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Highly Effective Catalytic Asymmetric Hydrogenations of α-Keto Esters and an α-Keto Acetal with New Neutral Chiral Pyrrolidinebisphosphine-Rhodium Complexes[1)]

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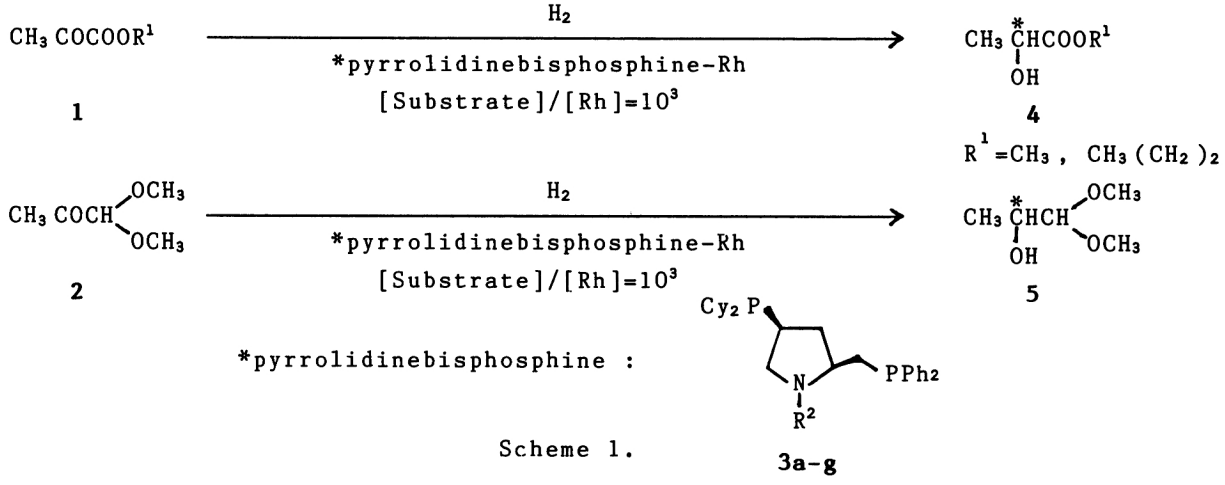
Synthesis of new chiral pyrrolidinebisphosphine-rhodium complexes and their application to the asymmetric hydrogenations of α-keto esters and an α-keto acetal are described. Among them, MCCPM-Rh gave the highest optical yield (87%) of the α-hydroxy ester and MCPM-Rh gave the 75% optical yield of the α-hydroxy acetal at the substrate to catalyst ratio (1000 : 1).

Recently, we have proposed a new concept, that one phosphino group of the bisphosphine ligands oriented *cis* to the prochiral group of substrate controls the enantioselectivity of asymmetric hydrogenation and the other oriented *trans* to the prochiral group accelarates its reaction rate, for the further development of extremely efficient chiral ligands in the asymmetric syntheses.[2,3)] And also, we have developed a new chiral pyrrolidinebisphosphine (BCPM) ligand, the neutral rhodium complex of which efficiently catalyzed the asymmetric hydrogenation of ketopantolactone leading to (*R*)-(-)-pantolactone in 90-92% optical yields even at high substrate to catalyst ratios (1000-10000 : 1).[2,3)]

We wish to describe here a systematic investigation of asymmetric hydrogenations of α-keto esters (**1**) and α-keto acetal (**2**) using new chiral pyrrolidinebisphosphines (**3**) [MCCPM (**3a**), BCCPM (**3b**), PCCPM (**3c**), MCPM (**3d**), BCPM (**3e**), PCPM (**3f**), PVCPM (**3g**)] and [Rh(1,5-cyclooctadiene)Cl]$_2$ as shown in Scheme 1.



1 **4** **2** **5** **3a-g**

Scheme 1.

