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NEW ENTRY TO THE PREPARATION OF CHIRAL BIS(DICYCLOHEXYLPHOSPHINO)ALKANE DERIVATIVES. USE FOR RHODIUM-CATALYZED HYDROGENATION OF CARBONYL COMPOUNDS

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Conversion has been achieved of two representative chiral diphosphines, (-)-DIOP and (*S*,*S*)-Chiraphos, into the corresponding bis(dicyclohexylphosphino)alkane derivatives, the latter being used for chiral ligands of the rhodium(I) catalyst in the homogeneous hydrogenation of prochiral carbonyl compounds.

Although inefficiency of the Wilkinson catalyst for homogeneous hydrogenation of simple carbonyl compounds into alcohols has long been known, there are many studies of the reaction by means of chiral catalysis of ordinary rhodium(I)-chiral diphosphine combinations.[1] Such hydrogenation, in fact, seems to rely on the high susceptibility of the specific carbonyl compounds examined to an activation by the catalyst. While an early study by Schrock and Osborn[2] has indicated that cationic rhodium complexes, which contain more basic phosphine such as $PPhMe_2$, do catalyze hydrogenation of acetone into isopropyl alcohol under ambient conditions.

Recently, Tani, Otsuka, et al.,[3] have reported that cationic Rh(I) complex of a cis-chelate bis(diisopropylphosphino)propane (and butane) show excellent catalytic activity for the hydrogenation of carbonyl compounds, and extended this finding to the asymmetric catalysis by using chiral basic diphosphines.[4]

Interested in the asymmetric hydrogenation of prochiral α-keto amides which are obtained by a palladium-catalyzed double carbonylation reactions,[5] we initiated studies on the conversion of commercially available (*R*,*R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane [(-)-DIOP] into the corresponding cyclohexyl analog [(-)-CyDIOP].[4] Our approach is outlined in Scheme 1.

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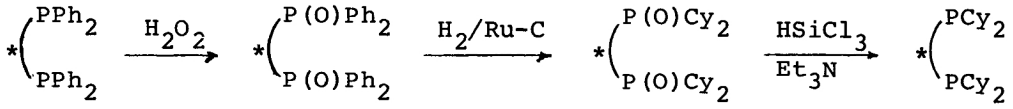


Scheme 1. (Cy = cyclohexyl)

We assumed that, once this approach be in hand, we may prepare a variety of cyclohexylated analogs of known chiral diphosphines mostly used for ligands in the asymmetric hydrogenation of dehydroamino acids.[6)]

(-)-DIOP (1.00 g, 2.0 mmol) was quantitatively oxidized with 30% H_2O_2 (0.5 mL) in acetone (20 mL) to give (-)-DIOP-oxide, $[\alpha]_D$ +14.9° (*c* 2, $CHCl_3$). Catalytic hydrogenation of diphenylphosphinyl groups was found to be rather sluggish.[7)] As a model reaction, hydrogenation of bis(diphenylphosphinyl)ethane (Diphos-oxide) with PtO_2, 5% Rh-C, and 5% Ru-C in methanol[8)] was carried out at 150 °C and 20 kg/cm^2 of hydrogen pressure for three days to give Cydiphos-oxide in 8.7, 12.5, and 99% yield, respectively. Although 5% Ru-C was most effective in this particular hydrogenation, hydrogen pressure exhibited marked effect on the hydrogenation of Diphos-oxide. Thus, under optimal conditions where the acetonide protecting group in the case of (-)-DIOP-oxide was confirmed to be intact, the catalytic hydrogenation proceeded smoothly at 70 kg/cm^2 at room temperature in 2 days. The following procedure is typical; (-)-DIOP-oxide (265 mg, 0.5 mmol) was dissolved in dry methanol (8 mL) and the solution was placed in a 50-mL micro autoclave. Ru-C (5%, 120 mg)[9)] was added to the solution. The hydrogenation was carried out at room temperature at 70 kg/cm^2 of initial hydrogen pressure for 48 h. After usual work-up there was obtained white powder of (-)-CyDIOP-oxide (272 mg, 98% yield), $[\alpha]_D$ -4.11° (*c* 0.5, PhH). ^{1}H NMR (90 MHz, $CDCl_3$) δ1.27(br centered, 20H), 1.39(s, 6H), 1.85(br centered, 24H), 2.35(br, 4H), and 4.08 ppm(m, 2H).

