Application of O₂–DMSO as Reoxidant in the Pd(II)-Catalyzed 1,4-Oxidation of 5-Substituted 1,3-Cyclohexadienes

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Palladium-catalyzed oxidation of 5-substituted 1,3-cyclohexadienes carrying a nucleophilic group in the side chain employing O₂–DMSO as the oxidant gave cyclization via 1,4-addition to the 1,3-diene. The nucleophilic groups employed were tosylamido and carboxy. In the reaction PdIII is most likely reduced to colloidal Pd0, which is subsequently reoxidized by O₂. The solvent DMSO prevents precipitation of metallic palladium by coordination to the colloidal particles. The stereochemistry of the palladium-catalyzed intramolecular 1,4-oxidation was controlled to some extent by the nature of the external nucleophile. Thus, in the intramolecular 1,4-oxyacyloxylation of 1 (hydroxy as nucleophile in the side chain) it was possible to direct the 1,4-addition towards cis or trans stereochemistry by variation of the external carboxylate nucleophile.

Palladium-catalyzed oxidations of olefins and dienes are of current interest in synthetic organic chemistry.1–3 The potential use of these reactions in industrial applications has led to the search for improved and inexpensive reoxidation systems. Recently, a number of new palladium-catalyzed oxidations of alkenes and dienes based on the use of molecular oxygen have been developed.4–7

The oxidation system O₂ in DMSO has recently been successfully used in the palladium-catalyzed oxidation of alkenes.5–7 In connection with our studies on palladium-catalyzed oxidation of conjugated dienes1–4,8 it was of interest to apply the O₂–DMSO system to these reactions. In this account we report on the use of O₂–DMSO as a reoxidant for palladium in intramolecular 1,4-additions of the 1,3-dienes 1, 2 and 3 (Scheme 1). An interesting observation is that the stereochemistry of the 1,4-addition depends on whether a carboxylic acid or its lithium salt is employed as the external nucleophile.

Results and discussion

Optimization of the stereochemistry in the oxyacyloxylation. Reaction of 1. Palladium-catalyzed oxidation of the diene alcohol 1 in DMSO by molecular oxygen in the presence of different carboxylic acids was studied. The catalyst used was palladium acetate. This reaction produces 5-acloxy-substituted hexahydrobenzofurans 4 together with some isomerized starting material. An important aspect of this reaction is the stereochemistry of the 1,4-addition over the 1,3-diene which, using p-benzoquinone as reoxidant, earlier was controlled by the concentration of chloride ion. As even small amounts of halide ion inhibit the reaction with O₂–DMSO as reoxidant other reaction conditions and additives were examined. It was found that the stereochemical outcome of the addition is strongly dependent on the nature of the external nucleophile. Thus, the use of a salt of the carboxylic acid gave the 1,4-trans addition product (>95% trans) whereas the use of the carboxylic acid itself favored the formation of the 1,4-cis addition product (Scheme 2, Table 1). Reaction of 1 in the presence of LiOAc in DMSO under 1 atm of O₂ produced 4a (>95% 1,4-trans addition) together with some aromatized starting material 5, the ratio 4a:5 being 4:1 (Table 1, entry 1 and 3). The isolated yield of 4a after work-up was 52%. An increase in temperature gave essentially the same result with a shorter reaction time. The use of lithium benzoate as the external nucleophile gave the

Scheme 1. Pd-catalyzed 1,4-oxidation by O₂ in DMSO.

