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# Palladium(II)-Catalyzed Asymmetric 1,4-Oxidation of 2-Phenyl-1,3-Cyclohexadiene

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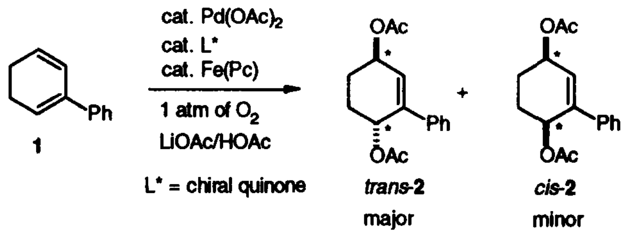
***Abstract***: Several new sulfoxide and amide substituted benzoquinones have been employed as ligands in the Pd(II)-catalyzed 1,4-oxidation of 2-phenyl-1,3-cyclohexadiene (**1**). The sulfoxide ligand **4** is a superior ligand in the reaction affording high yield in the functionalization of this sensitive 1,3-diene, and with this ligand the *trans*-diacetate was obtained with up to 45% enantiomeric excess. © 1997 Elsevier Science Ltd.

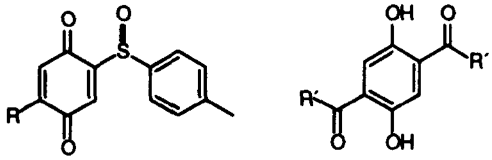
Palladium(II)-catalyzed 1,4-oxidation of 1,3-dienes is a useful reaction in the preparation of highly funtionalized compounds.[1] A wide range of nucleophiles is tolerated in the reaction which proceeds with a high degree of stereo- and regioselectivity. Both inter- and intramolecular versions of the reaction are available which have been utilized in natural product synthesis.[2] An asymmetric version of this reaction would therefore be highly desirable. Contrary to numerous reports of successful asymmetric Pd(0)-catalyzed reactions[3] there are only few reports of asymmetric Pd(II)-catalyzed reactions, especially regarding Pd(II)-catalyzed oxidation.[4] An exception to this is the recent elegant work by Hayashi on asymmetric Wacker-type oxidation of *o*-allylphenols.[4a]

**Scheme 1**



The 1,4-addition of two nucleophiles to conjugated dienes catalyzed by Pd(II) has been proven to involve the intermediacy of a ($\pi$-allyl)palladium species, which subsequently reacts with a second nucleophile affording the 1,4-functionalized product. The second nucleophilic attack is dramatically accelerated by ligands such as benzoquinone.[5] Since the intermediate $\pi$-allyl complex has been shown to be an equilibrating species[6] our approach to an asymmetric 1,4-oxidation has been the utilization of chiral benzoquinones. In this paper we report our preliminary results from catalytic 1,4-diacetoxylation of conjugated dienes (Scheme 1). A number of chiral benzoquinone ligands were prepared containing units that are known to coordinate to Pd(II), such as sulfoxides and amides (Figure 1).[7,8]

**Figure 1**



**3** R=H
**4** R= *t*-Bu

**5** R′= (-)-Menthoxy
**6** R′= (+)-NHCH(CH$_3$)Ph
**7** R′= (+)-CH$_3$NCH(CH$_3$)Ph
**8** R′= (+)-NHCH(CH$_3$)(1-napthyl)
**9** R′= (+)-NHCH(CH(CH$_3$)$_2$)CH$_2$OH

Employing the chiral ligands depicted in Figure 1 afforded the *trans*-diacetate with up to 21% enantiomeric excess in the 1,4-diacetoxylation of **1** (Table 1).[9] The sulfoxide ligands **3** - **4** and the amide ligand **6**, **8** - **9** were comparable ligands with respect to asymmetric induction and *trans*/*cis* selectivity. This was rather surprising when one takes into account their large structural differences. The only noticeable difference was with ligand **4** which afforded an excellent yield in the 1,4-oxidation of the very sensitive substrate **1**.[10] On the other hand ester **5** and amide **7** were poor ligands in the Pd(II)-catalyzed 1,4-oxidation affording low yield, stereoselectivity and no asymmetric induction.

