A New Palladium(II)-Catalyzed Asymmetric Chlorohydrin Synthesis

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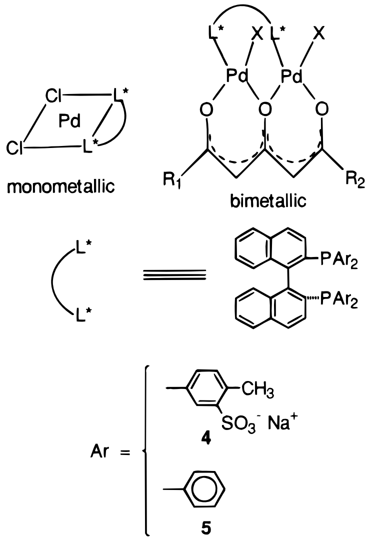
Received November 4, 1997

The Pd(II)-catalyzed oxidation of ethene in aqueous solution (Wacker reaction) gives exclusively acetaldehyde at low [Cl$^-$] (1.0 M). At high [Cl$^-$] (>2.5 M) and high [CuCl$_2$] (>3 M), formation of ethylene chlorohydrin occurs to an appreciable extent (Scheme 1).[1,2]

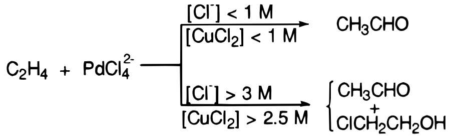
Previous studies in these laboratories have shown that substitution of chloride by pyridine in the coordination sphere of PdCl$_4^{2-}$ to give PdCl$_3$(pyridine)$^-$ resulted in the formation of chlorohydrin at [Cl$^-$] as low as 0.2 M.[3,4] At this low [Cl$^-$], PdCl$_4^{2-}$ gives only acetaldehyde at *any* [CuCl$_2$].

This finding opens up the possibility of an asymmetric chlorohydrin synthesis with α-olefins. Pd(II) catalysts containing chiral auxiliaries should produce optically active products. The logical starting point is the replacement of pyridine with a chiral amine L*. Scheme 2 outlines the general reaction scheme with monodentate chiral amines such as (CH$_3$)$_2$C*NH(CH$_3$)Ph. As shown, the two positional isomers, **2** and **3**, arise from the two possible modes of hydroxypalladation. The ratio **2**/**3** of about 4 for propene and 1-pentene is typical for a number of catalysts.

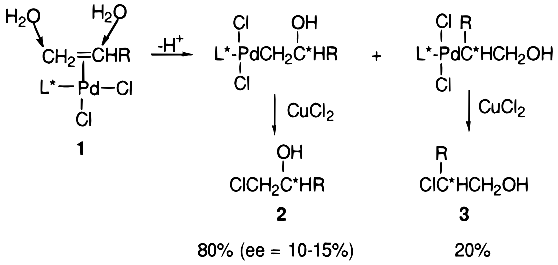
As expected, the optical purity of **2** was low, with ee's of 10−15%. Catalysts with chiral chelating diphosphines should give much higher optical purities. However, the monometallic Pd(II) complex containing a diphosphine ligand is a neutral species and thus insoluble in the reaction media. The solution to this problem involved two different approaches. One approach used sulfonated chiral ligands while the other involved bimetallic complexes with a bridging diphosphine ligand.[6] The structures of the two catalytic systems are shown below.



Scheme 1



Scheme 2



Synthesis of the tetrasulfonated ligand involved treatment of Tol-BINAP with H$_2$SO$_4$ containing 20% SO$_3$ at room temperature for 24 h followed by neutralization with NaOH.[7] Recrystallization from methanol provided pure samples. Reaction with K$_2$PdCl$_4$ or PdCl$_2$(PhCN)$_2$ provided the chiral catalyst. ^{31}P NMR measurements confirmed that all the tolyl rings were sulfonated. In these catalysts X = Cl.

Treatment of a solution of [Pd(CH$_3$CN)$_4$]BF$_4$ in CH$_3$CN with 1,3,5-pentanetriones gave the bimetallic triketone complexes. Addition of the chiral diphosphine ligand provided the chiral bimetallic complex. After purification, the products were characterized by elemental analysis and ^{1}H−^{13}C and ^{31}P NMR. As initially prepared, X is the CH$_3$CN ligand. However, in the actual reaction mixtures, CH$_3$CN is almost certainly replaced by Cl$^-$.

Gas uptake measurements using gas burets monitored the progress of the reactions.[8,9] Propene oxidation was monitored by propene consumption. With the other nongaseous olefins the gas was dioxygen. This is possible because the CuCl formed in the first oxidation step to form chlorohydrin readily reacts with dioxygen to give CuCl$_2$. Thus, as with the Wacker reaction, the chlorohydrin synthesis is a net air oxidation.

