CHEMISTRY LETTERS, pp. 2061-2064, 1986. 

# Synthesis of a New Chiral Pyrrolidine Ligand Bearing Two Different Types of Phosphino Groups and Their Effects on the Asymmetric Hydrogenation of Ketopantolactone[1)]

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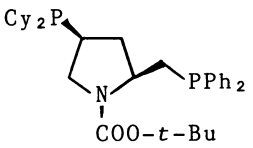
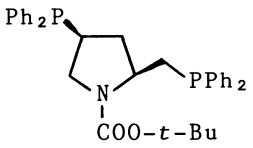
The respective functions of the two phosphino groups of the pyrrolidinebisphosphine ligands in the asymmetric hydrogenation of ketopantolactone were elucidated.

The new chiral ligand, (2*S*,4*S*)-*N*-(*t*-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine (BCPM, **1**) bearing the dicyclohexylphosphino group at the $C_4$ and the diphenylphosphinomethyl group at the $C_2$ position of the pyrrolidine ring was found to improve slightly the optical yield and dramatically the reaction rate as compared with BPPM ligand[2)] in the asymmetric hydrogenation of ketopantolactone.[3)] These results may indicate that the diphenylphosphino group oriented *cis* to the substrate carbonyl group plays an important role in determining the optical yield and the dicyclohexylphosphino group oriented *trans* to the carbonyl accelerates its hydrogenation rate.

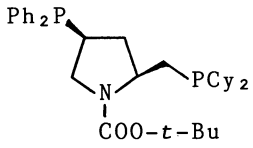
To confirm these conclusions, a new chiral pyrrolidinebisphosphine, (2*S*,4*S*)-*N*-(*t*-butoxycarbonyl)-2-[(dicyclohexylphosphino)methyl]-4-(diphenylphosphino)-pyrrolidine (BCPP, **3**) bearing the diphenylphosphino group located at the $C_4$-carbon and the dicyclohexylphosphinomethyl group situated on the $C_2$ of the pyrrolidine ring was synthesized and used for comparison with the related ligands, BPPM (**2**), BCPM (**1**), BCCP (**4**), in the asymmetric hydrogenation of ketopantolactone, the most conformationally rigid target of α-ketoesters. These results are listed in Scheme 1 and Table 1.



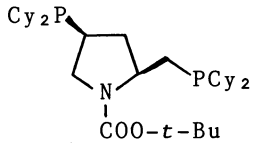

BCPM (**1**)



