

Palladium-Catalyzed Reactions in Aqueous Media. An Efficient Removal of Allyloxycarbonyl Protecting Group from Oxygen and Nitrogen

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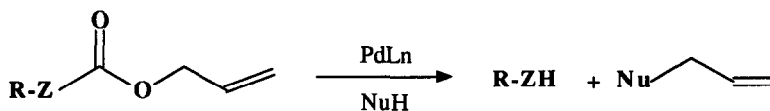
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Abstract : The Allyloxycarbonyl (Alloc) moiety can be removed smoothly and selectively in good yield (70-99%) from allylic esters, carbamates and carbonates by aqueous Pd (0) catalyzed allyl transfer to diethylamine as the accepting nucleophile. The method has been successfully used for deprotection of a wide range of secondary amines.

Palladium-catalyzed alkylation of carbonucleophiles and heteronucleophiles is a powerful tool in organic synthesis.¹ Palladium-catalyzed amination² has been successfully applied to the synthesis of secondary amines and tertiary amines by allylic alkylation with either primary amines^{2a} or secondary amines.^{2b,c} The use of π -allyl complexes of allylic carbonates was introduced by Tsuji³ and over the past few years we⁴ and others have emphasized the value of allyloxycarbonyl group in synthesis. The allyloxy moiety (Alloc) has also been introduced as protecting group⁵ of amines, alcohols and carboxylic acids. Different experimental conditions for removal have been proposed by several groups. The use of palladium (0) catalysts in the presence of various nucleophiles (e.g : formic acid,⁶ potassium 2-ethylhexanoate,⁷ morpholine,⁸ dimedone⁹ and tributyltin hydride¹⁰) is common (see Scheme I). For the cleavage of the Alloc moiety from the esters all these nucleophiles are suitable. (path (a) scheme II). However, deprotection of allyl carbamates is limited to primary amines or bulky secondary amines.⁶ Allylamine formation is observed due to attack of the free amino group, instead of trapping agent on the π -allyl intermediate (path (b) Z = NRR').

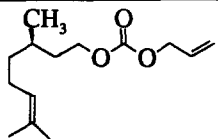
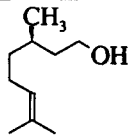
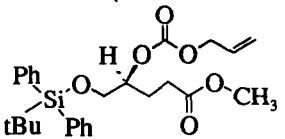
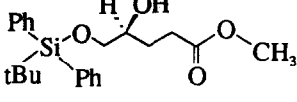
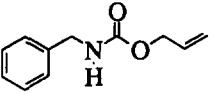
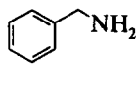
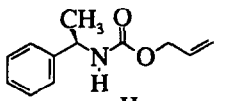
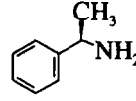
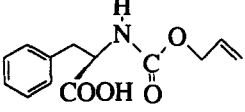
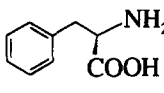
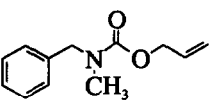
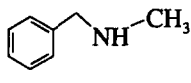
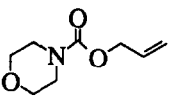
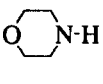
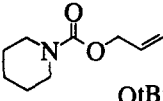
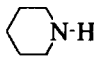
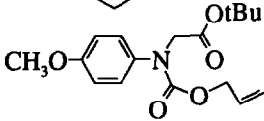
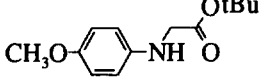
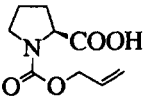
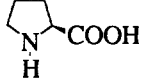
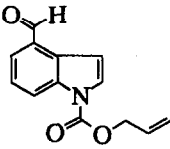
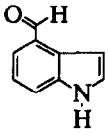


Scheme I

Our continuing interest in the area of palladium catalyzed reactions with heteronucleophiles² or carbonucleophiles⁴ was spurred by the idea that aqueous soluble palladium catalysts may be used in such reactions and two recent papers¹¹ prompt us to report here a simple and efficient system for the catalytic allyl transfer with water soluble Pd (0) catalyst namely Pd (OAc)₂ + TPPTS,¹² and diethylamine as allyl acceptor. Either homogeneous acetonitrile aqueous medium or biphasic system Et₂O / water are equally suitable for removal of alloc moiety from nitrogen and oxygen (see table).¹³