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Table 1. Variation of carboxylic acid and salt to control the 1,4-cis:1,4-trans selectivity.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCOOX</th>
<th>cis:trans</th>
<th>Major product 4</th>
<th>4:1:5</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOLi</td>
<td>&lt;5:95</td>
<td>4a</td>
<td>80:0:20</td>
<td>48 h RT</td>
</tr>
<tr>
<td>2</td>
<td>AcONa</td>
<td>&lt;5:95</td>
<td>4a</td>
<td>65:15:20</td>
<td>48 h RT</td>
</tr>
<tr>
<td>3</td>
<td>AcOLi</td>
<td>&lt;5:95</td>
<td>4a</td>
<td>80:0:20</td>
<td>24 h 40°C</td>
</tr>
<tr>
<td>4</td>
<td>PhCOOLi</td>
<td>&lt;5:95</td>
<td>4e</td>
<td>65:10:25</td>
<td>24 h 40°C</td>
</tr>
<tr>
<td>5</td>
<td>AcOH</td>
<td>50:50</td>
<td>4a,4c</td>
<td>70:17:13</td>
<td>24 h 40°C</td>
</tr>
<tr>
<td>6</td>
<td>PhCOOH</td>
<td>90:10</td>
<td>4d</td>
<td>34:23:43</td>
<td>36 h 40°C</td>
</tr>
<tr>
<td>7</td>
<td>o-CIC₆H₄COOH</td>
<td>93:7</td>
<td>4b</td>
<td>83:0:17</td>
<td>18 h 40°C</td>
</tr>
<tr>
<td>8</td>
<td>o-CIC₆H₄COOH</td>
<td>93:7</td>
<td>4b</td>
<td>87:0:13</td>
<td>48 h RT</td>
</tr>
<tr>
<td>9</td>
<td>o-CIC₆H₄COOH</td>
<td>94:6</td>
<td>4b</td>
<td>86:7:7</td>
<td>24 h RT</td>
</tr>
<tr>
<td>10</td>
<td>2,4-CIC₆H₄COOH</td>
<td>90:10</td>
<td>4b</td>
<td>85:5:15</td>
<td>48 h RT</td>
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<tr>
<td>11</td>
<td>2,4-CIC₆H₄COOH</td>
<td>80:20</td>
<td>5b</td>
<td>58:9:42</td>
<td>24 h 40°C</td>
</tr>
<tr>
<td>12</td>
<td>p-CIC₆H₄COOH</td>
<td>90:10</td>
<td>5b</td>
<td>46:15:39</td>
<td>24 h RT</td>
</tr>
<tr>
<td>13</td>
<td>p-FC₆H₄COOH</td>
<td>88:12</td>
<td>7b</td>
<td>78:14:8</td>
<td>24 h RT</td>
</tr>
<tr>
<td>14</td>
<td>o-BrC₆H₄COOH</td>
<td>94:6</td>
<td>7b</td>
<td>81:8:11</td>
<td>24 h RT</td>
</tr>
</tbody>
</table>

*The cis:trans ratio was determined using ¹H NMR integrals over the allylic bridge head protons. The data of the acetate adducts were compared with those reported in the literature. The acryloyloxy adducts were hydrolyzed to the corresponding alcohols 10 and 11. *Determined using the ¹H NMR integrals of the crude product.

Same stereoselectivity but a lower conversion and slightly more aromatic product 5 (entry 4). For acetic acid the selectivity 1,4-cis:1,4-trans was only 50:50 (entry 5) but the selectivity for 1,4-cis addition increased with the strength of the acid and was 90:10 for benzoic acid (entry 6) and 93:7 for o-chlorobenzoic acid (entries 7 and 8, Table 1).

Scheme 2. Controlling the stereoselectivity of the 1,4-addition over the 1,3-diene.

Attempts to use p-nitrobenzoic acid as the external nucleophile gave no reaction and the use of p-methoxybenzoic acid gave a very slow reaction.

**Reaction of 2.** The successful control of the 1,4-cis:1,4-trans selectivity with diene 1 encouraged us to try other dienes. In the case of cyclization of tosylamide 2 the selectivity for 1,4-trans addition with LiOAc as the external nucleophile was lower than for 1. Thus 6 was obtained as a 7:3 mixture of 1,4-trans and 1,4-cis addition products. The use of o-chlorobenzoic acid as the external nucleophile did not result in any product possibly due to the low nucleophilicity of the nitrogen at this lower pH (Scheme 3).

