CHEMISTRY LETTERS, pp.3-6, 1978. Published by the Chemical Society of Japan

PREPARATION OF CHIRAL AMINOPHOSPHINE LIGANDS AND THEIR USE IN ASYMMETRIC HOMOGENEOUS HYDROGENATION OF ITACONIC ACID

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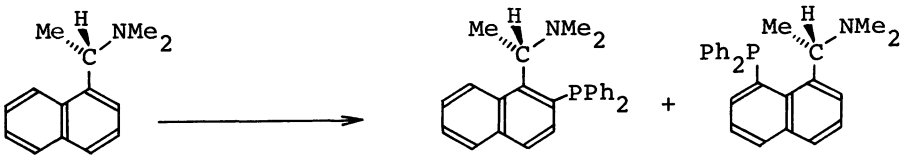
Optically active aminophosphines were prepared *via* ortho-directed metalation of appropriate arylamines followed by introduction of a diphenylphosphino group. These aminophosphines were used as ligands in the rhodium complex-catalyzed asymmetric hydrogenation of itaconic acid. Although moderate optical yields (up to 43% ee) were obtained, the stereochemical outcome with each ligand depended markedly on the chelate effect of the aminophosphines which played a significant role in both catalytic activity and enantioselectivity.

Tremendous success in asymmetric homogeneous hydrogenation of α-acetamidocinnamic acid catalyzed by chiral rhodium complexes with optically active diphosphine ligands has attracted much attention for stereochemical control of the reduction process by the chiral ligands.[1] Although the highest asymmetric induction is likely ascribed to an assisting coordination of very polar functional groups of the substrate to the metal, an attractive interaction between the substrate and functionalized ligands is expected as well to play an important role[2], *e.g.*, (S)-α-[(R)-1',2-bis(diphenylphosphino)ferrocenyl]ethyldimethylamine, abbreviated as (S)-(R)-BPPFA, is a diphosphine of the rigid chelate ligand, having a dimethylamino group conceivably suitable for such interaction.[3]

We have now examined six related monophosphines containing a dimethylamino group as ligands of a rhodium(I) complex. The aminophosphines were prepared from resolved α-phenyl, α-1-naphthyl (resolution with (-)-DAG[4]), and α-2-naphthylethyldimethylamine, respectively. The procedure involves directed ortho-metalation of the aromatic ring followed by introduction of a diphenylphosphino group.[5]

Scheme

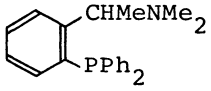
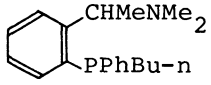
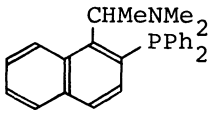
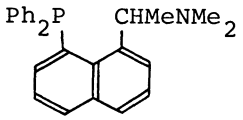
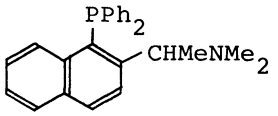
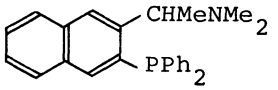


1,2-DPNEA 1,8-DPNEA

In the case of 1-naphthyl derivative, metalation at 2-position competed with that at 8-position giving rise to 1,2-DPNEA and 1,8-DPNEA, respectively, in a ratio of 3 :1 as depicted in the scheme.[6] 1,8-DPNEA seems to be a unique ligand incapable of forming a chelate complex (*vide infra*, Table 2), presumably due to a steric constraint of peri-positions.

Some physical data of chiral aminophosphines thus prepared are given in Table 1.

Table 1. Physical Properties of Chiral Aminophosphines

Aminophosphine[a]	Abbr.	Yield (%)	Mp (°C)	$[\alpha]_D^{25}$, deg (c, PhH)	$^4J_{P-H}$[b] (Hz)
	(S)-AMPHOS	70	80	-71.1 (0.70)	6.3
	(S)$_c$-(S)$_p$-AMPHOS-P*[c]	15	oil	-129 (0.79)	7.0
	(S)-1,2-DPNEA		54	-32.5 (0.71)	10.4
	(S)-1,8-DPNEA	35[d]	116	-94.5 (0.69)	14.0[e]
	(R)-2,1-DPNEA	56[d]	125	+124 (0.63)	12.0
	(R)-2,3-DPNEA		118	+16.0 (0.62)	5.6[f]

[a] All new compounds gave correct NMR and IR spectral and analytical data.
[b] Long-range coupling constant of a methine proton with a phosphorus nucleus.
[c] Resolved using (R)-tartaric acid (see ref. 7).
[d] Combined yield.
[e] $^5J_{P-H}$
[f] Structural assignment was made on the basis of this value as compared with that of AMPHOS.

