

# Tandem deprotection-coupling of $N^{\alpha}$ -Alloc-amino acids by use of ternary systems Pd cat./PhSiH<sub>3</sub>/carboxy-activated amino acid

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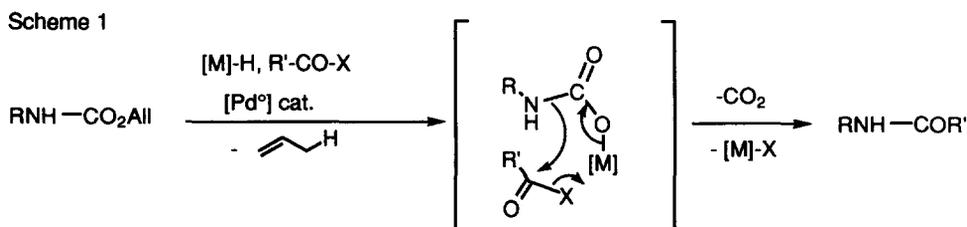
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## Abstract

$N^{\alpha}$ -allyloxycarbonyl derivatives of amino acids undergo smooth coupling with various carboxy-activated partners when treated with phenylsilane (PhSiH<sub>3</sub>) in the presence of catalytic amounts of tetrakis-(triphenylphosphine) palladium. © 1999 Elsevier Science Ltd. All rights reserved.

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Among the many nucleophiles which may be used as allyl group scavengers in the deprotection of  $N^{\alpha}$ -allyloxycarbonyl derivatives (Alloc-derivatives) of amines [1], pseudometallic hydrides (Bu<sub>3</sub>SnH, BH<sub>4</sub><sup>-</sup>, PhSiH<sub>3</sub>) present the particularity of leading not directly to the free amine, but, instead, to pseudometallic carbamates. If the catalytic deallylation reaction is carried out in the presence of an acylating species, then a neat transacylation process takes place. This process is thought to occur [2] through a concerted decarboxylative condensation between the intermediately formed pseudometallic carbamate and the acylating agent as represented in scheme 1. If so, the reaction takes place under virtually neutral conditions.



This tandem methodology has been applied to peptide bond formation between  $N^{\alpha}$ -allyloxycarbonyl-protected and carboxy-activated derivatives of amino acids either in the presence of tributyltin hydride as illustrated by Speckamp, Hiemstra and co-workers [2] or in the presence of alkali borohydrides as reported by Zhu and co-workers [3]. The first method however presents the inconvenients associated with the use of tin compounds (toxicity and difficulties in the elimination of by-products) while in the second one, the intrinsic

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nucleophilicity of borohydrides seriously limits the choice of the carboxy-activated component.

Some time ago [4], we introduced  $\text{PhSiH}_3$  as a new hydride species able to act as an efficient allyl group scavenger in the palladium catalysed deprotection of allyl carboxylates, carbamates and phenoxides. More recently [5], it was shown that advantage could be taken of the neutral conditions involved in the  $\text{PhSiH}_3$ /palladium mediated tandem deprotection-coupling procedure to avoid, in solid phase peptide synthesis, the formation of diketopiperazine when this reaction may be troublesome. In the present communication, we report on tandem deprotection-coupling reactions in solution, using the same system, between  $N^\alpha$ -Alloc-amino acid derivatives and various  $N^\alpha$ -protected carboxy-activated species and define the scope and limitations of this method [6].

The carboxy-activated amino acid derivatives first used in this study include  $N$ -hydroxysuccinimide esters, pentafluorophenyl esters, acid fluorides [7] and urethane-protected  $N$ -carboxyanhydrides (UNCAs) [8]. All reactions were carried out at room temperature in degassed dichloromethane (4 mL for 0.25 mmol of substrate) and under an argon atmosphere by mixing the methyl esters of  $N^\alpha$ -Alloc-amino acids with 2 equivalents of  $\text{PhSiH}_3$ , 1.1 equivalents of the carboxy-activated component and 2 mol% of  $\text{Pd}(\text{PPh}_3)_4$  used as the catalyst. The reactions were conveniently monitored by TLC or by IR spectroscopy by following the disappearance of the carbonyl absorption of the acyl activated species. Reaction times were found to range from *ca* 10 min to a few hours, depending on the reactants. Our most representative results are reported in table 1. Yields refer to isolate and purified (flash chromatography) products.

