Tetrahedron Letters, Vol.32, No.45, pp 6633-6636, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Palladium-Catalyzed Synthesis of Amides and Peptides

Eric C. Roos, Pablo Bernabé, Henk Hiemstra* and W. Nico Speckamp*

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

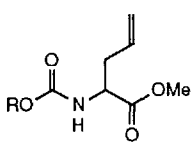
Bernard Kaptein and Wilhelmus H.J. Boesten

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

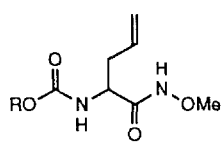
Key Words: allyloxycarbonyl, palladium(0), amides, peptide coupling, amino acids

Abstract: *When the Pd(0)-catalyzed hydrostannolysis of the N-allyloxycarbonyl group is carried out in the presence of an activated carbonyl compound, a coupling product is formed. This new method appears to be applicable to the synthesis of a wide range of amides and peptides.*

In recent years, we have investigated the Lewis acid-mediated reactions of α-methoxyglycine esters and amides with different types of π-nucleophiles.[1,2] When allylsilanes were used, these reactions led to *N*-protected γ,δ-unsaturated α-amino esters (e.g. **1a**-**1c**)[1a] and amides (e.g. **2a**-**2c**),[2b] respectively. For the subsequent deprotection step, at first the *N*-methoxycarbonyl (**1a**, **2a**) and the *N*-benzyloxycarbonyl group (**1b**, **2b**) were used. As these protective groups were, for various reasons, not able to serve our purposes completely, our attention turned to the use of the *N*-allyloxycarbonyl (Alloc) group. It was previously reported that this group was stable under various conditions, and that it could be removed with high yield and specificity in a catalytic fashion, using Pd(0)-complexes as the catalysts.[3-5]



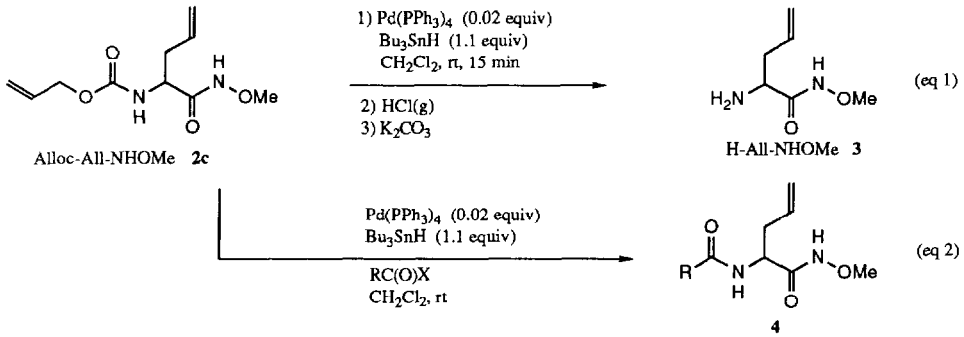
1a R = Me
1b R = Bn
1c R = allyl



2a R = Me
2b R = Bn
2c R = allyl

While the deprotection of **1c** and **2c** did not proceed successfully under various standard conditions, a free amine was indeed obtained in good yield when a modification of the method, as reported by Guibé and co-workers,[5] was used to deprotect **2c** to **3** (0.02 equiv $Pd(PPh_3)_4$, 1.1 equiv Bu_3SnH, CH_2Cl_2; then HCl(g); eq 1)[6]. In this reaction, Bu_3SnH transfers a hydride to the previously formed π-allylpalladium complex, leading to a tributyltin carbamate with concomitant evolution of propene; this intermediate tin carbamate is then cleaved by the proton donor to yield the free amine, carbon dioxide and Bu_3SnCl.

