Palladium-Catalyzed Transprotection of Allyloxycarbonyl-Protected Amines: Efficient One-Pot Formation of Amides and Dipeptides

Eric C. Roos,[1] Pablo Bernabé,[2] Henk Hiemstra,* and W. Nico Speckamp*

Department of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Bernard Kaptein and Wilhelmus H. J. Boesten

DSM Research, Department of Bio-Organic Chemistry, P.O. Box 18, 6160 MD Geleen, The Netherlands

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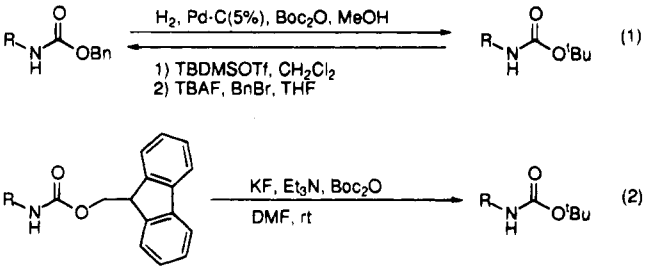
The synthetic utility of the *N*-(allyloxycarbonyl) (Alloc) substituent in α-amino acid derivatives is substantially extended beyond its well-known function as an amine protecting group. When the palladium-catalyzed deprotection is carried out by using tributyltin hydride as nucleophile (the Guibé method) *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 "transprotection" 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*-(benzyloxycarbonyl) (Z), *N*-(*tert*-butoxycarbonyl) (Boc), and more recently, the *N*-(allyloxycarbonyl) (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[3ab] and the reverse process (eq 1)[3c] 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]



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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 methyloxycarbonyl (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-

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(1) Present address: DSM Research, Department of Bio-Organic Chemistry, P. O. Box 18, 6160 MD Geleen, The Netherlands.

(2) ERASMUS exchange student on leave from the University of Santiago, Santiago de Compostela, Spain, Jan–June 1991.

(3) (a) Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 2983. (b) Bajwa, J. S. *Tetrahedron Lett.* **1992**, *33*, 2955. (c) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543.

(4) Li, W.-R.; Jiang, J.; Joullié, M. M. *Tetrahedron Lett.* **1993**, *34*, 1413.

(5) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.

(6) (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin, 1980; p 125–132.

(7) Some examples: (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991; pp 331–333. (b) Kocienski, P. J. *Protecting Groups*; Thieme: New York, 1994; pp 199–201. (c) Genêt, J. P.; Blart, E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Bernard, J. M. *Synlett* **1993**, 680, and refs cited therein.

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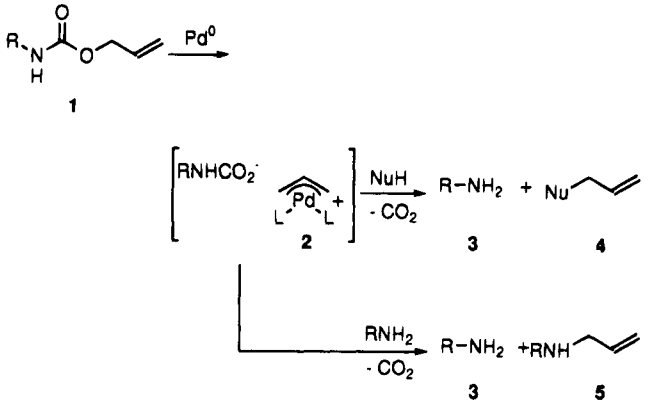
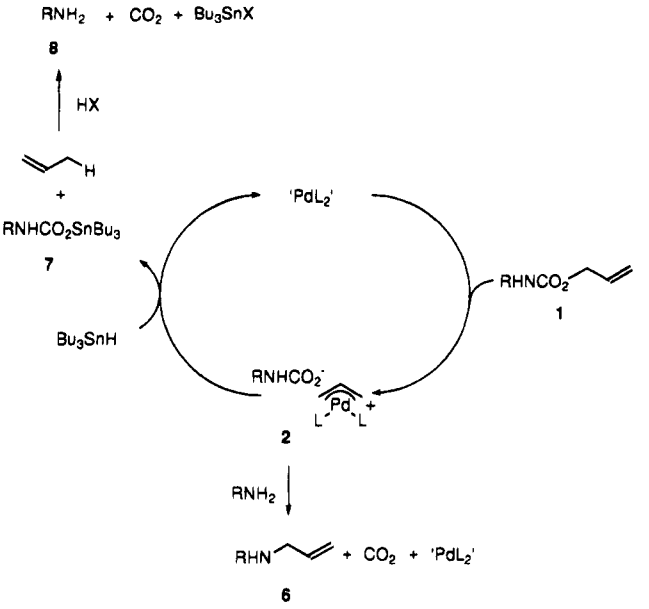
Scheme 1