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(1) For general discussion and references see: Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*; D. Reidel: Dordrecht, Holland, 1980; pp 41−84.

(2) (a) Stangl, H.; Jira, R. *Tetrahedron Lett.* **1970**, 3589. (b) Bäckwall, J. E.; Åkermark, B.; Ljunggren S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

(3) Francis, J. W.; Henry, P. M. *J. Mol. Catal. A: Chem.* **1995**, *99*, 77.

(4) A recent report of the oxychlorination of allylic amines and sulfides is another example of the effect of a neutral ligand on the chlorohydrin formation.[5]

(5) Lai, J.-Y.; Wang, F.-S.; Guo, G.-Z.; Dai, L.-X. *J. Org. Chem.* **1993**, *58*, 6944.

(6) These bimetallic catalysts are homogeneous analogues of the bimetallic heterogeneous catalysts studied previously in these laboratories. See: (a) Zaw, K.; Henry, P. M. *J. Mol. Catal. A: Chem.* **1995**, *101*, 187. (b) Henry, P. M.; Ma, X.; Noronha, G.; Zaw, K. *Inorg. Chim. Acta* **1995**, *ICA240/1-2*, 205.

(7) Amrani, Y.; Lecomte, L.; Sinou, D.; Bakos, J.; Toth, I.; Heil, B. *Organometallics* **1989**, *8*, 542.

(8) In a typical experiment, a 250-mL two-necked cone-shaped flask, with indented sides to increase the efficiency of stirring, was equipped with a magnetic stirring bar, subseal septum, and vacuum adapter. The flask was charged with 20 mL of H$_2$O, 5 mL of THF, 10.09 g (75 mmol) of CuCl$_2$, 0.212 g (5 mmol) of LiCl, and 0.1 mmol of catalyst. The flask was then placed in a constant-temperature bath at 25 °C and connected to the gas uptake system.[9] The system was evacuated for 10 min on the vacuum line with the stirrer running. The stirring was stopped and the system pressured to 1.0 atm with dioxygen. The olefin was added to the reaction mixture by syringe. The mercury in the gas buret and the leveling bulb were equalized, and a reading was taken. The stirrer was turned on to start the reaction. The pressure was kept constant at 1 atm by continuously leveling the mercury in the gas buret and bulb. Gas uptake readings were taken at regular intervals. The reaction was allowed to run until the reaction mixture was at least 0.25 M in total oxidation product. The oxidation product was separated from the reaction mixture by continuous extraction with ether overnight. The ether was dried over anhydrous MgSO$_4$ and removed by distillation. Analysis of the product was carried out by VPC and ^{1}H and^{13}C NMR.

(9) For a similar apparatus see: ref 1, p 57.

S0022-3263(97)02015-X CCC: $15.00

Table 1. Results for the Oxidation of Several Olefins by Ar-BINAP Catalysts in the Presence of $CuCl_2$[a]

run	Ar	cat. (config)	[LiCl] (M)	substrate	**2**/**3** ratio[b]	% ee of **2**	turnovers
1	**4**	mono(*R*)	0.20	propene	12	46	60[c]
2	**4**	mono(*R*)	0.20	$CH_2{=}CHC(O)CH_3$	>95	76	65[d]
3	**4**	mono(*R*)	0.20	$CH_2{=}CHCH_2OPh$	>95	68	72[d]
4	**5**	bim(*S*)[e]	0.10	propene	3.5	94[f]	195[c]
5	**5**	bim(*S*)[g]	0.22	1-pentene	4.0	81	200[d]
6	**5**	bim(*S*)[g]	2.20	1-hexene	18.7	87	155[d]
7	**5**	bim(*S*)[g]	0.30	$CH_2{=}CHCH_2OPh$	>95	93	170[d]
8	**5**	bim(*S*)[g]	0.20	$CH_2{=}CHCH_2O$(1-Naph)	>95	80	175[d]

[a] All runs contain 0.1−0.3 mmol of chiral catalyst in 25−50 mL of solvent and are 3−5 M in $CuCl_2$. Temperature = 25 °C. The solvent was a H_2O/THF mixture containing 30−90% THF by volume. [b] The reaction mixture also contained varying amounts of the Wacker ketone product (5−30%). [c] Measured by propene uptake using gas burets. [d] Dioxygen is oxidant; turnovers measured by O_2 uptake using gas burets. In calculating turnovers dioxygen is assumed to be a four-electron oxidant. [e] $R_1 = R_2 = CH_3$. [f] Absolute configuration was determined to be (*S*) by converting to the epoxide and comparing with an authentic sample. [g] $R_1 = CH_3$, $R_2 = Ph$.

