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A CHIRAL (HYDROXYALKYLFERROCENYL)PHOSPHINE LIGAND. HIGHLY STEREOSELECTIVE CATALYTIC ASYMMETRIC HYDROGENATION OF PROCHIRAL CARBONYL COMPOUNDS

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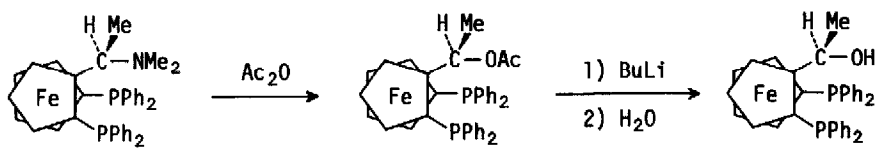
Recently, an increasing attention has been focused on a catalytic asymmetric hydrogenation of prochiral carbonyl compounds, which is achieved by means of certain chiral phosphine-rhodium complexes as catalysts.[1] However, the chiral rhodium catalysts thus far reported have not afforded so satisfactory results in their catalytic activity or in their asymmetry inducing ability as to make the asymmetric hydrogenation practically useful. In our recent studies on catalytic asymmetric hydrogenation of acrylic acids[2] and also on asymmetric Grignard cross-coupling reaction[3] using chiral (aminoalkylferrocenyl)phosphines, we have pointed out that attractive interactions between functional groups on a substrate and on a chiral ligand coordinated to a transition metal catalyst operate effectively in giving rise to a high asymmetric induction. Now we wish to report that a hydroxy group introduced into the side chain of a chiral ferrocenylphosphine ligand brings about a high degree of stereoselectivity in a rhodium complex-catalyzed asymmetric hydrogenation of carbonyl compounds.

A new chiral ferrocenylphosphine, (*R*)-α-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl alcohol (BPPFOH) was prepared starting with (*R*)-α-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]-ethyldimethylamine (BPPFA)[4] by the sequence shown below.



(*R*)-(*S*)-BPPFA (*R*)-(*S*)-BPPFOAc (*R*)-(*S*)-BPPFOH

(*R*)-(*S*)-BPPFA ($[\alpha]_D^{25}$ -349° (*c* 0.5, $CHCl_3$)) was treated with an excess of acetic anhydride at 100°C employing a modification of Nesmeyanov's procedure[5] to give (*R*)-α-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl acetate (BPPFOAc) ($[\alpha]_D^{25}$ -311° (*c* 0.5, $CHCl_3$), mp 153.5-155°C) in the epimeric pure form in 80% yield. The configuration *R* of the carbon central chirality of the BPPFOAc was inferred from the result that the same substitution reaction on α-dimethylaminoethylferrocene proceeded with nearly complete retention of enantiomeric configuration.[6] The acetate BPPFOAc was converted quantitatively into (*R*)-(*S*)-BPPFOH ($[\alpha]_D^{25}$ -285° (*c* 0.5, $CHCl_3$), mp 154-155°C) by treatment with n-BuLi in ether followed by hydrolysis. Lower yields were obtained with the usual direct acid or base hydrolysis of the acetate. A cationic rhodium complex, [Rh(COD)-{(*R*)-(*S*)-BPPFOH}]$^+ClO_4^-$ (abbr. (*R*)-(*S*)-BPPFOH-Rh$^+$)[8] was prepared from $[Rh(COD)Cl]_2$, $AgClO_4$ and (*R*)-(*S*)-BPPFOH according to the reported procedure (COD = 1,5-cyclooctadiene).[9]

Hydrogenation of prochiral carbonyl compounds was carried out in the presence of (*R*)-(*S*)-BPPFOH-Rh$^+$ (0.25-0.50 mol%) in MeOH solvent at 0-30°C and 50 atm initial hydrogen pressure (eq. 1).

$$R^1COR^2 \xrightarrow[(R)\text{-}(S)\text{-BPPFOH-Rh}^+/\text{MeOH}]{H_2\ (50\ \text{atm})} R^1\overset{*}{C}HR^2 \quad (1)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OH$$

1a: R^1 = Me, R^2 = Ph — 2a-2d
1b: R^1 = Et, R^2 = Ph
1c: R^1 = Me, R^2 = Bu^t
1d: R^1 = Me, R^2 = COOH