Scheme 2



hexanoate,[8] 5,5-dimethyl-1,3-cyclohexanedione (dimedone),[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 π-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 Guibé and co-workers, involves the use of tributyltin hydride (Bu_3SnH) as the allyl acceptor.[15] The mechanism proposed for this palladium-catalyzed hydrostannolytic cleavage of allyl carbamates is shown in Scheme 2. The first step in this process is the formation of the π-allylpalladium complex **2** from the starting Alloc-protected amine **1**. In a subsequent step, Bu_3SnH transfers a hydride ion to this complex, leading to the tributyltin carbamate **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_3SnH, 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 carbamate **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 Guibé 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]

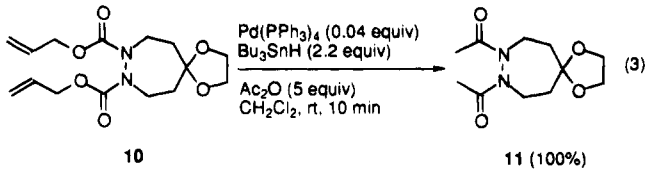
Results and Discussion

Attempted Deprotections of 9. During the course of our protective group studies, several literature methods[7-15] were applied to the Alloc-protected allylglycine derivative **9**. In the early experiments, the conditions of Noyori and co-workers were employed,[12b] using $Pd(PPh_3)_4$ in the presence of triphenylphosphine 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_3SnH method of Guibé.[15] Thus, **9** was reacted with $Pd(PPh_3)_4$ and Bu_3SnH in CH_2Cl_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 ^1H 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 Guibé's conditions, but in the presence of an excess of acetic anhydride *instead of acetic acid*, a clean, quantita-

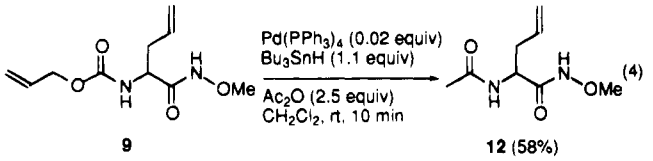
(8) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587.
(9) Kunz, H.; Unverzagt, C. *Angew. Chem.* **1984**, *96*, 426.
(10) Boullanger, P.; Descotes, G. *Tetrahedron Lett.* **1986**, *27*, 2599.
(11) Minami, I.; Ohashi, Y.; Shimizu, I.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 2449.
(12) (a) Hayakawa, Y.; Kato, H.; Uchiyama, M.; Kajino, H.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 2400. (b) Hayakawa, Y.; Wakabayashi, S.; Kato, H.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 1691.
(13) Kunz, H.; Waldmann, H. *Angew. Chem.* **1984**, *96*, 49.
(14) Some examples: (a) Merzouk, A.; Guibé, F.; Loffet, A. *Tetrahedron Lett.* **1992**, *33*, 477. (b) Blart, E.; Savignac, M.; Genêt, J. P. French Patent 92 04621.
(15) Dangles, O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984.
(16) Preliminary communication: (a) Roos, E. C.; Bernabé, P.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J. *Tetrahedron Lett.* **1991**, *32*, 6633. See also: (b) Roos, E. C.; Mooiweer, H. H.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J.; Kamphuis, J. *J. Org. Chem.* **1992**, *57*, 6769.

tive conversion into the corresponding *N,N*-diacetyl compound **11** was observed (eq 3).[17]



This fortuitous result prompted us to consider similar reactions with our amino acid derivatives. It was reasoned that if the Alloc group could be efficiently converted into a different acyl or alkoxycarbonyl group, the latter might be subsequently removed in a straightforward fashion.

The Transprotection: Synthesis of Amides and Carbamates. As a first experiment, analogous conditions as used for the conversion of **10** to **11** were applied to the Alloc-protected α-amino acid derivative **9**. Thus, **9** was reacted with a catalytic amount of $Pd(PPh_3)_4$ and 1.1 equiv of Bu_3SnH, in the presence of 2.5 equiv of acetic anhydride (eq 4), which furnished after a smooth and



rapid reaction the *N*-acetyl-α-amino acid derivative **12** in a moderate yield (58%). The formation of product **12** is the net result of a one-pot replacement of the allyloxycarbonyl 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**,[16b] and Alloc-protected L-alanine methyl ester (Alloc-L-Ala-OMe) **14**[18] were selected as Alloc protected α-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 CH_2Cl_2 under an atmosphere of dry nitrogen. $Pd(PPh_3)_4$ (0.02 equiv) was then added, and *immediately* after that Bu_3SnH (1.1 equiv) was added to the reaction mixture in one portion to exclude possible allylamine 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.

Table 1. Pd(0)-Catalyzed Coupling Reactions of Alloc Compounds

entry	precursor	carbonyl compound	product (yield)
1	Alloc-All-NHOMe **9**	**15**	**12** (58%)
2	**9**	**16**	**20** (89%)
3	**9**	**17**	**21** (60%)[a]
4	**13**	**16**	**22** (92%)
5	Alloc-Ala-OMe **14**	**18**	**23** (89%)
6	**14**	Ts-Cl **19**	**24** (89%)

[a] After treatment of the crude mixture with HCl/MeOH.

