SYNTHESIS OF ATROPISOMERIC BIPHENYLBISPHOSPHINE, 6,6'-BIS(DICYCLOHEXYLPHOSPHINO)-3,3'-DIMETHOXY-2,2',4,4'-TETRAMETHYL-1,1'-BIPHENYL AND ITS USE IN RHODIUM(I)-CATALYZED ASYMMETRIC HYDROGENATION[1)]

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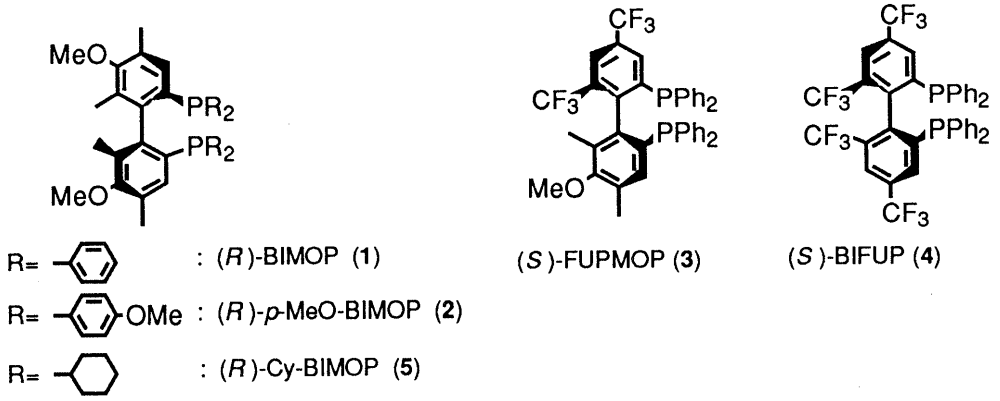
An optically pure atropisomeric biphenylbisphosphine, Cy-BIMOP, has been prepared, and its rhodium(I) complex showed higher catalytic activity and better enantioselectivity with the reverse configuration than BIMOP, *p*-MeO-BIMOP, and BINAP in the asymmetric hydrogentions of (*Z*)-α-acetamidocinnamic acid, itaconic acid, and its derivative.

KEYWORDS atropisomeric biphenylbisphosphine; rhodium(I) complex; asymmetric hydrogenation; optical resolution; enantioselectivity; acetamidocinnamic acid; itaconic acid; piperonylidenesuccinic acid

In much progress in the development of asymmetric hydrogenations with the complexes of transition metal and bisphosphine ligands, atropisomeric biarylbisphosphines such as BINAP,[2)] BIPHEMP,[3)] and BICHEP[4)] have been recently utilized for highly efficient ruthenium(II)- and rhodium(I)-catalyzed asymmetric hydrogenations of several functionalized ketones and olefins.

In previous communications,[5,6)] we reported the preparation of optically pure BIMOP (**1**), *p*-MeO-BIMOP (**2**), FUPMOP (**3**), and BIFUP (**4**), atropisomeric biphenylbisphosphines bearing electron-donating groups or/and electron-withdrawing groups on the biphenyl frameworks and the efficient asymmetric hydrogenations of β-keto ester and α,β-unsaturated carboxylic acid with their ruthenium(II) complex catalysts. We revealed that the steric effect and the electronic effect of the biphenyl framework have roles in the enantioselectivity and the catalytic activity, respectively, of the ruthenium(II)-catalyzed asymmetric hydrogenation of methyl acetoacetate, where BIMOP (**1**) and FUPMOP (**3**) bearing electron-donating groups at least on one phenyl group showed high catalytic activities, though BIFUP (**4**) bearing only electron-withdrawing groups exhibited much lower catalytic activity. These results prompted us to prepare a new atropisomeric biphenylbisphosphine bearing electron-donating groups on both the biphenyl framework and the phosphino groups.



This communication describes the synthesis of optically pure atropisomeric biphenylbisphosphine, 6,6'-bis(dicyclohexylphosphino)-3,3'-dimethoxy-2,2',4,4'-tetramethyl-1,1'-biphenyl (abbreviated to Cy-BIMOP) (**5**) and its use in rhodium(I)-catalyzed asymmetric hydrogenations of (*Z*)-α-acetamidocinnamic acid, itaconic acid, and its derivative.