**Reaction of 3.** Palladium-catalyzed oxidation of diene acid 3 employing o-chlorobenzoic acid as the external nucleophile resulted in 1,4-cis addition over the diene to give lactone 7 (>95% 1,4-cis addition). Surprisingly, change of the external nucleophile to lithium acetate did not give the expected 1,4-trans addition in this case but afforded lactone 8 via a 1,4-cis addition (Scheme 4). The reason for the difference between 1 and 3 in the reaction with lithium acetate is not clear. The high selectivity for 1,4-cis acyloxylation is interesting in the light of the moderate selectivity of the previous Pd-catalyzed procedure for this transformation. The present method is a major improvement over the previous method where the best result in the acyloxylation was 75% cis addition.

Scheme 3. Reactivity of the amide 2.

**Scheme 4. Reactivity of the acid 3.**

Mechanistic considerations. A side reaction in these 1,4-oxidation reactions is the aromatization of the starting diene. This aromatization could in principle take place directly from 1 but it is more likely that it proceeds via diene 9. Diene formation from (ν-allyl)palladium complexes is well known and formation of diene 9 followed by anti elimination of a hydrogen and the oxygen function would give 5 (Scheme 5). A possible explanation of the higher proportion of aromatized product in the O₂–DMSO reaction compared to the 1,4-benzoquinone–HOAc reactions is that the attack by the external nucleophile (e.g., AcO⁻) on the intermediate
(π-allyl)palladium complex is slower with the former system. As a consequence, the competing β-hydride elimination occurs to a larger extent. A change in temperature did not significantly change the ratio between 1,4-oxidation product and aromatized starting material.

Scheme 5. Possible mechanism for aromatization of 1.

The mechanism of palladium-catalyzed oxidations with the O₂-DMSO system has been discussed and considered to involve colloidal palladium(0). The role of DMSO would then be to dissolve such cluster-like particles. It is well known that sulfoxides coordinate to palladium(II) and the fact that they act as rate-accelerating ligands in palladium(II)-catalyzed reactions may also play an important role. The coordination properties of the DMSO may help to stabilize colloidal palladium by coordination to individual atoms in the cluster.

Conclusions. In conclusion, this newly developed method offers an inexpensive and environmentally safe reoxidation system. It is general, selective and in some cases this new method leads to an improvement of the stereoselectivity compared with the previous methods reported. An interesting aspect of the present procedure is that it can be run at a higher pH than the corresponding benzokainone-promoted palladium-catalyzed 1,4-oxidations. The latter oxidation system requires a weakly acidic solution whereas, with the present oxidation system (O₂-DMSO), the reaction tolerates a wider pH range and allows weakly basic conditions.

Experimental

¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were run on a Varian Unity 400 spectrometer. CDCl₃ was used as the solvent unless otherwise stated, and the chloroform signal at 7.26 ppm (for ¹H) or 77.0 ppm (for ¹³C) was used as the reference. IR spectra were obtained for thin films or CDCl₃ solutions on a Perkin-Elmer 1600 FT-IR instrument, and only the strongest/structurally most important peaks are listed. Merck silica gel 60 (240–400 mesh) was used for flash chromatography. The synthesis of the dienes 1, 2 and 3 were made according to known literature procedures. Compounds 10 and 12 were characterized by comparison with authentic samples prepared from the known acetates 4a and 8c by hydrolysis. Compound 11 was acetylated to give the corresponding known acetate 4c.

