Pergamon

Tetrahedron Letters, Vol. 36, No. 30, pp. 5397-5400, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00989-2

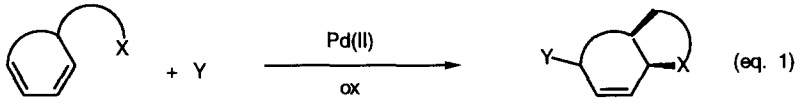
Palladium-Catalyzed Stereocontrolled *endo* Cyclization of 3-hydroxypropyl-1,3-cyclohexadiene Leading to Versatile Fused Tetrahydropyrans.

Elise B. Koroleva, Jan-E. Bäckvall, Pher G. Andersson*

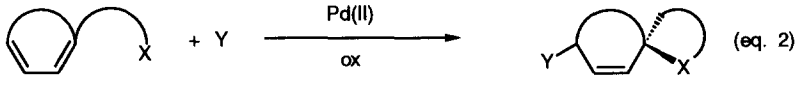
Department of Organic Chemistry, University of Uppsala
Box 531, S-751 21 Uppsala, Sweden

Abstract: A palladium-catalyzed synthesis of stereodefined fused tetrahydropyrans from 2-substituted 1,3-cyclohexadienes is presented. The reaction takes place via an intramolecular 1,4-oxidation of the conjugated diene via a (π-allyl)palladium intermediate. The stereochemical outcome of the reaction can be controlled to give *either cis or trans* 1,4-addition over the conjugated diene. The structure of the products was established by X-ray crystallography.

Palladium-catalyzed 1,4-oxidation of conjugated dienes has become a useful method for regio- and stereoselective functionalization of conjugated dienes.[1] Recent extension to intramolecular variants has opened new avenues towards the stereoselective synthesis of various heterocyclic systems.[2-5] In these reactions the side chain with the nucleophile has been situated in the 5- or 1-position of the diene (eq. 1 and 2). In both cases full control of the 1,4-relative stereochemistry was achieved.

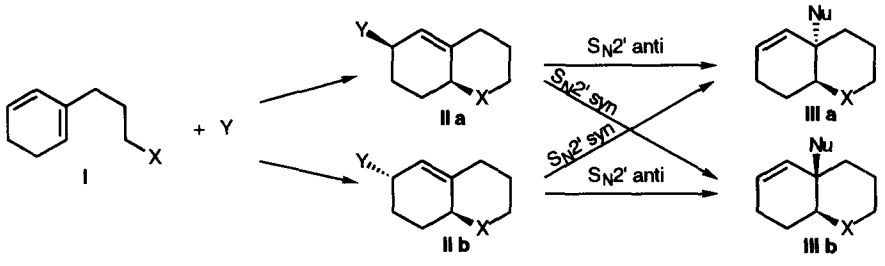


(eq. 1)



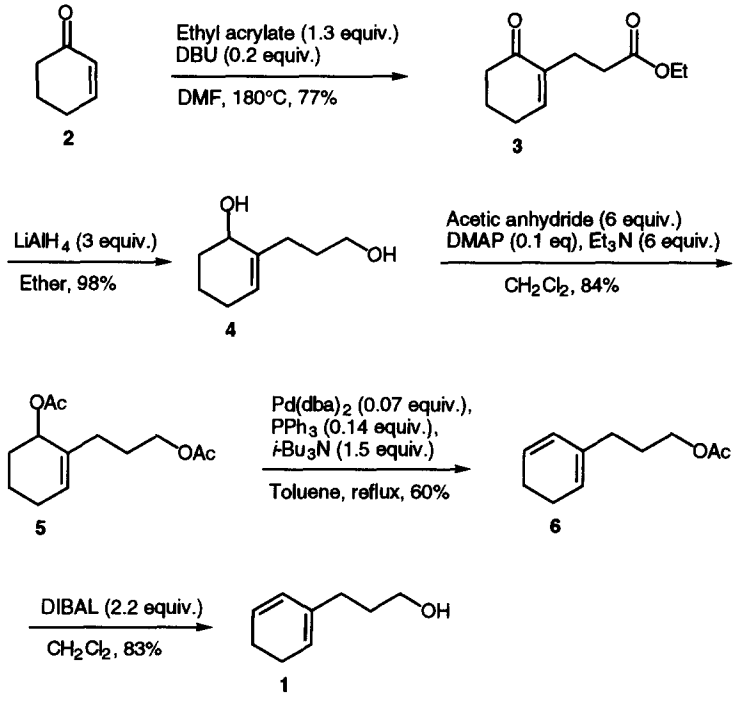
(eq. 2)

So far no studies have been made with a side chain in the 2-position. Such a cyclization would give rise to an *endo* cyclization to produce **II**. Since the Y group of these reactions is a versatile leaving group (*e.g.* carboxylate or halide) a stereospecific S_N2' substitution in **II** would give access to *cis*- or *trans*-fused heterocyclic systems **III** (Scheme 1). In this communication we report on intramolecular Pd-catalyzed 1,4-oxidation of **I** to **II** with alcohol as nucleophile in the side chain.