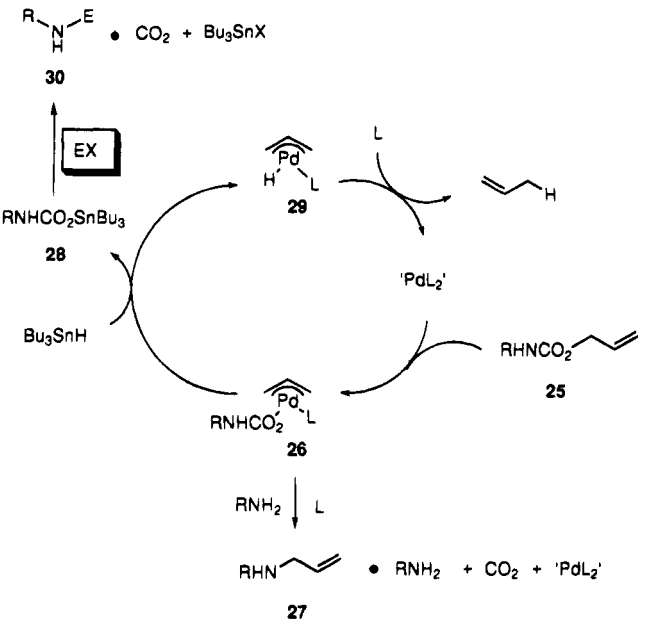
As already reported previously,[16b] the transprotection reaction turned out to be an excellent solution for our earlier encountered deprotection problems. γ,δ-Unsaturated Alloc-protected α-amino amides such as **9** and **13** could now be converted into the corresponding Boc derivatives **20** and **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 α-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.

(17) Rutjes, F. P. J. T. *Synthesis of Cyclic Hydrazines and α-Hydrazino Acid Derivatives via N-Acylhydrazonium Ions*. Ph.D. Thesis, University of Amsterdam, 1993.

(18) The latter compound was synthesized from L-Ala by using standard protective group chemistry. See, e.g.: Müller, E., Ed. *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1974; Band XV/1 + 2 (Synthese von Peptiden).

Scheme 3



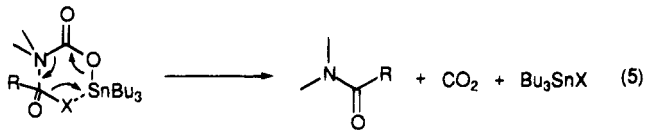
Evolution of gas from the reaction mixture was observed immediately after the addition of Bu_3SnH. However, in some of the reactions a second gas evolution was noticed after a reaction time of 10–30 min, sometimes spontaneous, sometimes after opening of the reaction flask. These observations substantiate 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 CO_2, 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 Bu_3SnH used. When a fresh or sufficiently purified batch of this reagent was used, the reactions proceeded as described above. However, when lower quality Bu_3SnH 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 Bu_3SnH 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.[19] One of these cases is the palladium(0)-catalyzed reduction of activated double bonds,[20] e.g., the conjugate reduction of α,β-unsaturated carbonyl compounds.[21] 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 hydrostannation of the double bond, occurs through an ionic rather than a radical mechanism,[19-21] 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.[20]

We suggest that in the reaction described here the palladium plays a similar role in the process of hydride transfer from Bu_3SnH to the allyl moiety (Scheme 3). This is envisaged to occur by reaction of the initially formed π-allylpalladium complex **26** (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 **28** and an intermediate palladium hydride species **29**. The hydride is then transferred *via* the metal to the allyl cation to release propene. That the use of unpurified Bu_3SnH 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



(5)

of CO_2 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.[22,23] Furthermore, the successful conversion of allyl carbamates into silyl carbamates by using palladium as the catalyst and Et_3SiH[5] or silylated amines[14a] as the nucleophile is known. Therefore, Bu_3SnH was replaced by Et_3SiH 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 Et_3SiH in this process, particularly because the use of this hydride donor instead of Bu_3SnH would be preferable.

The Transprotection: Synthesis of Dipeptides. Generally speaking, the coupling of two peptide fragments[18,24] requires three separate reaction steps, namely: (i) deprotection of the amine 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

