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A New Type of Atropisomeric Biphenylbisphosphine Ligand, (*R*)-MOC-BIMOP and Its Use in Efficient Asymmetric Hydrogenation of α-Aminoketone and Itaconic Acid[1)]

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Abstract: A new atropisomeric biphenylbisphosphine, MOC-BIMOP, has been prepared in enantiomerically pure form and its rhodium(I) complex proved to be an efficient catalyst in the asymmetric hydrogenations of α-aminoketone hydrochloride and itaconic acid. A possible mechanism of our origin has been described for the hydrogenations. .

Atropisomeric biarylbisphosphines such as BINAP,[2)] BIPHEMP,[3)] and BICHEP[4)] have been recognized as highly efficient chiral ligands for ruthenium(II)- and rhodium(I)-catalyzed asymmetric hydrogenations of several functionalized ketones and olefins.

We have recently reported the preparation of some new atropisomeric biarylbisphosphines, BIMOP,[5)] Cy-BIMOP,[6)] FUPMOP,[7)] and BIFUP,[7)] whose ruthenium(II) or rhodium(I) complexes were found to be efficient catalysts in the asymmetric hydrogenations of methyl acetoacetate, tiglic acid, and itaconic acid and its derivative.

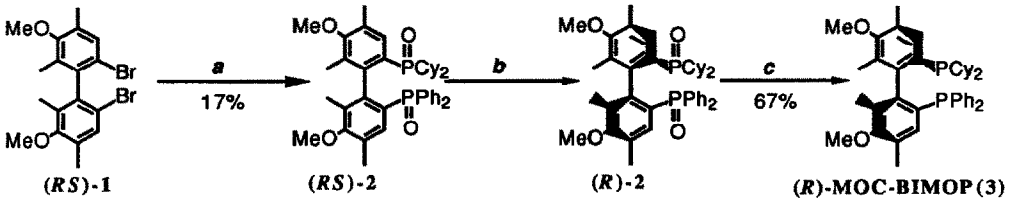
Previously, we presented "Respective Control Concept"[8)] for designing efficient chiral bisphosphine ligands and developed highly efficient unsymmetrical bisphosphine ligands such as BCPM and its analogues, the rhodium(I) complexes of which were shown to be excellent-catalysts for the asymmetric hydrogenations of some functionalized ketones and olefins.[9)]

This comuncation describes the synthesis of a new unsymmetrical biarylbisphosphine, 6-dicyclohexylphosphino-6'-diphenylphosphino-3,3'-dimethoxy-2,2',4,4'-tetramethyl-1,1'-biphenyl (abbreviated to MOC-BIMOP)(**3**) bearing both a dicyclohexylphosphino group and a diphenylphosphino group and its use in rhodium(I)-catalyzed asymmetric hydrogenations of α-aminoketone and itaconic acid.

Optically pure MOC-BIMOP (**3**) was prepared by the procedure shown in Scheme 1. 6,6'-Dibromo-3,3'-dimethoxy-2,2',4,4'-tetramethylbiphenyl (**1**)[5)] obtained from 1,3-dimethyl-2-nitrobenzene was mono-lithiated with *tert*-butyllithium and allowed to react with chlorodiphenylphosphine yielding the corresponding mono-phosphine, which was further lithiated without isolation, followed by phosphination with chlorodicyclo-hexylphosphine. After oxidation of the crude product with hydrogen peroxide, racemic MOC-BIMOPO (**2**) was isolated by silica gel column chromatography using AcOEt as the eluting solvent. Optical resolution of (*RS*)-(**2**) was carried out by HPLC with Chiral Pack OT(+) (Daicel) using isopropyl alcohol-hexane (9:1) as the eluent . From the first fractions, optically pure (*R*)-MOC-BIMOPO (**2**) was obtained. Reductive deoxygenation of (*R*)-(**2**) was carried out by heating at 160 °C with trichlorosilane in the presence of triethylamine affording

(*R*)-MOC-BIMOP (**3**), whose absolute configuration was determined by comparison of its CD spectrum with that of (*R*)-BIPHEMP.[3)]

Scheme 1.

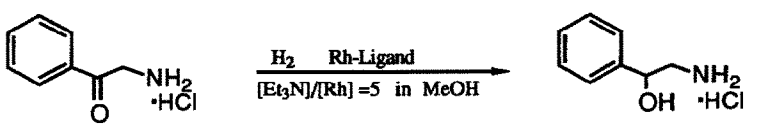


a 1. *t*-BuLi , $(C_6H_5)_2PCl$ / THF; 2. *t*-BuLi , $(cy\text{-}C_6H_{11})_2PCl$ / THF; 3. H_2O_2 aq / CH_2Cl_2;
b resolved by HPLC with CHIRALPAK OT (+) (Daicel);
c $HSiCl_3$, Et_3N / PhCl.