Optically pure Cy-BIMOP (**5**) was prepared by a similar procedure reported previously as shown in Chart 1. 6,6'-Dibromo-3,3'-dimethoxy-2,2',4,4'-tetramethylbiphenyl (**6**)[5)] prepared via 5 steps from 2,6-dimethylnitrobenzene was dilithiated with *tert*-butyllithium in tetrahydrofuran (THF) at -70 °C and allowed to react with chlorodicyclohexylphosphine affording the corresponding bisphosphine, which was directly converted to racemic Cy-BIMOPO (**7**) in 68% overall yield from **6** by oxidation with hydrogen

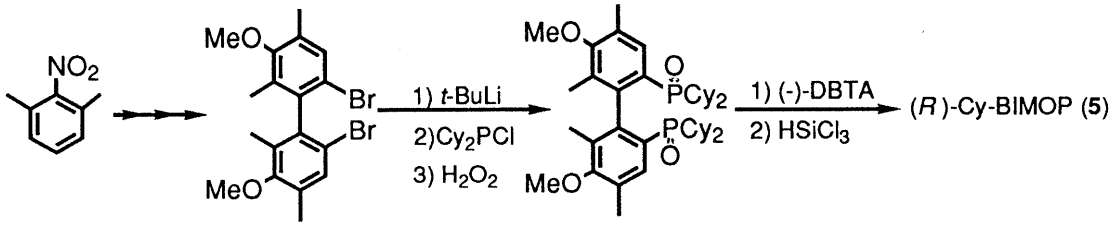
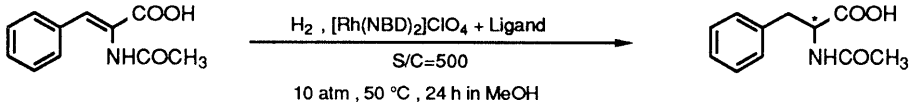


Chart 1

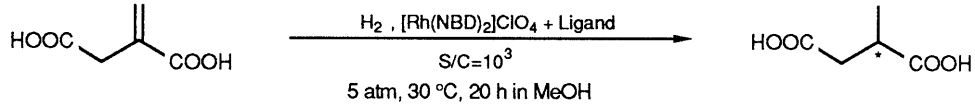
Table I. Asymmetric Hydrogenation of (*Z*)-α-Acetamidocinnamic Acid



Ligand	Convn.[b](%)	Optical Yield[c](%)	Confign.[d]
(*R*)-BINAP	42	15	*R*
(*R*)-BIMOP (**1**)	42	30	*R*
(*R*)-*p*-MeO-BIMOP (**2**)	100	44	*R*
(*R*)-Cy-BIMOP (**5**)	100	79	*S*

a) All hydrogenations were carried out in 0.1 M solution of the substrate. b) Determined by ^{1}H-NMR analysis.
c) Calculated on the basis of the reported value $[\alpha]_D^{20}$ +40.1° (c 1.00, MeOH) for the pure *S*-enantiomer.
d) Determined by the sign of optical rotation.

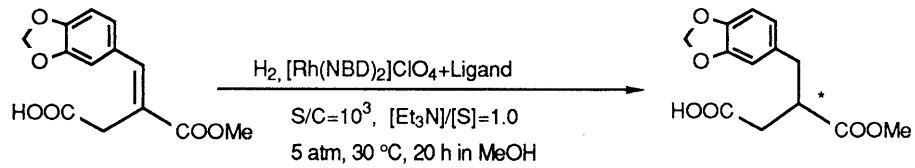
Table II. Asymmetric Hydrogenation of Itaconic Acid



Ligand	Convn.[b](%)	Optical Yield[c] (%)	Confign.[d]
(*R*)-BINAP	100	~0	---
(*R*)-BIMOP (**1**)	100	51	*S*
(*R*)-*p*-MeO-BIMOP (**2**)	100	57	*S*
(*R*)-Cy-BIMOP (**5**)	100	80	*R*

a) All hydrogenations were carried out in 0.5 M solution of the substrate. b) Determined by ^{1}H-NMR analysis.
c) Calculated on the basis of the reported value $[\alpha]_D^{20}$ +16.88° (c 2.16, EtOH) for the pure *R*-enantiomer.
d) Determined by the sign of optical rotation.

Table III. Asymmetric Hydrogenation of α–Piperonylidenesuccinic Acid Monomethyl Ester



Ligand	Convn.[b] (%)	Optical Yield[c] (%)	Confign.[d]
(*R*)-BINAP	24	~0	----
(*R*)-BIMOP (**1**)	72	56	*S*
(*R*)-*p*-MeO-BIMOP (**2**)	70	70	*S*
(*R*)-Cy-BIMOP (**5**)	100	73	*R*

a) All hydrogenations were carried out in 0.5 M solution of the substrate. b) Determined by ^{1}H-NMR analysis.
c) Calculated on the basis of the maximum optical rotation $[\alpha]_D^{20}$ +29.2° (c 2.00, MeOH) determined by HPLC analysis of the corresponding morpholino derivative on Chiralcel OC (Daicel).
d) Determined by the sign of optical rotation.