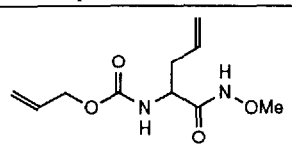
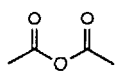
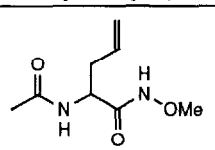
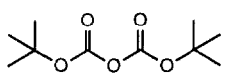
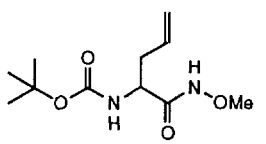
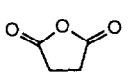
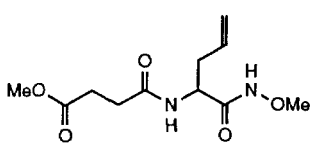
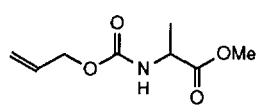
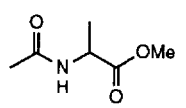
When it was discovered that the use of an activated electrophilic carbonyl moiety, instead of a proton donor, led to the formation of a new coupling product, our attention was focused on the use of this method for the synthesis of amides and peptides, analogous to **4** (eq 2).



Besides the already mentioned Alloc-All-OMe (**1c**) and Alloc-All-NHOMe (**2c**), several other Alloc precursors were prepared according to literature procedures.[7,8] These Alloc compounds were reacted with activated carbonyl compounds, using the following general procedure: 1 equiv of the Alloc compound and 1.05 equiv of the carbonyl compound were dissolved in dry CH_2Cl_2, under an atmosphere of dry nitrogen. Then $Pd(PPh_3)_4$ (0.02 equiv) was added, and immediately after this Bu_3SnH[9] (1.1 equiv) was added in one portion to the reaction mixture. The reaction was followed by TLC and in most cases shown to be completed within 5 min. The solvent was then evaporated, and the residue was chromatographed, using silica gel flash chromatography.

To study the scope of the reaction, several types of carbonyl compounds were used. The products, resulting from coupling reactions with anhydrides, acid chlorides and carbonates, are collected in Table I.

Table I. Pd(0)-catalyzed coupling reactions of Alloc compounds

entry	precursor	carbonyl compound	product (yield)	
1	 Alloc-All-NHOMe **2c**			**6** (60%)[a]
2	**2 c**			**7** (92%)
3	**2 c**			**8** (60%)[b]
4	 Alloc-Ala-OMe **5**			**9** (89%)

[a] In this case, 5 equiv of Ac_2O was used. [b] After treatment of the crude mixture with HCl/MeOH.

As shown in the Table, all of these types of carbonyl compounds gave rise to the introduction of a new acyl group; the (isolated) yields vary from good to excellent. The reactions in entries 1 and 2 could be called 'transprotections' and might prove to be very useful reactions in organic synthesis.[10] Apparently, all classes of compounds used in this study show a high reactivity towards the supposed intermediate tin carbamate.

Considering the high level of interest for peptide coupling,[11] we also studied the possibility of synthesizing peptides by this method, starting from Alloc-α-amino acid derivatives and activated α-amino esters. The results of this series of reactions are collected in Table II. The coupling reactions were performed in the same fashion as earlier described (*vide infra*); the products were usually purified by flash chromatography, although crystallization was in some cases possible.[12]

