



Selective Deprotective Method using Palladium-Water Soluble Catalysts

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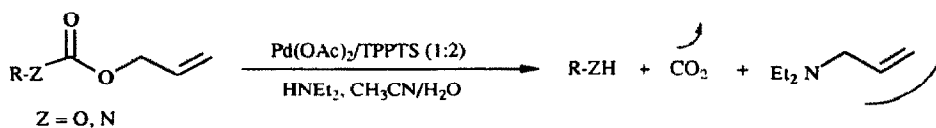
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Abstract : Allylcarboxy and Allyloxycarbonyl groups can be removed without affecting dimethylallylcarboxy and cinnamylcarboxy groups in the same molecule. using Pd(0) water soluble catalyst prepared *in situ*, with diethylamine as allyl scavenger. Homogeneous or biphasic media are suitable: the yields of deprotection are quantitative.

In previous publications¹⁻², we have shown that the palladium-water soluble catalyst prepared *in situ* from palladium(II) acetate and TPPTS³ is a practical catalytic system for various cross-coupling reactions and removal of allyloxycarbonyl from oxygen and nitrogen (scheme 1). The π -allyl methodology has emerged in recent years as a useful tool in protecting group chemistry⁴.



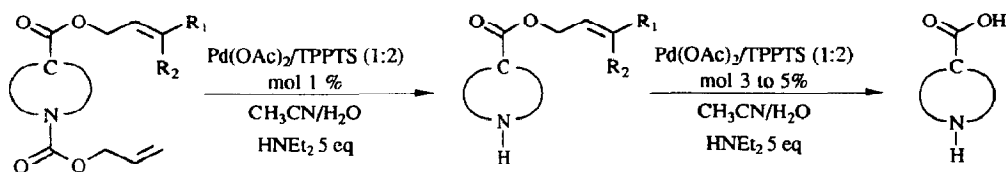
Scheme 1

Recently, we have compared the rate of deprotection of several phenyl acetic allyl esters under our previously reported homogeneous or biphasic aqueous conditions. We have found as shown in table 1 that, in homogeneous medium, the dimethylallyl group is cleaved at a lower rate than the cinnamyl group in the presence of 2 to 2.5% of palladium(0) (entries 2 and 3). Under the same conditions, the allyl group is removed at a significantly higher rate (entry 1). By comparison, under biphasic conditions, using butyronitrile and water as solvents, the cinnamyl and the dimethylallyl moieties remain intact in the presence of 5% of Pd(0) water soluble catalyst (entries 6 and 7), even after 3 days at room temperature; whereas the allyl group is still cleaved (10 min., RT) giving phenyl acetic acid in excellent yield (entry 5).

Table 1 : Deprotection of Phenylacetic Allyl Esters with Pd(OAc)₂ / TPPTS (1 : 2) Catalyst

Homogeneous : CH ₃ CN / H ₂ O					Biphasic : C ₃ H ₇ CN / H ₂ O				
Entry	Substrates	Cat. (mol %)	Time	Yield (%)	Entry	Substrates	Cat. (mol %)	Time	Yield (%)
1		2	5 min	100	5		5	10 min	100
2		2	20 min	100	6		5	72h	0
3		2.5	1h15	100	7		5	72h	0
4		0.5	8h	4					

Then we anticipated that it would be possible to cleave selectively, in the same molecule, an allyloxycarbonate in the presence of dimethylallyl carboxylate, which are readily available by addition of allyl chloroformate on the amino function followed by esterification of the carboxylic acid with the corresponding substituted allyl bromide, in the presence of DBU.



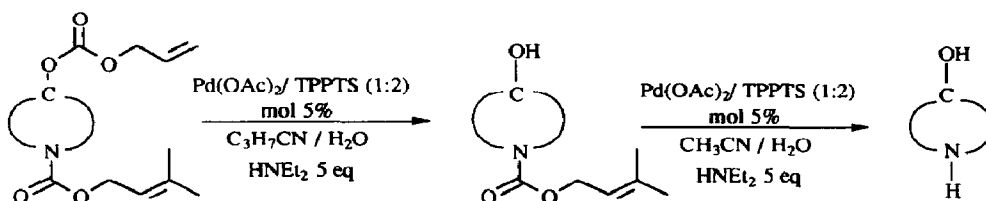
As shown in table 2, the allyloxycarbonate of isonipecotic acid (entry 1) was selectively and quantitatively cleaved under homogeneous conditions, in the presence of 1% of Pd(0), without affecting the dimethylallyl carboxylate. The latter was then deprotected using a higher amount of catalyst (mol 5%). The same scheme of selective deprotections was achieved on a base sensitive cephalosporin (entry 2); with 2.5% of water soluble catalyst the Alloc moiety was selectively removed to give the dimethylallyl carboxylate within 30 minutes, and then the carboxylic acid was recovered using 5% of Pd(0). We also applied these conditions of selective deprotection on amino acids: it was possible to cleave the N-allyloxycarbonate of the L-proline (entry 3) without affecting the carboxylic acid protected by the dimethylallyl moiety. Nevertheless, when the dimethylallyl group was replaced by the cinnamyl group, the use of 1% of Pd(0) in homogeneous medium led to complete removal of the allyloxycarbonyl group with a certain amount of the deprotected carboxylic acid⁵. In order to overcome this difficulty it was necessary to operate under biphasic conditions, in the presence of 1% of catalyst, giving the expected cinnamyl-L-prolinate in quantitative yield (entry 4).