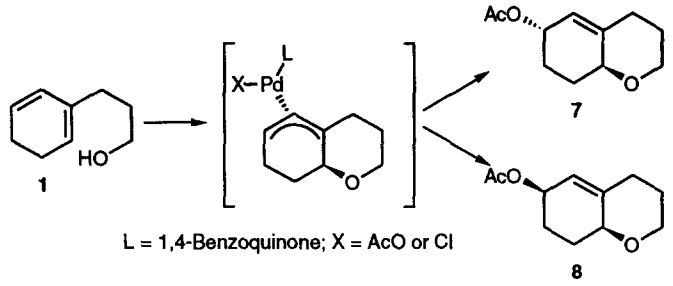
Scheme 1

The requisite starting material **1** for the cyclization was readily prepared from cyclohex-2-en-1-one in a few steps (Scheme 2). The vinylic alkylation of the unsaturated ketone with ethyl acrylate was performed according to a literature procedure.[6] Reduction of the resulting ketoester gave rise to the diol **4** which was subsequently acetylated to give the diacetate in high yield. Palladium-catalyzed elimination of HOAc from the allylic acetate furnished the conjugated diene acetate **6** which was transformed to **1** upon reductive cleavage of the acetate.



Scheme 2

The first attempts to cyclize **1** (Scheme 3) were performed in acetic acid / acetone (1 : 4) employing 5 mol% of $Pd(OAc)_2$ as the catalyst and 1,4-benzoquinone as the oxidant and resulted in extensive formation of aromatized starting material and Diels-Alder adducts between the diene and 1,4-benzoquinone. To overcome these problems, it was essential to add the diene slowly to the reaction mixture. Under these conditions (entry 1, Table I) the *trans*-acetate **7** was obtained in 69% yield and further improvment by changing the solvent to acetic acid (entry 2) led to a yield of 74% of **7**.[7] The stereochemistry of the second nucleophilic attack by acetate on the intermediate π-allyl palladium complex could be partially altered by the addition of lithium acetate to the reaction. In the presence of 5 and 10 equiv. (to the diene) of LiOAc the ratio between *cis* and *trans* acetates **7** and **8** were 1:1 and 2:1 respectively (entries 3 and 4). More efficient stereocontrol was obtained by the addition of lithium chloride and when 2 equiv. of LiCl (to the diene) *cis*-acetate **8**[8] was produced in 87% yield with excellent stereoselectivity (entry 5). Addition of both LiOAc and LiCl did not improve the yield (entry 6).



Scheme 3

Table I. Cyclization of **1** with acetate as external nucleophile.[a]

Entry	LiOAc (equiv)[b]	LiCl (equiv)[b]	Solvent	Stereochemistry	Yield
1	no	no	AcOH/acetone (1:4)	> 98% *trans*	69%
2	no	no	AcOH	> 98% *trans*	74%
3	yes (5)	no	AcOH	50% *cis*	35%
4	yes (10)	no	AcOH	66% *cis*	49%
5	no	yes (2)	AcOH	> 98% *cis*	87%
6	yes (2)	yes (2)	AcOH	> 98% *cis*	66%

a. For reaction conditions see reference 7. b. Based on the diene.

The proposed *trans* relation between the acetate and the tetrahydropyran oxygen in **7** was unambiguously assigned by X-ray crystallography, the result of which is presented in Figure 1.

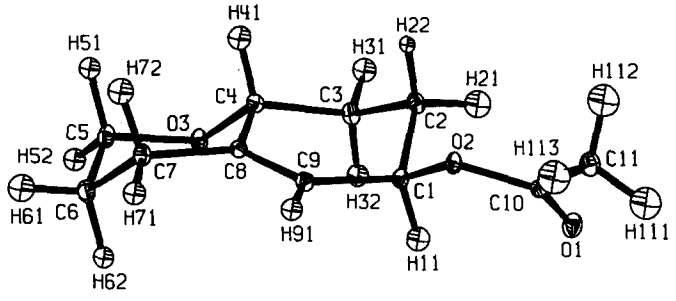
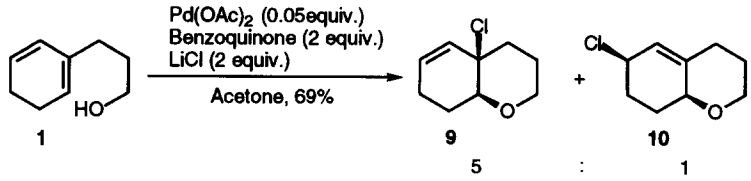


Figure 1. The bicyclic tetrahydrofuran **7** crystallises in space group $P2_1/c$ with cell dimensions a = 10.374(5), b = 6.514(3), c = 15.026(8) Å and β = 101.03(1)°. A structural model with 192 parameters was refined against 6340 reflexions measured with MoKα radiation at 25K giving a final resiual R(F) = 0.049.