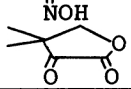
Chemical reduction of the phosphine oxide was also a crucial step. Attempted LAH reduction was inefficient but hydrosilane reduction[10)] was found satisfactory. (-)-CyDIOP-oxide (130 mg, 0.23 mmol) was suspended in a mixture of Et_3N (0.32 mL) and dry benzene (3 mL) under an argon atmosphere. To the mixture was added $HSiCl_3$ (0.23 mL) by a syringe, and the whole mixture was heated at 90 °C for 2 h with stirring. The oxide gradually dissolved and greasy materials formed. The reaction mixture was cooled and hydrolyzed with degassed 25% NaOH (4 mL). The organic layer was extracted with CH_2Cl_2 (3 × 10 mL) and the extracts were dried ($MgSO_4$). After evaporation of the solvent, a crude oil (120 mg) was treated with distilled CS_2 (3 mL) to give a deep red solution. The filtered solution was condensed to dryness to

leave pale brown crystals. The latter was decomposed in refluxing ethanol (2 mL) to give white solid (95 mg, 79% yield) of free CyDIOP, $[\alpha]_D$ -22.8° (*c* 0.90, PhH), optical purity being 94.6%.[4] ^{1}H NMR δ1.38(s, acetonide) and 3.81(m, methyne).

The same procedure could be applied to the preparation of Cy-chiraphos from (*S*,*S*)-2,3-bis(diphenylphosphino)butane (Chiraphos) as in the case of CyDIOP except that the hydrogenation was carried out at 80 kg/cm^2 of initial hydrogen pressure at 120 °C for 5 days. Cy-chiraphos,[11] $[\alpha]_D$ +17.0° (*c* 0.20, $CHCl_3$). ^{1}H NMR δ0.78-2.24(br m, Cy + Me, 50H) and 2.80(m, 2H).

Asymmetric hydrogenation of some α-keto amides and esters was examined. The following is the general procedure for hydrogenation; As a catalyst precursor neutral rhodium complex prepared in situ from 1/2[Rh(cod)Cl]$_2$ and CyDIOP (2×10^{-2} mmol each) was dissolved in degassed benzene-ethanol (3:1, 6 mL) ([Rh] = 3.3 mM). The catalyst in a micro autoclave was prehydrogenated by stirring for 1 h at room temperature under hydrogen (20 kg/cm^2). To this solution was added a given carbonyl compound (1.0 mmol, [substrate]/[Rh] = 50) and the mixture was stirred overnight at room temperature under hydrogen pressure (15 kg/cm^2). The complete conversion of the reaction was checked by GLC analysis, and the product was purified either by column chromatography or by distillation to determine optical yield. All results obtained are summarized in Table 1.

Table 1. Asymmetric Hydrogenation of Some α-Keto Carbonyl Compounds Catalyzed by Rh-CyDIOP

Run	Compound	Time / h	Yield[a] / %	$[\alpha]_D$/° (*c*, solvent)	Opt. yield[b] (% ee) (Confgn)
1	$PhCOCONHCH_2Ph$	12	72	+53.6 (0.82, $CHCl_3$)	71 (*S*)[c]
2	$PhCOCONHCH_2Ph$[d]	12	55	+30.4 (0.23, $CHCl_3$)	38 (*S*)
3	$PhCOCONEt_2$	36	—		
4	$PhCOCO_2Me$	12	63	-24.4 (0.53, AcMe)	21 (*R*)[e]
5	$PhCOCO_2Bu$-*t*	36	—		
6	Ph-C(=NOH)-CONHCH$_2$Ph	12	50	-29.0 (0.70, $CHCl_3$)	
7		12	69	-21.2 (0.30, H O)	45 (*R*)[f]

a) Isolated yield. b) Based on CyDIOP as 100% ee. c) See Ref. 12, optical yield was reported to be 77%. d) Rh-Cy-chiraphos as catalyst. e) Beilstein, 10 EIII, 454. f) See Ref. 1b.

Hydrogenation of *N*-benzylphenylglyoxylamide proceeded readily to yield (+)-(*S*)-*N*-benzylmandelamide with an optical yield 71% (Run 1), comparable to that reported by Tani and Otsuka, et al.[12] Methyl phenylglyoxylate also underwent hydrogenation smoothly, giving (-)-(*R*)-methyl mandelate with inferior enantioface selection (Run

4). It should be mentioned that no hydrogenation was observed under the present conditions with both *N,N*-diethyl amide and *t*-butyl ester presumably due to a strict steric influence. Finally, pantolactone was obtained with moderate optical yield (Run 7). No maximum rotation of phenylglycine amide has so far been given (Run 6).

In conclusion, a new method of preparation of CyDIOP by a simple three-step procedure as depicted in Scheme 1 is shown to be of significant use. In the same way, preparation of a cyclohexyl analog of CAPP[1b] has recently been presented.[13]

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