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The Use of Stabilized Carbon Nucleophiles in Palladium(II)-Catalyzed 1,4-Oxidation of Conjugated Dienes

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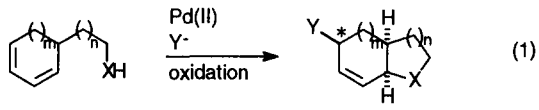
Abstract. Palladium(II)-catalyzed aerobic oxidation of conjugated dienes **3** having a stabilized carbon nucleophile in the side chain resulted in a carbocyclization with an overall 1,4-*cis*-addition to the diene. The reactions were carried under an atmosphere of molecular oxygen in DMSO. An interesting *exo*/*endo* selectivity of the electron-withdrawing groups in the tether led to a control of the relative stereochemistry between four stereogenic centers.

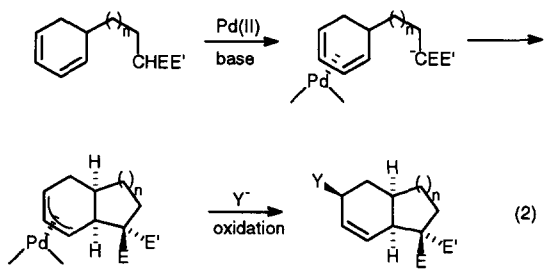
The palladium-catalyzed 1,4-oxidation of conjugated dienes in which two nucleophiles are added to the 1- and 4-position of the 1,3-diene has emerged into a synthetically useful reaction.[1-8] In the intermolecular reaction oxygen nucleophiles and halide anions are added to the diene in a highly regio- and stereoselective manner.[3,4] In the intramolecular version the reaction was extended to a number of heteroatom nucleophiles and in this way stereodefined fused heterocyclic systems are accessible (eq. 1).[5,6]



(1)

*Control of α-Y versus β-Y

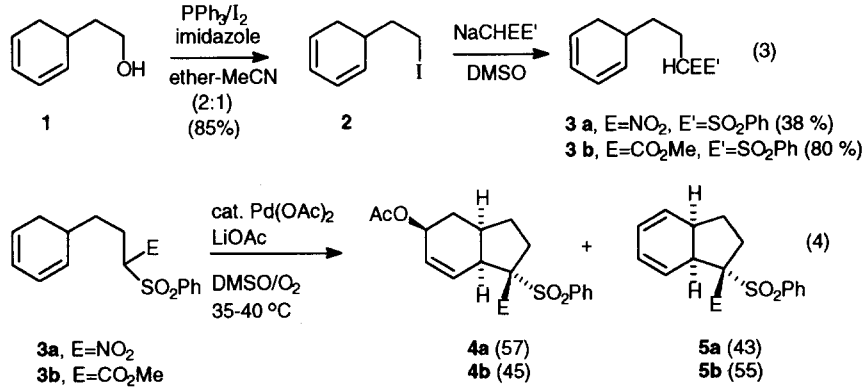
Recently the intramolecular reaction of equation 1 was extended to involve carbon-carbon bond formation via two different approaches:[7,8] (i) chloropalladation of an acetylene in the side chain generates a vinylpalladium species which reacts with the diene in a Heck-type addition, and (ii) an allylsilane was employed as nucleophile in the side chain. A more direct approach to obtain carbon-carbon bond formation would be to use a stabilized nucleophile in the side chain (eq. 2).



(2)

Attempts to employ the Pd(II)/benzoquinone electron transfer system with stabilized carbon nucleophiles (pK_a 5-7) in the side chain have so far been unsuccessful. However by changing to the O_2/DMSO oxidation system[9-11] we now have been able to realize this reaction pathway.

The starting materials for the palladium-catalyzed carbocyclization reaction were prepared according to equation 3. The diene alcohol[5b] was transformed to the requisite dienes **3** via the iodide **2**.[12] Palladium-catalyzed oxidation[13] of **3a** employing $Pd(OAc)_2$ as catalyst in DMSO in the presence of LiOAc and 1 atm of molecular oxygen resulted in complete consumption of the substrate (40 °C, 40h) and produced a 57:43 mixture between products **4a** and **5a** in a combined yield of 50% (eq. 4). The stereochemistry of products **4a** and **5a** was unambiguously assigned by NMR spectroscopy using NOE measurements.[14]

