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SYNTHESIS AND APPLICATION OF A NOVEL BISPHOSPHINE LIGAND, (-)-DIOCP, AS AN UNSYMMETRIZED DIOP TO PROVE THE GENERAL UTILITY OF NEW DESIGNING CONCEPT.$^{1)}$

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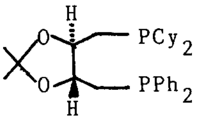
Abstract: A new chiral bisphosphine-Rh complex (DIOCP-Rh) was found to show excellent catalytic activity and good enantioselectivity for the asymmetric hydrogenation of ketopantolactone proving the general utility of new designing concept.

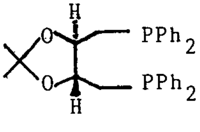
Previously, we have proposed a novel concept$^{2)}$ of developing the extremely efficient chiral ligands for the asymmetric hydrogenation and successfully realized the asymmetric synthesis of R-(-)-pantolactone in 90-92% ee with the high turnovers (10^{4-5}) from ketopantolactone catalyzed by a new chiral catalyst, BCPM-Rh complex.$^{3-5)}$

We wish to describe here a synthesis of a novel chiral ligand, [(4R,5R)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl(dicyclohexyl)-5-ylmethyl(diphenyl)]bisphosphine [(-)-DIOCP] (**1**), as an unsymmetrized (-)-DIOP (**2**), and its application to the asymmetric hydrogenation of ketopantolactone, the most conformationally rigid α-keto ester to prove the general utility of "Respective Control Concept" for designing the bisphosphine ligands which are highly effective for both reactivity and selectivity.$^{2)}$

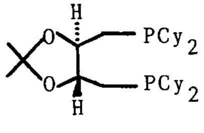
Recently, Tani$^{6)}$ and Yamamoto$^{7)}$ groups reported the synthesis of symmetric (-)-CyDIOP (**3**), the neutral rhodium complex of which showed excellent catalytic activity for the asymmetric hydrogenation of carbonyl compounds, especially α-keto ester derivertives, with lower optical yields than those catalyzed by an original DIOP-Rh complex.



(-)-DIOCP (**1**)



(-)-DIOP (**2**)

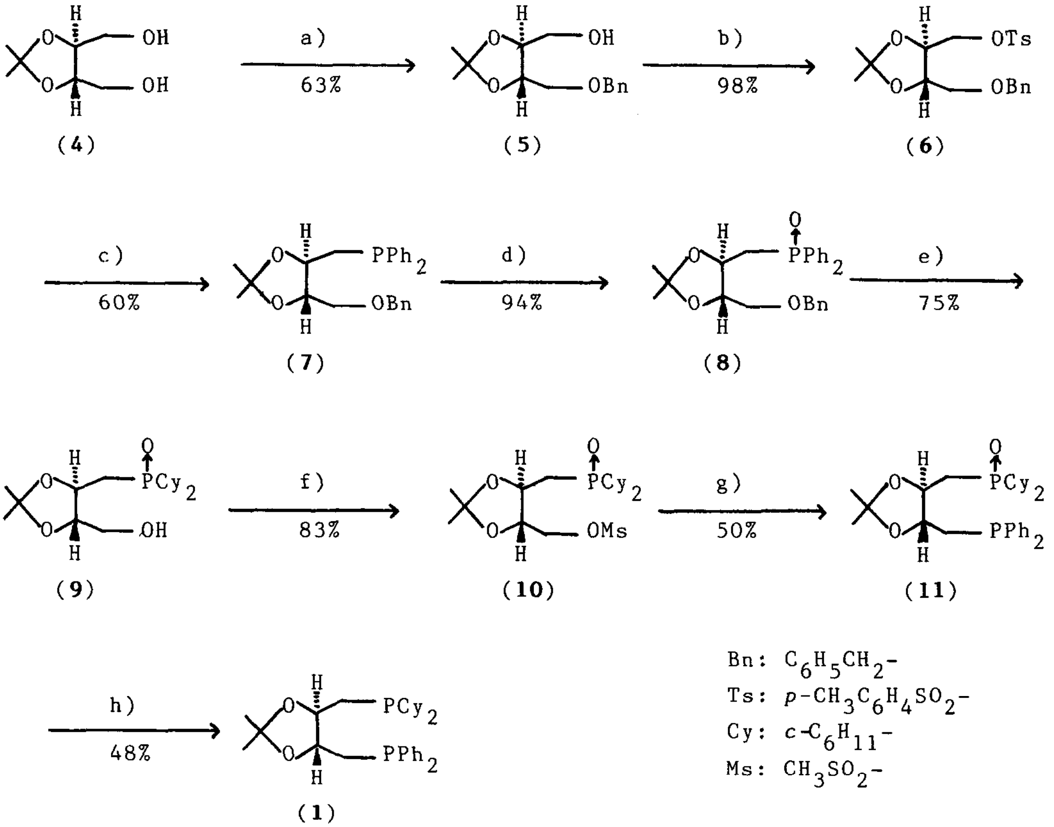


(-)-CyDIOP (**3**)

The new chiral bisphosphine ligand, (-)-DIOCP, was synthesized from 2,3-O-isopropylidene-L-threitol (**4**)[8] as shown in Scheme 1.

