2 Hz, 1 H), 5.14–5.04 (m, 2 H), 4.58–4.42 (m, 1 H), 4.11–4.05 (m, 1 H), 3.71 and 3.70 (s, 3 H), 2.95–2.47, 1.64–1.31 (m, 12 H), 0.69 (s, 6 H). ¹C NMR (50 MHz, most carbons show two peaks because of diastereomers): 173.2 and 173.0, 168.0, 155.8, 132.1 and 132.0, 118.9 and 118.8, 80.3, 64.0, 53.4 and 50.2, 41.1, 36.2 and 36.0, 28.2, 24.7, 24.6, 22.8 and 22.7, 22.0 and 21.8.

Boc-L-Phe-All-NHOMe (44). According to the general procedure B, starting from 31 mg (0.14 mmol) of 9, 158 mg (0.44 mmol) of 36, 10.1 mg (8.7 μmol) of Pd(PPh₃)₄, 130 μL (140 mg, 0.48 mmol) of Bu₃SnH, and 8.8 mL of CH₂Cl₂, there was obtained 135 mg (0.35 mmol, 79%) of 44, after flash chromatography (CH₂Cl₂/MeOH 19:1), as a mixture of diastereomers (50:50). IR: 3420, 3280, 1750–1600, 1490. ¹H NMR (300 MHz): 10.36 and 10.12 (2 x, s, 1 H), 7.25–7.18 (m, 5 H), 6.99 (d, J = 6.9 Hz, 1 H), 5.75–5.45 (m, 2 H), 5.08–5.02 (m, 2 H), 4.47–4.32 (m, 2 H), 3.69 (s, 3 H), 3.10–3.03 (m, 2 H), 2.45–2.36 (m, 2 H), 1.37 and 1.36 (s, 9 H). ¹C NMR (50 MHz, some carbons show two peaks because of diastereomers): 171.9 and 171.7, 167.8, 155.6, 136.3, 132.4 and 132.3, 129.2, 128.5, 126.9 and 118.9, 118.9, 80.3, 64.0, 53.4 and 50.2, 41.1, 36.2 and 36.0, 28.2, 24.7, 24.6, 22.8 and 22.7, 22.0 and 21.8.

Fmoc-L-Ala-All-NHOMe (45). According to the general procedure B, starting from 9 mg (0.44 mmol) of 14, 206 mg (0.44 mmol) of 34, 10 mg (8.9 μmol) of Pd(PPh₃)₄, 135 μL (142 mg, 0.49 mmol) of Bu₃SnH, and 9.0 mL of THF, there was obtained 88 mg (0.22 mmol, 50%) of 45, as a solid, after flash chromatography, Rf = 0.5 (EtOAc/ hexane 3:1). ¹H NMR (200 MHz): 7.74 (d, J = 7.3 Hz, 2 H), 7.58 (d, J = 7.2 Hz, 2 H), 7.42–7.25 (m, 4 H), 6.87 (d, J = 6.5 Hz, 1 H), 5.68 (d, J = 7.7 Hz, 1 H), 4.62–4.50 (m, 2 H), 4.38–4.22 (m, 2 H), 3.70–3.60 (m, 2 H), 2.95–2.80 (m, 2 H), 1.43–1.36 (m, 2 H), 1.35–1.28 (m, 2 H), 1.25–1.18 (m, 2 H), 0.90–0.84 (m, 2 H). ¹C NMR (200 MHz): 171.9, 167.8, 155.6, 136.3, 132.4 and 132.3, 129.2, 128.5, 126.9 and 118.9, 118.9, 80.3, 64.0, 53.4 and 50.2, 41.1, 36.2 and 36.0, 28.2, 24.7, 24.6, 22.8 and 22.7, 22.0 and 21.8.
1H), 4.39–4.30 (m, 3H), 4.23–4.16 (m, 1H), 3.72 (s, 3H), 1.42–1.37 (m, 6H). 13C NMR (50 MHz): 173.1, 172.0, 155.9, 143.8, 141.2, 127.7, 127.0, 125.0 and 119.9, 67.1, 52.4, 49.1, 48.0, 47.1, 18.8, 18.1.

Boc-L-Ala-L-Ala-OMe (46) from the O-Activated Amino Acid 32. According to the general procedure B, starting from 308 mg (1.64 mmol) of 14, 613 mg (1.73 mmol) of 32, 40.0 mg (34.6 pmol) of Pd(PPh3)4, 25.5 mg (1.81 mmol) of Bu3SnH, and 10.0 mL of CH2Cl2, there was obtained 404 mg (1.47 mmol, 90%) of 46, as a solid, after flash chromatography, Rf 0.36 (EtOAc/hexane 2:1). 1H NMR (200 MHz): 6.83 (d, J = 6.8 Hz, 1H), 5.19 (d, J = 7.5 Hz, 1H), 4.61–4.45 (m, 1H), 4.30–4.10 (m, 1H), 3.71 (s, 3H), 1.41–1.31 (m, 12H). 13C-NMR (50 MHz): 173.1, 172.3, 80.1, 52.3, 50.1, 48.0, 28.3, 18.3, 18.2. HRMS: calcd for C18H28N2O5 274.1529, found 274.1523. [α]25D: −57.7 (c 1.05; MeOH).

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Supplementary Material Available: Copies of 1H and 13C spectra of compounds 14, 20, 22–24, 37, and 39–46 (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm edition of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.