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Synthesis of (1R, 1R')-2,6-Bis[1-(diphenylphosphino)ethyl]pyridine and its Application in Asymmetric Transfer Hydrogenation

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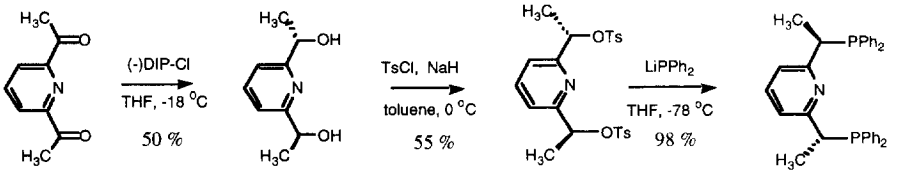
Abstract: *A C_2 symmetric tridentate ligand, (1R, 1R') 2,6-Bis[1-(diphenylphosphino)ethyl]pyridine, has been synthesized in enantiomerically pure form. A practical method to synthesize a variety of chiral pyridyl diols is reported. Asymmetric transfer hydrogenation is achieved using the tridentate ligand.*

A wide range of known chiral bidentate ligands with C_2 symmetry have been successfully used in asymmetric catalytic reactions.[1] While tridentate ligands can also be used in homogeneous catalysis,[2] it is surprising that C_2 symmetric chiral tridentate ligands have only very recently attracted attention for applications in this area. One family of C_2 symmetric tridentate ligands bearing three sp^2 nitrogens [chiral bis(oxazolinyl)pyridine[3] and bis(pyrazolyl)pyridine[4]] has been developed for asymmetric catalysis. Ru, Rh and Cu complexes of these ligands have been successfully employed in asymmetric hydrosilylation,[3] cyclopropanation[4,5] and Diels-Alder reactions.[6] A chiral pyridyl diol has been prepared for asymmetric epoxidation.[7] C_2 symmetric chiral tridentate ligands with two phosphines and a sp^2 carbon were recently used in an asymmetric aldol reaction.[8] Other pseudo C_2 symmetric chiral tridentate ligands with three phosphines, two phosphines and one nitrogen, or one nitrogen and two oxygens were also prepared and used to facilitate asymmetric reactions.[9] Herein, we report the synthesis of a novel C_2 symmetric tridentate ligand - (1R, 1R')-2,6-bis[1-(diphenylphosphino)ethyl]pyridine (**4**) (Figure 1).

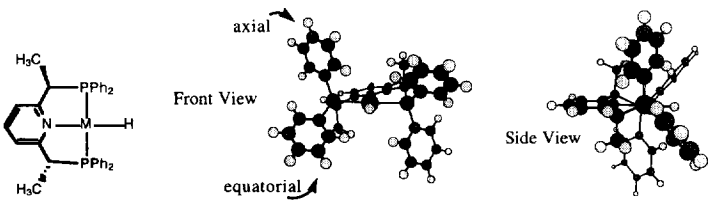


1 2 3 4

Figure 1

This ligand **4** has two chiral phosphine groups which can adopt trans positions in a transition metal complex and a pyridine nitrogen atom in the center. Such a ligand could bind metals in a planar geometry and create a well defined C_2 symmetric chiral environment. Figure 2 shows the possible orientations of the phenyl groups of this ligand in a transition metal complex based on calculations using a CAChe program. Two equatorial phenyl groups protrude into the P-M-P "in-plane" coordination site and two axial phenyls stay back. This calculated structure is in a good agreement with the crystal structure of metal complexes with a similar ligand {racemic 2,6-bis[1-(diphenylphosphino)ethyl]phenyl} reported by Venanzi.[10] In an octahedral coordination environment, transition metal complexes with this tridentate ligand should adopt a *meridional* geometry since the pyridine nitrogen can not effectively bind with the metal in the alternative *facial* coordination.

Figure 2



The key step in the synthesis of the tridentate ligand **4** is generation of the optically pure chiral pyridyl diol **2**. Although this diol **2** has been made through reduction of 2,6-diacetylpyridine **1** with baker's yeast,[11] we found that asymmetric reduction using Brown's chiral borane reagent (DIP-Cl) is more desirable on a laboratory scale.[12] GC analysis indicated that the (S, S) chiral diol **2** can be prepared in >98 % ee along with 5-10% meso (R, S) diol.[13] The meso diol can be removed by column chromatography. Alternatively, recrystallization of the corresponding di-p-bromobenzoate ester of the diol mixture can remove the meso compound and enrich the enantiomeric purity of the diol **2** to more than 99.9% ee.[11] Conversion of this pyridyl diol **2** to the ditosylate **3** was done using NaH in toluene. HPLC analysis showed that the enantiomeric purity of the diol **2** remained the same after this transformation.[14] Addition of $LiPPh_2$ to the ditosylate **3** gave the tridentate ligand **4** with complete inversion of configuration.[15]

