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Asymmetric α-hydroxy ketone synthesis by direct ketone oxidation using a bimetallic palladium(II) complex

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ABSTRACT

The oxidation of ketones by chiral bimetallic palladium(II) complexes in the presence of CuCl2 in THF-water solvents gave an enantioselective synthesis of α-hydroxyketones in a catalytic air oxidation. The ee’s ranged from 61% to 92%. The reaction was accelerated by addition of strong acid that presumably increases the rate of enolization.

Keywords: asymmetric synthesis
α-hydroxyketone
palladium catalysis
acloin
bimetallic palladium

Chiral α-hydroxy ketones (acyloins) are important intermediates for the asymmetric synthesis of natural products, fine chemicals, and drugs.1 For that reason, their enantioselective synthesis is of considerable interest and there have been a number of reports with various approaches to chiral α-hydroxy ketones.2 One general approach involves the preparation of enolates or enol derivatives,3 while another method involves catalytic asymmetric oxidation of (E)-enol phosphates by (salen) Mn(III) complexes.4 A recent approach to chiral α-hydroxy ketones involves the reactions of tin enolates with nitrosobenzene.5 Macmillan reported the direct proline-catalyzed oxyamination of aldehydes.6 The oxidation of carbonyl compounds by metal species is a well-known and widely studied reaction.7 and many of these reactions apparently proceed via oxidation of the enol tautomer. Thus, the oxidation of ketones by the two electron oxidants, Hg(II), Th(III) and Mn(VII)8 as well as some one-electron oxidants such as Mn(III)9 and tris(1,10-phenanthroline) complexes of Fe(III) and Ru(III)10 were postulated to involve the enol isomer. It has been shown that the Pd(II)-catalyzed carbonylation of ketones also proceeds via the enol isomer,11 and results indicated that the enol form of the ketone has a long enough lifetime to undergo Pd(II) catalyzed reactions. We also previously showed that Pd(II) in the presence of CO catalyzes conversion of cyclic ketones into diesters, proceeding via the enol isomer.12

We first observed α-hydroxy ketone formation in studies of the CuCl2 promoted chlorohydrin reaction catalyzed by the bimetallic complex A shown in Scheme 1.13 Treatment of a terminal alkene with a bimetallic complex A in the presence of LiCl with CuCl2 as re-oxidant produced the chiral chlorohydrin, along with some ketone and 2-hydroxy ketone as by-products. In a related study we showed that oxidation of ketones with Pd(II) bimetallic complex A as catalyst in the absence of LiCl and at lower concentration of CuCl2 produces predominantly the racemic α-hydroxy ketones.14 The results together suggest the possibility of a new and direct asymmetric synthesis of α-hydroxy ketones by incorporation of a chiral ligand in the place of the achiral ligand cyclohexane-1,2-diamine in the coordination sphere of bimetallic complex A. Herein we report the success of this direct approach and describe a new procedure for the direct asymmetric catalytic hydroxylation of ketones with oxygen.

Chiral bimetallic catalyst B (scheme 2) was chosen for this study because of its ease of preparation and success in asymmetric halohydrin formation. The complex was prepared from reacting tetrakis(acetonitrile) palladium(II) tetrafluoroborate complex with 1-phenylhexane-1,3,5-trione followed by (R)-BINAP as shown in scheme 2.13 The resulting asymmetric Pd(II) complex B was then utilized in asymmetric oxidation of various symmetrical and unsymmetrical ketones in aqueous solution of THF in the presence of cupric chloride, lithium chloride, and a catalytic amount of methanesulfonic acid.
The oxidation results are summarized in Table 1, and the absolute configurations of the resulting α-hydroxyl ketones were determined based on comparison of the sign of the optical rotation compared with literature values.\textsuperscript{15} We first examined the oxidation of the symmetrical cyclic ketone cyclohexanone (run 1) which produced a modest ee of 67% for the (R)-enantiomer, then proceeded with unsymmetrical aralkyl ketones. Propiophenone (run 2) also gave a modest ee of 68% for the (R)-enantiomer, while the same substrate in the absence of acid (run 3) was very slow in conversion (28% of SM consumed after 2d) but the asymmetric induction was higher (82%). Thus acid is beneficial for the forward progress of the reaction, since acid catalyzes ketone enolization, although higher acidity may ultimately compromise the ee of the product. The conversions for all other reactions were much higher, as workup was performed when >90% of starting material was consumed by GC. Run 4 with propiophenone included 2.0 M of LiCl in addition to cupric chloride, and resulted in a lower ee relative to Runs 3 and 4. Butyrophone gave the corresponding (R)-α-hydroxyketone in 71% ee, quite comparable to the 68% ee for the shorter homolog of Run 2. Asymmetric α-hydroxylation of the sterically larger 1,2-diphenylethanone afforded the (R)-enantiomer (Run 6), and replacing (R)-BINAP with (S)-BINAP produced the opposite enantiomer as expected, affording the (S)-2-hydroxyketone (Run 7). Employment of the more bulky 1-(3-chlorophenyl)-propan-1-one gave the (R)-α-hydroxyketone in 92% ee (Run 8), the highest observed in this series. The similar substrate 1-(3,5-difluorophenyl)-2-hydroxypropan-1-one gave the product with the (R)-configuration also in a high ee of 90%. Employing 3,3,3-trifluoro-1-phenylpropan-1-one afforded (R)-furin, with the opposite configuration relative to the generally-observed configuration (fluorine reverses the Cahn-Ingold-Prelog priorities), and the opposite configuration of what is drawn for Run 2. Run 11 employing furyl furfuryl ketone gave the α-hydroxyketone in quite high ee.

