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Palladium Catalysed allylic Substitution via in situ Activation of Allylic Alcohols[1]

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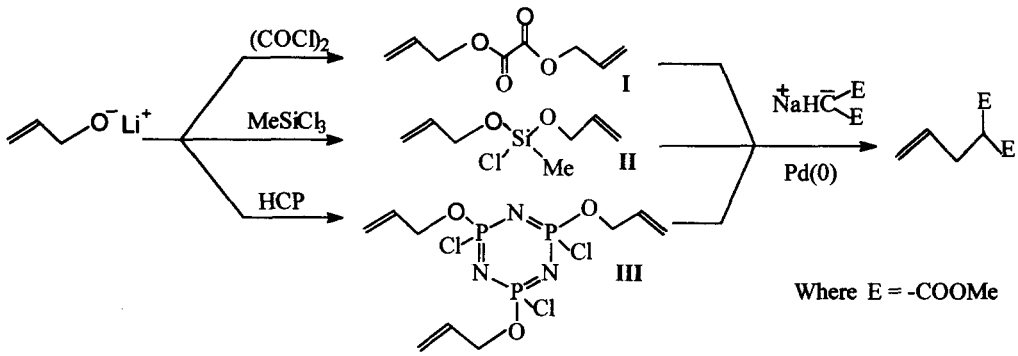
Abstract: In-situ activation of a variety of allylic alcohols by hexachlorophosphazene (or oxalyl chloride) followed by Pd(0) catalysed reactions with lithio dimethyl malonate leads to the regio and stereoselective alkylations in god yields. © 1997 Elsevier Science Ltd.

Carbon-carbon bond formation via π-allyl palladium intermediates is now a well established[2] procedure in organic synthesis. These π-allyl palladium intermediates are generally formed from allyl derivatives of the corresponding allylic alcohols. These derivatives are used in the form of acetates[2], carbonates[3], carbamates[4], phosphates[5] and related compounds[6] which are obtained from the corresponding allylic alcohols. Allylic alcohols themselves are rarely used[7] for such reactions due to the basic nature of the reaction medium. Recently Kocovský et al[8] have reported a novel *in situ* activation of allylic alcohols by triphenyl boron followed by their reaction with lithio diethyl malonate under Pd(0) catalysis leading to C-C bond formations in moderate to good yields. These reports prompted us to find some alternate reagents which could activate 2 or 3 molecules of allylic alcohols per one molecule of the activating agent. For this purpose, we chose three reagents viz. oxalyl chloride, methyltrichlorolsilane and hexachlorophosphazene (HCP). It was expected that allylic alcohols under basic conditions would be activated by these reagents to generate intermediates **I-III** (Scheme 1) which could undergo allylic C-C bond formations with compounds such as dimethyl malonate.

While reactions of **I** and **III** were clean and good yields of the final products were obtained, reactions with **II** were not encouraging. Thus, for example, reacton of **II**, derived from parent allyl alcohol, with sodio dimethyl malonate in the presence of Pd(0) gave the corresponding alkylated product in only 12% yield. We, therefore, did not pursue our studies with $MeSiCl_3$. Results with the other two reagents are summarised in the Table 1. It is clear that the high reactivity of oxalyl chloride and the high oxophilic character of phosphorous in HCP were responsible for the success of such alkylations. It was generally observed that activation of allylic alcohols via their sodium salts (prepared from NaH) with oxalyl chloride, $MeSiCl_3$ or HCP followed by the Pd catalysed alkylation was less clean and less yielding than the corresponding reactions carried out on lithium salts prepared using n-BuLi. Thus, for example, geraniol upon treatment with NaH and oxalyl chloride followed by its reaction with sodio dimethyl malonate gave a complex mixture of products along with 40% of the

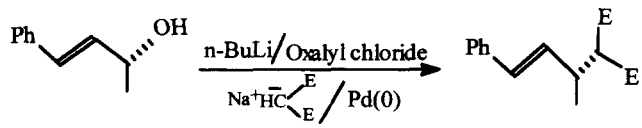
unreacted starting material. But when NaH was replaced by n-BuLi it led to a cleaner reaction yielding 68% of the desired product using oxalyl chloride and 60% using HCP. Even the parent allyl aclohol gave only 60% of the desired alkylated product in refluxing THF in 5hrs when used as its sodium salt whereas the lithio derivative yielded 85% of the product in only 3 hrs. This led us to use n-BuLi for the activation of allylic alcohols



Scheme 1

throughout the present study. It was also generally observed that oxalyl chloride was a better activator than HCP. Thus, when allyl alcohol was used a mixture of 6.8:1 of monoalkylated and dialkylated products was obtained using HCP. Whereas with oxalyl chloride formation of a 17:1 ratio of the same products was observed. Further, even this small amount of formation of the dialkylated product could be completely suppressed if the reaction mixture was highly diluted. A general experimental procedure is outlined in the reference section.[9]

