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Preliminary communication

A NEW METHOD FOR STEREOCONTROL IN PALLADIUM-CATALYZED REACTIONS OF ALLYLIC SUBSTRATES

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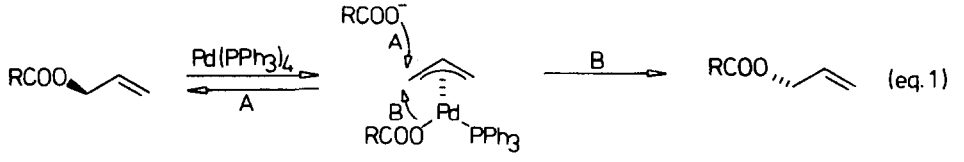
Summary

The $Pd(PPh_3)_4$-catalyzed reaction of *trans*-1-acetoxy-4-methoxy-2-cyclohexene (2) with amines led to a non-stereospecific substitution of the allylic acetoxy group as a result of isomerization of the starting material. Addition of lithium chloride had a remarkable effect on the stereochemical outcome of the reaction, and led to formation of the expected retention product without affecting the reaction rate.

Palladium-catalyzed nucleophilic substitution reactions of allylic substrates have become useful in organic synthesis [1]. Most of these reactions are mild, chemoselective, and usually stereospecific. Thus, stabilized carbon nucleophiles and heteroatom nucleophiles substitute the allylic leaving group with retention of configuration, which offers a useful alternative to the inversion obtained in S_N2 reactions [2,3]. However, one drawback with allylic carboxylates as substrates is that the nucleophilic substitution may sometimes proceed in a non-stereospecific manner as a result of palladium-catalyzed isomerization of the substrate [2,4,5]. This isomerization takes place as depicted in (eq. 1) [4], via a *cis*-migration of coordinated carboxylate [6,7] to the allyl group. For example, reaction of *cis*-3-acetoxy-5-carbomethoxy-1-cyclohexene with the anion of bis-(benzenesulfonyl)methane in the presence of $Pd(PPh_3)_4$ led to a 55/45 mixture of the *cis* and *trans* substitution product [4]. Furthermore, palladium(0)-



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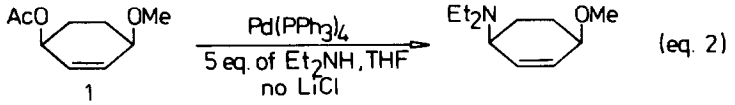
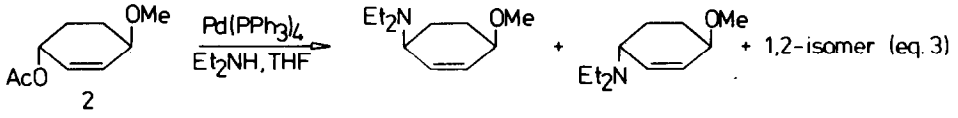
catalyzed reaction of the same substrate with diethylamine also led to a non-stereospecific substitution [8]. In the latter case the authors considered a *cis*-migration of coordinated amine in the intermediate (π-allyl)palladium complex as another possibility for the loss of stereospecificity.

We have previously observed a remarkable ligand effect of chloride ions in palladium-catalyzed reactions [7]. We now report that addition of lithium chloride is very effective in promoting a stereospecific palladium-catalyzed amination of allylic acetates.

Reaction of the allylic acetates **1** and **2** [7a] with diethylamine in the presence of catalytic amounts of $Pd(PPh_3)_4$ (4—6 mol%) proceeds smoothly (2—5 h) at 50°C to give the substitution products in good yield (70—90%). The substitution reaction of **1** takes place with retention of configuration at carbon (eq. 2)*, as expected for an oxidative addition with inversion [9], followed by a *trans*-attack by the amine on the (π-allyl)palladium intermediate [10]. The 1,4-isomer was selectively formed (>98% 1,4-selectivity). At 43% conversion the starting material was isolated and found to be an 80/20 mixture of **1** and **2**. This shows that **1** reacts faster than **2**.



In contrast to **1**, palladium-catalyzed amination of **2** led to a non-stereospecific reaction with the inversion product predominating (eq. 3)*. In this case the 1,2-isomer was also formed in a relative amount of 5—10%. Isolation of the starting material after 50% conversion from the reaction with 5 equivalents of diethylamine revealed that the ratio of **1**/**2** was 15/85. Hence, together with the



>98% *trans*	eq. Et_2NH	LiCl			
	5	—	88	/	12
	22	—	72	/	28
	5	added	48	/	52
	22	added	15	/	85

much higher reaction rate of **1** this ratio is large enough to account for the observed stereochemical outcome [11].

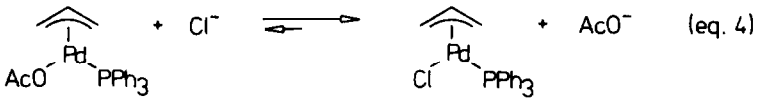
Addition of lithium chloride (0.2—1 equivalents to the substrate) had a drastic effect on the stereochemical outcome of the reaction [12]. For example, in one case the inversion/retention product ratio changed from 72/28 to 15/85 on addition of lithium chloride. It is noteworthy that the starting material isolated from the amination of **2** in the presence of lithium chloride was essentially unchanged with respect of the stereochemistry (>97% *trans*). However, presence of an average relative concentration of 2—3% of the *cis*-isomer **1** during the reac-

*The characterization and stereochemical assignment of the products in eq. 2 and 3 are given in ref. 10.

tion is enough to account for the 48/52 product ratio observed in the reaction involving 5 equivalents of diethylamine [11].

The analogous palladium-catalyzed amination of 2 with dimethylamine gave a 51/49 mixture of the retention and inversion products in the absence of lithium chloride, but selectively afforded the retention product (>90% retention) in the presence of lithium chloride.

The most likely reason for the observed effect of lithium chloride on the stereochemistry of the reaction is that chloride blocks the coordination of acetate in the intermediate (π-allyl)palladium complex (eq. 4). In this way the isomerization of the starting material, via *cis*-migration of acetate, is suppressed



(eq. 4)

(cf. eq. 1). Such an inhibition of *cis*-migration of acetate from palladium to a coordinated π-allyl group on addition of catalytic amounts of lithium chloride was previously observed in palladium-catalyzed 1,4-diacetoxylation of 1,3-dienes [7].

A polymer bound palladium catalyst has previously been used in the amination of allylic acetates to obtain a stereocontrol similar to the one reported here [8]. The simplicity of using lithium chloride, together with the fact that it does not affect the rate of the reaction, should make the present method synthetically useful for increasing the stereospecificity in palladium-catalyzed reactions of allylic substrates.

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11 If the oxidative addition of 1 to palladium(0) is assumed to be approximately 40—50 times faster than oxidative addition of 2 to palladium(0), this would lead to the observed stereochemical outcome.
12 In this case the relative amount of 1,2-isomer increased from 5—10% to about 20%. We were not able to conclusively determine the stereochemistry of the 1,2-isomer (cf. ref. 10).