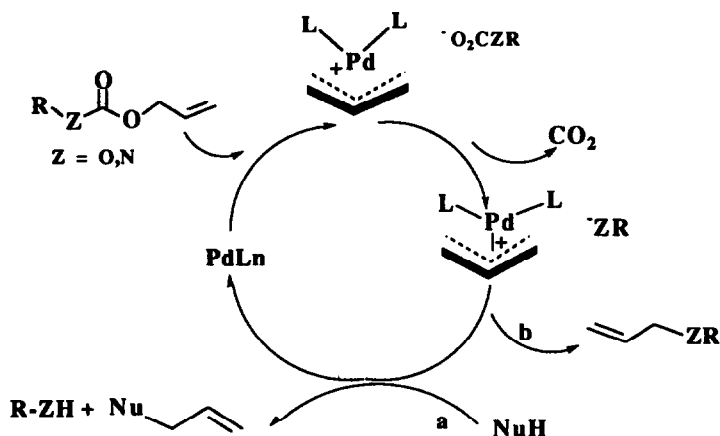
Diethylamine is generally used in a 2-2.5 fold excess. In more difficult cases (secondary amines), 8 to 40 fold excess can be used without any difficulty. The volatile diethylamine as well as N-allyl diethylamine can be readily separated from the deprotected amines, acids and alcohols.

Table : Deprotection of Alloc group with Pd / TPPTS, diethylamine

Entry	Substrates	Products	time / RT min	yield %
1			5	94 (a)
2			10	98 (a)
3			9	72 (a)
4			5	85 (a)
5			10	70 (a)
6			5	96 (c)
7			5	98 (a)(d)
8			5	93 (b)
9			45	99 (b)
10			15	90 (b)
11			10	73 (a)

(a): CH₃CN/H₂O, (b): Et₂O/H₂O, (c): HNEt₃/H₂O, (d): 3% N allylated amine (GC)

The allylic deprotection of allyloxycarbonyl group from citronellol proceeded at room temperature (5 min) in 94% yield (entry 1). Under these conditions the Alloc ester moiety can be removed selectively and quantitatively in the presence of *t*.butyl diphenylsilyl ether under these conditions (10min, RT) without any side reaction (entry 2)



The benzylamine and (-) α -methylbenzylamine carbamates were cleaved to the benzylamines in good yield (entry 3,4) under the same conditions after 9 min. The *N*-protected amino acid derived from phenyl alanine was deprotected without racemisation with Pd-TPPTS, HNEt₂ (entry 5). The deprotection of secondary amines is generally difficult using this technology.^{6a} Indeed the same conditions Pd-TPPTS, HNEt₂ (2.2 eq) used with *N*-protected carbamate of *N,N'* benzyl methylamine gave a 1:1 mixture of the free secondary amine and *N*-allyl *N,N'* methylbenzylamine. However, with a 40 fold excess of this volatile π allyl trapping nucleophile, the benzyl methylamine was recovered in 97% yield. Only a trace (3%) of *N*-allyl methylbenzylamine was detected (entry 6). Several others allyloxycarbamates derived from secondary amines (e.g. morpholine, piperidine and *N,N'*-*p*-methoxyphenyl-*t*-butylglycinate) reacted equally well on treatment with HNEt₂ (2.2-15 fold excess) in the presence of Pd(OAc)₂/TPPTS catalyst system (1-5 mol%) at room temperature within 5-45 min as shown in table (entries 7, 8 and 9). The above conditions are also useful for removal of *N*-allyloxycarbamate derived from optically active (-) proline. The reaction proceeded smoothly in quantitative yield without any formation of the *N*-allylated product (entry 10). The reactions were monitored by GC to completion and careful analysis was conducted to detect the undesired allyl *N,N'*dialkyl amine. The *N*-allyloxycarbonyl protected indole 4-carboxyaldehyde was cleanly deprotected under these conditions (10 min, RT) in 73 % yield (entry 11).

In summary, this aqueous palladium (0) - catalyzed deprotection of allyloxycarbonyl groups of allylic esters, carbamates and carbonates by using water soluble TPPTS as ligand occurs under very mild conditions. This technology allows easy separation of the organic product from the catalyst when a two phase system is used. Further studies of these conditions in other palladium catalyzed reactions and recycling of the catalyst are underway in our laboratory.

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