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Palladium-Catalyzed Intramolecular 1,4-Dialkoxylation of Cyclohexadienes: An Efficient Route to Highly Stereocontrolled Oxygen Heterocycles

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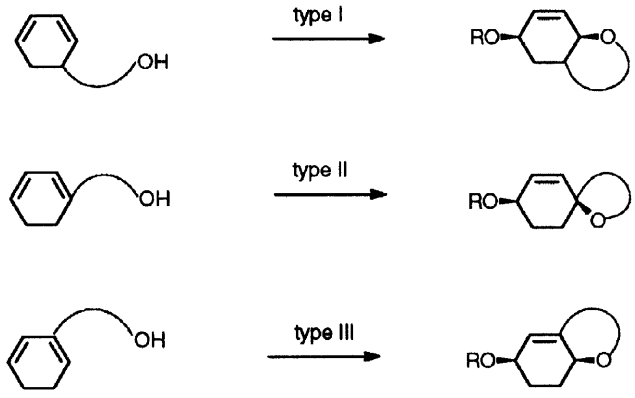
Abstract: New types of palladium(II)-catalyzed intramolecular 1,4-dialkoxylation of 1,3-cyclohexadienes are described. The reactions proceed with high regio- and stereoselectivity and provide an efficient route to novel stereodefined heterocycles such as oxaspirocyclic compounds and fused pyrans.

Palladium(II)-catalyzed 1,4-oxidation of 1,3-dienes has proved to be a valuable tool in organic synthesis in virtue of its high regio- and stereoselectivities.[1] Recently, an intramolecular variant of the palladium-catalyzed 1,4-oxidation has emerged as an efficient method for the stereoselective synthesis of various heterocyclic systems.[2] We have previously reported that 1,4-dialkoxylation of 1,3-dienes takes place when the 1,4-oxidation is performed in an alcohol as the solvent in the presence of a catalytic amount of a strong acid.[3,4] An extension of the 1,4-dialkoxylation to an intramolecular variant would provide a new synthetic avenue to a wide variety of oxygen heterocycles from readily available diene alcohols. There are three types of intramolecular 1,4-dialkoxylation in which the alcohol side chain is situated in different positions on the cyclohexadiene skeleton (Scheme 1). We have previously reported on the type I reaction, which proceeded with good to high stereoselectivity.[2e] Here we report the intramolecular 1,4-dialkoxylation of type II and III. Previously we have not been able to add two oxygen nucleophiles in a 1,4-*cis* fashion in the oxaspirocyclization reaction.

Scheme 1.



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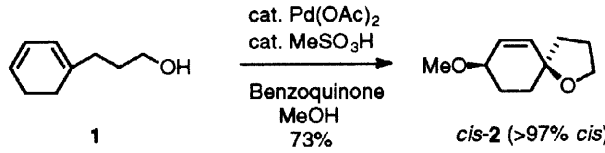
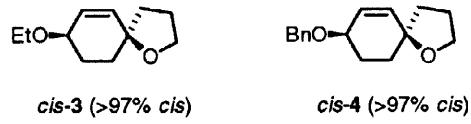
The diene alcohol **1**[5] was slowly added (5h) to a solution of 5 mol% of $Pd(OAc)_2$, 10 mol% of $MeSO_3H$, and 2 equiv of *p*-benzoquinone in MeOH at room temperature. An intramolecular 1,4-dialkoxylation took place to produce *cis*-**2** which was isolated in 73% yield by chromatography (eq 1). By altering the solvent alcohol to EtOH and BnOH, *cis*-**3** and *cis*-**4** were obtained in 80% and 60% isolated yield, respectively.

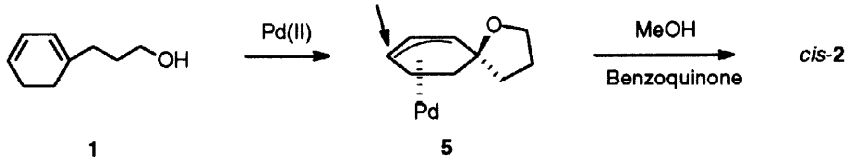


(1)

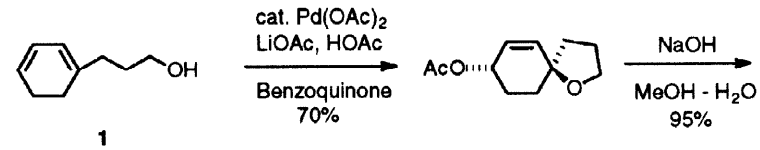


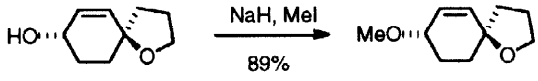
The *cis* stereochemistry was assigned in analogy with the intermolecular 1,4-dialkoxylation.[3] The stereochemical outcome can be rationalized by assuming an intramolecular *trans*-alkoxypalladation[6] of the diene alcohol to give π-allyl intermediate **5**, followed by an external *trans*-attack of the solvent alcohol to give *cis*-**2** (Scheme 2).

Scheme 2.