We have already revealed that unsymmetrical chiral bisphosphines, BCPM, MCCPM, DIOCP, etc. bearing both a dicyclohexylphosphino group and a diphenylphosphino group, are highly efficient ligands for rhodium(I)-catalyzed asymmetric hydrogenations of functionalized ketones and olefins, such as α–amino-ketone hydrochloride, ketopantolactone, and itaconic acid.[9, 10)]

So we carried out the asymmetric hydrogenations of α–aminoketone hydrochloride and itaconic acid with the Rh(I)-complex of (*R*)-MOC-BIMOP, and with those of (*R*)-BIMOP and (*R*)-Cy-BIMOP for comparison of their efficiency. Table 1 summarizes the results of the asymmetric hydrogenation of 2-aminoacetophenone hydrochloride. The Rh(I)-complex of (*R*)-MOC-BIMOP was found to have much better enantioselectivity than those of (*R*)-BIMOP and (*R*)-Cy-BIMOP, and higher catalytic activity than that of (*R*)-BIMOP.

Table 1. Asymmetric Hydrogenation of 2-Aminoacetophenone Hydrochloride

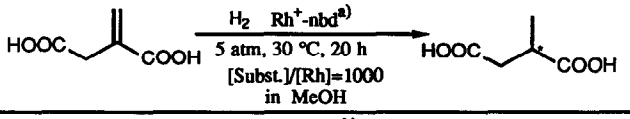


Ligand	Rh	[Subst.] / [Rh]	Condition atm/ °C / days	Convn.[c)](%)	O.Y.[d)](%)
(*R*)-MOC-BIMOP	Rh^{+} [a)]	1000	90/50/7	100	93(*R*)
(*R*)-Cy-BIMOP	Rh^{N} [b)]	500	50/50/4	100	55(*R*)
(*R*)-BIMOP	Rh^{N} [b)]	500	50/50/4	61	8(*S*)

a) Rh^{+} : $[Rh(nbd)_2]ClO_4$. b) Rh^{N}: $[Rh(nbd)Cl]_2$. c) Determined by ^{1}H-NMR analysis.
d) Determined by HPLC analysis of the corresponding *N*-benzoyl derivative on Chiralcel OD (Daicel).

The results of the asymmetric hydrogenation of itaconic acid summarized in Table 2 show that (*R*)-MOC-BIMOP has as high catalytic activity and enantioselectivity as (*R*)-Cy-BIMOP does.

Table 2. Asymmetric Hydrogenation of Itaconic Acid



Ligand	Convn.[b] (%)	O.Y.[c] (%)
(*R*)-BINAP	100	-----
(*R*)-BIMOP	100	51 (*S*)
(*R*)-Cy-BIMOP	100	80 (*R*)
(*R*)- MOC-BIMOP	100	71 (*R*)

a) Rh^+-nbd: $[Rh(NBD)_2]ClO_4$ + Ligand ([Ligand]/[Rh]= 1.1).

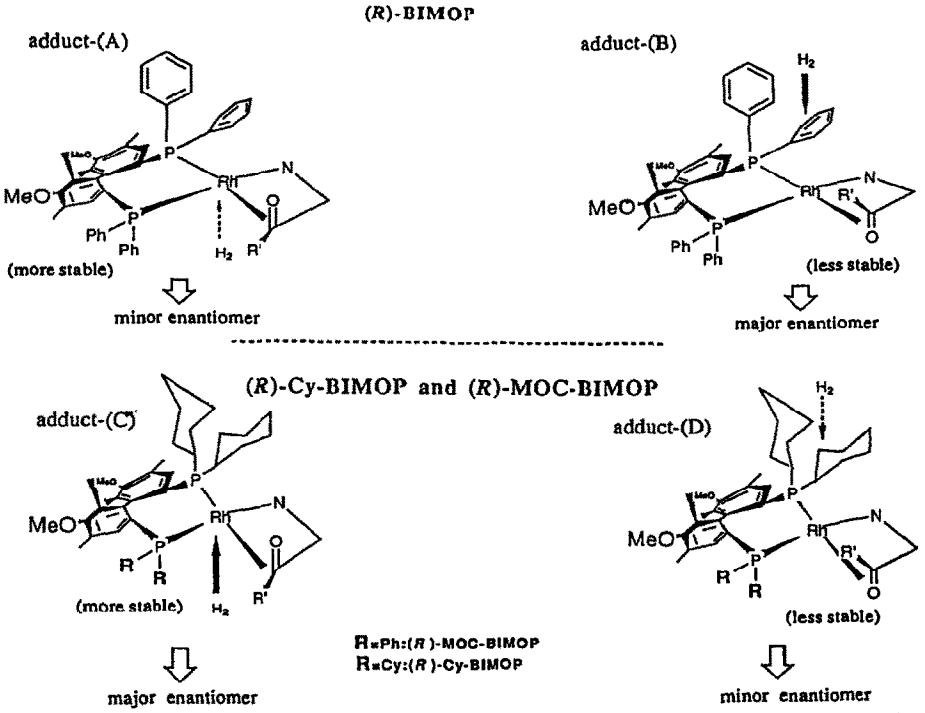
b) Determined by ^{1}H-NMR analysis. c) Calculated on the basis of the reported value $[\alpha]_D^{20}$ +16.88 (*c* 2.16, EtOH) for pure (*R*)-(+)-methylsuccinic acid (E. Berner and R. Leonerdsen, *Ann. Chem.*, 1939, **538**, 1.).

