# An Unexpected Pathway in the Palladium-catalysed Chemistry of Allyl Carbonates; the Transfer of Allyloxycarbonyl Groups without Loss of $CO_2$

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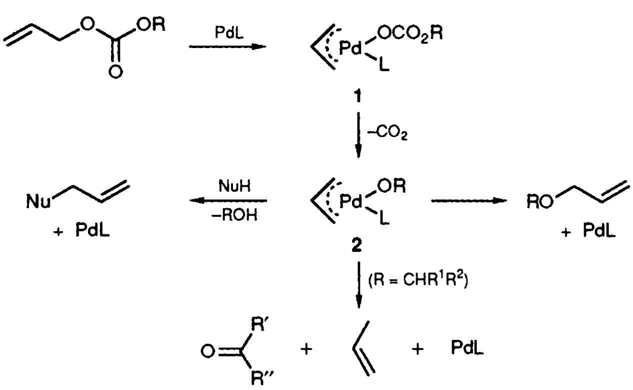
Treatment of hindered steroidal alcohols **4** and **11** with allyl ethyl carbonate in the presence of palladium complexes led to the steroidal allyl carbonates **10** and **12**, as opposed to the expected allyl ethers; these reactions are exceptional in that carbon dioxide is not lost from the carbonate, and suggest an alternative to the generally accepted mechanism for the interaction of Pd catalysts with allyl carbonates.

Allyl alkyl carbonates have come to play an important role in palladium-catalysed synthetic methodology,[1] having been employed in reactions leading to (for example) allylated C-nucleophiles, cyclopentanoids, enones (from ketones), ketones,[2] allyl ethers[2–5] and alcohols[2,3] (as part of a protection–deprotection sequence). For all these conversions, it is generally understood that the mechanism proceeds *via* the oxidative addition of the allyl carbonate to a palladium(0) species to give a π-allyl palladium complex **1**, followed by loss of carbon dioxide giving **2** and further transformations as illustrated in Scheme 1. We now report the observation of a reaction that, remarkably, does not conform to this pattern and which suggests that the interplay of allyl carbonates and $Pd^0$ species may be more complex than previously thought.

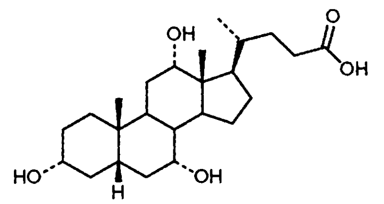
In connection with our programme on the synthesis of 'cholaphanes',[6] macrocyclic host molecules derived from cholic acid **3**, we were interested in the allylation of the steroidal 7α- and/or 12α-hydroxy groups. Working initially with the 3,7-diacetoxy methyl ester **4** we found that conventional methods such as NaH, $Bu_4N^+I^-$ and $CH_2{=}CHCH_2Br$ or



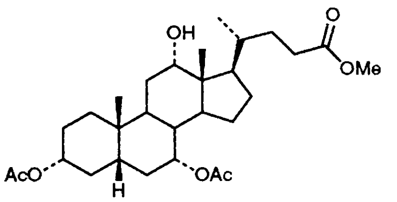
Scheme 1

$Pr^i_2NEt$ and $CH_2{=}CHCH_2Br$ were unsuccessful, probably because of the hindered nature of the (axial) 12α-OH.[7] We thus turned to the method of Sinou and coworkers,[4] in which the alcohol is treated with allyl ethyl carbonate (**5**) and catalytic amounts of [$Pd_2(dba)_3$] (dba = dibenzylideneacetone) and 1,4-bis(diphenylphosphino)butane (dppb) (Scheme 2). The discoverers suggest, reasonably, that this transformation proceeds *via* reaction of **5** with a $Pd^0$ species as in Scheme 1 to give an ethoxy complex **7**, which ionises, exchanges ethanol for the substrate alcohol to give **8**, and then collapses to the product **6**.