Table 1 lists some representative results. As discussed above, all reactions were catalytic oxidations. The catalytic turnovers, listed in the last column, do not represent the maximum number obtainable. In all cases, the reaction rate had not diminished at the termination point, and many more turnovers are possible.

Previous studies suggested that the degree of sulfonation could be an important factor in determining ee values.[7,10] In the hydrogenation of imines by rhodium(I) catalysts containing a sulfonated chiral diphosphine, it was found that the optical purity depended on the degree of sulfonation.[10] When the degree of sulfonation was about 4 the % ee of the product was only 19%. However, when the degree of sulfonation was about 1.5 the optical purity rose to 96% ee. Thus, the use of catalysts with monosufonated BINAP probably would increase ee values with the monometallic sulfonated catalysts in the present studies.

The **2**/**3** ratio for the monometallic catalyst (runs 1−3) was high, indicating the formation of **3** is not a serious problem. Only propene gave any detectable amount of **3**. Even in this case it was less than 10% of the total. Steric factors must account for this trend in **2**/**3** ratios. For the bimetallic catalyst, the **2**/**3** ratio is about 4 for propene and 1-pentene (runs 4 and 5) but increases to almost 20 for 1-hexene (run 6). The reason for the latter jump is not certain but could result from the change in [Cl^-]. As with the sulfonated catalyst, the allyl ethers gave no **3** (runs 7 and 8).

The optical purities with the bimetallic catalyst were higher than with the sulfonated monometallic catalyst, ranging from modest to good. In all cases, the ee was over 80% and rose to over 90% in two runs (4 and 7). Simple steric factors cannot explain these trends. Thus, the 94% ee obtained for propene in run 4 is the highest value obtained. In run 8, these factors would predict a higher % ee for the 1-naphthyl ether.

The high asymmetric induction obtained with the bimetallic catalysts is probably the most unexpected and interesting result of the present work. Formally, the bimetallic catalyst, with one phosphine per Pd(II), is analogous to the monometallic catalyst **1** in Scheme 2. Two factors almost certainly explain the high enantioselectivity observed. The first is the rigid structure of the bridging diphosphine ligand. Without the free rotation of the monodentate ligand in **1** the asymmetric induction is increased. The second factor is the coordination sphere of the Pd(II). With a bidentate β-diketone and a phosphine ligand, there is only one open coordination site available to the olefin. The site is adjacent to the chiral phosphine ligand where the asymmetric induction will be the highest. Note that in catalyst **1** the site trans to the chiral ligand would experience little chiral induction.

The discovery of a new asymmetric chlorohydrin synthesis increases the present stable of transition-metal-catalyzed chiral syntheses. It differs from previous asymmetric oxidation reactions, such as asymmetric epoxidation of allylic alcohols,[11a] epoxidation of unfunctionalized olefin,[11b] and asymmetric dihydroxylation[11c] in that it is a catalytic air oxidation. The closest comparison to the present reaction is the Pd(II)-catalyzed synthesis of chiral chlorhydrins using an olefin containing a chiral allylic amine ligand.[5] This very interesting conversion gives a chiral chlorohydrin containing the chiral amine in poor to modest optical purities (ee = 1−77%). As the chiral agent is monodentate, the system is analogous to catalyst **1** in Scheme 2. The fact that the optical yields were generally higher than those obtained with **1** can be rationalized by the fact the system is rigid in the same fashion as the bimetallic catalyst in the present studies. In addition, as opposed to catalyst **1**, the olefin is forced next to the chiral center.

An interesting possibility is the formation of other asymmetric products by variation of reaction conditions. The reaction consists of two distinct steps, addition and decomposition. In chloride-free media, nucleophiles other than chloride could be involved in the decomposition step, and better nucleophiles than water could be the attacking species in the first step. Thus, preparation of chiral bromohydrins and iodohydrins as well as chiral dibromides is a viable possibility.

Probably the main practical application of this new technology will be the preparation of chlorohydrins from allyl ethers. Thus, the chlorohydrin from allyl-1-naphthyl ether is a precursor for (−)-propranolol, the β-adrenergic blocker.[12]

Future work will concentrate on defining the scope of the reaction and improving optical yields. The latter effort involves the testing of other chiral auxiliaries and determination of the effect of [Cl^-] and solvent composition on % ee's.

Supporting Information Available: Text describing experimental procedures and characterization data (6 pages).

JO972015U

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