The results are summarized in Table 1, which contains also data obtained with some other rhodium catalysts for comparison. Acetophenone (1a) was hydrogenated quantitatively and rapidly at 23°C in the presence of (*R*)-(*S*)-BPPFOH-Rh$^+$ to give (*R*)-1-phenylethanol (2a) with an optical purity of 40%. An in situ catalyst (abbr. (*R*)-(*S*)-BPPFOH-Rh) formed from (*R*)-(*S*)-BPPFOH and $[Rh(1,5\text{-hexadiene})Cl]_2$ showed almost the same degree of stereoselectivity though the chemical yield was rather low. The asymmetric hydrogenation of 1a has been reported using [Rh(NBD){(*R*)-$(PhCH_2)MePhP\}_2]^+ClO_4^-$,[1a] [Rh(NBD){(*R*)-$EtMePhP\}_2]^+PF_6^-$,[1b] and [Rh(NBD){(-)-DIOP}]$^+ClO_4^-$,[1d] and in only 8.6%, 0.24%, and 8.1% optical yield, respectively. (*R*)-(*S*)-BPPFOH-Rh$^+$ was also fairly effective for the hydrogenation of propiophenone (1b) and pinacolone (1c). Of particular interest are the high optical yields attained with BPPFOH in the hydrogenation of pyruvic acid (1d). These values (59-83%) are comparable to those reported for asymmetric reduction of α-keto esters via hydrosilylation[10] and are highest ever known for asymmetric hydrogenation of carbonyl

Table 1. Asymmetric Hydrogenation of Carbonyl Compounds.

Substrate	Catalyst[a]	Reaction Conditions	Conversion (%)	$[\alpha]_D$[b]	Optical Yield (%)[c] (Configuration)
MeCOPh	(*R*)-(*S*)-BPPFOH-Rh$^+$	0°C, 8 hr	96	+18.6	43 (*R*)
MeCOPh	(*R*)-(*S*)-BPPFOH-Rh$^+$	23°C, 3 hr	100	+17.2	40 (*R*)
MeCOPh	(*R*)-(*S*)-BPPFOH-Rh	30°C, 47 hr	71	+15.3	35 (*R*)
MeCOPh	(*R*)-(*S*)-BPPFA-Rh$^+$	20°C, 65 hr	80	-6.7	15 (*S*)
EtCOPh	(*R*)-(*S*)-BPPFOH-Rh$^+$	20°C, 4 hr	94	+8.70	31 (*R*)
MeCOBu-*t*	(*R*)-(*S*)-BPPFOH-Rh$^+$	28°C, 2 hr	100	-3.29	43 (*R*)
MeCOCOOH	(*R*)-(*S*)-BPPFOH-Rh$^+$	23°C, 45 min	100	+4.86	59 (*R*)
MeCOCOOH	(*R*)-(*S*)-BPPFOH-Rh$^+$	0°C, 7 hr	100	+5.60	68 (*R*)
MeCOCOOH[d]	(*R*)-(*S*)-BPPFOH-Rh$^+$	20°C, 16 hr	100	+6.79	83 (*R*)
MeCOCOOH	(*R*)-(*S*)-BPPFOH-Rh	20°C, 24 hr	100	+4.51	55 (*R*)
MeCOCOOH	(*R*)-(*S*)-BPPFA-Rh$^+$	20°C, 4 hr	100	-1.28	16 (*S*)
MeCOCOOH	(*S*)-BPPEF-Rh	20°C, 48 hr	71	-1.28	16 (*S*)
MeCOCOOH	(-)-DIOP-Rh	20°C, 110 hr	44	+0.47	6 (*R*)

[a] (*R*)-(*S*)-BPPFA-Rh$^+$ = [Rh(COD){(*R*)-(*S*)-BPPFA}]$^+$$ClO_4^-$, (*S*)-BPPEF-Rh = (*S*)-BPPEF + $\frac{1}{2}[Rh(C_6H_{10})Cl]_2$, (-)-DIOP-Rh = (-)-DIOP + $\frac{1}{2}[Rh(C_6H_{10})Cl]_2$.

[b] In the case of pyruvic acid, produced lactic acid was esterified to methyl lactate, of which the specific rotation was measured.

[c] Optical yields are calcurated from the specific rotation of pure enantiomers: (*S*)-1-phenylethanol; $[\alpha]_D^{21}$ -43.5° (neat),[13] (*S*)-1-phenylpropanol; $[\alpha]_D^{22}$ -28.1° (neat),[13] (*S*)-3,3-dimethylbutan-2-ol; $[\alpha]_D^{20}$ +7.84° (neat),[14] (*R*)-methyl lactate; $[\alpha]_D^{19}$ +8.2° (neat).[15]

[d] One equiv. of Et_3N was added.

compounds.

The ability of BPPFOH ligand to cause high asymmetric induction can probably be ascribed to hydrogen bonding possible between the carbonyl group on a substrate and the hydroxy group on BPPFOH, which may increase conformational rigidity in diastereomeric transition states or intermediates.[11] The hydrogenated products with lower optical purity and with reversed configuration *S* were obtained with (*R*)-(*S*)-BPPFA and (*S*)-1,1'-bis(diphenylphosphino)-2-ethylferrocene ((*S*)-BPPEF),[12] which are both analogous to (*R*)-(*S*)-BPPFOH but lack the hydroxy group. This fact may well support the above mentioned participation of the hydroxy group in asymmetric hydrogenation of carbonyl compounds.

We are investigating the design and preparation of proper chiral ligands for a given catalytic asymmetric reaction using chiral ferrocenylphosphines which have superiority over others in permitting one to introduce desirable functional groups onto the phosphine ligands.

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