General procedure for palladium(II)-catalyzed cyclization of dienes. Method A. To the diene (1 mmol in 1 ml of DMSO), was added 8–12 equiv. of acid or the salt of an acid. The atmosphere was changed to oxygen by applying a vacuum immediately followed by inlet of O₂. This procedure was repeated once. The solution was stirred for 5 min, after which Pd(OAc)₂ (0.1 mmol) was added by opening the vessel while a slow stream of oxygen was maintained. Once again the vessel was evacuated followed by inlet of O₂. When the reaction was finished according to TLC, water (20 ml) was added and the product was extracted with pentane–ether 50:50 (3 × 15 ml). When an acid was used as second nucleophile the combined organic layers were washed once with Na₂CO₃(sat) (20 ml) to remove the acid. The organic phase was subsequently washed once with water (20 ml) and once with brine (20 ml) and then dried (MgSO₄). The solvent was removed under reduced pressure and the crude product was examined by NMR spectroscopy.

When a salt was used as the external nucleophile the same work-up procedure was employed except for the Na₂CO₃ wash.

Method B. To 3 ml of dry DMSO was added 0.1 mmol of Pd(OAc)₂ and 6 equiv. of acid or the salt of an acid. The atmosphere was changed to molecular oxygen using the above described procedure. After 5 min the diene, 1 mmol, was added via a syringe.

Stereocontrolled oxyacyloxylation. Method A was used and the amount of external nucleophile was 8–12 equiv. The temperature and reaction time are indicated in Table 1. The same work-up as in Method A was used and the crude product was examined by ¹H NMR spectroscopy.

5-Acetoxy-2,3,3a,4,5,7a-hexahydro-(3az,5a,7az)-benzofuran (4a). Method B, 6 equiv. of LiOAc, was used and the same work-up as in Method A was employed. Compound 1 (248 mg, 2.00 mmol) gave 4a (163 mg, 1.04 mmol, 52% yield, >95% trans) after flash chromatography in pentane–ether 75:25. The spectral data were in accordance with those reported in the literature.

5-(o-chlorobenzoyloxy)-2,3,3a,4,5,7a-hexahydro-(3az,5β,7az)-benzofuran (4b). Method B, 6 equiv. of o-chlorobenzoic acid, was used and the same work-up as in Method A was employed. Compound 1 (248 mg, 2.00 mmol) gave 4b (348 mg, 1.26 mmol, 63% yield, 92:8 cis:trans) after flash chromatography in pentane–ether 50:50. Rₜ(pentane–ether 50:50) 0.53. ¹H NMR (400 MHz; CDCl₃): δ 7.80 (1 H, dd, J = 7.8, 1.7 Hz), 7.42 (2 H, m), 7.30 (1 H, m), 6.00 (2 H, s), 5.53 (1 H, m), 4.11 (1 H, m), 4.03 (1 H, m), 3.82 (1 H, ddd, J = 8.6, 8.5, 5.6 Hz), 2.47 (1 H, br), 2.22 (1 H, m), 2.13 (1 H, m), 1.77 (1 H, m), 1.64 (1 H, m). ¹³C NMR (100 MHz; CDCl₃): δ 165.3, 133.7, 132.5, 131.3, 131.2, 131.0, 130.2, 128.2, 126.5, 73.6, 70.7, 67.2, 34.6, 32.2, 30.3. IR: ν = 1730 cm⁻¹.
5-Benzoyloxy-2,3,4,5,7a-hexahydro-(3ax,5β,7ax)-benzofuran (4d). Method B, 6 equiv. of benzoic acid, was used and the same work-up as in Method A was employed. Compound 1 (62 mg, 0.5 mmol) gave 4d (55 mg, 0.23 mmol, 45% yield, 81:19 cis:trans) after flash chromatography in pentane–ether 75:25. \( R_f \) (pentane–ether 75:25) 0.35. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \( δ \) 8.04 (2 H, dd, \( J = 8.4, 1.4 \) Hz), 7.56 (1 H, m), 7.44 (2 H, m), 6.00 (2 H, m), 5.52 (1 H, m), 4.13 (1 H, m), 4.05 (1 H, m), 3.84 (1 H, app dt, \( J = 8.5, 5.6 \) Hz), 2.49 (1 H, m), 2.22 (1 H, m), 2.11 (1 H, m), 1.78 (1 H, m), 1.64 (1 H, app dt, \( J = 12.4, 9.8 \) Hz). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): \( δ \) 166.1, 133.0, 131.6, 130.3, 129.6, 128.3, 128.1, 73.7, 69.9, 67.2, 34.7, 32.3, 30.5. IR: \( v_{\text{max}} \) (CDCl\(_3\))/cm\(^{-1}\) 1716.