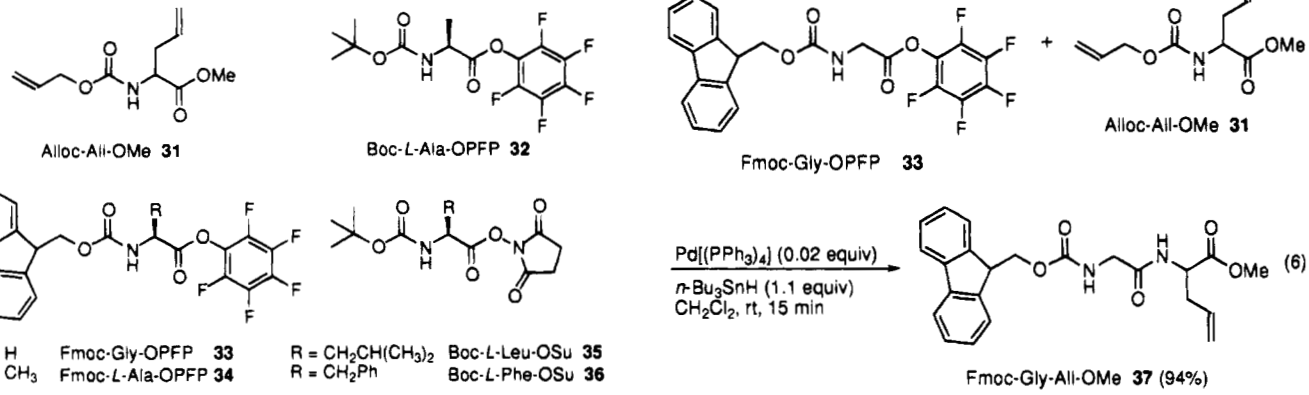
(19) Keinan, E.; Gleize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477.
(20) Guibé, F.; Zigna, A.; Balavoine, G. *J. Organomet. Chem.* **1986**, *306*, 257.
(21) Four, P.; Guibé, F. *Tetrahedron Lett.* **1982**, *23*, 1825.
(22) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
(23) See, e.g.: Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487 and references cited therein.
(24) Some recent examples: (a) Carpino, L. A.; Mansour, E.-S. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611. (b) Carpino, L. A.; Chao, H. G.; Beyermann, M.; Bienert, M. *J. Org. Chem.* **1991**, *56*, 2635. (c) Thaler, A.; Seebach, D.; Cardinaux, F. *Helv. Chim. Acta* **1991**, *74*, 617. (d) Thaler, A.; Seebach, D.; Cardinaux, F. *Helv. Chim. Acta* **1991**, *74*, 628.

Table 2. Pd(0)-Catalyzed Synthesis of Dipeptides

entry	precursor	active α-amino ester	product (yield, %)
1	Alloc-All-OMe **31**	Fmoc-Gly-OPFP (**33**)	Fmoc-Gly-All-OMe (**37**) (94)
2	**31**	Fmoc-L-Ala-OPFP (**34**)	Fmoc-L-Ala-All-OMe (**39**) (99)
3	**31**	Boc-L-Leu-OSu (**35**)	Boc-L-Leu-All-OMe (**40**) (93)
4	Alloc-All-NHOMe **9**	Fmoc-Gly-OPFP (**33**)	Fmoc-Gly-All-NHOMe (**41**) (80)
5	**9**	Fmoc-L-Ala-OPFP (**34**)	Fmoc-L-Ala-All-OMe (**42**) (64)
6	**9**	Boc-L-Leu-OSu (**35**)	Boc-L-Leu-All-NHOMe (**43**) (79)
7	**9**	Boc-L-Phe-OSu (**36**)	Boc-L-Phe-All-NHOMe (**44**) (79)
8	Alloc-L-Ala-OMe **14**	Fmoc-L-Ala-OPFP (**34**)	Fmoc-L-Ala-L-Ala-OMe (**45**) (50)
9	**14**	Boc-L-Ala-OPFP (**32**)	Boc-L-Ala-L-Ala-OMe (**46**) (90)[a]
10	**14**	Boc-L-Ala-OH/DCC/HOBT (**38**)	Boc-L-Ala-L-Ala-OMe (**46**) (96)[b]

[a] $[\alpha]^{27}_D$ −57.7 (*c* 1.05; MeOH) (lit.[25] $[\alpha]^{20}_D$ −57.8 (*c* 1; MeOH). [b] $[\alpha]^{27}_D$ −53.3 (*c* 1.02; MeOH).

Chart 1



second and third step can be performed in one pot by activating the carboxylic moiety *in situ* using coupling reagents such as dicyclohexylcarbodiimide (DCC).

We set out to test the possibility of applying the transprotection process described above to the synthesis of peptides. This method would, if equally successful, 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.

Our study was directed at the synthesis of a number of dipeptides, starting from various Alloc-protected α-amino acid derivatives and a number of active α-amino esters. The Alloc-protected fragments used included Alloc-All-NHOMe (**9**), Alloc-Ala-OMe (**14**), and Alloc-All-OMe (**31**), the latter being prepared by standard *N*-acyliminium ion chemistry (Chart 1). The active α-amino esters **32**−**36**, employed in these reactions, contained different protective groups on the amine nitrogen (Boc and Fmoc), as well as two different activating groups that are well-known in peptide chemistry, namely the pentafluorophenyl (OPFP) and the *N*-hydroxysuccinimide (OSu) ester. These fragments were easily prepared following standard procedures.[18]

An example of the coupling reactions performed with these compounds is depicted in eq 6. When the standard transprotection procedure was used, racemic Alloc-All-OMe (**31**) was reacted with 1.05 equiv of Fmoc-Gly-OPFP (**33**) in the presence of a catalytic amount of $Pd(PPh_3)_4$ and 1.1 equiv of Bu_3SnH. 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-OMe (**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 process, already reported for the deprotection by Guibé and co-workers,[15] was confirmed by synthesizing Boc-L-Ala-L-Ala-OMe (**46**) from Boc-L-Ala-OPFP (**32**) and Alloc-L-Ala-OMe (**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.[25]

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-L-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.[16b] Tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) was purchased from Aldrich and stored at 4 °C under exclusion of light. The preparation of 2-[(allyloxycarbonylamino]-*N*-methoxy-4-pentenamide (Alloc-All-NHOMe; **9**), 2-[(allyloxycarbonyl)amino]-2-(3-cyclopentenyl)-*N*-methoxyacetamide (**13**), 2-[(*tert*-butyloxycarbonyl)amino]-*N*-methoxy-4-pentenamide (**20**) and 2-[(*tert*-butyloxycarbonyl)amino]-2-(3-cyclopentenyl)-*N*-methoxyacetamide (**22**) were described previously.[16b] Fmoc-Gly-

(25) Ueda, T.; Saito, M.; Kato, T.; Izumiya, N. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 568.