Selective benzylation of **4** with benzyl bromide in the presence of a phase transfer catalyst, tetrabutylammonium iodide (TBAI), gave the monobenzylated compound (**5**). The following tosylation of the free hydroxyl group of **5** was carried out with tosyl chloride in pyridine to afford **6**.[9] Phosphination with sodium diphenylphosphide in dioxane-THF proceeded to give the monophosphino compound (**7**).[9] Subsequent oxidation of **7** with 10% H_2O_2

Scheme 1



Bn: $C_6H_5CH_2$-
Ts: p-$CH_3C_6H_4SO_2$-
Cy: c-C_6H_{11}-
Ms: CH_3SO_2-

mp. 52.5-54 °C
$[\alpha]_D^{23}$ -24.1° (c0.80, benzene)

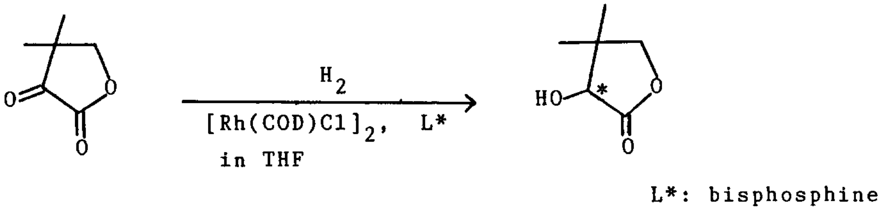
Reagents: a) NaH, $PhCH_2Br$, $Bu_4N{\cdot}I$/THF; b) TsCl/pyridine; c) Ph_2PNa/dioxane THF; d) 10% H_2O_2 aq./MeOH; e) Raney Ni (W-6)/EtOH; f) MsCl/pyridine; g) Ph_2PLi/THF; h) $HSiCl_3$-NEt_3/benzene.

aq. in MeOH gave the monophosphine oxide (**8**).9) Although several attempts to cleave the benzyl group of **8** by usual hydrogenolysis with Pd-C catalyst were unsuccessful, both debenzylation and hydrogenation of **8** were found to proceed smoothly by using Raney nickel catalyst at 70 °C for 24 hr to give the dicyclohexylphosphinyl compound (**9**).9) Mesylation of **9** with mesyl chloride in pyridine and subsequent phosphination of the mesylate (**10**)9) with lithium diphenylphosphide gave the phosphinyl compound (**11**).9) Reduction of the phosphine oxide (**11**) was achieved by refluxing with $HSiCl_3$-NEt_3 in benzene under argon followed by treatment with 30% NaOH aq. to give (-)-DIOCP (**1**).9)

Asymmetric hydrogenations of ketopantolactone were carried out with ketopantolactone (10 mmol) in THF (10 ml) under the conditions as described in Table 1.

The table clearly indicated that DIOCP-Rh ([sub]/[Rh]=10^3, 72% ee) showed stronger catalytic activity than DIOP-Rh ([sub]/[Rh]=10^2,) and better optical yields than DIOP-Rh (52% ee) and CyDIOP-Rh (45% ee7), under milder conditions). Although the rate enhancement (x10) of (-)-DIOCP compared to (-)-DIOP was considerably weaker than that (x10^2) of BCPM to BPPM, these facts may sufficiently suggest that the prochiral keto group orients selectively <u>trans</u> to the dicyclohexylphosphino group of (-)-DIOCP in the rate determining step, and also selectively <u>cis</u> to the diphenylphosphino group in the enantioselecting step.10) Therefore, as one of the possible mechanisms

Table 1. Asymmetric hydrogenations of ketopantolactone



ligands	[substrate]/[Rh]$^{a)}$	atm/°C/hr	conversion$^{b)}$ (%)	opt. yield (config.)$^{c)}$ (%)
(-)-DIOCP	10^3	50/50/45	100	72 (R)
(-)-DIOCP	10^3	15/50/70	100	75 (R)
(-)-DIOCP	10^4	50/50/45	67	57 (R)
(-)-DIOP	10^2	50/50/45	100	52 (R)
(-)-DIOP	10^3	50/50/45	45	37 (R)
(-)-CyDIOP$^{d)}$	50	15/rt/12	100	45 (R)

a) $[Rh(COD)Cl]_2$/bisphosphine molar ratio = 1 : 2.4 (COD:1,5-cyclooctadiene). *b)* Determined by GLC analysis. *c)* Calculated using $[\alpha]_D^{23}$ -50.7° (c 2.05, H_2O) for pure (R)-(-)-pantolactone. *d)* Ref. 7).

for the asymmetric hydrogenation of ketopantolactone catalyzed by bisphosphine-neutral rhodium complexes, the oxidative addition of hydrogen to the catalyst-substrate complexes[11)] seems to be the most important rate-determining and also enantioselecting step as similarly indicated by Halpern et al.[12)] for the asymmetric hydrogenation of α-acetaminocinnamic acid.

It should be noted that the respective control concept for designing highly effective chiral bisphosphine ligands has the general utility capable of improving even the C_2-symmetric bisphosphine ligands such as DIOP. Further investigations along this line are actively under way.

References and Notes

1) Asymmetric Reactions Catalyzed by Chiral Metal Complexes XXV.
2) "Respective Control Concept": One phosphino group of the bisphosphine ligands controls selectively the chiral induction and the other accelerates the reaction rate.
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9) Satisfactory analytical and spectral data were obtained for these compounds.
10) The asymmetric hydrogenation of methyl pyruvate catalyzed by DIOCP-Rh complex also proceeded faster than that by DIOP-Rh, and both reactions gave almost the same optical yield.
11) The clear effect of the hydrogen pressure on the optical yield of R-(-)-pantolactone was not observed.
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