5-Benzoyloxy-2,3,3a,4,5,7a-hexahydrd-(3ax,5a,7ax)-benzofuran (4e). Method B, 6 equiv. of lithium benzoate, was used and the same work-up as in Method A was employed. Compound 1 (62 mg, 0.5 mmol) gave 4e (59 mg, 0.24 mmol, 48% yield, >95% trans) after flash chromatography in pentane–ether 75:25. \( R_f \) (pentane–ether 75:25) 0.35. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \( δ \) 8.03 (2 H, m), 7.55 (1 H, m), 7.43 (2 H, m), 6.08 (2 H, m), 5.51 (1 H, m), 4.27 (1 H, dd, \( J = 6.3, 2.7 \) Hz), 3.97 (1 H, app dt, \( J = 8.2, 5.8 \) Hz), 3.81 (1 H, app dt, \( J = 8.4, 6.4 \) Hz), 2.65 (1 H, m), 2.18 (1 H, m), 1.97 (2 H, m), 1.75 (1 H, m). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): \( δ \) 166.0, 132.9, 131.1, 130.4, 129.6, 128.3, 128.3, 73.8, 66.9, 66.7, 33.3, 31.0, 30.1. IR: \( v_{\text{max}} \) (CDCl\(_3\))/cm\(^{-1}\) 1712.

Acetoxy tosylamide (6). Method B with 6 equiv. of LiOAc. The same work-up as in Method A was employed except that EtOAc was used to extract the product. Compound 2 (56 mg, 0.20 mmol) gave 6 (45 mg, 0.13 mmol, 63% yield, 1,4-tr:1,4-cis=7:3) after flash chromatography using pentane–EtO\(_2\)O 1:1 as the eluent. The spectral data were in accordance with those reported in the literature.

Lactone 7. Method B, 6 equiv. of o-chlorobenzoic acid, was used. Work-up was done by evaporating the solvent off under reduced pressure. Compound 3 (69 mg, 0.50 mmol) gave 7 (81 mg, 0.28 mmol, 56% yield, >95% cis) after flash chromatography in pentane–ether 20:80. \( R_f \) (pentane–ether 20:80) 0.26. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \( δ \) 7.80 (1 H, ddd, \( J = 7.6, 2.1, 0.6 \) Hz), 7.45 (2 H, m), 7.33 (1 H, ddd, \( J = 7.6, 6.5, 2.1 \) Hz), 6.21 (1 H, m), 6.08 (1 H, ddd, \( J = 10.2, 3.8, 2.0 \) Hz), 5.58 (1 H, m), 4.83 (1 H, m), 2.86 (1 H, dd, \( J = 17.0, 8.4 \) Hz), 2.77 (1 H, m), 2.50 (1 H, dd, \( J = 17.0, 2.6 \) Hz), 2.24 (1 H, m), 1.72 (1 H, ddd, \( J = 13.0, 11.6, 9 \) Hz), \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): \( δ \) 175.4, 165.1, 133.8, 133.5, 132.8, 131.3, 131.2, 129.7, 126.7, 125.5, 74.0, 68.4, 35.8, 31.6, 29.2

Lactone 8. Method B, 6 equiv. of LiOAc, was used with the same work-up as in Method A except that EtOAc was used to extract the product. Compound 3 (69 mg, 0.50 mmol) gave 7 (50 mg, 0.26 mmol, 51% yield, >95% cis) after flash chromatography using pentane–EtO\(_2\)O 2:8 as the eluent. The spectral data were in accordance with those earlier reported in the literature.