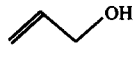
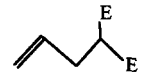
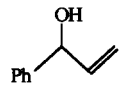
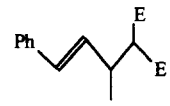
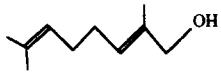
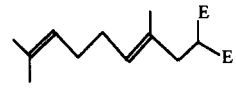
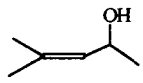
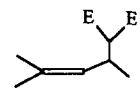
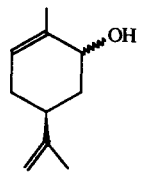
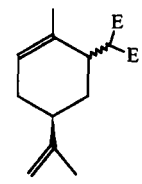
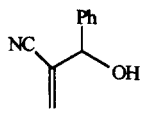
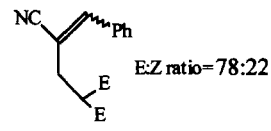
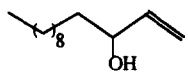
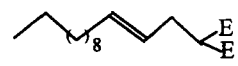
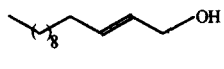
To assess the stereochemical behaviour of the reaction when alkylation was carried out with optically pure allylic alcohol **IV**[10] {$[\alpha]^{25}{}_{D}$ = + 7.53° (c=2, $CHCl_3$)} using oxalyl chloride the corresponding alkylated product **V** was obtained in 61% chemical yield with retention of configuration as indicated by the sign of rotation $[\alpha]^{25}{}_{D}$ = +19.3° (C=2, $CHCl_3$). The enantiomeric purity of the starting alcohol and the alkylated product are more or less same (≈ 27%)[11] thereby indicating that under the present reaction conditions there is no loss of optical activity on account of facial isomerisation of the resultant Pd-η^3 complexes.[12]



IV **V**

In summary we believe that the two procedures developed by us are useful variations of the literature procedures for Pd(0) catalysed *in situ* alkylations of allylic alcohols. We believe that among the two procedures the one utilising oxalyl chloride should find use in organic synthesis since the by products are water soluble and the yields are higher.

Table 1: Palladium Catalysed Allylic Substitution via *in situ* Activation of Allylic Alcohols

S.No	Allylic Alcohol	Alkylated Product#	Reaction with HCP: Yield (%)/ Time (hr)	Reaction with Oxalyl Chloride: Yield(%)/Time (hr)
1.			68/3(i)	84/3(ii)
2.			66/3	79/2
3.			63/3	--
4.			62/4	74/3
5.			60/3	68/2
6.			59/4	--
7.			65/4*	63/4*
8.		 E:Z ratio=78:22	--	70/2
9.			--	64/3*
10.			--	68/3

E: -COOMe. (i) 10% of the dimer i.e.  was also formed. (ii) 3% of the dimer was formed.

* Yield is based on the recovered starting material.

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9. To a stirred solution of an allylic alcohol (4 mmol) in THF (2 ml) at 0°C, 2.86 ml of 1.4 M n-BuLi (4 mmol) is added dropwise at 0 °C. After stirring the reaction mixture for 5min. at the same temperature 2 mmol (85 μl) of oxalyl chloride [or a THF solution of HCP (1.4 mmol)] is added rapidly. The cloudy white reaction mixture is stirred for 10 min. at 0 °C). A mixture of Ph_3P (104 mg, 10 mol%) and freshly prepared Pd(0) (5 mol%, 230 mg) are added to the reaction mixture and while warming sodium salt of diethyl malonate (4 mmol) (prepared from NaH and diethyl malonate, 1.1 : 1), is added rapidly. The resultant mixture is refluxed for the time indicated in the Table 1. Usual work up with diethyl ether after the removal of THF gave a crude product which was purified by column chromatography.

10. The optically active alcohol **IV** was prepared by enzymatic resolution of the corresponding acetate using pig liver acetone powder (cf. Vankar, P.S.; Bhattacharya, I. and Vankar, Y.D. *Tetrahedron: Asymmetry* **1996**, *7*, 1683 and references cited therein) and compared the rotation with the literature (cf. Kenyon, J.; Partridge, S.M. and Phillips, H. *J. Chem. Soc.* **1936**, 85 and Starý, I. and Kocovský, P *J. Am. Chem. Soc.* **1989**, *111*, 4981) data and then assigned the absolute configuration and the enantiomeric purity.

11. The alkylated product and its optical purity was compared with the literature data (cf. Starý, I. and Kocovský, P. *J. Am. Chem. Soc.* **1989**, *111*, 4981).

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