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## Asymmetric $\alpha$ -hydroxy ketone synthesis by direct ketone oxidation using a bimetallic palladium(II) complex

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### ABSTRACT

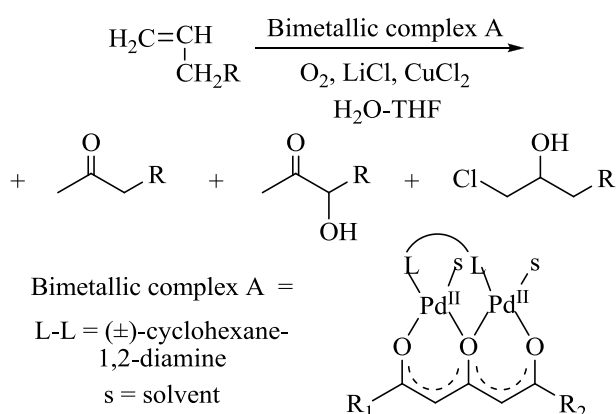
The oxidation of ketones by chiral bimetallic palladium(II) complexes in the presence of CuCl<sub>2</sub> in THF-water solvents gave an enantioselective synthesis of  $\alpha$ -hydroxyketones in a catalytic air oxidation. The ee's ranged from 61% to 92%. The reaction was accelerated by addition of strong acid that presumably increases the rate of enolization.

Chiral  $\alpha$ -hydroxy ketones (acyloins) are important intermediates for the asymmetric synthesis of natural products, fine chemicals, and drugs.<sup>1</sup> For that reason, their enantioselective synthesis is of considerable interest and there have been a number of reports with various approaches to chiral  $\alpha$ -hydroxy ketones.<sup>2</sup> One general approach involves the preparation of enolates or enol derivatives,<sup>3</sup> while another method involves catalytic asymmetric oxidation of (E)-enol phosphates by (salen) Mn(III) complexes.<sup>4</sup> A recent approach to chiral  $\alpha$ -hydroxy ketones involves the reactions of tin enolates with nitrosobenzene.<sup>5</sup> Macmillan reported the direct proline-catalyzed oxyamination of aldehydes.<sup>6</sup>

The oxidation of carbonyl compounds by metal species is a well-known and widely studied reaction,<sup>7</sup> 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), Tl(III) and Mn(VII)<sup>8</sup> as well as some one-electron oxidants such as Mn(III)<sup>9</sup> and tris(1,10-phenanthroline) complexes of Fe(III) and Ru(III)<sup>10</sup> 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,<sup>11</sup> 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.<sup>12</sup>

We first observed  $\alpha$ -hydroxy ketone formation in studies of the CuCl<sub>2</sub> promoted chlorohydrin reaction catalyzed by the bimetallic complex A shown in Scheme 1.<sup>13</sup> Treatment of a terminal alkene with a bimetallic complex A in the presence of LiCl with CuCl<sub>2</sub> 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 CuCl<sub>2</sub> produces predominantly the racemic  $\alpha$ -hydroxy ketones.<sup>14</sup> The results together suggest the possibility of a new and direct asymmetric synthesis of  $\alpha$ -hydroxyketones 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.<sup>13</sup> 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.



**Scheme 1.** Alkene oxidation with bis-Pd(II) catalyst affording chlorohydrin plus ketone and hydroxyketone by-products.

The oxidation results are summarized in Table 1, and the absolute configurations of the resulting  $\alpha$ -hydroxy ketones were determined based on comparison of the sign of the optical rotation compared with literature values.<sup>15</sup> 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. Butyrophenone gave the corresponding (R)- $\alpha$ -hydroxyketone in 71% ee, quite comparable to the 68% ee for the shorter homolog of Run 2. Asymmetric  $\alpha$ -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)- $\alpha$ -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)-furoin, 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 Table 1. Run 11 employing furyl furfuryl ketone gave the  $\alpha$ -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  $\pi$ -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 (H<sub>2</sub>O) on the  $\beta$ -carbon of the enol forms  $\sigma$ -complex **13**. Decomposition of  $\sigma$ -complex **13** to afford the  $\alpha$ -hydroxyketone must occur by hydride transfer from the hydrogen attached to oxygen on the  $\alpha$ -carbon since

hydride transfer from the hydrogen on the  $\beta$ -carbon would destroy the chirality. Bimetallic Pd(II) complex B is regenerated by oxidation with CuCl<sub>2</sub> and the resulting CuCl is oxidized by dioxygen to complete the catalytic cycle.