Assignment of the stereochemistry of 4b. 25 mg (90 μmol) of 4b were stirred in 5 ml 5% KOH in MeOH–H\(_2\)O 9:1 at 40 °C for 3 h. The solvent was evaporated and the residual crude mixture was purified by flash chromatography using pentane–EtO\(_2\)O (1:1) as the eluent to give 10 mg of the alcohol 11 (79%).

Assignment of the stereochemistry of 4d. The assignment of 4d was carried out in analogy with that of 4b to give the alcohol 11 as the major stereoisomer.

Assignment of the stereochemistry of 4e. The assignment of 4e was carried out in analogy with that of 4b to give the alcohol 10 as the major stereoisomer.

Assignment of the stereochemistry of lactone 7. 35 mg (120 μmol) of 7 were stirred in 5 ml 5% KOH in MeOH–H\(_2\)O 9:1 at 40 °C for 2 h. The reaction mixture was then acidified using HCl (conc.) and stirred for 1 h. The solvent was evaporated off and the residual crude mixture was purified by flash chromatography using EtOAc as the eluent to give 15 mg (97 μmol) of alcohol 12 (81%).

trans Alcohol 10. 24 mg (132 μmol) of 4a were stirred in 3 ml of 5% KOH in MeOH–H\(_2\)O 9:1 at 40 °C for 2 h. The solvent was evaporated off and the residual crude mixture was purified by flash chromatography using pentane–EtO\(_2\)O (1:1) as the eluent to give 15 mg (108 μmol, 82%) of the trans alcohol 10.

\[ \text{HO}_3\text{C} - \text{H} \]
\[ \text{HO}_3\text{C} \]
\[ \text{HO}_3\text{C} \]

10

11

\( R_f \) (pentane–ether 50:50) 0.14. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \( δ \) 5.99 (1 H, m), 5.88 (1 H, ddd, \( J = 10.1, 3.7, 1.2 \) Hz), 4.25 (1 H, br), 4.22 (1 H, m), 3.91 (1 H, m), 3.76 (1 H, app dt, \( J = 8.2, 6.7 \) Hz), 2.58 (1 H, m), 2.10 (1 H, m), 1.88 (1 H, ddd, \( J = 13.3, 8.8, 4.6 \) Hz), 1.78–1.63 (2 H, m), 1.58 (1 H, br). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): \( δ \) 132.3, 129.0, 73.9, 66.8, 63.5, 33.5, 33.3, 30.7.

cis Alcohol 11. The reaction was performed as described for 10 using 4b to give the cis-alcohol 11.
Assignment of the stereochemistry of alcohol 11. 11 (10 mg, 71 μmol), was dissolved in 2 ml CH₂Cl₂ containing 14 μl (107 μmol, 1.5 equiv.) NE₂Cl. To this solution was added 7 μl (107 μmol, 1.5 equiv.) AcCl and the reaction mixture was stirred for 2 h. The solvent was evaporated off and the crude product was purified by flash chromatography using pentane: Et₂O 75:25 as the eluent to give 4e (10 mg, 55 μmol, 77%) with NMR data in accordance with those reported in the literature.⁶⁸

Lactone alcohol 12. 35 mg (120 μmol) of 8 were stirred in 5 ml 5% KOH in MeOH-H₂O 9:1 at 40 °C for 2 h. The reaction mixture was then acidified with HCl (conc.) and stirred for 1 h. The solvent was evaporated off and the residual crude mixture was purified by flash chromatography using EtOAc as the eluent to give 15 mg (97 μmol, 81%) of the alcohol 12.

References and notes

13. When a carbon nucleophile was used in place of an oxygen nucleophile, the diene corresponding to 9 was isolated. In this case the diene is more stable due to the lower leaving-group ability of the carbon: Rönn, M. Unpublished results.

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