In order to synthesize this ligand and other related tridentate ligands on a large scale, we have investigated several methods to prepare the starting 2,6-diketopyridines. Figure 3 demonstrates a practical method for the synthesis of various 2,6-diketopyridines through the coupling of 2,6-pyridinedicarboxylic acid chloride **6** with cuprate reagents. Multigram amounts (e.g., 50 g) of diketopyridines can be easily obtained through this reaction. Combination of this efficient ketone formation with the asymmetric reduction is useful for the practical synthesis of many chiral pyridyl diols. A recent synthesis of **8** through the highly enantioselective reduction (100 % ee) of diketone **7** using (-) DIP-Cl as the reducing agent has been reported.[16] However, the preparation of **7** required two low yielding steps (coupling between 2,6-dibromopyridine and ^tBuCHO followed by Jones oxidation). Our procedure for the synthesis of **7** was proceeded in high yield (82%) with the cheap starting material, diacid chloride **6**. In an analogous manner as described by a literature procedure,[17] chiral pyridyl diol **8** was made by us with 100% ee.[13]

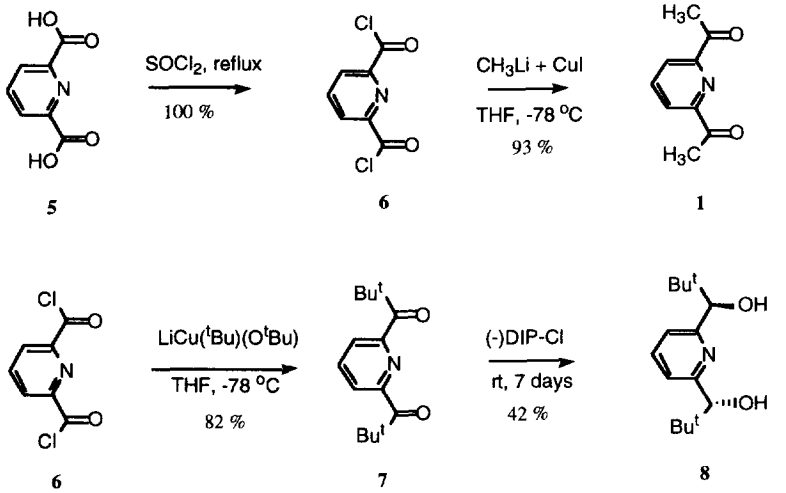
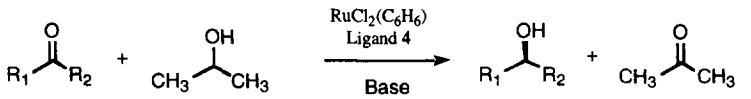
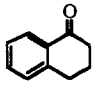
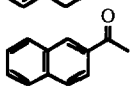
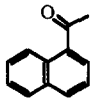


Figure 3

Studies on the application of this new C_2 symmetric tridentate ligand **4** in a variety of asymmetric reactions are in progress. Herein we report results of asymmetric transfer hydrogenation of aromatic ketones catalyzed by chiral ruthenium (II) complexes (Table 1). Transition metal complexes with chiral phosphorus and nitrogen ligands have been used to promote asymmetric transfer hydrogenation.[18, 19] Chelating bidentate diphosphines are not effective ligands for asymmetric transfer hydrogenation of simple aromatic ketones (20 to 80% conversion, 1.5 to 34 % ee).[19a,b] Using $RuCl_2(C_6H_6)$ as a precursor with tridentate ligand **4**, the asymmetric transfer hydrogenation is more effective (33 % to 98 % conversion, 30 to 74 % ee) than many bidentate phosphine systems. Although the enantioselectivity in this system is moderate, fine-tuning of the ligand's steric and electronic properties could lead to development of a promising new reagent for asymmetric transfer hydrogenation.

Table 1. Ruthenium-catalyzed Asymmetric Transfer Hydrogenation[a]



Substrate	Base	Base Equiv	Time (h)	Yield (%)	ee (%)[c]
	NaOMe	5	24	91	35 (R)
	NaOMe	5	24	67	48 (R)[b]
	NaH	10	24	93	40 (R)
	NaOMe	25	24	33	74 (R)
	NaOMe	25	24	92	42 (R)
	NaOMe	25	24	98	30 (R)

a.The reaction was carried out at room temperature using 2 M solution of a ketone (200 mmol) in 10 mL of 2-propanol; substrate /catatyst = 100:1. b. the reaction was performed in 40 mL of 2-propanol. c. ee% was measured by G. C. with a β cyclodextrin column.

Acknowledgments

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13 Enantioselectivities were determined by G.C. with a SUPELCO β-DEX^{TM} column, 30 m x 0.25 mm.

14. Enantioselectivities were determined by HPLC using a CHIRALCEL OD column with hexane/isopropanol (90:10).

15. NMR data for compound **4**: ^{1}HNMR ($CDCl_3$) δ 7.70-7.55 (m, 4H), 7.50 -7.35 (m, 6H), 7.31 (t, J = 7.7 Hz, 1H), 7.25-7.05 (m, 10H), 7.31 (t, J = 7.7 Hz, 2H), 7.25-7.05 (m, 10H), 6.95 (d, J = 7.7 Hz, 2H), 3.76 (dd, J = 6.9 Hz and 7.1 Hz, 2H), 1.37 (dd, J = 14.7 Hz and 7.1 Hz, 6H); ^{13}CNMR ($CDCl_3$) δ 162.4, 137.4, 137.2, 136.2, 134.0, 133.0, 128.9, 128.2, 127.9, 127.7, 119.8, 41.4, 18.9; ^{31}P NMR ($CDCl_3$) δ 1.6.

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