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PREPARATION OF NEW CHIRAL PYRROLIDINEBISPHOSPHINES AS HIGHLY EFFECTIVE LIGANDS FOR CATALYTIC ASYMMETRIC SYNTHESIS OF *R*-(-)-PANTOLACTONE[1)]

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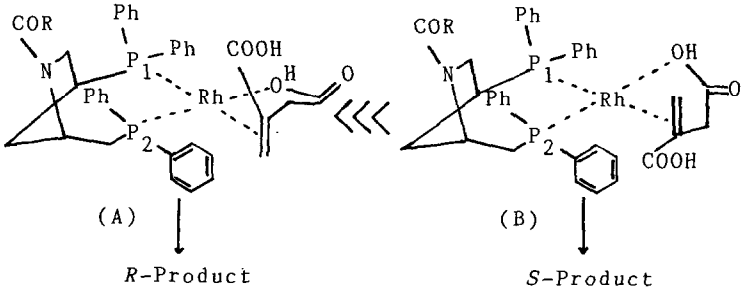
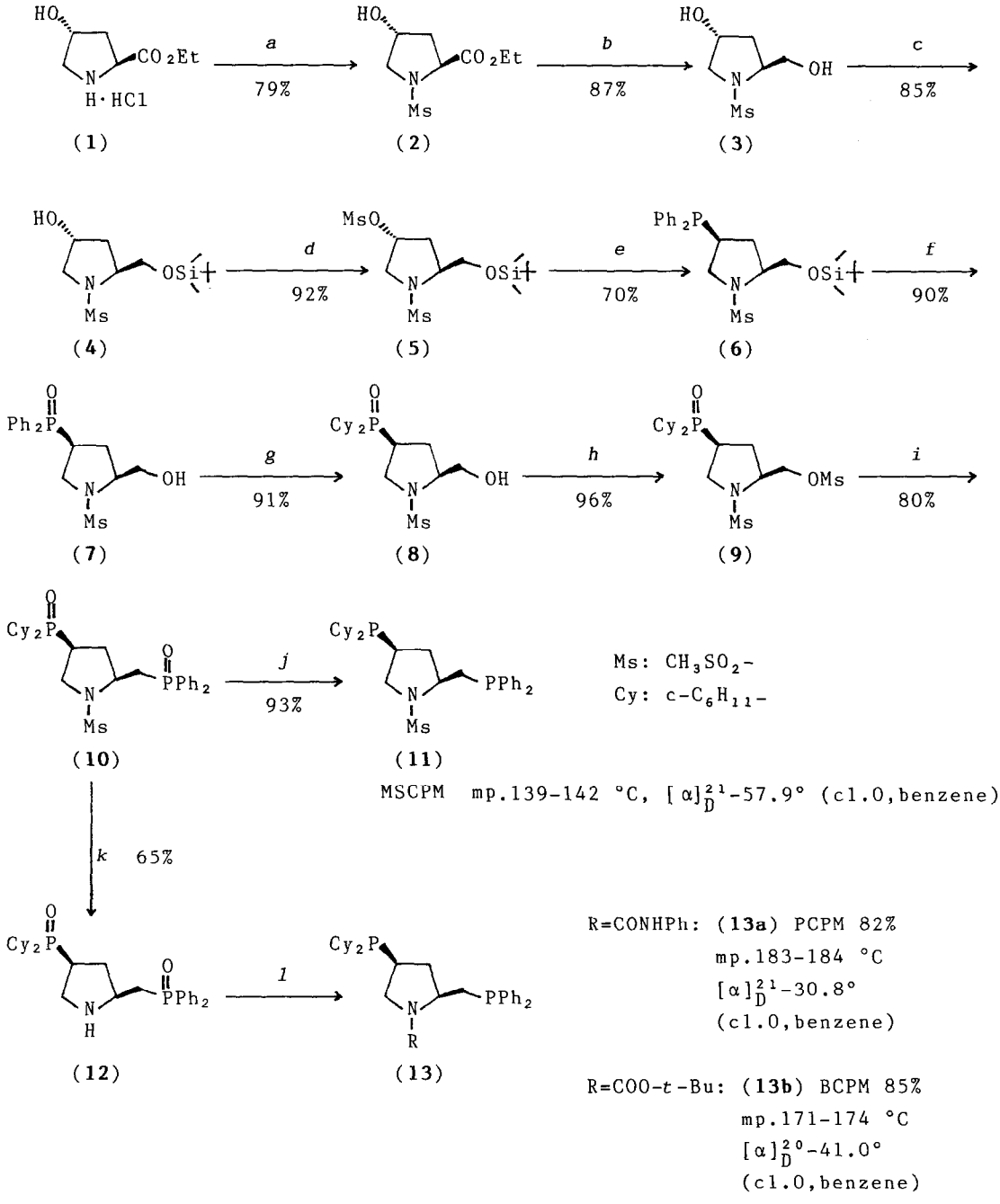
Abstract: New chiral pyrrolidinebisphosphines, MSCPM, PCPM and BCPM, were prepared. Among them, BCPM was found to be the most effective ligand for catalytic asymmetric synthesis of *R*-(-)-pantolactone.