OPFP (**33**) and Fmoc-L-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-L-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 × 250 mL). The combined organic fractions were washed with 2 N aqueous HCl and water, dried (Na_2SO_4), and concentrated *in vacuo* to give Alloc-L-Ala-OH (5.88 g, 34 mmol, 30%) as a colorless oil. ^{1}H 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 $NaHCO_3$ and extracted with $CHCl_3$ (3×). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give 1.02 g (5.45 mmol, 94%) of **14** as a colorless oil. ^{1}H 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 CH_2Cl_2. To this mixture a solution of $Pd(PPh_3)_4$) (0.02 equiv) in the same solvent was added, immediately followed by the addition of Bu_3SnH (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-pentenamide (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 $Pd(PPh_3)_4$, 68 μL (74 mg, 0.25 mmol) of Bu_3SnH, and 5.0 mL of CH_2Cl_2, there was obtained 25 mg (0.13 mmol, 58%) of **12**, as a solid, after flash chromatography, R_f 0.37 (CH_2Cl_2/acetone 2:1). ^{1}H NMR (200 MHz): 10.47 (s, 1 H), 6.95 (d, J = 7.5 Hz, 1 H), 5.83–5.62 (m, 1 H), 5.16–5.07 (m, 2 H), 4.50–4.34 (m, 1 H), 3.73 (s, 3 H), 2.54–2.33 (m, 2 H), 2.00 (s, 3 H).

2-(3-(Methoxycarbonyl)propionyl)-*N*-methoxy-4-pentenamide (21). According to the general procedure A, starting from 61 mg (0.29 mmol) of **9**, 30 mg (0.30 mmol) of succinic anhydride (**17**), 6.6 mg (5.7 μmol) of $Pd(PPh_3)_4$ dissolved in 1 mL of THF, 87 μL (92 mg, 0.31 mmol) of Bu_3SnH, and 5.7 mL of THF, there was obtained a crude product, which was dissolved in a 1.5 N solution of HCl in methanol (3.0 mL). After being stirred for 3 h at rt the solvent and the excess of HCl were removed *in vacuo* and the residue was chromatographed to give 42 mg (0.17 mmol, 60%) of **21**, R_f 0.31 (EtOAc/hexane 2:1). ^{1}H NMR: 6.22 (d, J = 7.1 Hz, 1 H), 5.73–5.56 (m, 1 H), 5.14–5.06 (m, 2 H), 4.70–4.61 (m, 1 H), 3.73 and 3.67 (2 × s, 3 H), 2.70–2.48 (m, 6 H). ^{13}C NMR: 173.1, 172.1, 171.0, 132.1, 119.1, 52.3, 51.8, 51.6, 36.4, 30.8, 29.2.

Methyl 2-(Acetylamino)propanoate (23). According to the general procedure A, starting from 205 mg (1.10 mmol) of **14**, 82 μL (91 mg, 1.15 mmol) of acetyl chloride (**18**), 25.3 mg (21.9 μmol) of $Pd(PPh_3)_4$, 325 μL (351 mg, 1.21 mmol) of Bu_3SnH, and 8.0 mL of CH_2Cl_2, there was obtained 141 mg (0.98 mmol, 89%) of **23**, as a yellow solid, after flash chromatography (EtOAc), and washing with EtOAc. ^{1}H NMR (200 MHz): 6.45 (br.s, 1 H), 4.62–4.46 (m, 1 H), 3.69 (s, 3 H), 1.96 (s, 3 H), 1.34 (d, 2 H, J = 7.2 Hz, 2 H). ^{13}C NMR (50 MHz): 173.5, 169.6, 52.0, 47.9, 22.8, 18.2.

Methyl 2-[(4-Toluenesulfonyl)amino]propanoate (24). According to the general procedure A, starting from 114 mg (0.61 mmol) of **14**, 128 mg (0.67 mmol) of tosyl chloride (**19**), 14.1 mg (12.2 μmol) of $Pd(PPh_3)_4$, 180 μL (195 mg, 0.67 mmol) of Bu_3SnH, and 5.0 mL of CH_2Cl_2, there was obtained 139 mg (0.54 mmol, 89%) of **24**, as a colorless oil, after flash chromatography, R_f 0.68 (EtOAc/hexane 1.3:1). IR ($CHCl_3$): 3340, 3020, 1740, 1595, 1340, 1160. ^{1}H NMR (200 MHz): 7.70 (d, J = 8.3 Hz, 2 H) and 7.26 (d, J = 8.2 Hz, 2 H)(Ar), 5.54 (d, J = 8.5 Hz, 1 H), 4.09–3.87 (m, 1 H), 3.49 (s, 3 H), 2.37 (s, 3 H), 1.33 (d, J = 7.1 Hz, 2 H). ^{13}C NMR (50 MHz): 172.4, 143.4, 137.0, 129.5, 127.0, 52.3, 51.3, 21.3, 19.5. MS: M^+ = 257; $(M - CO_2Me)^+$ = 198.

