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

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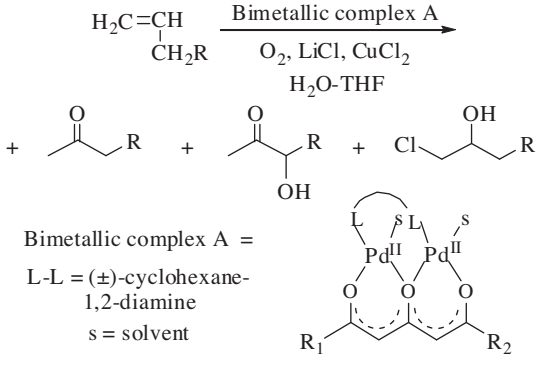
ABSTRACT

The oxidation of ketones by a chiral bimetallic palladium(II) complex in the presence of $CuCl_2$ in THF–water solvents gave an enantioselective synthesis of α-hydroxyketones in catalytic oxidation utilizing an atmosphere of oxygen. 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 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), Tl(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 the 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 the conversion of cyclic ketones into diesters, proceeding via the enol isomer.[12]

We first observed α-hydroxy ketone formation in studies of the $CuCl_2$ promoted chlorohydrin reaction catalyzed by the bimetallic complex A shown in Scheme 1.[13] Treatment of a terminal alkene with bimetallic complex A in the presence of LiCl with $CuCl_2$ as re-oxidant produced the chiral chlorohydrin, along with some



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

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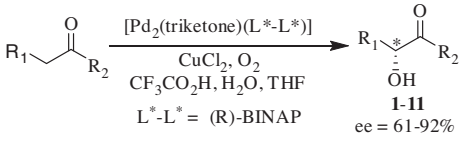
ketone and 2-hydroxy ketone as by-products. In a related study we showed that oxidation of ketones with Pd(II) bimetallic complex A as catalyst in the absence of LiCl and at lower concentration of $CuCl_2$ produces predominantly the racemic α-hydroxy ketones.[14] The results together suggest the possibility of a new and direct asymmetric synthesis of α-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 α-hydroxylation of ketones.

Chiral bimetallic catalyst B (Table 1) was chosen for this study because of its ease of preparation and success in asymmetric halohydrin formation. The complex was prepared by reacting tetrakis(acetonitrile) palladium(II) tetrafluoroborate complex with 1-phenylhexane-1,3,5-trione followed by (*R*)-BINAP.[13] The resulting asymmetric Pd(II) complex B was then utilized in asymmetric oxidation of various symmetrical and unsymmetrical ketones in an aqueous solution of THF in the presence of cupric chloride, lithium chloride, and a catalytic amount of trifluoroacetic acid.

The oxidation results are summarized in Table 1, and the absolute configurations of the resulting α-hydroxy ketones were determined based on the comparison of the sign of optical rotation with literature values.[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 the conversion (28% of SM consumed after 2 days) 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, and workup was performed when >90% of the 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 Run 3. 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 (*S*)-2-hydroxyketone (Run 7). Employment of the more bulky 1-(3-chlorophenyl)-propan-1-one gave (*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*)-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 α-hydroxyketone in quite high ee.

Table 1
Asymmetric synthesis of α-hydroxyl ketones using chiral bimetallic palladium complex B[a]



Run	R_1	R_2	Yield[b] (%)	ee[c] (%)	*R*/*S*
1	$CH_2CH_2CH_2CH_2$		64	67	*R*[g]
2	CH_3	Ph	64	68	*R*[h]
3[d]	CH_3	Ph	36	82	*R*[h]
4[e]	CH_3	Ph	52	51	*R*[h]
5	CH_3CH_2	Ph	61	71	*R*[i]
6	Ph	Ph	52	85	*R*[j]
7[f]	Ph	Ph	52	87	*S*[j]
8	CH_3	(3-Cl)Ph	56	92	*R*[k]
9	CH_3	3,5-di-F-Ph	53	90	*R*[l]
10	CF_3	Ph	48	89	*R*[m]
11	2-furyl	2-furyl	72	91	*R*[n]