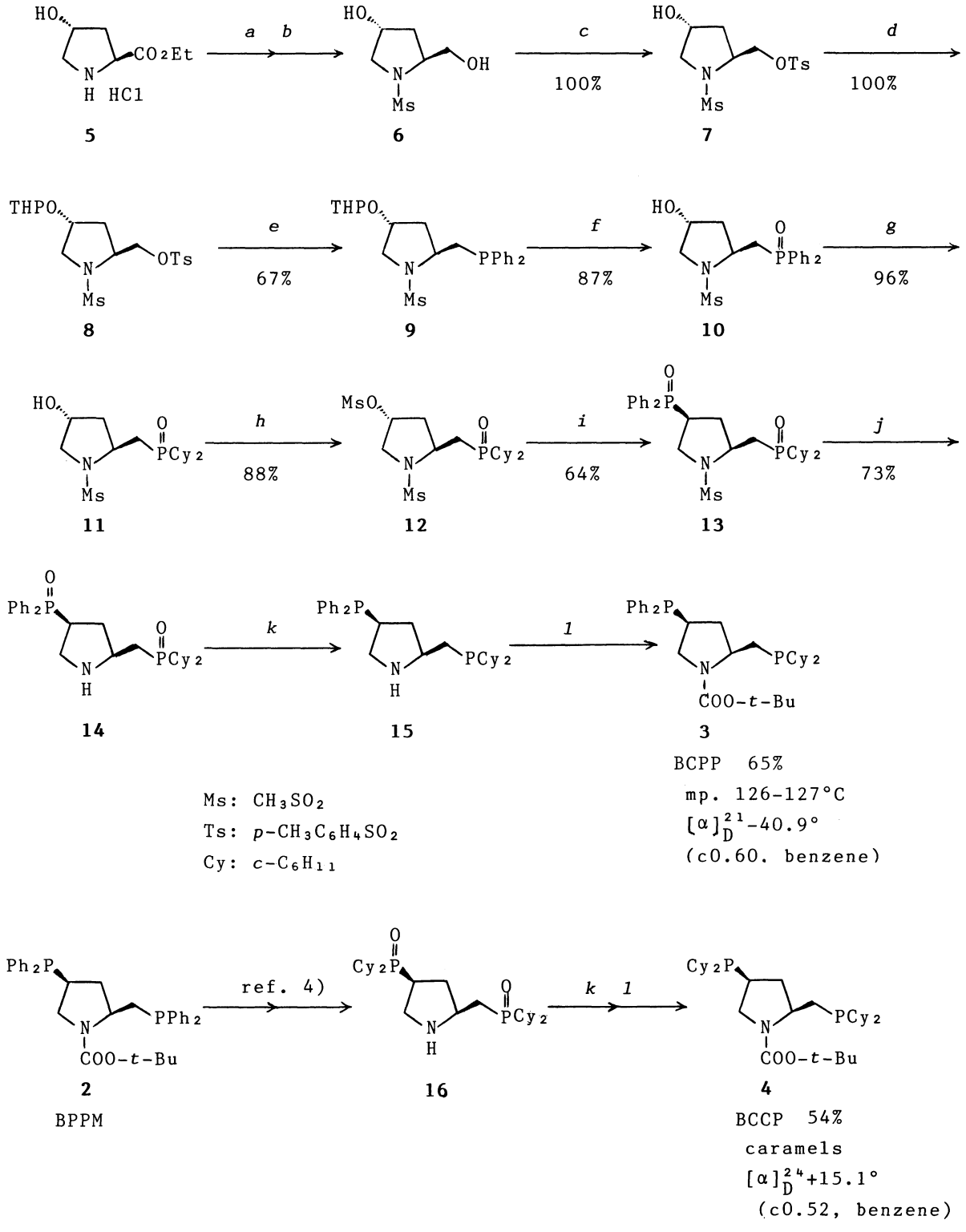

BPPM (**2**)




BCPP (**3**)




BCCP (**4**)

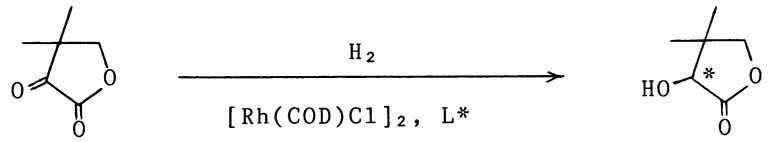



Scheme 1. *Reagents*, *a*) MsCl *b*) $LiAlH_4$ *c*) TsCl *d*) DHP *e*) $Ph_2PNa$ *f*) 10% $H_2O_2$, PTSA-MeOH *g*) 5% $Rh-Al_2O_3$ *h*)MsCl *i*) $Ph_2PNa$ *j*) 48% HBr-phenol *k*) $HSiCl_3-NEt_3$ *l*) $(t\text{-}BuOCO)_2O$

The chiral pyrrolidinebisphosphine, BCPP (**3**) was synthesized from 4-hydroxy-L-proline ethyl ester hydrochloride (**5**) as shown in Scheme 1. *N*-Protection of **5** with mesyl chloride followed by reduction with $LiAlH_4$ gave a diol (**6**).[3] Selective tosylation of the primary alcohol was carried out by the reaction with tosyl chloride in pyridine at -25 °C overnight. After the protection of the free alcohol with 2,3-dihydropyran (DHP) in the presence of *p*-toluensulfonic acid (PTSA), diphenylphosphination with sodium diphenylphosphide in dioxane-THF at room temperature gave a monophosphino compound (**9**). Oxidation of **9** with 10% $H_2O_2$ in MeOH and subsequent cleavage of the THP ether gave the phosphine oxide (**10**). The phosphinyl compound (**10**) was then hydrogenated in MeOH with hydrogen (150 atm) at 150 °C for 2 d over 5% Rh-$Al_2O_3$ to afford the dicyclohexylphosphinyl compound (**11**). Mesylation of the alcohol of **11** was followed by phosphination to give the phosphinophosphinyl compound, which was susceptible to oxidation and isolated as the bisphosphinyl compound (**13**). Demesylation of **13** by heating with 48% HBr and phenol followed by treatment with NaOH gave the free amine (**14**). Reduction of the phosphine oxide (**14**) was achieved by refluxing with $HSiCl_3$-$NEt_3$ in toluene under argon and subsequent treatment with 30% NaOH. The resulting bisphosphino compound (**15**) was converted to (2*S*,4*S*)-*N*-(*t*-butoxycarbonyl)-2-[(dicyclohexylphosphino)-methyl]-4-(diphenylphosphino)pyrrolidine (BCPP, **3**) by the reaction with di-*t*-butyl dicarbonate.