Methyl 2-[(Allyloxycarbonyl)amino]-4-pentenoate (Alloc-All-OMe, 31). Allyltrimethylsilane (3.30 mL, 2.37 g, 20.73 mmol) was added to a solution of methyl 2-[(allyloxycarbonyl)amino]-2-methoxyacetate[16b] (2.11 g, 10.36 mmol) in CH_2Cl_2 (54.0 mL). After the solution was cooled to 0 °C, BF_3·OEt_2 (1.91 mL, 2.21 g, 15.55 mmol) was added. After the mixture was stirred for 2.5 h at rt, 3 more equiv of Lewis acid was added and the reaction mixture was stirred for another 20 h at room temperature. The reaction mixture was then poured onto ice-cold aqueous saturated $NaHCO_3$. After extraction with CH_2Cl_2 (3×), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give 2.16 g (10.14 mmol, 98%) of **31**, as a colorless oil, R_f 0.64 (EtOAc/hexane 1:1.5). ^{1}H NMR: 5.99–5.78 (m, 1 H), 5.74–5.57 (m, 1 H), 5.09–5.03 (m, 4 H), 4.55 (d, J = 5.5 Hz, 2 H), 4.48–4.38 (m, 1 H), 3.73 (s, 3 H), 2.58–2.48 (m, 2 H). ^{13}C NMR: 172.1, 155.5, 132.6, 132.0, 119.2, 117.7, 65.8, 53.3, 52.3, 36.7. The product was used without further purification in the following reactions.

Boc-L-Ala-OPFP (32). To a vigorously stirred solution of L-alanine (8.9 g, 100 mmol) in *t*-BuOH (75 mL) were added a 2 N aqueous solution of NaOH (55 mL, 0.11 mmol) and di-*tert*-butyl dicarbonate (21.8 g, 100 mol) dropwise in such a way that the pH was kept between 8 and 9.5. After being stirred at rt for 16 h, the reaction mixture was carefully acidified with an aqueous solution of $KHSO_4$ (22.4 g in 150 mL of water), washed with CH_2Cl_2 (3×), dried ($MgSO_4$), and concentrated *in vacuo* to give Boc-L-Ala-OH (17.4 g, 92 mmol, 92%) as a colorless oil. ^{1}H NMR: 10.7 (s, 1 H), 6.91 (br s, 1 H), 5.15 (d, J = 6.9 Hz, 1 H), 4.38–4.16 (m, 1 H), 1.44–1.41 (m, 12 H). A 4.5 g (23.8 mmol) portion of this compound was dissolved in 1,4-dioxane (115 mL), and pentafluorophenol (4.8 g, 26.1 mmol) was added. The stirred solution was cooled to 0 °C, and dicyclohexylcarbodiimide (DCC) (5.0 g, 28.6 mmol) was added. After being stirred for 1 h at 0 °C and 17 h at rt the resulting suspension was filtered and evaporated. After the mixture was washed with hexane, a portion of **32** (5.8 g, 16.3 mmol, 69%) was obtained as a white powder. ^{1}H NMR: 5.08 (br s, 1 H), 4.65 (t, J = 7.2 Hz, 1 H), 1.58 (d, J = 7.2 Hz, 3 H), 1.46 (s, 9 H).

General Procedure B for the Pd(0) Catalyzed Coupling Reactions of Alloc-Protected α-Amino Acids with Activated α-Amino Esters. The activated

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 CH_2Cl_2. To this mixture was added $Pd(PPh_3)_4$) (0.02 equiv) (as such or as a 4 mM solution of in the same solvent), immediately followed by the addition of Bu_3SnH (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 $Pd(PPh_3)_4$, 69 μL (74 mg, 0.26 mmol) of Bu_3SnH, and 4.6 mL of CH_2Cl_2, there was obtained 89 mg (0.22 mmol, 94%) of **37**, as a colorless oil which solidified upon standing, after flash chromatography (EtOAc/hexane 3:1). Mp : 118–119 °C. IR ($CHCl_3$): 3440, 1760–1695, 1695–1625, 1505, 1445. ^1H NMR (200 MHz): 7.75 (d, J = 7.5 Hz, 2 H), 7.58 (d, J = 7.2 Hz, 2 H), 7.42–7.25 (m, 4 H), 6.88 (d, J = 7.1 Hz, 1 H), 5.86 (d, J = 5.2 Hz, 1 H), 5.72–5.59 (m, 1 H), 5.12–5.04 (m, 2 H), 4.69 (m, 1 H), 4.39 (d, J = 6.8 Hz, 2 H), 4.21 (t, J = 6.8 Hz, 1 H), 3.94 (d, J = 5.2 Hz, 2 H), 3.71 (s, 3 H), 2.59–2.49 (m, 2 H). ^{13}C NMR (50 MHz): 171.8, 168.9, 156.6, 143.6 and 141.2, 131.8, 127.6, 127.0, 124.9 and 119.9, 119.3, 67.3, 52.4 and 51.6, 46.9, 44.2, 36.2. Anal. Calcd for $C_{23}H_{24}N_2O_5$ (408.45): C, 67.63; H, 5.92; Found: C, 67.09; H, 6.22.

