Asymmetric Hydrogenation of α-Keto Acid Derivatives with Rh(I)-Chiral Diphosphinite System. Effect of Halide Counterion on the Asymmetric Induction

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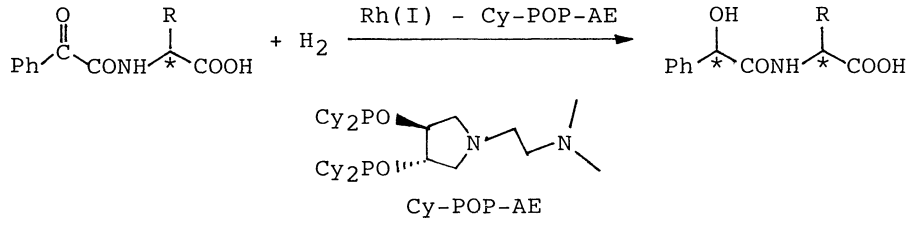
Synopsis. A chiral diphosphinite ligand having dicyclohexylphosphinooxy and dimethylamino moieties (Cy-POP-AE) was effective for the asymmetric hydrogenation of *N*-(benzoylformyl) amino acids by a Rh(I) catalyst under mild conditions. A neutral rhodium(I) precursor enabled a double asymmetric induction in methanol, while a cationic precursor caused an asymmetric induction controlled mainly by the substrate chirality.

Catalytic asymmetric reactions have recently attracted much attention regarding selective syntheses of chiral bioactive substances.[1] The Rh(I)-catalyzed asymmetric hydrogenation of olefinic compounds has achieved prominent success with various chiral ligands under mild conditions.[2] In the case of the hydrogenation of carbonyl groups, a high hydrogen pressure is required,[3,4] and only a few cases have been reported in which the carbonyl moiety could be hydrogenated under mild conditions.[5] Peralkylmonophosphine or -diphosphine ligands with a high σ-donating character have been reported to be effective for the Rh(I)-catalyzed hydrogenation of carbonyl groups under atmospheric hydrogen pressure.[5b]

We have reported the selective asymmetric hydrogenation of *N*-protected dehydrodipeptides with Rh(I)-chiral diphosphinite (3*S*,4*S*)-1-[2-(dimethylamino)-ethyl]-3,4-bis(diarylphosphinooxy)pyrrolidine: POP-AE's[6]) or Rh(I)–diphosphine [2-[2-(dimethylamino)-ethyl]-1,3-propanediyl]bis[diphenylphosphine]: DPP-AE[7]). In these Rh(I) catalyst systems an electrostatic interaction between the ligand and substrate played an important role. We report here that the Rh(I)-catalyzed hydrogenation of benzoylformic acid derivatives with a chiral amino acid residue can proceed under atmospheric hydrogen pressure using a modified POP-AE containing the dicyclohexylphosphinooxy moiety of strongly σ-donating character (Cy-POP-AE) and that the counteranion species of the Rh(I) catalyst severely affects the stereoselectivity.

Results and Discussion

The Cy-POP-AE ligand was prepared in six steps from diethyl (+)-tartrate. The chemical shift of Cy-POP-AE in ^{31}P NMR was in good agreement with the value reported for the Cy-proNOP ((2*S*)-1-dicyclohexylphosphino-2-[(dicyclohexylphosphinooxy)methyl]pyrrolidine).[8] With $[Rh(cod)_2]BF_4$–Cy-POP-AE system, the hydrogenation of benzoylformic acid could proceed smoothly under atmospheric pressure and at ambient temperature in a dichloromethane solution to give (*S*)-product. Polar solvents inclined to need a long time for the reaction and to lower the stereoselectivity (Table 1).



Scheme 1.

Table 1. Asymmetric Hydrogenation of α-Keto Acid Derivatives with Rh(I)–Cy-POP-AE Catalyst

Run	Substrate	Solvent	Time / h	Conv. / %	% e.e.	% d.e.
1	PhCOCOOH	EtOH	100	90	2 (*S*)	
2		CH_2Cl_2	20	100	10 (*S*)	
3	PhCOCO-β-Ala-OH	MeOH	24	100	38 (*R*)	
4	PhCOCO-(*S*)-Ala-OH	$CHCl_3$	48	100		23 (*R*,*S*)
5		EtOH	48	100		52 (*R*,*S*)
6		MeOH	48	100		56 (*R*,*S*)

Hydrogenation was performed under atmospheric hydrogen pressure at room temperature. Substrate/Cy-POP-AE/Rh=50/1.4/1, Rh precursor was $[Rh(cod)_2]BF_4$.