Table II. Pd(0)-catalyzed synthesis of dipeptides

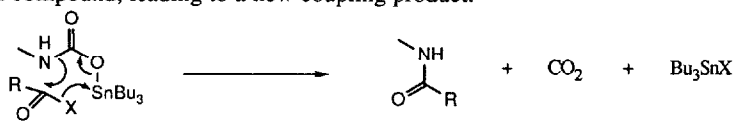
entry	precursor	active α-amino ester	product (yield)
1	Alloc-All-OMe **1c**	Fmoc-Gly-OPFP **10**	Fmoc-Gly-All-OMe **16** (94%)
2	**1c**	Fmoc-Ala-OPFP **11**	Fmoc-Ala-All-OMe **17** (100%)
3	**1c**	^{t}BOC-Leu-OSu **12**	^{t}BOC-Leu-All-OMe **18** (93%)
4	Alloc-All-NHOMe **2c**	Fmoc-Ala-OPFP **11**	Fmoc-Ala-All-NHOMe **19** (64%)
5	**2c**	^{t}BOC-Leu-OSu **12**	^{t}BOC-Leu-All-NHOMe **20** (80%)
6	**2c**	^{t}BOC-Phe-OSu **13**	^{t}BOC-Phe-All-NHOMe **21** (80%)
7	Alloc-L-Ala-OMe **5**	^{t}BOC-L-Ala-OPFP **14**	^{t}BOC-L-Ala-L-Ala-OMe **22** (90%) $[\alpha]^{27}_D$ = -57.7 (c=1; MeOH) lit.[13] $[\alpha]^{20}_D$ = -57.8 (c=1; MeOH)
8	**5**	^{t}BOC-L-Ala-OH/ DCC/HOBT **15**	^{t}BOC-L-Ala-L-Ala-OMe **22** (96%) $[\alpha]^{27}_D$ = -53.3 (c=1; MeOH)

In these reactions, the reactivity of the carbonyl moiety rests upon the use of activated esters, such as pentafluorophenyl (PFP) or *N*-hydroxysuccinimide (Su) esters, or upon *in situ* activation of the acid by using the DCC/HOBT method.[7] In the latter case, the amino acid was previously mixed with 1 equiv of HOBT and 1 equiv of DCC in CH_2Cl_2; the mixture was stirred at room temperature for 30 min, then transferred to the reaction flask and the coupling reaction was performed.

The use of all these different activating groups resulted in high yield-product formation. Even simple activation with DCC/HOBT led to a dipeptide in excellent yield under these catalytic conditions. Moreover, the reactions appeared to proceed without any notable racemization, as was shown by comparison of the $[\alpha]^{20}_D$ values of ^{t}BOC-Ala-Ala-OMe (**22**) with that reported in the literature.[13] This result is in accordance with the racemization-free Pd(0)-catalyzed deprotection of Alloc compounds, as reported by Guibé and co-workers.[5]

As an explanation for these results we suggest that the presence of the tin significantly enhances

the nucleophilicity of the nitrogen in the intermediate tin carbamate. With the rapid evolution of carbon dioxide as the driving force, this intermediate then can react via a 6-membered transition state with an activated carbonyl compound, leading to a new coupling product.



In conclusion, we have described a new and mild method for synthesizing amides and peptides. This is based upon reaction of Alloc-protected amines with activated carbonyl compounds, using catalytic conditions. The reactions proceed very rapidly and in high yields. In this fashion, dipeptides are synthesized in a one-pot procedure with no evident racemization. To the best of our knowledge, the first Pd(0)-catalyzed synthesis of peptides is herewith described.

Acknowledgement: We thank Organon B.V. (Oss, The Netherlands) for providing some of the activated α-amino esters and Mr. F.P.J.T. Rutjes for helpful discussions. These investigations were supported (in part) by the Netherlands' Foundation for Chemical Research with financial aid from the Netherlands' Technology Foundation.