Table 1

Tandem deprotection coupling of  $N^\alpha$ -Alloc amino acid derivatives with  $N$ -hydroxysuccinimide or pentafluorophenyl esters of  $N^\alpha$ -protected amino acids, with UNCAs and with  $N^\alpha$ -protected amino acid fluorides

Entry	Acyl-activated derivative	Alloc derivative	Coupling product	Reaction time (min)	Yield <sup>a</sup> (%)
1	Boc-Ala-OSu	Alloc-Phe-OMe	Boc-Ala-Phe-OMe	15	86
2	Boc-Ala-OSu	Alloc-Pro-OMe	Boc-Ala-Pro-OMe	45	73
3	Fmoc-Ala-OPfp	Alloc-Phe-OMe	Fmoc-Ala-Phe-OMe	<90	100
4	Fmoc-Ala-OPfp	Alloc-Pro-OMe	Fmoc-Ala-Pro-OMe	50	86
5	Fmoc-Ala-OPfp	Alloc-Aib-OMe	Fmoc-Ala-Aib-OMe	(b)	29
6	Z-Ala-NCA	Alloc-Phe-OMe	Z-Ala-Phe-OMe	20	90
7	Z-Ala-NCA	Alloc-Pro-OMe	Z-Ala-Pro-OMe	10	100
8	Z-Ala-NCA	Alloc-Leu-OMe	Z-Ala-Leu-OMe	10	94
9	Z-Ala-NCA	Alloc-Val-OMe	Z-Ala-Val-OMe	10	90
10	Z-Ala-NCA	Alloc-Aib-OMe	Z-Ala-Aib-OMe	(b)	90
11	Z-Ala-NCA	Alloc-MeAib-OMe	Z-Ala-MeAib-OMe	(b)	45

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Table 1 (continued)

Entry	Acyl-activated derivative	Alloc derivative	Coupling product	Reaction time (min)	Yield <sup>b</sup> (%)
12	Fmoc-Ala-F	Alloc-Phe-OMe	Fmoc-Ala-Phe-OMe	30	96
13	Fmoc-Ala-F	Alloc-Pro-OMe	Fmoc-Ala-Pro-OMe	40	72
14	Fmoc-Ala-F	Alloc-Leu-OMe	Fmoc-Ala-Leu-OMe	70	90
15	Fmoc-Ala-F	Alloc-Val-OMe	Fmoc-Ala-Val-OMe	60	88
16	Fmoc-Ala-F	Alloc-Aib-OMe	Fmoc-Ala-Aib-OMe	(b)	77
17	Fmoc-Ala-F	Alloc-MeAib-OMe	Fmoc-Ala-MeAib-OMe	(b)	76
18	Fmoc-Phe-F	Alloc-Aib-OMe	Fmoc-Phe-Aib-OMe	(b)	87
19	Fmoc-Phe-F	Alloc-MeAib-OMe	Fmoc-Phe-MeAib-OMe	(b)	65
20	Fmoc-Aib-F	Alloc-Aib-OMe	Fmoc-Aib-Aib-OMe	(b)	88
21	Fmoc-Aib-F	Alloc-MeAib-OMe	No coupling	(b)	

<sup>a</sup>Isolated yields (chromatography); <sup>b</sup>The reaction was allowed to proceed for 12h.

Inspection of table I shows that, under our conditions, smooth coupling takes place between unhindered partners with all the carboxy activated species under study. However, as the steric demand of the reaction increases, UNCAs and acyl fluorides prove to be more efficient than *N*-hydroxysuccinimide or pentafluorophenyl esters (compare entry 5 with entries 10 and 16). Concerning acyl fluoride activation, couplings of two aminoisobutyric (Aib) residues (entry 20), or of Alloc-Aib-OMe or Alloc-MeAib-OMe (methyl  $N^{\alpha}$ -Alloc,  $N^{\alpha}$ -methyl-aminoisobutyrate) with Fmoc-Ala-F or Fmoc-Phe-F (entries 17-19) were achieved in fair to good yields. High yields were usually obtained in the coupling reactions of the NCA derivative of *Z*-alanine (entries 6-11), but comparison of entries 11 and 17 seems to indicate that, in our conditions, UNCAs are more sensitive to steric hindrance than acyl fluorides. Finally, attempts to couple Alloc-MeAib-OMe with Fmoc-Aib-F were unsuccessful, which marks the limits of the method [9].