Chiral aminophosphines were used as ligands in the rhodium complex-catalyzed asymmetric hydrogenation of itaconic acid, a rather simple 1,1-disubstituted olefinic acid, for which asymmetric reduction using a rhodium(I)-chiral phosphine catalyst system had not been very successful.[8]

Under the standard reaction conditions given in eq. 1, where the catalyst apparently contains two equivalents of chiral ligand per rhodium atom, reduction of itaconic acid proceeded smoothly at room temperature to give in most cases quantitatively α-methylsuccinic acid with poor to moderate optical yields.[9] All results obtained are summarized in Table 2.

Table 2. Optical Yields of Asymmetric Homogeneous Hydrogenation of Itaconic Acid at Room Temperature

Ligand (L*)	Optical yield (% ee)	
	Neutral catalyst[a]	Cationic catalyst[b]
(S)-AMPHOS	18 (R)[c]	18 (R)
$(S)_C$-$(S)_P$-AMPHOS-P*	20 (S)[d]	17 (S)
(S)-1,2-DPNEA	41 (R)	43 (R)
(S)-1,8-DPNEA	20 (S)	—[e]
(R)-2,1-DPNEA	—[f]	Racemic
(R)-2,3-DPNEA	3.5 (S)	15 (S)

[a] Neutral catalyst prepared *in situ*: $1/2[(1,5\text{-}C_6\text{-}H_{10})RhCl]_2$ + 2 L* (L*/Rh = 2).
[b] Cationic catalyst: $[Rh(COD)L^*]^+ClO_4^-$ (COD = 1,5-Cyclooctadiene) (L*/Rh = 1).
[c] When L*/Rh = 1 (50°C), 5.8% ee (R) was obtained.
[d] Racemate at phosphorus atom gave 3.6% ee (S).
[e] Cationic complex with chelate ligand could not be isolated.
[f] Very low conversion: When L*/Rh = 1 (at 50°C), 5.0% ee (S) was obtained.

$$CH_2{=}C(CH_2\text{-}CO_2H)\text{-}CO_2H \xrightarrow[\text{PhH-MeOH (1 : 3 v/v)}]{H_2\,(20\ kg/cm^2)/[Rh^*]} CH_3\text{-}\overset{*}{C}H(CH_2\text{-}CO_2H)\text{-}CO_2H \qquad (1)$$

[Rh*] : $1/2[(1,5\text{-}C_6H_{10})RhCl]_2$ + 2L* (2.5 mM)

Substrate/[Rh*] = 200 (0.5 mol%)

The table indicates that prediction of the preferred configuration and relative magnitude of optical yields of the products with these chiral ligand systems is difficult.

However, several interesting observations can be made from this data: (i) The best optical yield was obtained with (S)-1,2-DPNEA (41% ee), comparable with that using (-)-DIOP (44% ee) or (S)-(R)-BPPFA (33% ee). (ii) AMPHOS-P* brought about the inverse enantioselectivity as compared with AMPHOS. (iii) A sharp contrast of enantioselectivity was observed between (S)-1,2- and (S)-1,8-DPNEA as ligands. Such inversion of enantioselectivity was also observed in the case of reduction of α-acetamidoacrylic acid. The facts suggest that 1,8-DPNEA behaves differently as a ligand of the neutral rhodium complex from 1,2-DPNEA, and (iv) 2,1-DPNEA in the neutral catalyst prevented hydrogenation itself even at 50°C.

We have isolated some DPNEA-rhodium cationic complexes which contain one molecule of DPNEA per rhodium atom as a chelate ligand.[10] Using these cationic catalysts, we have carried out the hydrogenation of itaconic acid under the standard conditions (cf. eq. 1), the results being also summarized in Table 2. Essentially

the same results as with the neutral catalysts were obtained in upper three cases. It should be mentioned, however, that no stable cationic complex with 1,8-DPNEA was isolated. It is very likely that 1,8-DPNEA can not form chelate even in the neutral rhodium complex. This is the reason why 1,8-DPNEA brings about a different enantioselectivity from that of 1,2-DPNEA.

Although we have observed apparent difference in catalytic activities between neutral catalysts and cationic ones described above, the chelate effects of the aminophosphines, if available, seem to be of importance for a significant enantioselectivity in the present asymmetric hydrogenation. Such a chelate effect of 2,1-DPNEA also accounts for the exceptional inactivity of the neutral complex, where a stable bis-chelate formation saturates the coordination sites. Further studies to substantiate the effects discussed are in progress.

We are indebted to Dr. D. Valentine, Jr., Hoffmann-La Roche, for a generous gift of (-)-DAG,[4] and to Dr. Y. Ishido, Tokyo Institute of Technology, for valuable suggestion as to the use of DAG.

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(Received November 4, 1977)