**Table 1.** Asymmetric synthesis of  $\alpha$ -hydroxy ketones using chiral bimetallic palladium complex B<sup>a</sup>

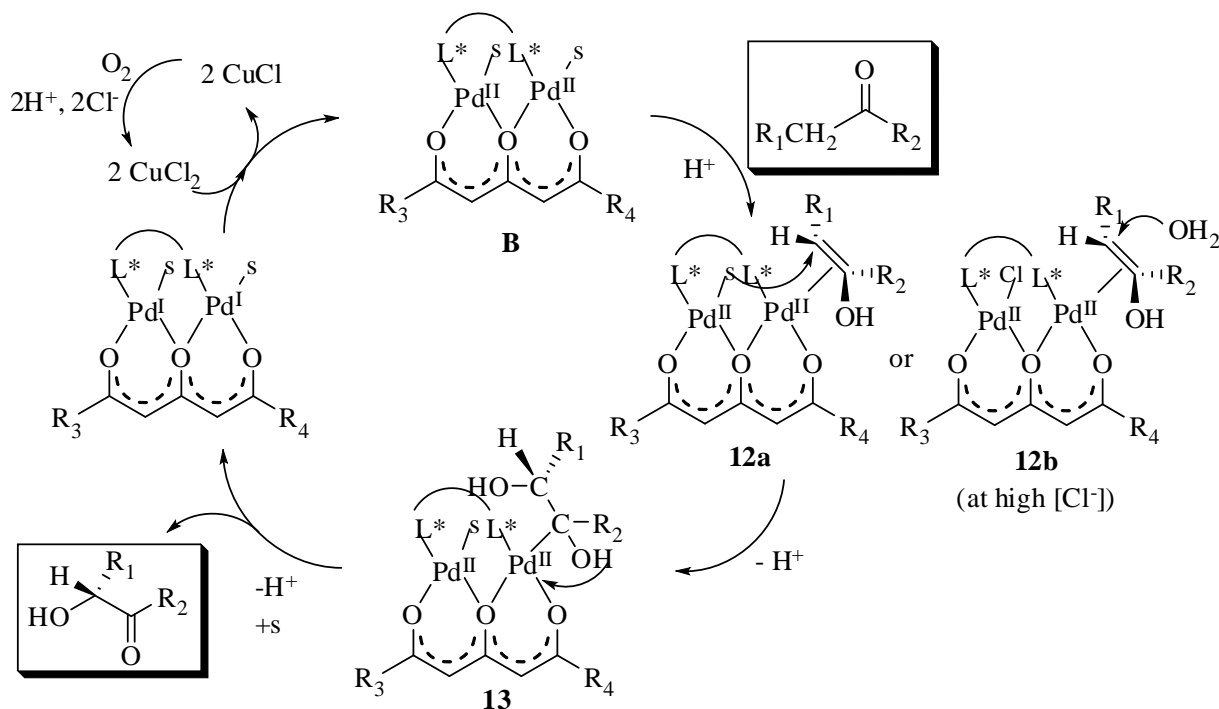
Run	R <sub>1</sub>	R <sub>2</sub>	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)	R/S
1	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>		64	67	R <sup>g</sup>
2	CH <sub>3</sub>	Ph	64	68	R <sup>h</sup>
3 <sup>d</sup>	CH <sub>3</sub>	Ph	36	82	R <sup>h</sup>
4 <sup>e</sup>	CH <sub>3</sub>	Ph	52	51	R <sup>h</sup>
5	CH <sub>3</sub> CH <sub>2</sub>	Ph	61	71	R <sup>i</sup>
6	Ph	Ph	52	85	R <sup>j</sup>
7 <sup>f</sup>	Ph	Ph	52	87	S <sup>j</sup>
8	CH <sub>3</sub>	(3-Cl)Ph	56	92	R <sup>k</sup>
9	CH <sub>3</sub>	3,5-di-F-Ph	53	90	R <sup>l</sup>
10	CF <sub>3</sub>	Ph	48	89	R <sup>m</sup>
11	2-furyl	2-furyl	72	91	R <sup>n</sup>