peroxide. Optical resolution of racemic **7** was achieved by using (2*R*, 3*R*)-(-)-2,3-*O*-dibenzoyltartaric acid ((-)-DBTA) as a resolving agent. Repeated recrystallization of the complex from methanol gave a diastereomerically pure complex of (*R*)-Cy-BIMOPO ((*R*)-**7**) and (-)-DBTA in 40% yield. Free (*R*)-**7** was obtained by treating the complex with aq. sodium hydroxide in dichloromethane. The phosphinyl groups were reduced by heating at 140 °C for 4 h with a large excess of trichlorosilane in chlorobenzene to afford optically pure (*R*)-Cy-BIMOP (**5**)[7] in 64% yield. The absolute configuration was determined by comparison of its CD spectrum with that of (*R*)-BIPHEMP.[8]

First, the ruthenium (II)-catalyzed asymmetric hydrogenation of methyl acetoacetate was carried out for evaluation of the capability of (*R*)-Cy-BIMOP (**5**) and for comparison with **1**, **2**, **3**, and **4**. Unexpectedly, the hydrogenation catalyzed by (*R*)-Cy-BIMOP (**5**)-ruthenium (II) complex did not proceed smoothly even under a hydrogen pressure of 90 atm at 30-40 °C for 40 h. As reported previously,[6] the (*S*)-BIFUP (**4**)-ruthenium(II) complex also showed very low catalytic activity. These results may suggest that the complex formation of the bisphosphine-ruthenium-monohydride by oxidative addition of hydrogen to the intermediate considered as a rate-determining step retards since, in Cy-BIMOP (**5**) bearing only electron-donating groups, the bisphosphine-ruthenium-monohydride complex is unstable and in BIFUP (**4**) bearing only electron-withdrawing groups the oxidative addition of hydrogen becomes slower.

We have already reported that bisphosphine ligands bearing electron-donating groups have important roles in effective asymmetric hydrogeantions of ketones and olefins using their rhodium(I) complex.[9] Therefore, we next carried out the asymmetric hydrogenation of functionalized olefins such as (*Z*)-α-acetamidocinnamic acid and itaconic acids with the rhodium(I) complex of (*R*)-Cy-BIMOP (**5**). Asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid was carried out using the cationic rhodium(I) complex of BIMOPs (**1**, **2**, **5**) (molar ratio: substrate/catalyst (S/C)=500) in methanol under a hydrogen pressure of 10 atm at 50 °C for 24 h. The results summarized in Table I show that the ligands bearing more electron-donating groups have higher catalytic activity and better enantioselectivity. Itaconic acid and α-piperonylidenesuccinic acid half-ester were also hydrogenated using their cationic complex (S/C=1000) in methanol under a hydrogen pressure of 5 atm at 30 °C for 20 h. Tables II and III show that (*R*)-Cy-BIMOP (**5**) was the most effective ligand for exhibiting higher enantioselectivity and catalytic activity though all the reactions proceeded completely in itaconic acid under these conditions. Thus, in the the ligands having a biphenyl framework, it has been revealed that the electron-donating groups give higher catalytic activity and better enantioselectivity to the rhodium(I) complex catalyst. In addition, the direction of the enantioselection of (*R*)-Cy-BIMOP (**5**) bearing dicyclohexylphosphino groups was reverse to that of the other ones, **1**, **2**, and (*R*)-BINAP, bearing diphenylphosphino groups. Previously, it was reported that an isolated (*R*)-BINAP-rhodium(I) complex gave the (*S*)-products in high optical yields from (*Z*)-α-(acylamino)acrylic acids but the diene coordinated starting complex or a dinuclear complex showed much lower selectivity.[10] Although the reason for the different enantioselectivity between (*R*)-Cy-BIMOP (**5**) and the others is not clearly understood so far, it is likely that in the ligands of biarylbis(diphenylphosphine) type, a dinuclear rhodium complex formed *in situ* has higher catalytic activity with different enantioselectivity than a mononuclear rhodium complex, or an intermediary complex bearing the chelation of the olefin group and the α-carboxylic group to the rhodium shows higher activity than the complex bearing the β-carbonyl or carboxylic chelation, resulting in different selectivity.

Further investigations along this line are in progress to clarify the mechanism of the enantioselectivity in the hydrogenation of functionalized olefins.

ACKNOWLEDGEMENT The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan.

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7) (*R*)-Cy-BIMOP (**5**): mp 185-186 °C, $[\alpha]_D^{19}$ -56.5° (c 1.16, $CHCl_3$). *Anal.* Calcd for $C_{42}H_{64}O_2P_2$: C, 76.10; H, 9.73. Found: C, 76.04; H, 9.59. ^{1}H-NMR δ ($CDCl_3$): 0.90-1.90 (44H, m, 4xC_6H_{11}), 1.80 (6H, s, 2xCH_3), 2.35 (6H, s, 2xCH_3), 3.72 (6H, s, 2xOCH_3), 7.09 (2H, s, arom. H).
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(Received September 3, 1991)