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Carbon-Carbon Bond Formation in Palladium(II)-Catalyzed Intramolecular 1,4-Oxidation of Conjugated Dienes

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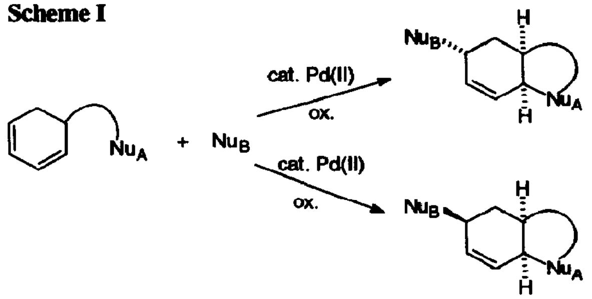
Abstract: Palladium(II)-catalyzed 1,4-oxidation of conjugated dienes involving a carbocyclization has been developed. Chloropalladation of the triple bond in a dienyne and subsequent addition of the vinylpalladium to the conjugated diene creates a (π-allyl)palladium intermediate, which undergoes a quinone-induced chloride attack to give the product. The overall 1,4-addition of the vinylic carbon and the chloro group across the diene occurs in an anti fashion.

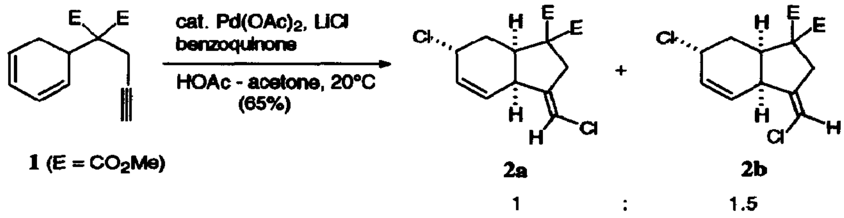
We have recently developed a number of intramolecular palladium-catalyzed 1,4-oxidations of conjugated dienes (Scheme I).[1-4] In these reactions two nucleophiles are added across the diene[5] of which one adds intramolecularly. The 1,4-addition to the diene is highly regio- and stereoselective and often a useful dual stereocontrol is obtained. So far only heteroatom nucleophiles have been employed and it was therefore of great interest to extend these intramolecular 1,4-oxidations to carbon nucleophiles. In the present communication we report on our recent progress in realizing palladium(II)-catalyzed carbon-carbon bond formation in 1,4-oxidation of conjugated dienes.

Scheme I



We first tried to use dienes with a stabilized carbon nucleophile in the side chain to bring about a palladium-catalyzed reaction according to Scheme I. However, all attempts to induce a carbocyclization by this approach have so far been unsuccessful. Another possibility to obtain a carbocyclization would be via a Heck- [redacted] chloropalladation.[7] The latter approach seemed particularly attractive since it involves a Pd(II) chloride salt and would be compatible with the rest of the catalytic cycle.

Reaction of dienyne 1[8] with LiCl and benzoquinone in the presence of palladium acetate (10 mol%) as the catalyst afforded a mixture of products **2a** and **2b** in a ratio of 1:1.5. The reaction was run at room temperature



(1)

in acetic acid - acetone. We were able to assign the structures of the products **2** from their ^{1}H NMR spectra.[9] For confirmation, an X-ray crystal structure[10] of the major isomer was determined (Fig. 1). In this way the relative stereochemistry between the allylic chloro group and the vinylic carbon was firmly established.

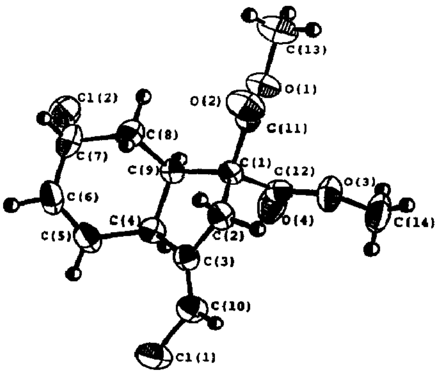
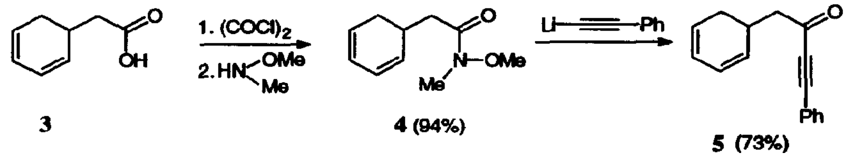
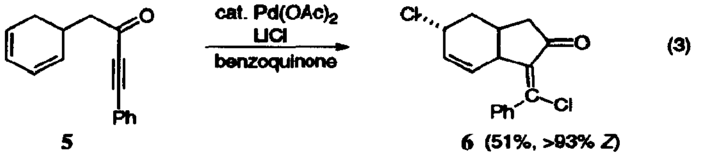


Figure 1. ORTEP drawing of **2b**.