Fmoc-L-Ala-All-OMe (39). According to the general procedure B, starting from 47 mg (0.22 mmol) of **31**, 108 mg (0.23 mmol) of **34**, 5.1 mg (4.4 μmol) of $Pd(PPh_3)_4$, 66 μL (71 mg, 0.25 mmol) of Bu_3SnH, and 4.4 mL of CH_2Cl_2, there was obtained 92 mg (0.22 mmol, 99%) of **39**, as a solid, after flash chromatography (EtOAc/hexane 3:1), as a mixture of diastereomers (50:50). Mp: 144–147 °C. IR ($CHCl_3$): 3420, 1730, 1710, 1675, 1495, 1445. ^1H NMR (200 MHz): 7.76 (d, J = 7.4 Hz, 2 H), 7.59 (d, J = 7.2 Hz, 2 H), 7.43–7.26 (m, 4 H)(Ar), 6.78–6.67 (m, 1 H), 5.72–5.50 (m, 2 H), 5.12–5.04 (m, 2 H), 4.72–4.62 (m, 1 H), 4.38 (d, J = 6.6 Hz, 2 H), 4.40–4.14 (m, 2 H), 3.72 and 3.71 (s, 3 H), 2.59–2.44 (m, 2 H), 1.40 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (50 MHz, some carbons show two peaks because of diastereomers): 171.9, 171.8 and 171.7, 155.9, 143.8 and 141.3, 132.0 and 131.9, 127.7, 127.0, 125.0 and 119.9, 119.3, 67.2, 52.3, 51.7 and 51.5, 49.8, 47.1, 36.4 and 36.3, 18.9 and 18.6. Anal. Calcd for $C_{24}H_{26}N_2O_5$ (422.48): C, 68.23; H, 6.20. Found: C, 68.15; H, 6.24.

Boc-L-Leu-All-OMe (40). According to the general procedure B, starting from 50 mg (0.23 mmol) of **31**, 81 mg (0.25 mmol) of **35**, 5.4 mg (4.7 μmol) of $Pd(PPh_3)_4$, 69 μL (75 mg, 0.26 mmol) of Bu_3SnH, and 4.7 mL of CH_2Cl_2, there was obtained 75 mg (0.21 mmol, 93%) of **40**, after flash chromatography, R_f 0.37 (CH_2Cl_2/ MeOH 19:1), as a mixture of diastereomers (50:50). IR ($CHCl_3$): 3430, 1735, 1700, 1670, 1495. ^1H NMR (200 MHz): 5.70–5.53 (m, 1 H), 5.10–5.03 (m, 2 H), 4.65–4.56 (m, 1 H), 4.20–4.05 (s, 1 H), 3.69 (s, 3 H), 2.55–2.41 (m, 2 H), 1.71–1.40 (m, 12 H), 0.88 (d, J = 4.5 Hz, 6 H). ^{13}C NMR (50 MHz, some carbons show two peaks because of diastereomers): 172.2, 171.8 and 171.7, 155.5, 132.1 and 132.0, 119.0 and 118.9, 79.9, 52.1, 51.6 and 51.5, 41.1, 36.3, 28.2, 24.7, 24.6, 22.8 and 22.7, 21.8.

Fmoc-Gly-All-NHOMe (41). According to the general procedure B, starting from 44 mg (0.19 mmol) of **9**, 97 mg (0.20 mmol) of **33**, 4.5 mg (3.8 μmol) of $Pd(PPh_3)_4$, 57 μL (62 mg, 0.21 mmol) of Bu_3SnH, and 4.0 mL of CH_2Cl_2, there was obtained 64 mg (0.15 mmol, 80%) of **41**, as a solid, after washing with hexane. mp 163–164 °C. ^1H NMR (200 MHz): 7.72 (d, J = 7.1 Hz, 2 H), 7.56 (d, J = 7.1 Hz, 2 H), 7.40–7.23 (m, 4 H), 5.71–5.58 (m, 1 H), 5.11–5.03 (m, 2 H), 4.37 (d, J = 7.2 Hz, 2 H), 4.27–4.14 (m, 2 H), 3.90–3.67 (m, 5 H), 2.48–2.33 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3/CD_3OD$): 169.8, 168.1, 156.9, 143.5 and 141.1, 132.1, 127.5, 126.9, 124.8 and 119.8, 118.7, 67.0, 63.8, 50.1, 46.9, 43.9, 36.1.