Table 2. Effect of the Halide Ion on the Double Asymmetric Induction in the Hydrogenation of PhCOCO-AA-OH

Run	Ligand	Substrate	Rh precursor	% d.e.
1	Cy-POP-AE	PhCOCO-(*S*)-Ala-OH	Rh^+	56 (*R*,*S*)
2			Rh^N	67 (*R*,*S*)
3		PhCOCO-(*R*)-Ala-OH	Rh^+	12 (*S*,*R*)
4			Rh^N	5 (*R*,*R*)
5		PhCOCO-(*S*)-Phe-OH	Rh^+	47 (*S*,*S*)
6			Rh^N	7 (*S*,*S*)
7		PhCOCO-(*R*)-Phe-OH	Rh^+	53 (*R*,*R*)
8			Rh^N	50 (*R*,*R*)
9		PhCOCO-(*S*)-Ala-OMe	Rh^N	33 (*R*,*S*)
10		PhCOCO-(*S*)-Ala-OH+NEt_3	Rh^N	50 (*R*,*S*)
11	Cy-POP-IP	PhCOCO-(*S*)-Ala-OH	Rh^N	49 (*R*,*S*)
12		PhCOCO-(*R*)-Phe-OH	Rh^N	41 (*R*,*R*)

Hydrogenation was performed under atmospheric hydrogen pressure at room temperature in methanol. Substrate/ligand/Rh=50/1.4/1, Rh^+=$[Rh(cod)_2]BF_4$, Rh^N=$[RhCl(cod)]_2$.

In the case of PhCOCO-β-Ala-OH with an achiral amino acid unit, the direction of asymmetric induction was (*R*)-selective, opposite to the reaction of PhCOCOOH. It was noted that solvent effect on the reaction of *N*-(benzoylformyl) amino acid was reversed to the reaction of benzoylformic acid (Table 1, Runs 4—6). The increase in the solvent polarity raised both the reactivity and stereoselectivity; this tendency was the same as observed in the cases of dehydrodipeptides with a free carboxyl group.[7] On the other hand, a high stereoselectivity was reported in less polar solvents for the hydrogenation of *N*-(benzoylformyl) amino acid esters.[5b]

In reactions of *N*-(benzoylformyl) amino acids, the kinds of rhodium precursors showed a striking effect on the direction of asymmetric induction (Table 2, Runs 1—8). In the case of cationic precursors, the newly developed chirality was mainly controlled by the chirality of the amino acid unit, though the direction of asymmetric induction was strongly dependent on the structure of the amino acid unit (Runs 1 and 5, 3 and 7). A neutral rhodium precursor, however, amplified the asymmetric induction through the chirality of Cy-POP-AE (*R*-selectivity) and relatively high stereoselectivities were observed by a double asymmetric induction in matched pairs;[9] a good selectivity of 67% (*R*,*S*) was obtained in the case of PhCOCO-(*S*)-Ala-OH. A comparison of the ^{31}P NMR spectra of the reaction systems in CD_3OD using $[Rh(cod)Cl]_2$ and $[Rh(cod)_2]BF_4$ precursors indicated the presence of the Rh(I)Cl species in methanol for the system using $[Rh(cod)Cl]_2$, as well as the cationic Rh(I) species. These results indicate that the active rhodium species coordinated by chloride caused a double asymmetric induction in methanol. This halide ion effect makes a sharp contrast to the hydrogenation of dehydroamino acids or dehydrodipeptides in methanol solvent where no conspicuous difference was observed between the reactions with cationic and neutral rhodium(I) precursors.[2,6]