We also studied the dienyne derivative **5** in the palladium-catalyzed carbocyclization reaction. Dienyne **5** was obtained according to equation 2. The known diene acid **3**[2,11] was transformed to methoxyamide **4**. Subsequent reaction of **4** with the appropriate lithium acetylide cleanly afforded the requisite starting material **5**.[12]



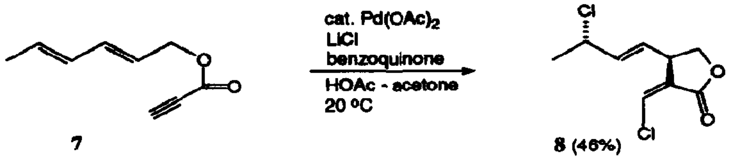
(2)



(3)

Palladium-catalyzed reaction of dienyne **5**, employing the same reaction conditions as used for **1**, afforded cyclized product **6** (eq. 3). The reaction was highly stereoselective with respect to the 1,4-addition across the conjugated diene. In this case the formation of the vinylic carbon-chloro bond was stereoselective to give mainly the *Z*-double bond (>93% *Z*), as determined by NOE. The reaction sequence in eqs. 2 and 3 was performed with the butyl acetylene analog with comparable results. In the latter case we were not able to unambiguously determine the double bond stereochemistry of the cyclized product.

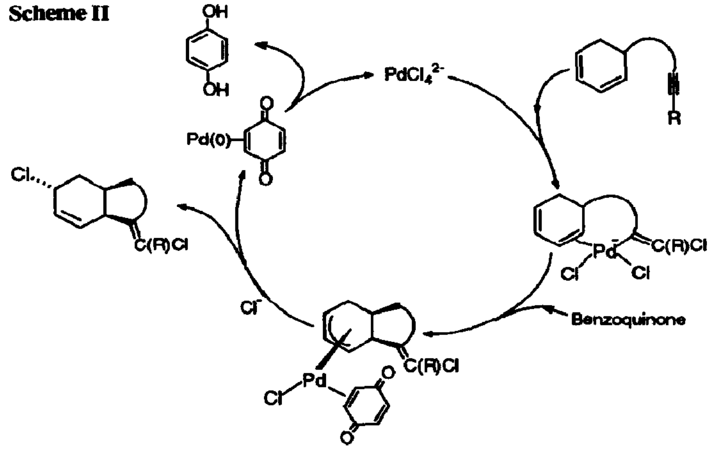
The corresponding reaction of acyclic dienyne **7** gave lactone **8** as the product. Again the reaction resulted in an overall stereoselective anti 1,4-addition of carbon and chloride across the diene. As in the reaction of **5** formation of the vinylic carbon-chloro bond was stereoselective (85-90% *Z*).



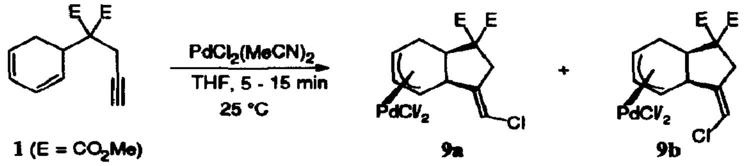
7 **8** (46%)

A likely mechanism for the palladium(II)-catalyzed 1,4-oxidation involving C-C-bond formation is given in Scheme II. Chloropalladation of the triple bond would produce a vinylpalladium species which can add to the diene in a Heck-type reaction. The latter reaction gives a (π-allyl)palladium complex, which will be attacked by a chloride nucleophile. It is interesting to note that the reaction conditions (LiCl, *p*-benzoquinone, HOAc-acetone, 20 °C) are the same as those employed in the analogous intramolecular palladium-catalyzed 1,4-addition of a nitrogen or oxygen nucleophile and a chloride.[2-4] The left part of the catalytic cycle of Scheme II is mechanistically identical to the catalytic cycle of the latter reactions.