New chiral *N*-substituted pyrrolidinebisphosphines (**3a-g**) were prepared by the reactions of the pyrrolidinebisphosphine (**3**: R^2=H) with the corresponding isocyanates, chloroformates or dicarbonate and acyl chloride, respectively.[4)]

The table shows that the newly synthesized pyrrolidinebisphosphines (**3**) gave higher optical yields at a higher substrate to catalyst molar ratio (1000 : 1) than BPPM (optical yield, 66.3%; molar ratio, 200 : 1) for the hydrogenation of methyl pyruvate.[5)] The highest optical yield was achieved by using MCCPM (**3a**) as a chiral ligand for asymmetric hydrogenation of methyl pyruvate. On the other hand, *n*-propyl pyruvate was hydrogenated with MCCPM-Rh in a lower optical yield than methyl pyruvate, although the former was hydrogenated with higher enantioselectivity than the latter in the use of BPPM-Rh.[5)]

The *N*-carbamoyl (**3a-c**) or the *N*-alkoxycarbonyl (**3d-f**) ligands brought about higher enantioselectivities and turnovers than the corresponding *N*-acyl one (**3g**). The *N*-substituents having methyl (MCCPM (**3a**) and MCPM (**3d**)) or phenyl (PCCPM (**3c**) and PCPM (**3f**)) groups also gave higher optical yields than those having *t*-butyl ones (BCCPM (**3b**) and BCPM (**3e**)), respectively.

Even in the case of the α-keto acetal (**2**), the less reactive carbonyl compound, the hydrogenation proceeded smoothly as indicated in Table. The *N*-substituent effects of **3** were also observed clearly on the optical yields of the asymmetric hydrogenation product (**5**). Thus, the *t*-butoxycarbonyl group (BCPM (**3e**): 71% ee) works better than the corresponding acyl (PVCPM (**3g**): 47% ee) and carbamoyl (PCCPM (**3c**): 7% ee) groups. Furthermore, in a series of the alkoxycarbonyl groups, the ligand having the methyl group (MCPM (**3d**): 75% ee) gave the higher optical yield than that having *t*-butyl (BCPM (**3e**): 71% ee) or phenyl (PCPM (**3f**): 64% ee) groups. Therefore, it should be noted that the *N*-substituents of **3** played important roles in affecting the optical yields of **4** and **5**.[6)]

In a typical experiment, the asymmetric hydrogenation of methyl pyruvate (1.531g, 15 mmol) was carried out in dry peroxide-free THF (10 ml) at 20 °C, for 24 h under an initial hydrogen pressure of 20 atm in the presence of the rhodium catalyst (10^{-1} mol%) which was prepared *in situ* from [Rh(1,5-cyclooctadiene)Cl]$_2$ (3.7 mg) and MCCPM (9.4 mg). After the reaction was completed, the reaction mixture was distilled to give (*R*)-(+)-methyl lactate in an almost quantitative yield: $[\alpha]_D^{22}$ +7.17° (neat).

To the best of our knowledge, the neutral rhodium complexes of new chiral pyrrolidinebisphosphines (**3**) are the most effective catalysts so far reported for the asymmetric hydrogenation of α-keto esters and first applied to the hydrogenation of α-keto acetal.

Although their enantioselectivities must be improved, for example, by matching the *N*-substituents of **3** to the structures of the substrates, these asymmetric hydrogenations catalyzed by newly designed pyrrolidinebisphosphine-rhodium complexes may efficiently give rise to several chiral α-hydroxy acid and α-hydroxy aldehyde derivatives as chiral building blocks for the synthesis of useful chiral compounds.

Table 1. Asymmetric Hydrogenations of α-Keto Esters[a] and an α-Keto Acetal[b]