<sup>a</sup>All runs contain 0.08-0.2 mmol of catalyst in 20 mL 1:1 H<sub>2</sub>O/THF, 0.5 M in CuCl<sub>2</sub>, with a catalytic amount of CH<sub>3</sub>SO<sub>3</sub>H. t = 25°C. <sup>b</sup>Yields for isolated products after column chromatography. Absolute configuration as drawn *except* for Run 10. <sup>c</sup>ee's were determined by <sup>1</sup>H NMR utilizing Eu(hfc)<sub>3</sub> chiral shift reagent. <sup>d</sup>No acid catalyst was used in this run. <sup>e</sup>Contains 2.0 M of LiCl in addition to CuCl<sub>2</sub>. <sup>f</sup>(S)-BINAP was used rather than (R)-BINAP. <sup>g</sup>For (R) [α]<sub>D</sub><sup>20</sup> = +26.20 (c 1.35, CHCl<sub>3</sub>)<sup>15b</sup>; run 1: [α]<sub>D</sub><sup>20</sup> = +14.0 (c 2.0, CHCl<sub>3</sub>). <sup>h</sup>For (R) [α]<sub>D</sub><sup>20</sup> = +81.0 (c=1.5, CHCl<sub>3</sub>), ee = 96%<sup>15b</sup>, [α]<sub>D</sub><sup>20</sup> = +82.2 (c=2.0, CHCl<sub>3</sub>)<sup>15c</sup>; run 2: [α]<sub>D</sub><sup>20</sup> = +60.3 (c 2.0, CHCl<sub>3</sub>), run 3: [α]<sub>D</sub><sup>20</sup> = +69.8 (c 2.0, CHCl<sub>3</sub>), run 4: [α]<sub>D</sub><sup>20</sup> = +46.2 (c 2.0, CHCl<sub>3</sub>). <sup>i</sup>For (S) [α]<sub>D</sub><sup>20</sup> = -30.8 (c=2.24, CHCl<sub>3</sub>), ee = 95% in Davis<sup>15d</sup>, but for (S) [α]<sub>D</sub><sup>20</sup> = +40.5 (c=0.3, CHCl<sub>3</sub>) in Krawczyk<sup>15e</sup>; run 5: [α]<sub>D</sub><sup>20</sup> = +23.7 (c 2.0, CHCl<sub>3</sub>). <sup>j</sup>For (R) [α]<sub>D</sub><sup>20</sup> = -170.1 (c=1.0, benzene)<sup>15b</sup>, [α]<sub>D</sub><sup>20</sup> = -230.5 (c=1.0, benzene)<sup>15f</sup>; for (S) [α]<sub>D</sub><sup>20</sup> = +138.4 (c=0.25, CHCl<sub>3</sub>)<sup>15c</sup>, [α]<sub>D</sub><sup>20</sup> = +114.9 (c=1.5, acetone)<sup>15e</sup>; run 6 [α]<sub>D</sub><sup>20</sup> = -139.6 (c 0.2, CHCl<sub>3</sub>), run 7 [α]<sub>D</sub><sup>20</sup> = +141.8 (c 0.2, CHCl<sub>3</sub>). <sup>k</sup>For (R) [α]<sub>D</sub><sup>20</sup> = +64.2 (c=1.2, CHCl<sub>3</sub>)<sup>15g</sup>, run 8: [α]<sub>D</sub><sup>20</sup> = +66.5 (c 2.0, CHCl<sub>3</sub>). <sup>l</sup>For (R) [α]<sub>D</sub><sup>20</sup> = +50.0 (c=1.0, CHCl<sub>3</sub>)<sup>15h</sup>, run 9 [α]<sub>D</sub><sup>20</sup> = +46.8 (c 2.0, CHCl<sub>3</sub>). <sup>m</sup>For (S) [α]<sub>D</sub><sup>20</sup> = +8.6 (c=0.2, CHCl<sub>3</sub>)<sup>15h</sup>, run 10 [α]<sub>D</sub><sup>20</sup> = -7.8 (c 0.2, CHCl<sub>3</sub>). <sup>n</sup>For (R) [α]<sub>D</sub><sup>20</sup> = +62.7 (c=0.9, CHCl<sub>3</sub>)<sup>15h</sup>, run 11 [α]<sub>D</sub><sup>20</sup> = +59.2 (c 1.0, CHCl<sub>3</sub>).

The result of Run 4 that was conducted at high [Cl<sup>-</sup>] affording a lower ee suggests that the mode of H<sub>2</sub>O addition may be different from the conditions of other runs. In this case of high [Cl<sup>-</sup>], the chloride ion would replace the solvent in the coordination sphere of Pd(II) discouraging syn hydroxypalladation with the result that anti hydroxypalladation represented by **12b** in Scheme 3 becomes a possibility. Several earlier studies showed that anti hydroxy palladation predominates at high concentration of LiCl.<sup>16</sup>

In most cases the enantioselectivities were at least 70% and they reached a maximum of 92%. The E/Z enol ratio would be expected to impact the enantioselectivity, but as noted the two stereoisomers would have both different binding constants to the catalyst, and different rates of attack once bound. Further, the presence of excess chloride decreases the enantioselectivities. With modest increases in enantioselectivities, which may be realized by varying chiral auxiliaries and reaction conditions, this catalytic air oxidation procedure should compete with much more elaborate and involved procedures for preparing optically active

**Scheme 2.** Proposed mechanism for the asymmetric  $\alpha$ -hydroxylation of ketones



$\alpha$ -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.

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