Palladium-catalysed Cyclisation and Cyclisation–Carbonylation of Unsaturated *C*-Glycoside Derivatives. The Importance of Relative Stereochemistry

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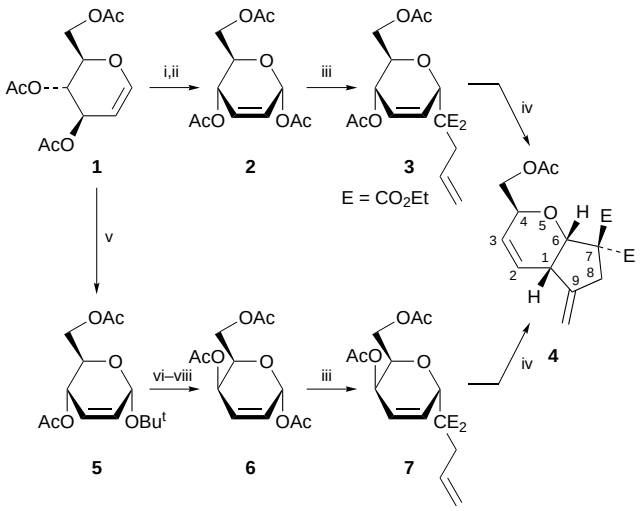
The Pd-catalysed 'metallo-ene type' cyclisation and cyclisation–carbonylation of selected 2,3-unsaturated *C*-glycosides is described and attention is drawn to the importance of relative stereochemistry in the latter type of reactions.

The palladium(0)-catalysed intramolecular carbocyclisation of allyl acetates with alkenes, a type of palladium-ene reaction,[1] exemplifies an attractive methodology leading to usefully functionalised five- and six-membered carbo- and hetero-cyclic compounds. Not only are these reactions regio- and most often stereo-selective, but they are also entropically favoured.

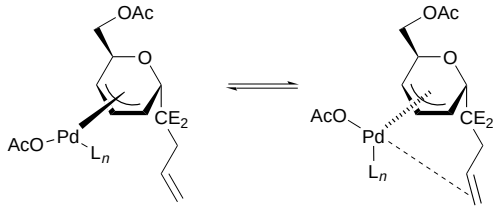
Palladium-catalysed cyclisation onto carbohydrate templates[2] offers a fast and efficient route to chiral, highly functionalised polycyclic compounds that can be transformed into versatile synthetic intermediates. Recently, we described the Pd^0-catalysed cyclisation of selected pseudoglycal 1,6-diene and 1,6-enyne derivatives for the synthesis of *cis*-annulated pyranoside products.[3] We herein describe[4] the formation of 5,6-bicyclic systems by palladium(0)-catalysed cyclisation of acetoxy-1,6-diene and 1,6-enyne *C*-glycoside derivatives. The catalysing properties of palladium were also exploited in the preparation of the starting material *C*-glycosides **3** and **7** (Scheme 2).



Scheme 2 *Reagents and conditions*: i, water–1,4-dioxane, reflux; ii, Ac_2O, py (**1** to **2**; 93%); iii, diethyl allylmalonate, NaH, $Pd(PPh_3)_4$, THF (90%); iv, $Pd(PPh_3)_4$, HOAc, 70 °C (83–89%); v, Bu^tOH, $BF_3{\cdot}Et_2O$,THF (75%); vi, K_2CO_3, MeOH (99%); vii, PPh_3, HOAc, DEAD,THF (93%); viii, Ac_2O, $ZnCl_2$, $CH_2Cl_2Cl_2$, 0 °C (85%)

'Metallo-ene type' cyclisation of **3** in acetic acid[13] at 70 °C in the presence of a catalytic amount of $Pd(PPh_3)_4$ afforded the *cis*-fused annulated *C*-glycoside derivative **4** as the sole product. The same product was obtained, in a somewhat reduced reaction time and in a slightly higher yield, when the isomeric *C*-glycoside **7** was subjected to similar reaction conditions.