Substrate	Ligand (**3a-g**: R^2=)	Convn./%[c]	Opt. yield/%[d]	Confign.
$CH_3COCOOCH_3$	MCCPM (**3a**: R^2=$CONHCH_3$)	100	87	*R*
	BCCPM (**3b**: R^2=CONH-*t*-Bu)	100	75	*R*
	PCCPM (**3c**: R^2=CONHPh)	100	85	*R*
	MCPM (**3d**: R^2=$COOCH_3$)	100	84	*R*
	BCPM (**3e**: R^2=COO-*t*-Bu)	100	76	*R*
	PCPM (**3f**: R^2=COOPh)	100	86	*R*
	PVCPM (**3g**: R^2=CO-*t*-Bu)	72	52	*R*
$CH_3COCOO(CH_2)_2CH_3$	MCCPM (**3a**: R^2=$CONHCH_3$)	100	74	*R*
$CH_3COCH(OCH_3)_2$	BCCPM (**3b**: R^2=CONH-*t*-Bu)	100	7	*R*[e]
	BCPM (**3e**: R^2=COO-*t*-Bu)	100	71	*R*[e]
	PVCPM (**3g**: R^2=CO-*t*-Bu)	100	47	*R*[e]
	MCPM (**3d**: R^2=$COOCH_3$)	100	75	*R*[e]
	PCPM (**3f**: R^2=COOPh)	100	64	*R*[e]

a) All hydrogenations were run with 15 mmol of substrate (**1**), 7.5×10^{-3} mmol of [Rh(1,5-cyclooctadiene)Cl]$_2$ and 18×10^{-3} mmol of a chiral pyrrolidinebisphosphine (**3**) in 10 ml THF at 20 °C for 24 h under an initial hydrogen pressure of 20 atm.[5] *b*) All hydrogenations were run with 15 mmol of substrate (**2**), 7.5×10^{-3} mmol of [Rh(1,5-cyclooctadiene)Cl]$_2$ and 18×10^{-3} mmol of **3** in 10 ml THF at 50 °C for 48 h under an initial hydrogen pressure of 50 atm. *c*) Determined by GLC analysis. *d*) Caluculated using the reported optical rotations of pure enantiomers: (*S*)-(-)-methyl lactate; $[\alpha]_D^{20}$ -8.25° (neat),[7a] (*S*)-(-)-*n*-propyl lactate; $[\alpha]_D^{18}$ -12.1° (neat),[7b] and determined by ^{1}H-NMR spectra using chiral shift reagent [Eu(hfc)$_3$] for **5**. *e*) See, Ref. 8.

Further investigations along this line are actively under way.

References

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3) T. Moromoto, H. Takahashi, K. Fujii, M. Chiba, and K. Achiwa, Chem. Lett., 1986, 2061.
4) MCCPM (**3a**); mp 142-143.5 °C, $[\alpha]_D^{23}$ -29.7° (c 0.62, benzene), BCCPM (**3b**); mp 159-161 °C, $[\alpha]_D^{23}$ -15.5° (c 1.00, benzene), PCCPM (**3c**); This ligand, first named PCPM (Ref. 2), was renamed PCCPM. MCPM (**3d**); mp 149-151 °C, $[\alpha]_D^{21}$ -52.2° (c 0.50, benzene), PCPM (**3f**); mp ca. 120 °C (decomp.), $[\alpha]_D^{21}$ -44.5° (c 0.82, benzene), PVCPM (**2g**); mp 201-203 °C, $[\alpha]_D^{22}$ -5.5° (c 0.62, benzene).

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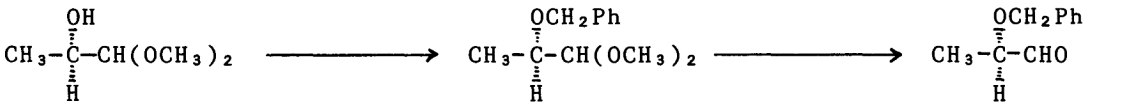
6) Previously, *N*-substituent effects of pyrrolidinebisphosphines (BPPM and its analogues) were reported on the optical yields of the product in the asymmetric hydrogenation of ketopantolactone (K. Achiwa, T. Kogure, and I. Ojima, Chem. Lett., 1978, 297.).
7) a) T. Purdie and J. C. Irvine, J. Chem. Soc., 1899, 483; b) E. Wassmer and P. A. Guye, Chem. Zentralbl., 1903, 1419.
8) The absolute configuration of (*R*)-(+)-**5** was determined as indicated below.



(*R*)-(+)-**5** (*R*)-(+)-**6** (*R*)-(+)-**7**[9]

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