In order to confirm the stereochemistry of the reaction, *trans*-**2** was synthesized independently (eq 2). A *trans*-oxaspirocyclization of **1** afforded spirocyclic ether in 70% yield isolated as a single diastereomer.[2b] Hydrolysis of the acetate and subsequent etherification of the alcohol afforded *trans*-**2** as a single diastereomer (eq 2). Compounds *cis*-**2** and *trans*-**2** showed different NMR spectra.[7]





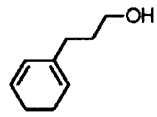
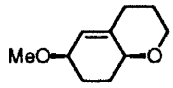
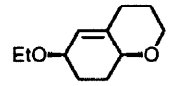
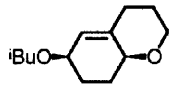
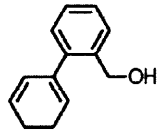
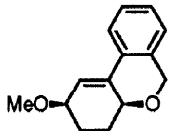
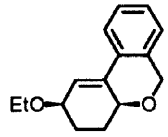
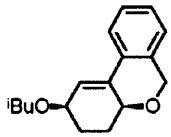
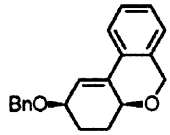
(2)

trans-**2** (>97% *trans*)

Next, the analogous reaction of type III diene alcohol[8] was examined and the results are listed in Table 1. The reactions of **6** proceeded smoothly with high regio- and stereoselectivities (entry 1-3). Interestingly, the construction of the isochroman ring system,[9] which is otherwise difficult to achieve, was realized in a stereoselective manner (entry 4-7). It is noteworthy that almost complete loss of stereochemistry of all the

products from diene alcohol **7** was observed when the reactions were carried out at a longer reaction time (12h). Since it was possible to obtain the *cis*-product predominantly (entry 4-7) at shorter reaction times (0.5-2h), this suggests that acid-catalyzed epimerization of the product via a vinylogous benzyl cation intermediate occurs. In some of the reactions it was not possible to completely avoid the secondary acid-catalyzed epimerization (entry 4 and 7). Moreover, this acid-catalyzed epimerization would explain the moderate stereoselectivities observed in some of the type I dialkoxylations previously reported.[2e]

Table 1. Palladium-Catalyzed Intramolecular 1,4-Dialkoxylation of 1,3-Cyclohexadienes (type III)[a]

entry	starting material	solvent	reaction time (h)[b]	product	yield (%)[c]	stereo-chem.
1	 **6**	MeOH	5 + 5		76	>97% cis
2		EtOH	5 + 5		87	>97% cis
3		^{i}BuOH	5 + 5		96	>97% cis
4	 **7**	MeOH	2 + 0.5		90	92% cis
5		EtOH	2 + 1		77	>97% cis
6		^{i}BuOH	2 + 3		96	95% cis
7		BnOH	2 + 2		80	82% cis

[a] The reactions were performed in the appropriate alcohol (5 mL/mmol) using 5 mol% of $Pd(OAc)_2$, 10 mol% of $MeSO_3H$, and 2 equiv of *p*-benzoquinone. [b] The first figure refers to the addition time of starting material and the second figure refers to the reaction time after completed addition. [c] Isolated yields.

In summary, we have developed stereoselective intramolecular 1,4-dialkoxylations of diene alcohols in which the alcohol side chains are situated in 1- and 2-position of the 1,3-cyclohexadiene skeleton. The development of an enantioselective version of these reactions as well as their application to natural product synthesis are the subjects of a current investigation.

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Visiting student from Kyoto University, Japan

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5. Diene alcohol **1** was prepared according to the procedure described in ref. 2h.
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7. *Cis*-**2** : ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.81 (dd, J = 10.4, 2.8 Hz, 1H), 5.66 (d, J = 10.4 Hz, 1H), 3.90-3.84 (m, 1H), 3.82-3.76 (m, 1H), 3.73-3.68 (m, 1H), 3.34 (s, 3H), 2.00-1.70 (m, 8H); ^{13}C -NMR (100MHz, $CDCl_3$): δ 134.2, 129.3, 79.1, 74.5, 67.3, 55.6, 37.5, 32.0, 26.0, 25.8. *Trans*-**2** : ^{1}H-NMR (400MHz, $CDCl_3$): δ 5.81 (dd, J = 10.0, 3.2 Hz, 1H), 5.69 (d, J = 10.0 Hz, 1H), 3.92-3.80 (m, 2H), 3.80-3.76 (m, 1H), 3.37 (s, 3H), 2.12-1.55 (m, 8H); ^{13}C -NMR (100MHz, $CDCl_3$): δ 135.0, 128.4, 80.2, 74.4, 67.4, 55.9, 37.3, 32.4, 26.9, 26.1.
8. Diene alcohol **6** was prepared by a procedure described in ref. 2i, and **7** was prepared by a method recently developed in our laboratory (Karlström, A. S. E.; Bäckvall, J. E. unpublished results).
9. For other methods for the synthesis of the isochroman ring system, see: (a) Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1995**, *36*, 7047. (b) Ponaras, A. A.; Zaim, Ö. *Tetrahedron Lett.* **1993**, *34*, 2879.