In a recent comparative study, Carpino, Beyerman and coworkers have shown that acyl chlorides are better reagents than acyl fluorides for coupling of highly hindered partners [9]. First attempts to use *N*-protected amino acid chlorides in our reactions failed, as a result of catalyst poisoning<sup>2</sup>. One-pot deprotections-transacylations with acyl chlorides were nevertheless found to be possible, provided that the  $N^{\alpha}$ -Alloc derivative was *sequentially* reacted with Pd/PhSiH<sub>3</sub> and (after *ca* 20 min) with the acylating agents. Our results are reported in Table 2. The reaction conditions (dilution, temperature) are the same as those of coupling reactions described in table 1. Yields still refer to pure chromatographed compounds.

Coupling of Fmoc-Ala-Cl with various  $N^{\alpha}$ -Alloc derivatives of amino acids takes place readily and in very satisfactory yields (entries 1-4) while coupling, in fair yields, of hindered

<sup>2</sup> This poisoning which leaves  $N^{\alpha}$ -Alloc derivatives unprotected is very likely to be due to oxidative addition of the acyl chloride to palladium. Contrary to what is observed with tributyltin hydride (Four, P.; Guibé, F. J. Org. Chem. 1981; 46: 4439-4445), PhSiH<sub>3</sub> is inert towards such oxidative addition complexes and do not reduce them to aldehydes.

partners (that is Aib-MeAib or even MeAib-MeAib), using  $N\alpha$ -tosyl-protected<sup>3</sup> amino acyl chlorides becomes now possible. These latter reactions which were very conveniently monitored by following the disappearance of the IR carbonyl absorption of the acyl chloride ( $1800\text{ cm}^{-1}$ ) as well as that of the intermediate silyl carbamate<sup>4</sup> ( $1685\text{ cm}^{-1}$ ) requires however longer time.

Table 2

Tandem deprotection coupling of  $N\alpha$ -Alloc amino acid derivatives with  $N\alpha$ -protected amino acyl chlorides

Entry	$N$ -protected amino acyl chloride	Alloc derivative	Coupling product	Reaction time (min)	Yield <sup>a</sup> (%)
1	Fmoc-Ala-Cl	Alloc-Phe-OMe	Fmoc-Ala-Phe-OMe	10 min	96
2	Fmoc-Ala-Cl	Alloc-Pro-OMe	Fmoc-Ala-Pro-OMe	10 min	72
3	Fmoc-Ala-Cl	Alloc-Leu-OMe	Fmoc-Ala-Leu-OMe	10 min	90
4	Fmoc-Ala-Cl	Alloc-Val-OMe	Fmoc-Ala-Val-OMe	10 min	88
5	Ts-Aib-Cl	Alloc-MeAib-OMe	Ts-Aib-MeAib-OMe	4 h	65
6	Ts-MeAib-Cl	Alloc-MeAib-OMe	Ts-MeAib-MeAib-OMe	8 h	60

<sup>a</sup>Isolated yields (chromatography) .

To conclude, the tandem deprotection-coupling procedure using  $N\alpha$ -Alloc derivatives of aminoacids described in this communication allows the smooth coupling of even hindered partners under virtually neutral conditions. Applications of this methodology to base sensitive substates are currently under study in our group.

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<sup>3</sup> Urethane-protected  $\alpha$ -aminoisobutyryl chlorides are unstable, quickly rearranging to oxazolones [6,9]; The tosyl group is not easily removed from nitrogen, but other, more easily deblocked sulfonyl protecting groups have recently been proposed in the literature ( see [9] and: Vedejs, E.; Lin, S.; Klapars, A.; Wang, J. *J. Am. Chem. Soc.* 1996; 118, 9796-9798).

<sup>4</sup> Upon reaction with  $\text{PhSiH}_3$  (2 equiv.) in the presence of palladium catalyst, the carbonyl absorption of the allyl carbamate of a primary amine such as *p*-methylbenzyl amine shifts from  $1722\text{ cm}^{-1}$  to  $1711\text{ cm}^{-1}$  while that of Alloc-MeAib-OMe shifts from  $1700\text{ cm}^{-1}$  to  $1685\text{ cm}^{-1}$  ( $\text{CH}_2\text{Cl}_2$  as the solvent). We attribute these new absorbances, which disappear instantaneously upon addition of small amount of water, to the corresponding silyl carbamates. Efforts to gain more information, especially by NMR spectroscopy, on the structure of such carbamates which should be of general structure  $(\text{R-NH-COO})_n\text{SiH}_{(3-n)}\text{Ph}$ , were not conclusive.