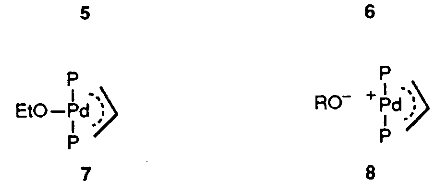
When the above method was applied to **4** we were pleased to find that a clean reaction occurred to give a relatively non-polar product. However, to our surprise we discovered that the product was not the allyl ether **9** but the carbonate **10**.† It transpired that this reaction occurred under a variety of conditions. Thus, successful experiments (yield of **10** ⩾ 70%) were conducted using [$Pd_2(dba)_3$][8] in tetrahydrofuran (THF) with $Ph_3P$, dppb or 1,2-bis(diphenylphosphino)ethane (dppe), and in benzene with dppb.‡ It was also possible to employ $Pd(OAc)_2$ as the source of palladium; indeed the highest yield of **10** (94%) was obtained using the latter salt (4.2 mol%) and dppb (8.6 mol%) in neat **5** at 60 °C for 18 h. Confirmation that the reaction has some degree of generality was provided by an experiment in which the 7,12-diol **11** was treated with $Pd(OAc)_2$ (4.6 mol%) and $Ph_3P$ (24 mol%), again in neat **5** (70 °C for 12 h), to give dicarbonate **12** in 70% yield.



**3**



**4**



Scheme 2

Some of the Pd-catalysed reactions of **4** did give small amounts of the allyl ether **9** (the original target), the proportions of which tended to increase with time and also with temperature. Formation of **9** was favoured by using $Ph_3P$ as ligand and $Pd(OAc)_2$ as the source of palladium, and conducting the reaction in neat **5**. However, after extensive optimisation we were unable to obtain more than a modest yield of **9**, the best methods being (*a*) $Pd(OAc)_2$ (6.4 mol%) and $Ph_3P$ (30 mol%) in neat **5** at 70 °C for 62 h (42% yield), (*b*) $Pd(OAc)_2$ (5.6 mol%), dppb (12 mol%), $Et_3N$ (7 equiv.) and **5** (18 equiv.) in THF at reflux for 27 h (49% yield). Conditions essentially similar to (*b*) could also be used to convert **10** to **9** in 45% yield, the remainder of the product being alcohol **4**.

To clarify the mechanistic possibilities for the allyloxycarbonyl transfer, the following experiments were undertaken. Firstly, reactions were attempted in which either the phosphine or the source of palladium was omitted from the mixture. In neither case was any product detected, confirming that both components of the catalyst system were required. Secondly, carbonate **5** was replaced by diethyl carbonate. Once again, no reaction occurred, establishing that the allyl group was also necessary for the reaction. Indeed, it should be pointed out that at no stage during this study did we detect any steroidal *ethyl* carbonates in the product mixtures.

Thirdly, it was of interest to determine whether allylic rearrangement could take place within the allyloxycarbonyl system under the conditions of the reaction.§ Thus, the specifically deuteriated carbonate **13** was prepared,[9] treated with [$Pd_2(dba)_3$] and dppb in refluxing THF for 20 min, then recovered from the mixture. Analysis by $^1H$ NMR showed that extensive scrambling had occurred, the $CD_2$ units being partitioned in the ratio *ca.* 3:2 between positions 1 and 3 of the allyl group. Not surprisingly, when **13** was used as reagent in the allyloxycarbonylation of **4** under similar conditions (but over 4 h), the allyl group in the product had also rearranged

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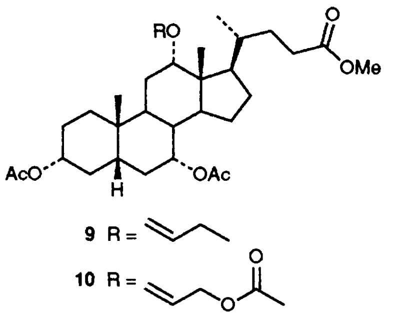
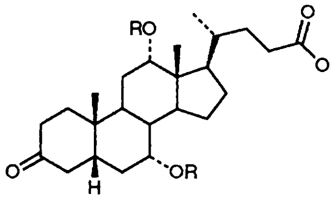
† *Spectroscopic data for* **9**: $\delta_H$ ($CDCl_3$, 300 MHz) 5.98 (1 H, ddt, *J* 17.2, 10.4, 5.2 Hz, $CH_2{=}C\mathit{H}CH_2O$), 5.34 (1 H, br d, *J* 17.2 Hz, $C\mathit{H}{=}CHCH_2O$), 5.17 (1 H, br d, *J* 10.4 Hz, $C\mathit{H}CHCH_2O$), 4.88 (1 H, br s, 7β-H), 4.57 (1 H, m, 3β-H), 4.09, 3.84 (2 H, br ABq, *J* 13.1 Hz, $CH_2{=}CHC\mathit{H}_2O$) 3.66 (3 H, s, $OCH_3$), 3.57 (1 H, s, 12β-H), 2.06 (3 H, s, OAc), 2.04 (3 H, s, OAc), 0.92 (3 H, s, 19-Me), 0.92 (3 H, d, *J* 6.1 Hz, 21-Me) and 0.68 (3 H, s, 18-Me); $\delta_C$ (75.5 MHz, $CDCl_3$) 174.62 (C-24), 170.58 and 170.50 [2 × $O\mathit{C}(O)CH_3$], 135.73 ($CH_2{=}\mathit{C}HCH_2O$), 115.44 ($\mathit{C}H_2{=}CHCH_2O$), 80.52 (C-12), 74.08 (C-3), 70.78 (C-7), 69.32 ($CH_2{=}CH\mathit{C}H_2O$), 51.77 ($O\mathit{C}H_3$), 46.47 (C-13), 46.05, 42.82, 40.94, 37.98, 35.02, 34.77, 34.53, 34.30 (C-10), 31.23, 30.85 (2 × $\mathit{C}H_2$), 28.29, 27.25, 26.77, 23.05, 22.94, 22.62 (C-19), 21.59 and 21.40 [2 × $OC(O)\mathit{C}H_3$], 17.39 (C-21) and 12.47 (C-18).