**Table 1.** Chiral ligands used in the 1,4-oxidation of **1**.[a]

| Entry | Ligand | T °C | % yield, **2**[b] | *trans*/*cis* | %ee *trans*[c] |
|---|---|---|---|---|---|
| 1 | *p*-benzoq. | 21 | 54 | 89/11 | - |
| 2 | **3** | 21 | 33 | 83/17 | 21 |
| 3 | **4** | 21 | 82 | 93/7 | 19 |
| 4 | **5** | 50 | 42[d] | 63/37 | 0 |
| 5 | **6** | 28 | 58 | 88/12 | 14[f] |
| 6 | **7** | 21 | 4 | 76/24 | 0 |
| 7 | **8** | 4 | 35 | 95/5 | 20[f] |
| 8 | **9** | 21 | 34 | 85/15 | 17[f] |

[a] Reaction conditions: 0.5 mmol scale, 10 mol% Pd(OAc)$_2$, 3 mol% iron(II) phthalocyanine (Fe(Pc)), 1.2 eq. LiOAc x 2H$_2$O, 20 mol% of L in 0.25 mL/1 mL of acetone/acetic acid under an oxygen atmosphere. [b] Isolated yield by column chromatography. [c] The enantiomeric excess was determined by HPLC on a Chiralcel OD-H column using 5% *i*-PrOH in hexane, 0.5 mL/min. In entries 2 and 3 the major enantiomer is the opposite to that of entries 5,7 and 8.[9] [d] Slow addition.

The promising result with ligand **4** demanded a closer look at various reaction parameters such as temperature, solvent, ratio of ligand to palladium, and the effect of additives. Alteration of the Pd/ligand ratio was found to strongly affect the asymmetric induction and with a ratio of 10/1 of Pd/**4** the *trans*-diacetate **2** was isolated with 38% enantiomeric excess (Table 2). By using less amount of ligand the yield and the stereoselectivity in the reaction decreased.

**Table 2.** 1,4-Oxidation of diene **1** with ligand **4**[a]

| Pd:4 | mol% Pd | mol% 4 | %yield, 2[b] | *trans*/*cis* | %ee *trans*[c] |
|---|---|---|---|---|---|
| 1:2 | 10 | 20 | 82 | 93/7 | 19 |
| 1:1 | 10 | 10 | 47 | 92/8 | 22 |
| 5:1 | 20 | 4 | 46 | 90/10 | 33 |
| 10:1 | 20 | 2 | 38 | 86/14 | 38 |

[a] Reaction conditions: 0.5 mmol scale 3 mol% Fe(Pc), 1.2 eq. LiOAc x 2 $H_2O$, in 1 mL HOAc and 0.25 mL acetone under an oxygen atmosphere at rt. for 24 h. [b] Isolated yield by column chromatography. [c] The enantiomeric excess was determined by HPLC on a Chiralcel OD-H column using 5% *i*-PrOH in hexane, 0.5 mL/min.

During the examination of different reaction parameters, one of the more interesting observations was that acetonitrile as an additive had a beneficial effect on the reaction.[11] Utilizing variable amounts of acetonitrile in the reaction, it was possible to increase the asymmetric induction up to 45% ee (Table 3). Unfortunately, this was achieved at the expense of the yield and stereoselectivity of the reaction.

**Table 3.** Amount of acetonitrile as additive utilizing 10 mol% of ligand **4**[a]

| $CH_3CN$:Pd | %yield, 2[b] | *trans/cis* | %ee *trans*[c] |
|---|---|---|---|
| 0 | 88 | 91/9 | 28 |
| 1:1 | 89 | 90/10 | 30 |
| 10:1 | 58 | 80/20 | 33 |
| 50:1 | 29 | 70/30 | 39 |
| 766[d]:1 | 27 | 60/40 | 45 |

[a] Reaction conditions: 0.5 mmol scale, 10 mol% $Pd(OAc)_2$ 10 mol% 4, 3 mol% Fe(Pc), 2 eq. LiOAc x 2 $H_2O$, in 2 mL HOAc under an oxygen atmosphere at rt. for 24 h. [b] Isolated yield by column chromatography. [c] The enantiomeric excess was determined by HPLC on a Chiralcel OD-H column using 5% *i*-PrOH in hexane, 0.5 mL/min. [d] 2 mL of $CH_3CN$, 10 equiv. of HOAc.

In summary, we have reported the first example of an asymmetric palladium(II)-catalyzed 1,4-oxidation of 1,3-cyclohexadiene. Several ligands were employed in the reaction affording a moderate asymmetric induction. By variation of reaction conditions, with sulfoxide ligand **4**, the *trans*-diacetate **2** was obtained with up to 45 % enantiomeric excess. Ligand **4** is a superior ligand, compared to any other benzoquinone ligands since it affords good yields and a good *trans/cis* selectivity in the oxidation of sensitive dienes such as **1**. The use of **4** in palladium(II)-catalyzed 1,4-oxidation of dienes is therefore a substantial improvement of the experimental procedure. The scope of the reaction and the preparation of a new generation of ligands are currently under investigation.

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\# Visiting student from Kyoto University, Japan

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11. Other reaction parameters such as solvents and other additives were found to affect the reaction, though not as dramatically.

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