[a] All runs contain 0.08–0.2 mmol of catalyst in 20 mL 4:1 THF/H_2O, 0.5 M in $CuCl_2$, with a catalytic amount of CF_3CO_2H. t = 25 °C.
[b] Yields for isolated products after column chromatography. Absolute configuration as drawn except for run 10.
[c] ee's were determined by ^1H NMR utilizing Eu(hfc)$_3$ chiral shift reagent.
[d] No acid catalyst was used in this run.
[e] Contains 2.0 M of LiCl in addition to $CuCl_2$.
[f] (*S*)-BINAP was used rather than (*R*)-BINAP.
[g] For (*R*) $[\alpha]_D^{20}$ = +26.20 (c = 1.35, $CHCl_3$)[15a]; Run 1: $[\alpha]_D^{20}$ = +14.0 (c = 2.0, $CHCl_3$).
[h] For (*R*) $[\alpha]_D^{20}$ = +81.0 (c = 1.5, $CHCl_3$), ee = 96%[15b]; $[\alpha]_D^{20}$ = +82.2 (c = 2.0, $CHCl_3$)[15c]; Run 2: $[\alpha]_D^{20}$ = +60.3 (c = 2.0, $CHCl_3$); Run 3: $[\alpha]_D^{20}$ = +69.8 (c = 2.0, $CHCl_3$); Run 4: $[\alpha]_D^{20}$ = +46.2 (c = 2.0, $CHCl_3$).
[i] For (*S*) $[\alpha]_D^{20}$ = −30.8 (c = 2.24, $CHCl_3$), ee = 95% in Davis,[15d] but for (*S*) $[\alpha]_D^{20}$ = +40.5 (c = 0.3, $CHCl_3$) in Krawczyk[15c]; Run 5: $[\alpha]_D^{20}$ = +23.7 (c = 2.0, $CHCl_3$).
[j] For (*R*) $[\alpha]_D^{20}$ = −170.1 (c = 1.0, benzene)[15b]; $[\alpha]_D^{20}$ = −230.5 (c = 1.0, benzene)[15f]; for (*S*) $[\alpha]_D^{20}$ = +138.4 (c = 0.25, $CHCl_3$)[15c], $[\alpha]_D^{20}$ = +114.9 (c = 1.5, acetone)[15e]; Run 6 $[\alpha]_D^{20}$ = −139.6 (c = 0.2, $CHCl_3$); Run 7 $[\alpha]_D^{20}$ = +141.8 (c = 0.2, $CHCl_3$).
[k] For (*R*) $[\alpha]_D^{20}$ = +64.2 (c = 1.2, $CHCl_3$)[15g]; Run 8: $[\alpha]_D^{20}$ = +66.5 (c = 2.0, $CHCl_3$).
[l] For (*R*) $[\alpha]_D^{20}$ = +50.0 (c = 1.0, $CHCl_3$)[15h]; Run 9 $[\alpha]_D^{20}$ = +46.8 (c = 2.0, $CHCl_3$).
[m] For (*S*) $[\alpha]_D^{20}$ = +8.6 (c = 0.2, $CHCl_3$)[15h]; Run 10 $[\alpha]_D^{20}$ = −7.8 (c = 0.2, $CHCl_3$).
[n] For (*R*) $[\alpha]_D^{20}$ = +62.7 (c = 0.9, $CHCl_3$)[15h]; Run 11 $[\alpha]_D^{20}$ = +59.2 (c = 1.0, $CHCl_3$).

Mechanistically, we propose that the α-hydroxylation involves initial enolization, which is accelerated by acid, giving rise to a π-bound enol palladium species. An equilibrating mixture of *E* and *Z*-enols should exist in solution, although the two stereoisomers may have quite different binding constants to palladium. A 2,1-insertion involving a palladium-bound solvent water molecule should install the α-hydroxyl, and reductive elimination then affords the product plus the reduced catalyst, which is reoxidized by $CuCl_2$, and the resulting CuCl is oxidized by oxygen to complete the catalytic cycle. Running the reaction under an inert atmosphere led to only slightly lower isolated yields of products and with no impact on enantioselectivities, consistent with the presence of excess $CuCl_2$.

The result of Run 4 that was conducted at high [Cl^-] affording a lower ee suggests that the mode of H_2O addition may be different from that of other runs. In this case of high [Cl^-], the chloride ion would replace the solvent in the coordination sphere of Pd(II) discouraging syn hydroxypalladation (2,1-insertion) and giving rise to the possibility of nucleophilic attack of water on the π-complex, leading to the opposite stereochemistry. Several earlier studies showed that anti-hydroxypalladation predominates at a high concentration of LiCl.[16]

In summary, enantioselectivities of the catalytic alpha-hydroxylation were at least 70% and 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 different binding constants to the palladium 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 oxidation procedure should compete with much more elaborate and involved procedures for preparing optically active α-hydroxy ketones. Ongoing work is focused on understanding the mechanism, improving the enantioselectivities, and exploring other nucleophiles.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.066.

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