For **10** $\delta_H$ ($CDCl_3$, 300 MHz) 5.99 (1 H, ddt, *J* 17.2, 10.4, 5.8 Hz, $CH_2{=}C\mathit{H}CH_2O$), 5.41 (1 H, br d, *J* 17.2 Hz, $C\mathit{H}{=}CHCH_2O$), 5.31 (1 H, br d, *J* 10.4 Hz, $C\mathit{H}{=}CHCH_2O$), 4.96 (1 H, s, 12β-H), 4.90 (1 H, br s, 7β-H), 4.69–4.66 (2 H, m, $CH{=}CHC\mathit{H}_2O$), 4.57 (1 H, m, 3β-H), 3.66 (3 H, s, $OCH_3$), 2.08 (3 H, s, OAc), 2.04 (3 H, s, OAc), 0.93 (3 H, s, 19-Me), 0.85 (3 H, d, *J* 6.3 Hz, 21-Me) and 0.75 (3 H, s, 18-Me); $\delta_C$ (75.5 MHz, $CDCl_3$) 174.08 (C-24), 170.13 and 170.09 [2 × $O\mathit{C}(O)CH_3$], 154.16 [$CH_2O\mathit{C}(O)O$], 131.57 ($CH_2{=}\mathit{C}HCH_2O$), 118.57 ($\mathit{C}H_2{=}CHCH_2O$), 79.28 (C-12), 73.62 (C-3), 70.17 (C-7), 67.86 ($CH_2{=}CH\mathit{C}H_2O$), 51.14 ($O\mathit{C}H_3$), 46.85 (C-13), 45.01, 42.89, 40.55, 37.36, 34.31 (C-12 and $\mathit{C}H_2$), 34.18, 33.98, 30.88, 30.56, 30.36, 28.55, 26.80, 26.32, 25.25, 22.42, 22.17 and 21.38 [2 × $OC(O)\mathit{C}H_3$], 21.11 (C-19), 17.15 (C-21) and 11.96 (C-18).

‡ Reactions performed at 70 °C over 15–24 h with 12–21 equiv. of **5**. Products were isolated by evaporation followed by flash chromatography.

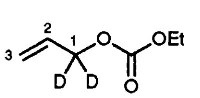
§ We are grateful to a referee for prompting us to try these experiments, and also for suggesting mechanism (*c*) in Scheme 3.