(2*S*,4*S*)-*N*-(*t*-Butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(dicyclohexyl-phosphino)methyl]pyrrolidine (BCCP, **4**) was prepared from BPPM (**2**) by the method reported previously.[4]

The asymmetric hydrogenation of ketopantolactone was carried out with the substrate (10 mmol), [Rh(1,5-cyclooctadiene)Cl]$_2$ ($0.5\times10^{-2}$ mmol), and bisphosphine ligand ($1.1\times10^{-2}$ mmol) under hydrogen (50 atm) at 50 °C for 45 h in THF (10 ml). For BCPM (**1**) and BCCP (**4**), the hydrogenation with [bisphosphine ligand]/[Rh]/[substrate]=1.3/1.0/$10^4$ was also examined. Table 1 shows the optical yield and the configuration of the product.




L*: bisphosphine

Scheme 2.

From the table, BPPM (**2**) and BCPM (**1**), the ligands which have the diphenylphosphinomethyl group on the $C_2$ position of the pyrrolidine ring gave the higher optical yields than BCPP (**3**) and BCCP (**4**), the ligands which bear the dicyclohexylphosphinomethyl group on the same $C_2$ position, and also BCPM (**1**) and BCCP (**4**), the ligands bearing the dicyclohexylphosphino group on the $C_4$ position accelerated more dramatically the hydrogenation rate of the carbonyl group (>$10^2$ times) than BPPM (**2**) and BCPP (**3**), the ligands having the diphenylphosphino group on the same

Table 1. Asymmetric Hydrogenation of Ketopantolactone [a)]

| Ligand | [Substrate]/[Rh] | Conv./%[b)] | Opt. yield/%[c)] | Config. |
|---|---|---|---|---|
| BPPM (**2**) | $10^2$ | 100 | 81[d)] | *R* |
| | $10^3$ | 44 | 72 | *R* |
| BCPM (**1**) | $10^3$ | 100 | 91[e)] | *R* |
| | $10^4$ | 100.0 | 90 | *R* |
| BCPP (**3**) | $10^3$ | 75 | 9 | *R* |
| BCCP (**4**) | $10^4$ | 100.0 | 61 | *S* |

*a*) All hydrogenations were carried out with [substrate] = 1.0 M in THF. *b*) Determined by GLC analysis. *c*) Calculated using $[\alpha]_D^{25}$ -50.7° (c2.05, $H_2O$)[5)] for pure *R*-(-)-pantolactone. *d*) Ref. 2*a*. *e*) Ref. 3.

$C_4$ position.

Marked different effects of the dicyclohexylphosphino groups at the $C_2$ positions between BCPP (**3**) and BCCP (**4**) on the optical yields (the *R*-product (9%) with **3** and the *S*-product (61%) with **4**) may be rationalized by the assumption that the conformation of the dicyclohexylphosphino group is more sensitive to that of the other phosphino group than the diphenylphosphino group of BPPM and BCPM.

These experimental findings that one phosphino group of the bisphosphine ligands controls selectively the chiral induction and the other accelerates the reaction rate may provide the new concept for the further development of extremely efficient chiral ligands in the catalytic asymmetric syntheses.

Further investigations along this line are actively under way.

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(Received September 22, 1986)