In addition, it is noteworthy that the direction of the enantioselection of (*R*)-Cy-BIMOP and (*R*)-MOC-BIMOP bearing one or two dicyclohexylphosphino group(s) was reversed to that of (*R*)-BIMOP in the hydrogenation of 2-aminoacetophenone hydrochloride. It can be explained by the mechanism described below. In the asymmetric hydrogenation catalyzed by typical bisphosphine-Rh(I) complexes, it is usually considered that the predominantly produced enantiomer is derived from the minor diastereomer (adduct-(B)) of the [Rh(ligand)substrate]$^+$ complex rather than the major one (adduct-(A)) because the minor (or the less stable) diastereomer has much higher reactivity toward H_2 than the major (or the more stable) one.[11] But in the asymmetric hydrogenation of 2-aminoacetophenone hydrochloride catalyzed by Rh(I) complexes of (*R*)-MOC-BIMOP and (*R*)-Cy-BIMOP bearing one or two dicyclohexylphosphino group(s), the major enantiomer of the product was the (*R*)-product derived from the more stable adduct-(C). In the case of (*R*)-MOC-BIMOP and (*R*)-Cy-BIMOP, it is considered that the transition state energy in the oxidative addition of the hydrogen molecule to the adduct-(D) from the upper apical side becomes more higher than that to the adduct-(C) from the down apical side because the oxidative addition of the hydrogen molecule from the upper apical side to the Rh atom is hindered by the Cy-group edged axially.[12] Therefore the (*R*)-enantiomer *via* the adduct-(C) in the case of 2-aminoacetophenone hydrochloride was predominantly derived in comparison with the (*S*)-enantiomer *via* the adduct-(D).

On the other hand, in the asymmetric hydrogenation of itaconic acid catalyzed by the Rh(I)-complex of (*R*)-BIMOP the major product was the (*S*)-enantiomer derived from the more stable adduct-(A). This result cannot be explained by the mechanism described in the asymmetric hydrogenation of α–aminoketone hydrochloride. It is likely that in the case of the ligands bearing two diphenylphosphino groups a dinuclear rhodium complex[13] formed *in situ* exhibits higher catalytic activity with different enantioselectivity than a mononuclear rhodium complex.

Thus, we have synthesized a new chiral ligand MOC-BIMOP, which is an efficient ligand in Rh(I)-catalyzed asymmetric hydrogenation of 2-aminoacetophenone hydrochloride. In addition, we presented the mechanism of our origin on the basis of the results in the asymmetric hydrogenations of α–aminoketone hydrochloride catalyzed by the Rh(I)-complexes of (*R*)-Cy-BIMOP and (*R*)-MOC-BIMOP bearing one or two dicyclohexylphosphino group(s).

Figure1. A Possible Mechanism in Asymmetric Hydrogenation of α-Aminoketone Hydrochloride



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12) ^{31}P-NMR analysis data of [Rh((*R*)-MOC-BIMOP)(nbd)]ClO_4 and [Rh((*R*)-FUPMOP)(nbd)]ClO_4 suggested that the interatomic distance of $P_1(Cy_2)$-Rh is shorter than that of $P_2(Ph_2)$-Rh and the P_1-P_2 distance of MOC-BIMOP (bearing a dicyclohexylphosphino group) is longer than that of FUPMOP (bearing diphenylphosphino groups). These results show that Cy_2-groups are sterically much more crowded than Ph_2-groups ; [Rh((*R*)-MOC-BIMOP)(nbd)]ClO_4: $J_{(Rh\text{-}P_1)}$=163.1Hz, $J_{(Rh\text{-}P_2)}$=142.1Hz, $J_{P_1\text{-}P_2}$=32.4 Hz ; [Rh((*R*)-FUPMOP)(nbd)]ClO_4: $J_{(Rh\text{-}P_1)}$=159.3 Hz (MOP), $J_{(Rh\text{-}P_2)}$=154.5 Hz (FUP), $J_{P_1\text{-}P_2}$=35.3 Hz.
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