Palladium(II)-catalysed Intramolecular Oxypalladation/Functionalisation of Carbohydrate-derived Cyclic Alkenes. Regioselective Formation of Substituted Di- and Tetra-hydropyrans

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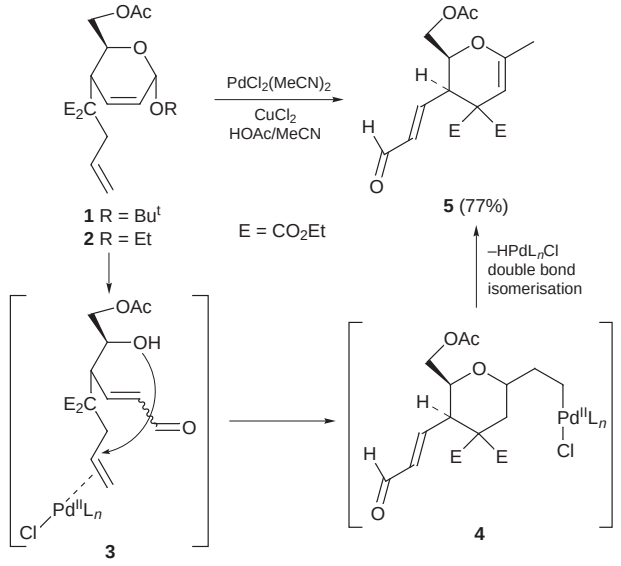
A palladium(II)-promoted domino process converts easily prepared pseudoglycals into highly functionalised, chiral di- and tetra-hydropyran structures in high yields.

Polyether antibiotics are a large group of natural products that are acclaimed for their antimicrobial[1] and cardiovascular activity.[2] The frameworks of these compounds are dominated by the presence of 2,5-disubstituted tetrahydrofurans, substituted tetrahydropyrans and spiroketal systems.

In a domino process, the readily prepared[6] C-4 substituted pseudoglucal **1** was transformed into the highly functionalised, chiral dihydropyran product **5** (Scheme 1) upon treatment with $PdCl_2(MeCN)_2$ and $CuCl_2$ in acetic acid–acetonitrile at room temperature.



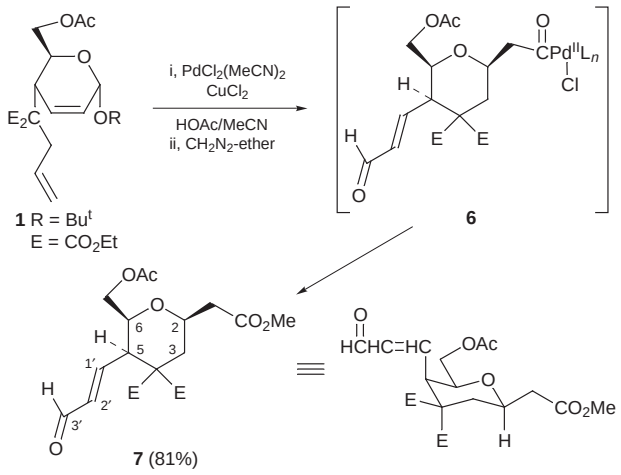
Scheme 1

In like manner, the ethyl pseudoglucal **2** was also converted into **5**, thus illustrating that the nature of the anomeric functionality is not significant in this case.