Fmoc-L-Ala-All-NHOMe (42). According to the general procedure B, starting from 41 mg (0.18 mmol) of **9**, 88 mg (0.19 mmol) of **34**, 4.2 mg (3.6 μmol) of $Pd(PPh_3)_4$, 53 μL (58 mg, 0.20 mmol) of Bu_3SnH, and 3.6 mL of CH_2Cl_2, there was obtained 79 mg (0.18 mmol, 100%) of **42** after washing with hexane and 50 mg (0.11 mmol, 64%) after flash chromatography (CH_2Cl_2/MeOH 9:1), as a mixture of diastereomers (50:50). ^1H NMR (200 MHz): 7.54 (d, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.1 Hz, 2 H), 7.05–7.26 (m, 4 H), 5.38–5.55 (m, 1 H), 4.84–4.93 (m, 2 H), 4.26–3.92 (m, 7 H), 3.46 (s, 3 H), 2.35–2.22 (m, 2 H), 1.12 (d, J = 7.1 Hz, 3 H). ^{13}C NMR (50 MHz, some carbons show two peaks because of diastereomers): 173.3 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 $Pd(PPh_3)_4$, 40 μL (43 mg, 0.15 mmol) of Bu_3SnH, and 2.7 mL of CH_2Cl_2, there was obtained 38 mg (0.11 mmol, 79%) of **43**, as a colorless oil, after flash chromatography, R_f 0.34 (EtOAc/hexane 2:1), as a mixture of diastereomers (50:50). IR ($CHCl_3$): 3460, 3300, 1750, 1640, 1510. ^1H NMR (300 MHz): 10.38 and 10.30 (s, 1 H), 5.77–5.62 (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), 2.55–2.47, 1.64–1.31 (m, 12 H), 0.89 (m, 6 H). ^{13}C 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 100 mg (0.44 mmol) of **9**, 158 mg (0.44 mmol) of **36**, 10.1 mg (8.7 μmol) of $Pd(PPh_3)_4$, 130 μL (140 mg, 0.48 mmol) of Bu_3SnH, and 8.8 mL of CH_2Cl_2, there was obtained 135 mg (0.35 mmol, 79%) of **44**, after flash chromatography (CH_2Cl_2/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 × 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). ^{13}C 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, 56.0 and 55.2, 50.2, 38.2, 36.2 and 35.8, 28.2.

Fmoc-L-Ala-L-Ala-OMe (45). According to the general procedure B, starting from 83 mg (0.44 mmol) of **14**, 206 mg (0.44 mmol) of **34**, 10 mg (8.9 μmol) of $Pd(PPh_3)_4$, 135 μL (142 mg, 0.49 mmol) of Bu_3SnH, and 9.0 mL of THF, there was obtained 88 mg (0.22 mmol, 50%) of **45**, as a solid, after flash chromatography, R_f 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,

1 H), 4.39–4.30 (m, 3 H), 4.23–4.16 (m, 1 H), 3.72 (s, 3 H), 1.42–1.37 (m, 6 H). ^{13}C 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 μmol) of $Pd(PPh_3)_4$, 486 μL (526 mg, 1.81 mmol) of Bu_3SnH, and 10.0 mL of CH_2Cl_2, there was obtained 404 mg (1.47 mmol, 90%) of **46**, as a solid, after flash chromatography, R_f 0.36 (EtOAc/hexane 2:1). ^{1}H NMR (200 MHz): 6.83 (d, J = 6.8 Hz, 1 H), 5.19 (d, J = 7.5 Hz, 1 H), 4.61–4.45 (m, 1 H), 4.30–4.10 (m, 1 H), 3.71 (s, 3 H), 1.41–1.31 (m, 12 H). ^{13}C-NMR (50 MHz): 173.1, 172.3, 80.1, 52.3, 50.1, 48.0, 28.3, 18.3, 18.2. HRMS: calcd for $C_{12}H_{22}N_2O_5$ 274.1529, found 274.1523. $[\alpha]^{25}_D$: −57.7 (*c* 1.05; MeOH).

Boc-L-Ala-L-Ala-OMe (46) by Coupling of Alloc-L-Ala-OMe with *in Situ* O-Activated Boc-L-Ala-OH Using DCC/HOBT. To a stirred solution of Boc-L-Ala-OH (209 mg, 1.10 mmol) in CH_2Cl_2 (5.0 mL) were added HOBT·H_2O (149 mg, 1.10 mmol) and DCC (228 mg, 1.10 mmol). The reaction mixture was stirred at room temperature for 1 h. After this the mixture (**38**), which now contained the *N*-protected, *in situ* *O*-activated α-amino acid, was then transferred *via* a syringe into a solution of Alloc-L-Ala-OMe (**14**, 207 mg, 110 mmol) in CH_2Cl_2 (5.0 mL). To this mixture was added $Pd(PPh_3)_4$ (25.5 mg, 22.1 μmol), immediately followed by the addition of Bu_3SnH (327 μL, 354 mg, 1.22 mmol). After being stirred for 30 min the reaction mixture was filtered (to remove DCU), concentrated *in vacuo*, and chromatographed to give 290 mg (1.06 mmol, 96%) of **46**. Spectroscopic data: *vide supra*. $[\alpha]^{25}_D$: −53.3 (*c* 1.02; MeOH).

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Supplementary Material Available: Copies of ^{1}H and ^{13}C 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.

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