The reaction system of Cy-POP-AE-PhCOCO-(*S*)-Ala-OH afforded higher stereoselectivity than the systems of Cy-POP-AE-PhCOCO-(*S*)-Ala-OMe or Cy-POP-IP-PhCOCO-(*S*)-Ala-OH (Cy-POP-IP: an analog of Cy-POP-AE having an isopentyl unit instead of 2-(dimethylamino)ethyl group); this difference was ascribed to a contribution of the electrostatic interaction between the carboxyl group of PhCOCO-(*S*)-Ala-OH and the amino group of Cy-POP-AE to the asymmetric induction. The lowered stereoselectivity by amine addition also supported this conclusion.[7]

The present results imply that Rh(I)Cl-Cy-POP-AE system would be useful for the asymmetric hydrogenation of *N*-(acylfomyl) amino acid under atmospheric hydrogen pressure utilizing double asymmetric induction in a polar alcoholic solution.

Experimental

(3*S*,4*S*)-1-[2-(Dimethylamino)ethyl]-3,4-bis(dicyclohexylphosphinooxy)pyrrolidine (Cy-POP-AE). (3*S*,4*S*)-1-[2-(Dimethylamino)ethyl]-3,4-pyrrolidinediol was prepared from diethyl (+)-tartrate in five steps, as was described previously.[6] To a THF solution (50 ml) of this diol (1.7 g, 9.8 mmol) containing 60 mmol of triethylamine, was added dropwise chlorodicyclohexylphosphine (5.0 g, 21 mmol) in 20 ml THF at 0 °C; the mixture was stirred overnight. Hydrochloride salt of triethylamine was filtered and the filtrate was evaporated to dryness to give white solids. These solids were dissolved in 30 ml hexane; undissolved tetracyclohexyldiphosphine and pentavalent phosphorus compounds were filtrated off at −20 °C. The filtrate was evaporated and residual solids were recrystallized from dry ether at −50 °C to afford Cy-POP-AE (3.6 g, 49%) as white crystals: Found: C, 67.28; H, 10.84; N, 4.44%. Calcd for $C_{32}H_{60}N_2O_2P_2$: C, 67.81; H, 10.67; N, 4.94%; ^1H NMR ($CDCl_3$) δ=0.8—2.1 (44H, m, *c*-C_6H_{11}), 2.25 (6H, s, -NCH_3), 2.3—3.1 (8H, m, -NCH_2-CH_2N-, -CH_2-NCH_2-), 3.8—4.3 (2H, m, O-CH-); ^{31}P NMR ($CDCl_3$) δ=144.4; MS *m*/*z*=567 (MH^+) (FAB, *m*-nitrobenzyl alcohol matrix); $[\alpha]_D^{20}$ =+55.1° (*c* 0.17, $CHCl_3$).

(3*S*,4*S*)-1-Isopentyl-3,4-bis(dicyclohexylphosphinooxy)-pyrrolidine (Cy-POP-IP). Cy-POP-IP was prepared from (3*S*,4*S*)-1-isopentyl-3,4-pyrrolidinediol similarly to Cy-POP-AE and recrystallization from dry ether at −50 °C afforded Cy-POP-IP (38%) as white crystals: Found: C, 69.60; H, 11.07; N, 2.29%. Calcd for $C_{33}H_{61}NO_2P_2$: C, 70.05; H, 10.87; N, 2.48%; ^1H NMR ($CDCl_3$) δ=0.8 (6H, d, *J*=6.5 Hz, CH_3), 0.8—2.1 (47H, m, *c*-C_6H_{11}-, -CH_2CH-), 2.2—3.1 (6H,

m, N-CH_2-), 3.9—4.3 (2H, m, O-CH-); ^{31}P NMR ($CDCl_3$) δ=144.4; MS m/z=566 (MH^+) (FAB, *m*-nitrobenzyl alcohol matrix); $[\alpha]_D^{20}$=+61.7° (*c* 0.21, $CHCl_3$).