References and notes

1. (a) Mooiweer, H.H.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron* **1989**, *45*, 4627. (b) Mooiweer, H.H.; Ettema, K.W.A.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron* **1990**, *46*, 2291.
2. (a) Roos, E.C.; Hiemstra, H.; Speckamp, W.N.; Kaptein, B.; Kamphuis, J.; Schoemaker, H.E. *J. Org. Chem.*, submitted for publication. (b) Roos, E.C.; Mooiweer, H.H.; Hiemstra, H.; Speckamp, W.N.; Kaptein, B.; Kamphuis, J.; Schoemaker, H.E., manuscript in preparation.
3. Minami, I.; Ohashi, Y.; Shimizu, I.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 2449.
4. Hayakawa, Y.; Kato, H.; Uchiyama, M.; Kajino, H.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 2400.
5. Dangles, O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984.
6. Rutjes, F.P.J.T.; Paz, M.M.; Hiemstra, H.; Speckamp, W.N., previous paper in this issue.
7. Müller, E., Ed.; *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1974, Band XV/1 + 2 (Synthese von Peptiden).
8. Keller, O.; Keller, W.E.; Van Look, G.; Wersin, G. *Org. Synth.* **1985**, *63*, 160.
9. The quality of the Bu_3SnH proved to be crucial in these reactions. For purification methods, see: Klinger, R.J.; Mochida, K.; Kochi, J.K. *J. Am. Chem. Soc.* **1979**, *101*, 6626.
10. Cf. Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 2983. In this work a similar reaction is described, starting from a *N*-benzyloxycarbonyl protected amine. Introduction of the *N*-tert-butoxycarbonyl group by way of $Pd(OAc)_2$-Et_3SiH reaction requires however significantly longer reaction times and probably may involve the free amine.
11. Some recent examples: (a) Thaler, A.; Seebach, D. *Helv. Chim. Acta* **1991**, *74*, 617-643, and references cited therein. (b) Carpino, L.A.; Mansour, E.M.E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611. (c) Carpino, L.A.; Chao, H.G.; Beyermann, M.; Bienert, M. *ibid.* **1991**, *56*, 2635.
12. All new products were appropriately characterized by IR, ^1H NMR, ^{13}C NMR, accurate mass and microanalytical data. Experimental data for **16**: According to the general procedure (*vide infra*), starting from 47 mg (0.22 mmol) of **1c**, 108 mg (0.23 mmol) of **10**, 5.1 mg (4.4 μmol) of $Pd(PPh_3)_4$, 66 μL (0.71 mg, 0.25 mmol) of Bu_3SnH and 4.4 mL of CH_2Cl_2, 92 mg (0.22 mmol, 100%) of **16** was obtained as a crystalline compound, after flash chromatography, R_f 0.50 (EtOAc : hexane = 3 : 1), mp 144-147 °C. IR: 3420, 3000, 2950, 1730, 1710, 1675, 1495, 1445, 1220, 990, 920. ^1H NMR (200 MHz, $CDCl_3$): [7.76 (d, 2 H, J = 7.4 Hz), 7.59 (d, 2 H, J = 7.2 Hz), 7.43-7.26 (m, 4 H)](FMOC), 6.78-6.67 (m, 1 H, N*H*), 5.72-5.50 (m, 2 H, C*H*=CH_2, N*H*), 5.12-5.04 (m, 2 H, CH=C*H*$_2$), 4.72-4.62 (m, 1 H, C*H*-CH_3), 4.38 (d, 2 H, J = 6.6 Hz, CH_2 in FMOC), 3.71 (s, 3 H, CH_3O), 2.59-2.44 (m, 2 H, CH_2-CH=CH_2), 1.40 (d, 3 H, J = 6.9 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): 171.9 (*C*(O)-O), 171.7 (*C*(O)-NH), 155.9 (O-*C*(O)-NH), 143.8 and 141.3 (quat. in FMOC), 131.9 (*C*H=CH_2), 127.7 and 127.0 and 125.0 and 119.9 (tert. in FMOC), 119.3 (CH=*C*H$_2$), 67.2 (-CH_2-O), 52.3 (CH_3-O), 51.7 and 51.5 (*C*H-), 47.1 (*C*H in FMOC), 36.3 (CH_2-CH=CH_2), 18.9 and 18.6 (CH_3-). Anal. Calcd. for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20. Found: C, 68.15; H, 6.24.
13. Ueda, T.; Saito, M.; Kato, T.; Izumiya, N. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 568.

(Received in UK 2 September 1991)