Interestingly, no formation of allylic chloride from nucleophilic attack by chloride on the intermediate π-allyl palladium complex was observed when an excess of LiCl (2 equiv. to the diene) was used in the reaction.[9] In order to produce the allylic chloride it was necessary to change the solvent to acetone. This indeed allowed for the chloride to add to the intermediate π-allyl complex although the regioselectivity was now changed into mainly 1,2-addition over the 1,3-diene (Scheme 4).[10]



Scheme 4

Acknowledgements. We are indebted to Dr. Torbjörn Gustafsson and Mr. Hilding Karlsson for obtaining the X-ray structure of **7**. This work was supported financially by the Swedish Natural Science Research Council.

References and Notes:

(1) (a) Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem* **1984**, 49, 4619. (b) Bäckvall, J. E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, 44, 492. (c) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, 107, 3676.

(2) (a) Bäckvall, J. E.; Andersson, P. G.; Vågberg, J. O. *Tetrahedron Lett.* **1989**, 30, 137. (b) Bäckvall, J. E.; Granberg, K. L.; Andersson, P. G.; Gatti, R.; Gogoll, A. *J. Org. Chem.*, **1993**, *58*, 5645.

(3) Bäckvall J. E., Andersson P. G. *J. Am. Chem. Soc.* **1992**, 114, 6374.

(4) Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1990**, 112, 3683.

(5) Bäckvall, J. E.; Andersson, P. G. *J. Org. Chem.* **1991**, 56, 2274.

(6) Hwu,J. R.; Hakimelahi, G. H.; Chou C.-T. *Tetrahedron Lett.* **1992**, 43, 6469.

(7) Typical experimental procedure and spectroscopic data for **7**: $Pd(OAc)_2$ (16 mg, 0.072 mmol), *p*-benzoquinone (155 mg, 1.44 mmol) and $LiOAc{\cdot}2H_2O$ (147 mg, 1.44 mmol) were dissolved in glacial acetic acid (9 mL). To this solution was added, via syringe pump, the dienol **1** (100 mg, 0.72 mmol) dissolved in glacial acetic acid (1 mL) during 16h. After complete addition, the reaction was stirred at rt for an additional 8h. The mixture was then poured into ether (10 mL) and washed with 2 M NaOH (3x5 mL), dried ($MgSO_4$) and evaporated at reduced pressure. Chromatography on silica gel (15% ether in pentane) gave **7** (105 mg, 0.53 mmol, 74%) as colorless crystals. mp 47 - 48°C; ^{1}H NMR δ 5.41 (s, 1 H), 5.32 (m, 1H), 3.98 (dddd, J = 11.5, 4.1, 2.0, 2.0 Hz, 1 H), 3.89 (t, J = 4.6 Hz, 1 H), 3.55 (ddd, J = 11.3, 11.3, 4 Hz, 1 H), 2.31 (dt, J = 2.2 Hz, 1 H), 2.25 (td, J = 0.8 Hz, 1 H), 2.19 (m, 2 H), 2.09 (s, 3 H), 1.76 (m, 1 H), 1.72 (m, 1 H), 1.56 (m, 2 H); ^{13}C NMR δ 170.0, 140.7, 121.5, 73.9, 69.6, 67.8, 31.5, 27.8, 27.2, 26.5, 21.3; IR (CCl_4): 2940, 1737, 1364, 1239, 1100, 1088, 1022 cm^{-1}.

(8) Spectroscopic data for **8**: ^{1}H NMR δ 5.54 (s, 1 H), 5.14 (m, 1H), 4 (dt, J = 2, 1.5 Hz, 1 H), 3.81 (t, J = 6.22 Hz, 1 H), 3.53 (td, J = 11.3, 11.3, 4 Hz, 1 H), 2.33 (dt, J = 2.2 Hz, 1 H), 2.2 (td, J = 0.8 Hz, 1 H), 2.05 (s, 3 H, CH_3), 1.89 (m, 2 H), 1.84 (m, 1 H), 1.76 (m, 1 H), 1.7 (m, 2 H) ; ^{13}C NMR δ 145.8, 133.9, 119.8, 74.1, 67.7, 50.6, 31.4, 29.0, 27.4, 25.9, 21.4; IR (CCl_4): 2939, 1735, 1364, 1241, 1095 cm^{-1}.

(9) Normally the use of 2 equiv. of lithium chloride results in the exclusive formation of allylic *cis*-chlorides, see references 1b and 1c.

(10) Spectroscopic data for **9**: ^{1}H NMR δ 5.78 (dt, J = 10.1, 3.5 Hz, 1 H), 5.6 (app. d, J = 10 Hz, 1 H), 3.85 (m, 2 H), 3.5 (m, 1 H), 1.95 (m, 2 H), 1.78 (m, 2 H), 1.63 (m, 2 H), 1.45 (m, 2 H); ^{13}C NMR δ 131.9, 129.0, 94.2, 37.9, 34.9, 26.0, 24.9, 20.5 10.3; MS 136, 117, 91, 77, 65, 51.

(*Received in UK* 20 *March* 1995; *revised* 31 *May* 1995; *accepted* 2 *June* 1995)