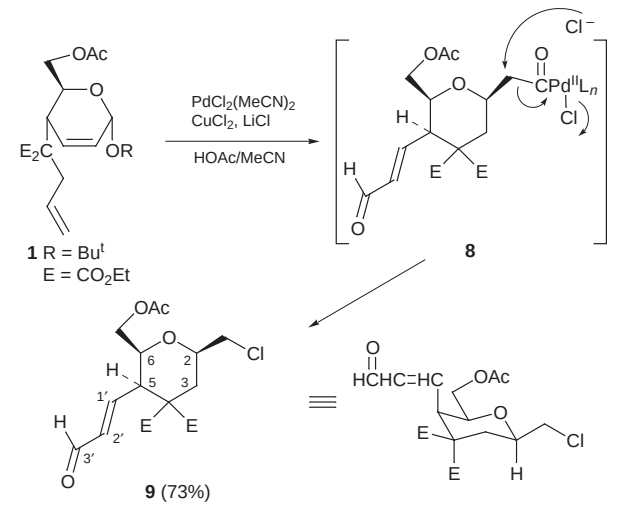
In the presence of carbon monoxide, the intramolecular palladium-catalysed alkoxycarbonylation of the terminal alkene of **1** provided **7**, after methylation by diazomethane ether, in an isolated yield of 81% (Scheme 2).

When the reaction of **1** was conducted under Wacker-like conditions in the presence of a large excess of LiCl, the reaction was terminated by chloride anion capture[7] to furnish **9** in a yield of 73% (Scheme 3).

Semmelhack *et al.*[8] rationalized the frequent preferential formation of *cis*-2,6-disubstituted tetrahydropyrans on the basis that the intermediate hydroxyalkene assumes a pseudo-chair conformation in approaching the transition state for nucleophilic addition (Scheme 4). To avoid energetically unfavourable pseudo-axial interactions between the hydrogen atom on the nucleophile-bearing carbon and the Pd^{II}–alkene complex, the latter group assumes a pseudo-equatorial conformation (**11**) which results in the formation of the *cis*-2,6-disubstituted tetrahydropyran.

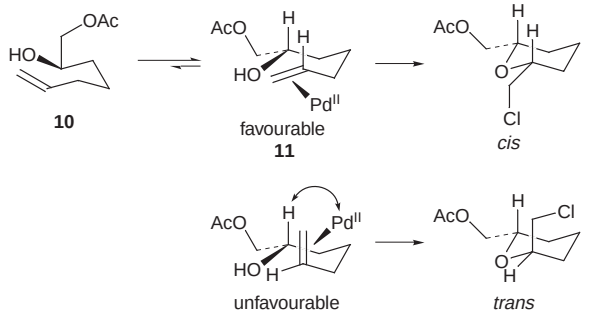


Scheme 2



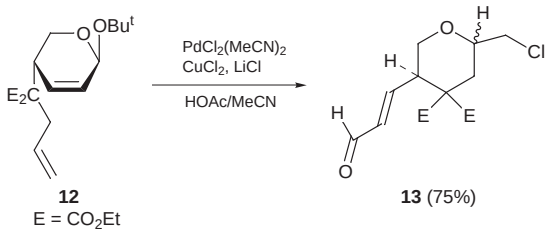
Scheme 3

*To receive any correspondence.



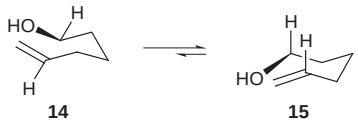
Scheme 4

In the case of the hexose-derived substrates, the conformationally mobile hydroxyalkene **11** is in equilibrium with minute amounts of the energetically less favoured **10**, where the CH_2OAc substituent occupies a pseudo-axial position. Therefore, when the same reaction was conducted with **12**, a mixture of C-2α and β-products (**13**) (*ca.* 2:3 by ^{1}H NMR) was obtained (Scheme 5).



Scheme 5

This finding is explained in terms of a rapid and facile interconversion between two pseudo-chair conformers **14** and **15** (Scheme 6) in the absence of a group to 'lock' the substrate into a preferred conformation and serves to highlight the crucial rule of the C-6 acetoxymethyl substituent in the stereocontrolled formation of the C-2 stereocentre of **7** and **9**.



Scheme 6

In conclusion, we have developed a novel palladium(II)-promoted domino process for the conversion of simple glycals into highly functionalised di- and tetra-hydropyrans in high yields in only three steps. The propenal substituents formed in all of the products create interesting opportunities for further elaboration of these structures for their ultimate application in natural product synthesis.

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Techniques used: NMR, MS, polarimetry

Schemes: 6

References: 8

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