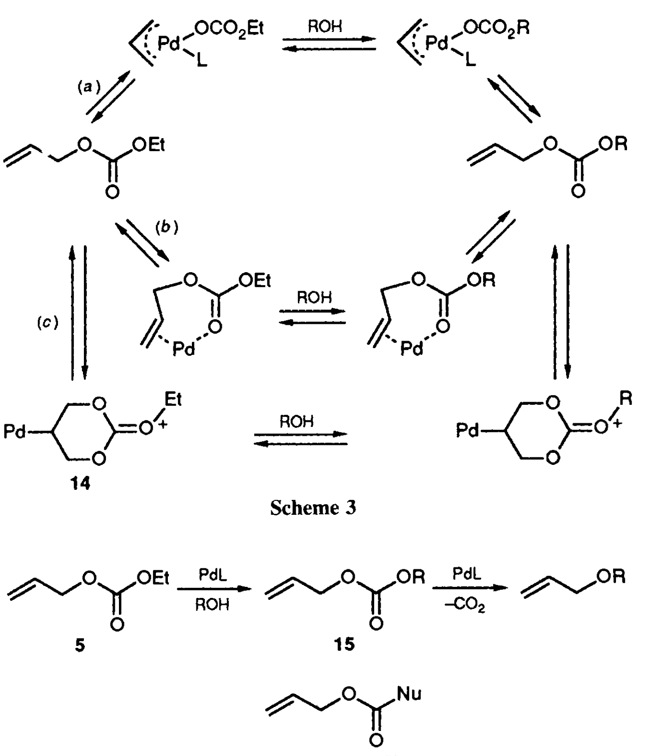


**11** R = H

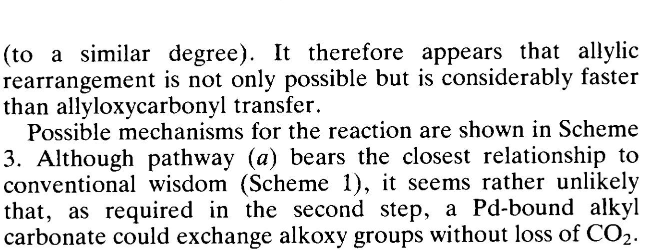
**12** R =



**13**



**Scheme 3**



**16** NuH = nucleophilic reagent

**Scheme 4**

(to a similar degree). It therefore appears that allylic rearrangement is not only possible but is considerably faster than allyloxycarbonyl transfer.

Possible mechanisms for the reaction are shown in Scheme 3. Although pathway (*a*) bears the closest relationship to conventional wisdom (Scheme 1), it seems rather unlikely that, as required in the second step, a Pd-bound alkyl carbonate could exchange alkoxy groups without loss of $CO_2$. Pathway (*b*) can account for the allyloxycarbonyl transfer, but cannot by itself accommodate the allylic rearrangement. The most satisfying option would appear to be pathway (*c*), in which intermediate **14** provides a staging post for allylic rearrangement and should be activated towards attack by ROH because of its electron-deficient nature. With regard to the formation of allyl ether **9**, although our results do not actually exclude the mechanism proposed by Sinou *et al.*,[4]¶ they clearly suggest an alternative in which the ether is formed *via* Pd-catalysed $CO_2$ extrusion from the corresponding carbonate‖ (Scheme 4). The success of the Sinou allylation would be dependent on the substrate-derived carbonate **15** collapsing substantially more rapidly than reagent **5**. This is presuambly the case for the highly-oxygenated substrates used by the French workers, but not for our hindered steroidal alcohols.

Irrespective of the detailed mechanism, our results are significant because they demonstrate that the Pd-catalysed reactions of alkyl allyl carbonates need *not* always involve the loss of carbon dioxide to give intermediates **2** (Scheme 1). Indeed, the fact that allyloxycarbonyl groups may be transferred between alkoxy groups raises the possibility that they may also be donated intact to other nucleophiles. It is therefore conceivable that a number of the allylations referred to in the first paragraph might follow a pathway analogous to that in Scheme 4, in which carbonate and nucleophile interact to form an intermediate **16** which then loses $CO_2$ in a separate step.

Synthetically, it might seem at first sight that the results are of little interest. However, we have found that carbonate **10** is in fact remarkably difficult to prepare using standard methodology. Thus, no reaction occurred when **4** was treated with allyl chloroformate and pyridine in THF,[10] even in the presence of dimethylaminopyridine (DMAP). Although further work is needed, the Pd-catalysed method may turn out to be generally useful for the protection of hindered hydroxy groups as allyl carbonates.

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¶ The allyloxycarbonyl transfer is presumably reversible, so that it is always possible for the substrate alcohol to be regenerated from its allyl carbonate and proceed to react with an allyl–Pd intermediate such as **7**. The experiment involving carbonate **10** as starting material is not inconsistent with this mechanism, as it resulted in the production of some alcohol **4** (possibly by reaction with traces of moisture) and was performed in the presence of several equivalents of allyl ethyl carbonate **5**.

‖ Literature precedent for such a process may be found in refs. 3 and 5.

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