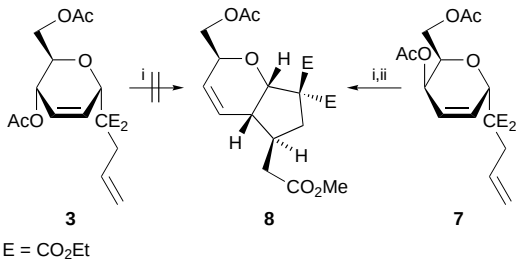
Although the precise mechanism for the cyclisation reaction is as yet unknown, it has been established that it proceeds in a suprafacial manner, *i.e.* the alkene inserts predominantly into an intermediate π- (or σ-)allylpalladium species, *cis* relative to the palladium atom.[1] The observation that both the *cis* and *trans* substituted allyl acetate derivatives **3** and **7** gave the same *cis* annulated cyclisation product **4**, analogous to observations made by Oppolzer,[14] presumably implies a relatively slow *trans–cis* isomerisation



Scheme 3

(Scheme 3) of the intermediate π-allylpalladium complex, allowing the palladium to be situated *syn* to the 'enophile'.

Additional useful functionality was incorporated into the molecule when the cyclised alkylpalladium intermediate was trapped[1] with carbon monoxide instead of undergoing a β-elimination termination step. The *trans* disposed *C*-glycoside **7** was converted (Scheme 4) into the cyclised carboxylic acid product (isolated as the methyl carboxylate derivative **8**) by $Pd_2(dba)_3{\cdot}CHCl_3$/trio-*o*-tolylphosphine catalysis (dba = dibenzylideneacetone) in acetic acid at 46 °C in the presence of carbon monoxide (1 atm).



Scheme 4 *Reagents and conditions*: i, $Pd_2(dba)_3{\cdot}CHCl_3$, tri-*o*-tolylphosphine, CO (1 atm), HOAc, 46 °C; ii, CH_2N_2–diethyl ether, CH_2Cl_2, 0 °C (**7** to **8**; 80%)

Interestingly, similar treatment of **3** under prolonged reaction conditions produced only unreacted starting material (Scheme 4). This phenomenon can best be ascribed to a decrease in the electron density at the metal centre caused by the strong π-acceptor properties of the CO ligand,

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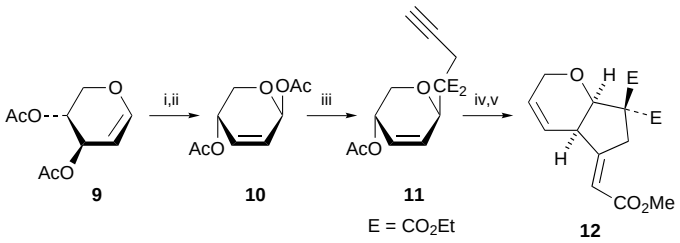

Scheme 5 *Reagents and conditions:* i, Bu^tOH, I_2, THF, reflux (70%); Ac_2O, $ZnCl_2$ (90%); iii, dimethyl prop-2-ymylmalonate, $Pd(PPh_3)_4$, NaH, THF (50%); iv, $Pd_2(dba)_3{\cdot}CHCl_3$, tri-*o*-tolylphosphine, CO (1 atm), HOAc, 46 °C; v, CH_2N_2-diethyl ether, CH_2Cl_2, 0 °C (**11** to **12**, 65%)

thereby suppressing π-allylpalladium complex formation.[16] As a consequence, the rate of *trans–cis* isomerisation so dramatically decreased and only the *trans* substituted allyl acetate **7**, which has favourable relative stereochemistry, undergoes cyclisation–carbonylation.

Finally, cyclisation–carbonylation of the enyne **11** (Scheme 5) under the above reaction conditions proceeded faster[17] with the alkyne 'enophile', as compared to the alkene 'enophile', to furnish **12**, after diazomethane methylation, in a high yield.

In conclusion, we believe that this facile palladium catalysed preparation of chiral, functionalised 5,6-bicyclic systems will be of value in the preparation of intermediates for the synthesis of polycyclic natural products. Furthermore, attention is drawn to the importance of paying due consideration to the relative stereochemistry of a precursor when planning and executing a palladium catalysed cyclisation–carbonylation reaction.

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Techniques used: NMR (^1H, ^{13}C and ROSY), ms, polarimetry

Schemes: 5

References: 21

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