A mechanistic hypothesis is shown in Scheme 3. Enolization is accelerated by acid and the enol form is stabilized by complexation to the Pd(II). Addition of the enol to Pd(II) in complex B should form the most stable σ-complex intermediate 12 where both bulky groups Ph and R3 are anti to the bulky BINAP ligand. The E-enol is shown in 12a; an equilibrium mixture of E and Z-enols would exist in solution, yet the two stereoisomers may have quite different binding to the palladium. Intramolecular syn attack by the solvent (H2O) on the β-carbon of the enol forms σ-complex 13. Decomposition of σ-complex 13 to afford the α-hydroxyketone must occur by hydride transfer from the hydrogen attached to oxygen on the α-carbon since hydride transfer from the hydrogen on the β-carbon would destroy the chirality. Bimetallic Pd(II) complex B is regenerated by oxidation with CuCl2 and the resulting CuCl is oxidized by dioxygen to complete the catalytic cycle.

**Table 1. Asymmetric synthesis of α-hydroxyl ketones using chiral bimetallic palladium complex B**

<table>
<thead>
<tr>
<th>Run</th>
<th>R1</th>
<th>R2</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt; (%)</th>
<th>R/S</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>CH2CH2CH2CH2</td>
<td>64</td>
<td>67</td>
<td>R&lt;sup&gt;s&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CH3</td>
<td>64</td>
<td>68</td>
<td>R&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CH3</td>
<td>36</td>
<td>82</td>
<td>R&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CH3</td>
<td>52</td>
<td>51</td>
<td>R&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CH3</td>
<td>61</td>
<td>71</td>
<td>R&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>52</td>
<td>85</td>
<td>R&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>52</td>
<td>87</td>
<td>S&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CH3</td>
<td>56</td>
<td>92</td>
<td>R&lt;sup&gt;k&lt;/sup&gt;</td>
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</tr>
<tr>
<td>9</td>
<td>CH3</td>
<td>53</td>
<td>90</td>
<td>R&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
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<td>89</td>
<td>R&lt;sup&gt;m&lt;/sup&gt;</td>
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</tr>
<tr>
<td>11</td>
<td>2-furfuryl</td>
<td>72</td>
<td>91</td>
<td>R&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> All runs contains 0.08-0.2 mmol of catalyst in 20 mL 1:1 H2O/THF, 0.5 M in CuCl2, with a catalytic amount of CH3SOH. t = 25°C.  
<sup>b</sup> Yields for isolated products after column chromatography.  
<sup>c</sup> Absolute configuration as drawn except for Run 10; ee’s were determined by 1H NMR utilizing E/Z-biaryl.  
<sup>d</sup> No acid catalyst was used in this run.  
<sup>e</sup> Contains 2.0 M of LiCl in addition to CuCl2.  
<sup>f</sup> The oxidation results are summarized in Table 1, and the absolute configurations of the resulting α-hydroxyl ketones were determined based on comparison of the sign of the optical rotation compared with literature values.  
<sup>g</sup> Addition of the enol to Pd(II) in Run 11 employing furyl furfuryl ketone gave the opposite configuration also in a high ee of 90%. Employing 3,3,3-trifluoro-1-phenylpropan-1-one afforded (R)-furin, with the opposite configuration relative to the generally-observed configuration (fluorine reverses the Cahn-Ingold-Prelog priorities), and the opposite configuration of what is drawn for Run 2. Run 11 employing furyl furfuryl ketone gave the α-hydroxyketone in quite high ee.
α-hydroxy ketones. Ongoing work is aimed at improving the enantioselectivities and exploring other nucleophiles.

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Supporting Information Available. Supplementary data associated with this article can be found, in the online version.

References and notes