Previously, we developed the chiral pyrrolidinebisphosphine named as BPPM which was found to be the most effective chiral ligand for catalytic asymmetric synthesis of α-amino acids, α-methylsuccinic acid, and *R*-(-)-pantolactone.[2)]

Furthermore, our studies on the mechanism of asymmetric hydrogenation of itaconic acid with BPPM-Rh^+ complex using ^{31}P-NMR spectroscopy indicated the intermediary key structure of BPPM-Rh^+-itaconic acid complex as shown in Fig.1, where the conformation of diphenyl groups substituted on the phosphine-2 played a more important role in determining the asymmetric induction than that on the phosphine-1.[3,4)]

Fig.1





Ms: CH_3SO_2-

Cy: c-C_6H_{11}-

MSCPM mp.139-142 °C, $[\alpha]_D^{21}$-57.9° (c1.0,benzene)

R=CONHPh: (**13a**) PCPM 82%
mp.183-184 °C
$[\alpha]_D^{21}$-30.8°
(c1.0,benzene)

R=COO-*t*-Bu: (**13b**) BCPM 85%
mp.171-174 °C
$[\alpha]_D^{20}$-41.0°
(c1.0,benzene)

Scheme 1. *Reagents*, *a*) MsCl *b*) $LiAlH_4$ *c*) TBDMSC *d*) MsCl *e*) Ph_2PNa *f*) 10% H_2O_2, 3% HCl-MeOH *g*) 5% Rh-Al_2O_3 *h*) MsCl *i*) Ph_2PNa *j*) $HSiCl_3$-NEt_3 *k*) 48% HBr-phenol *l*) $HSiCl_3$-NEt_3, PhNCO for (**13a**) or $(t\text{-BuOCO})_2O$ for (**13b**)

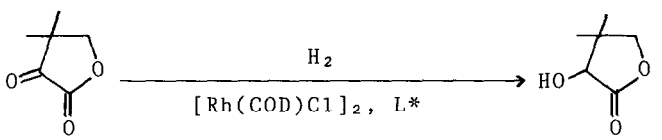
From these[2,3] and the other facts[5], we now prepared the (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]-pyrrolidine (BCPM) where dicyclohexyl groups on the phosphine-1 were expected to accelerate the reactivity and improve the optical yield of asymmetric hydrogenation of trans-coordinated carbonyl group, and also diphenyl groups on the phosphine-2 to keep the high stereoselectivity.

The chiral pyrrolidinebisphosphines, (2*S*,4*S*)-*N*-substituted-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidines (**11**,**13a**,**13b**), were synthesized from 4-hydroxy-L-proline ethyl ester hydrochloride (Scheme 1).

N-Protection of **1** with methanesulfonyl chloride was followed by reduction with $LiAlH_4$ in THF to produce a diol (**3**). After the selective protection of the primary alcohol with *tert*-butyldimethylsilyl chloride in THF, mesylation of the free alcohol and subsequent phosphination with sodium diphenylphosphide in dioxane-THF proceeded to give monophosphino compound (**6**). Oxidation of **6** with 10% hydrogen peroxide in MeOH and subsequent desilylation with 3% methanolic hydrogen chloride gave the phosphine oxide (**7**). The phosphinyl compound (**7**) was then hydrogenated in MeOH with hydrogen (150 atm) at 150 °C for 2 days over 5% $Rh-Al_2O_3$ to give the dicyclohexylphosphinyl compound (**8**). Mesylation of the primary alcohol of **8** followed by usual phosphination and oxidation gave the bisphosphinyl compound (**10**). Reduction of the phosphine oxide was achieved by refluxing with $HSiCl_3$-NEt_3 in CH_3CN under argon and followed by treatment with 30% NaOH. The resulting product was purified by recrystallization to give (2*S*,4*S*)-*N*-(methanesulfonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (MSCPM, **11**). The other *N*-substituted pyrrolidinebisphosphines were synthesized as follows. Demesylation of **10** was achieved by heating with 48% HBr and phenol[6] to give the free amine (**12**), which was then transformed into (2*S*,4*S*)-*N*-(phenylcarbamoyl)- and (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (PCPM **13a**, BCPM **13b**) by the reduction and subsequent reactions with phenylisocyanate and di-*tert*-butyl dicarbonate, respectively.[7]

Asymmetric hydrogenation of ketopantolactone was carried out with the substrate (5.0 mmol), $[Rh(COD)Cl]_2$ (2.5×10^{-2} mmol) and bisphosphine ligand (5.5×10^{-2} mmol) under hydrogen (50 atm) at 50 °C for 45 hr in THF (5 ml). The hydrogenation with [BCPM (**13b**)]/[Rh]/[substrate]=1.1/1.0/1000 was also examined (Scheme 2). Table 1 shows the optical yield and the configuration of the product.

Scheme 2



L*: bisphosphine

Table 1. Asymmetric Hydrogenation of Ketopantolactone.[a)]

ligands	[substrate]/[Rh]	conv. (%)[b)]	$[\alpha]_D$	opt. yield (%)[c)]	config.
MSCPM (**11**)	100	100	-33.6°	66.3	*R*
PCPM (**13a**)	100	100	-36.9°	72.8	*R*
BCPM (**13b**)	100	100	-46.6°	92.0	*R*
BCPM (**13b**)[d)]	100	100	-44.7°	88.2	*R*
BCPM (**13b**)	1000	100	-45.9°	90.5	*R*

a) All hydrogenations were carried out with [substrate]=1.0 M in THF unless otherwise noted. *b*) Determined by GLC analysis.
c) $[\alpha]_D^{25}$-50.7° (c2.05, H_2O).[8)] *d*) Solvent: benzene.

R-(-)-Pantolactone of very high optical purity was obtained when BCPM (**13b**) was used as a ligand. The stereoselectivity of over 91%-92% with [substrate]=1.0 M was achieved.

It should be emphasized that the present asymmetric hydrogenation catalyzed by BCPM-Rh proceeds smoothly with the high enatioselectivity (opt. yield >90.5%) at even a high substrate to catalyst ratio (1000 : 1).

Further investigations along this line are actively under way.

Referrences and Notes

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