Scheme II



Evidence for the mechanism in Scheme II was provided by the reaction of **1** (1 equiv.) with $PdCl_2(MeCN)_2$ (1 equiv.) in THF which gave (π-allyl)palladium complexes **9a** and **9b** as the only products.[13] Interestingly, the ratio **9a**:**9b** decreased when the reaction was run more diluted, reflecting that **9a** and **9b** are formed via a bimolecular and an intramolecular reaction, respectively. Complete conversion was observed within 5 minutes when the reaction was run in THF-d_8 in an NMR tube. The rapid formation of **9a** and **9b** as the only observable products eliminates an alternative pathway for formation of **2a** and **2b** via chloropalladation of the diene and subsequent insertion of acetylene into the allylpalladium bond.[14]



1 (E = CO_2Me) **9a** **9b**

	9a		9b
[1] = [$PdCl_2(MeCN)_2$] = 0,26 M	1.3	:	1
[1] = [$PdCl_2(MeCN)_2$] = 0,026 M	1	:	1.8

An interesting feature of this new carbon-carbon bond forming reaction is that it is catalyzed by Pd(II), and as a result the stereodefined allylic chloride is stable under the reaction conditions.[15,16] These stereodefined allylic chlorides are useful synthetic intermediates since the chloro group can be stereospecifically substituted with either retention or inversion by a number of nucleophiles.[4a,5c]

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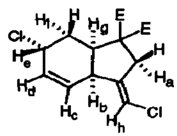
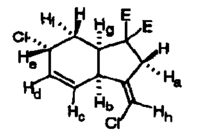
7. Ma, S; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120.
8. Obtained from reaction of propargylic bromide with sodium dimethyl (2,4-cyclohexadien-1-yl) malonate.[2a,3b]
9. *NOE-measurement*: The stereochemistry of the exocyclic double bond was determined to be *E* in **2a** (H_h gave NOE effects to H_b and H_c) and *Z* in **2b** (H_h gave an NOE effect to H_a). Since NOE was observed between H_b and H_g in both isomers the cis ring junction was established. In neither case did H_e give any detectable NOE to H_g.



2a



2b

10. *Crystal data* for **2b**: $C_{14}H_{16}Cl_2O_4$, $M = 319.18$, triclinic space group P1, a = 11.175(3) Å, b = 11.725(4) Å, c = 6.034(2) Å, $\alpha = 91.14(3)°$, $\beta = 101.02(3)°$, $\gamma = 82.68(2)°$, V = 769.6(4) $Å^3$, Z = 2, $D_{calc} = 1.377$ gcm^{-3}, R(F) = 0.063, $R_w(F) = 0.081$, crystal size: 0.55 x 0.10 x 0.07 mm, $\mu_{calc} = 4.3$ cm^{-1}. *Experimental*: Data were measured on a Rigaku AFC6R X-ray diffractometer (graphite monochromatized Mo-Kα radiation; 9 KW rotating-anode generator) using an ω-2θ scan-mode to a maximum 2θ value of 50.0°. Weak reflections ($I < 50\sigma(I)$) were rescanned to give good counting statistics. Stationary background counts were recorded on each side of the reflection. Of the 2857 reflections measured, 2706 were unique. Five representative reflections were monitored every 50 reflections; these showed an overall decrease of 4.7%. A linear correction factor was applied. An empirical absorption correction, based on azimuthal scans of several reflections, resulted in correction factors ranging from 0.95 to 1.00. The data were also corrected for Lorentz and polarization effects.
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12. The use of methoxyamides in the reaction with Grignard or organolithium reagents to provide ketones has been described by Weinreb: Nahm, S. Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815, see also Cupps, T.L.; Boutin; R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972.
13. The assignment of **9a** and **9b** was done by NOE. It was also demonstrated that **9a** → **2a** and **9b** → **2b** on reaction with LiCl and *p*-benzoquinone.
14. For the reaction of (π-allyl)palladium intermediates with acetylenes leading to carbocyclization see: Oppolzer, W.; Robyr, C. *Tetrahedron* **1994**, *50*, 415 and refs cited therein.
15. (a) It has been demonstrated that allylic chlorides react within minutes at room temperature with palladium(0) phosphine complexes:[4a,5c,15b] (b) Granberg, K. L.; Bäckvall, J.E. *J. Am. Chem. Soc.* **1992**, *114*, 6858.
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