Substrates. *N*-(Benzoylformyl) amino acids (PhCOCO-AA-OH: AA=(*S*)- and (*R*)-Ala, (*S*)- and (*R*)-Phe, and β-Ala) were prepared by condensation of benzoylformic acid with amino acid methyl ester hydrochloride in THF using dicyclohexylcarbodiimide, 1-hydroxy-1*H*-benzotriazole, and *N*-methylmorpholine (or triethylamine) at 0 °C followed by hydrolysis according to methods described in the literature.[10]

N-(Benzoylformyl)-(*S*)- and (*R*)-alanine were obtained as crystals (73—75%), while *N*-(benzoylformyl)-(*S*)- and (*R*)-phenylalanine were very viscous oil; the latter were purified as dicyclohexylammonium salt,[11] then converted to free acid by potassium hydrogensulfate. *N*-(Benzoylformyl)-β-alanine was obtained as pale-yellow solids (77%).

Hydrogenations. The catalyst solution of Rh(I)-Cy-POP-AE or -Cy-POP-IP was prepared from $[Rh(cod)_2]BF_4$ or $[Rh(cod)Cl]_2$ and the ligand in 5 ml of solvent (Rh 0.01 mmol; ligand/Rh=1.1—1.5). It was then transferred to a reaction vessel containing 0.5 mmol of the substrate using a fine stainless tube so as to avoid contamination with oxygen. Degassing was repeated three times and the solution was stirred for 30 min under N_2 followed by H_2 introduction. After the reaction, the solution was diluted with methanol and rhodium was removed using a Dowex 50 cation-exchange resin. The solution was evaporated to dryness and the products were converted to methyl esters in methanol-HCl. The diastereomeric excess was determined by an NMR method using $Eu(hfc)_3$ in CD_3OD-$CDCl_3$ monitoring the methine proton of the mandelic acid unit in the product.

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References

1) "Asymmetric Catalysis (NATO ASI Series E 103)," ed by B. Bosnich, Martinus Nijhoff, Dordrecht (1986); "Asymmetric Synthesis," ed by J. D. Morrison, Academic, Orlando (1985), Vol. 5.

2) H. B. Kagan, "Comprehensive Organometallic Chemistry," ed by G. Wilkinson, Pergamon, Oxford (1982), Vol. 8, Chap. 53; J. M. Brown and P. A. Chaloner, "Homogeneous Catalysis with Metal Phosphine Complexes," ed by L. H. Pignolet, Plenum, New York (1983), Chap. 4.

3) P. Bonvicini, A. Levi, G. Modena, and G. Scorrano, *J. Chem. Soc., Chem. Commun.*, **1972**, 1188; T. Hayashi, A. Katsumura, M. Konishi, and M. Kumada, *Tetrahedron Lett.*, **1979**, 425; S. Törös, B. Heil, L. Kollár, and L. Markó, *J. Organomet. Chem.*, **197**, 85 (1980); J. Bakos, I. Tóth, B. Heil, and L. Markó, *ibid.*, **279**, 23 (1985).

4) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, and R. Noyori, *J. Am. Chem. Soc.*, **110**, 629 (1988).

5) a) K. Tani, K. Suwa, E. Tanigawa, T. Yoshida, T. Okano, and S. Otsuka, *Chem. Lett.*, **1982**, 261; K. Tani, E. Tanigawa, Y. Tatsuno, and S. Otsuka, *J. Organomet. Chem.*, **279**, 87 (1985); K. Yamamoto and S. U. Rehman, *Chem. Lett.*, **1984**, 1603. b) K. Tani, E. Tanigawa, Y. Tatsuno, and S. Otsuka, *Chem. Lett.*, **1986**, 737.

6) M. Yatagai, M. Zama, T. Yamagishi, and M. Hida, *Bull. Chem. Soc. Jpn.*, **57**, 739 (1984); M. Yatagai, T. Yamagishi, and M. Hida, *ibid.*, **57**, 823 (1984).

7) T. Yamagishi, S. Ikeda, M. Yatagai, M. Yamaguchi, and M. Hida, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 1787.

8) A. Karim, A. Mortreux, F. Petit, G. Buono, G. Peiffer, and C. Siv, *J. Organomet. Chem.*, **317**, 93 (1986).

9) S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, **24**, 1 (1985).

10) W. König and R. Geiger, *Chem. Ber.*, **103**, 788, 2024 (1970).

11) M. Bodanszky and A. Bodanszky, "The Practice of Peptide Synthesis," Springer-Verlag, Heiderberg (1984), pp. 19—20.