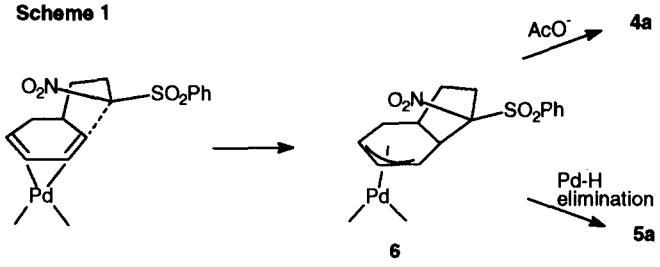


Compound **4a** was obtained as a single isomer with the relative stereochemistry shown in equation 4. Thus, the relative stereochemistry between four stereogenic centers is controlled in one single reaction. The 1,4-addition to the diene occurs with overall *syn* stereochemistry, which is a result of a trans carbopalladation[15] of the double bond of the diene to give a π-(allyl)palladium intermediate (eq. 2) followed by external *anti* attack by acetate (Y = OAc). Because of the bulkiness of the $PhSO_2$ group compared to the nitro group the former will point away from the cyclohexadiene in the transition state conformation and end up in the *exo* position in the π-allyl intermediate **6** (Scheme 1). External nucleophilic attack by acetate on **6** produces **4a** as a single isomer. Diene formation via elimination of palladium and a hydrogen[16,17] competes with nucleophilic attack by acetate and accounts for product **5a**, which also was obtained as a single isomer.

The use of **3b** as substrate gave a mixture of the two compounds **4b** and **5b** (45:55) in a combined yield of 40%. In this case the $PhSO_2$ *exo*/*endo* selectivity was lower (4:1) probably due to the larger size of the ester group compared to the nitro group.

The low selectivity of **4** versus **5** is most likely due to a slow nucleophilic attack on the π-allyl intermediate **6**, leading to competing β-hydride elimination (Scheme 1). The activation of the π-allyl complex by coordination of DMSO[18] or molecular oxygen is rather weak and leads only to a moderate rate of nucleophilic attack.

Scheme 1



We have demonstrated a new carbon-carbon bond formation reaction employing *catalytic* amounts of palladium. Furthermore, the possibility to control the relative stereochemistry between four stereocenters in one reaction could prove useful in *e.g.* synthesis of natural products. This highly convenient method is now under further development.

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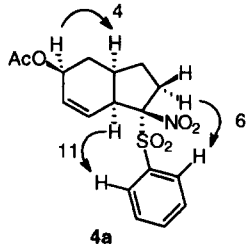
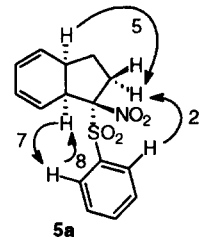
13. **General procedure for cyclization of 3a.** To $Pd(OAc)_2$ (22 mg, 0.1 mmol) and LiOAc (300 mg, 3 mmol) in DMSO (2 ml) under an atmosphere of oxygen was added **3a** (150 mg, 0.5 mmol). The reaction was stirred at 40 °C for 40 h. Water (10 ml) was added and the products were extracted with EtOAc (3x20 ml). The combined organic layers were washed with water (3x10 ml) and dried ($MgSO_4$). Evaporation followed by purification using flash chromatography gave **4a** and **5a** in 50 % combined yield.
Spectral data for 4a ^{1}H NMR (400 MHz) δ; 7.99 (2 H, m), 7.75 (1 H, m), 7.62 (2 H, m), 5.73 (1 H, m), 5.32 (1 H, ddd, J= 10.4, 4.3, 2.0 Hz), 5.21 (1 H, m), 3.43 (1 H, m), 3.13 (1 H, m), 2.93 (1 H, ddd, J=15.4, 8.8, 2.0 Hz), 2.65 (1 H, m), 2.25 (1 H, m), 2.02 (3 H, s), 1.96 (1 H, m), 1.86 (1 H, m), 1.30 (1 H, m); **Spectral data for 5a** ^{1}H NMR (400 MHz) δ; 7.98 (2 H, m), 7.74 (1 H, m), 7.61 (2 H, m), 5.91 (1 H, m), 5.79 (1 H, m), 5.62 (1 H, app. dt, J= 9.6, 3.7, 1.1 Hz), 5.11 (1 H, m), 3.66 (1 H, ddd, J= 11.3, 5.0, 1.8 Hz), 3.26 (1 H, m), 2.85 (1 H, d, J=7.0 Hz), 2.83 (1 H, d, J=7.0 Hz), 2.40 (1 H, m), 2.09 (1 H, m).
14. NOE in %.



4a



5a

15. Carbopalladation of olefins[15a] and dienes[15b] with stabilized carbon nucleophiles is known to occur with trans stereochemistry: (a) Kurosawa, H.; Majima, T.; Asada, N. *J. Am. Chem. Soc.* **1980**, *102*, 6996. (b) Stille, J. K.; Fox, D. B. *J. Am. Chem. Soc.* **1970**, *92*, 1274.
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17. Although this elimination has previously assumed to occur via *syn* β-elimination, recent studies indicate that an *anti* elimination of a proton and palladium(0) is a competing pathway: Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1.
18. For nucleophilic attack on (π-allyl)palladium complex in DMSO see: Tsuji, J. *Tetrahedron Lett.* **1965**, 4387.

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