Table 2 : Selective Cleavage of Allyloxycarbonates in the presence of Substituted Allyl Carboxylates

Entry	Substrate	Product	Time (min)	Yield ^{c)} (%)	Product	Time (min)	Yield ^{d)} (%)
1			20	96		10	100
2			30	100 ^{a)}		60	100
3			30	99		45	100
4			30	89 ^{b)}		40	86

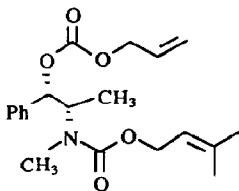
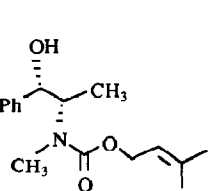
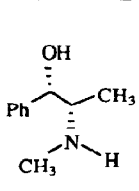
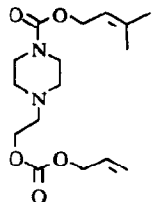
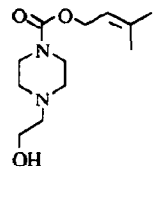
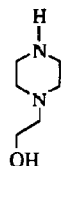
a) Pd(0) : mol 2.5%; b) solvent : butyronitrile-water; c) crude product; d) isolated yield.

Then, we investigated the selective cleavage of allyloxycarbonates in the presence of dimethylallylcarbamates⁶ (table 3).



A first attempt to cleave selectively the allyloxycarbonate from (1R, 2S)-(-)-ephedrine doubly protected, under homogeneous conditions, using 1% of Pd(0), led to total deprotection of the amino function together with partial removal of the dimethylallyloxycarbonyl group. Taking advantage of a biphasic medium, the reaction was thus conducted in a butyronitrile-water system with 5% of Pd(0); under these conditions, the allyloxycarbonyl group was smoothly removed from oxygen without affecting the dimethylallylcarbamate. In a second step, the amine could be deprotected using an homogeneous medium, with acetonitrile as co-solvent, to recover the parent molecule within 15 minutes, with 100% yield (entry 1). An other example on 1-(2-hydroxy ethyl)-piperazine gave similar results, and thus confirmed the selective cleavage of an allyloxycarbonate in the presence of N-dimethylallylcarbamate in the same molecule (entry 2).

Table 3 : Selective Cleavage of Allyloxycarbonates in the Presence of Dimethylallyl Carbamates

Entry	Substrate	Product	Time (min)	Yield ^{a)} (%)	Product	Time (min)	Yield ^{b)} (%)
1			20	100		15	100
2			20	100		15	100

a) Pd(0): mol 5% / butyronitrile-water / crude product; b) Pd(0) : mol 5% / acetonitrile-water / isolated yield

In summary, to our knowledge, this palladium(0) technology⁷ constitutes the first example of a selective deprotection of allyl carbamates in the presence of substituted allyl carboxylates, based on π -allyl methodology. In the same way, allyloxycarbonates are selectively removed without affecting dimethylallyl carbamates in the same molecule. These conditions offer new opportunities for fine chemical syntheses and are of practical importance from an industrial view point.

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References and notes

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- @TPPTS : (m-Sulfonated triphenylphosphine)
- For some proposed systems of deprotection based on palladium(0) mediated reactions see : a) Hayakawa, Y.; Wakabayashi, S.; Kato, H. and Noyori, R. *J. Am. Chem. Soc.* **1990**, 112, 1691-1696; b) Jeffrey, P.D. and McCombie, S.W. *J. Org. Chem.* **1982**, 47, 587-590; c) Kunz, H.; Waldermann, H. and Klinkhammer, U. *Helv. Chim. Acta* **1988**, 71, 1868-1874; Guibé, F. and Saint M'Leux, Y. *Tetrahedron Lett.* **1981**, 22, 3591-3594; d) Mermouk, A.; Guibé, F. and Loffet, A. *Tetrahedron Lett.* **1992**, 33, 477-480; e) Garo-Helion, F.; Mermouk, A. and Guibé, F. *J. Org. Chem.* **1993**, 58, 6109-6113.
- When the substrate was treated with 1% of Pd(0) under homogeneous conditions, the cinnamyl carboxylate was partially cleaved and the reaction gave a mixture of the selectively N-deprotected proline with the fully deprotected product in the ratio (65 : 35).
- The N-dimethylallyloxycarbonates are prepared by addition of the dimethylallyloxycarbonyl triethylammonium chloride on the corresponding amines. The procedure will be published in due course.
- For palladium mediated reactions in aqueous media see also : a) Casalnuovo, L. and Calabrese, J.C. *J. Am. Chem. Soc.* **1990**, 112, 4324-4330; b) Safi, M. and D. Sinou *Tetrahedron Lett.* **1991**, 32, 2025-2028; c) Bugamin, N.A.; More, P.G. and Beleskaya, I.P. *J. Organomet. Chem.* **1989**, 371, 397-401.
Typical procedure : A solution of the doubly protected substrate (1 mmol), Pd(OAc)₂ (1%), TPPTS (2%) and diethylamine (5 mmol) in butyronitrile/water or acetonitrile-water (3 ml/0.5 ml) was stirred at room temperature, under argon atmosphere. After completion the mixture can be filtered on silica gel and the solvent was evaporated in vacuo. Otherwise, it was treated with water and extracted by AcOEt (3x5 ml); the organic layer was dried over MgSO₄ and concentrated in vacuo. The clean crude product was directly engaged in the second deprotection with 3 to 5% of Pd(OAc)₂ and 6 to 10% of TPPTS. The reaction mixture was treated as described above, and the crude product was purified by flash chromatography if necessary.

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