New Chiral Diphosphine Ligands Designed to Have a Narrow Dihedral Angle in the Biaryl Backbone

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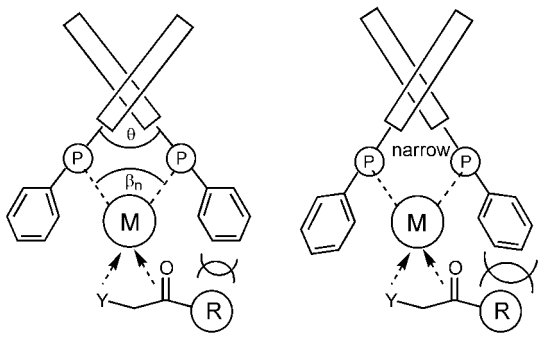
Abstract: A series of novel optically active diphosphine ligands, (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diarylphosphine)s (**6**), which are called SEGPHOS, has been designed and synthesized with dihedral angles in the Ru complexes being less than that in the corresponding BINAP-Ru complex. The stereorecognition abilities of SEGPHOS-Ru complex catalysts in the asymmetric catalytic hydrogenation of a wide variety of carbonyl compounds are superior to those observed with BINAP-Ru complex catalysts.

Keywords: asymmetric catalysis; homogeneous catalysis; hydrogenation; P ligands, ruthenium

In asymmetric catalysis using chiral transition-metal complexes, binaphthyl or biphenyl groups have often been used as chiral scaffolds to produce an excellent asymmetric environment.[1] Among these ligands with chiral binaphthyl or biphenyl bridges, the most representative example is the C_2 symmetric 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (**1**).[2] Changes in the steric and/or electronic properties of the ligands are known to dramatically influence the selectivity and the reactivity of transition-metal complexes. The framework of chiral ligands not only sways the enantioselectivity but can also remarkably change the reactivities of the metal complexes. During the course of our research on the development of chiral diphosphine ligands, we were interested to see if varying the dihedral angle of the chiral backbone would have an effect on the enantioselectivity of asymmetric hydrogenation. Additionally, in spite of a sparsity of information in the literature concerning the mechanism of the asymmetric control, one of the predominant factors could be the dihedral angle in the chiral backbone. This correlates to the natural bite angle in metal complexes.[3] The dihedral angles of the binaphthyl or biphenyl systems are expected to exert influence on the effect of the steric bulk of the diphenylphosphino group as illustrated in Figure 1. This working hypothesis is based on steric considerations and does not consider the electronic properties of the complex, or the metal's valence.

Additionally, the following experimental results support our working hypothesis. Thus, the enantioselectivities in the hydrogenation of 2-oxo-1-propanol (**2a**) to (2*R*)-1,2-propanediol (**3a**) are influenced re-



β_n: Natural bite angle
θ: Dihedral angle

Figure 1. Steric considerations based on the effect of varying the dihedral angle (θ) in biaryl backbone.

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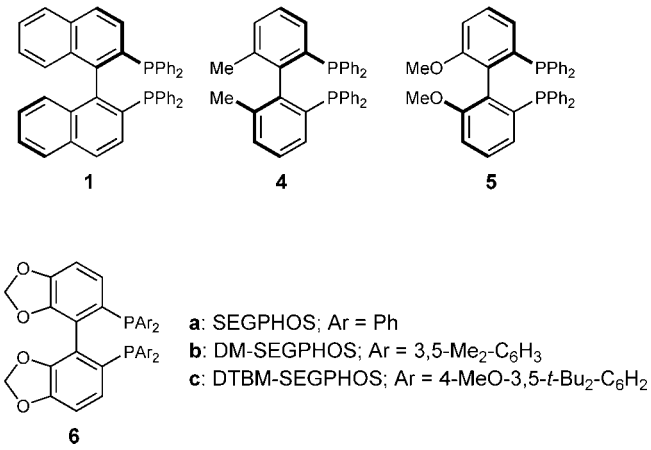


Figure 2. Structures of ligands **1**, **4**, **5**, and **6**.

markably by the choice of ligand, and increase in the following order: BINAP **1** (89.0% ee), BIPHEMP **4** (92.5% ee), and MeO-BIPHEP **5** (96.0% ee) (Figure 2). As estimated by a CAChe MM2 calculation, the selectivities are lineally related to the dihedral angles in the Ru-complexes of these ligands: BINAP (73.49°), BIPHEMP (72.07°), MeO-BIPHEP (68.56°). In order to produce new diphosphine ligands with a narrower dihedral angle than BINAP, we used the bi-1,3-benzodioxole system as the chiral framework, because the methylenedioxy moiety could be considered to be less sterically hindered. Thus, we have designed and synthesized novel optically active diphosphine ligands, (4,4′-bi-1,3-benzodioxole)-5,5′-diyl-bis(diarylphosphine)s (**6a–c**; Figure 2), which are called SEGPHOS. Estimation of the dihedral angle of the atropisomeric bi-1,3-benzodioxole system in SEGPHOS **6a**–Ru complex using molecular mechanics calculations gave a result of 64.99°.

The preparation of these diphosphines was achieved using the oxidative homo-coupling of 5-diarylphosphinyl-1,3-benzodioxoles at the C4 position as the key reaction.[4] The synthesis of SEGPHOS **6a** is shown in Scheme 1; ligands **6b** and **6c** can be also prepared by a similar coupling reaction.

The absolute configuration of (+)-**8** was determined by X-ray analysis of the complex of (+)-**8** with (2*S*,3*S*)-(+)-*O*,*O*′-dibenzoyltartaric acid [(+)-DBT]. From the internal comparison with (+)-DBT, the absolute configuration of (+)-SEGPHOSO is defined to be *R*. The X-ray structure analysis revealed that the dihedral angle θ between the least-square planes through the two 1,3-benzodioxole rings is 71.65° [in the 1 : 1 complex of (*S*)-Cy-BINAPO and (–)-DBT, the dihedral angle of the two naphthalene rings is 79.4°].[5]

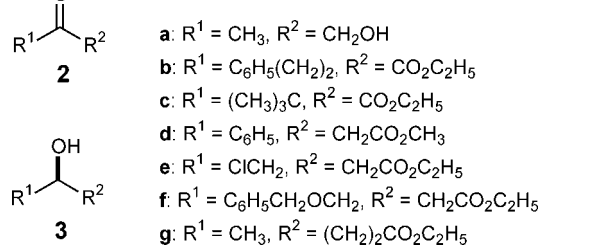
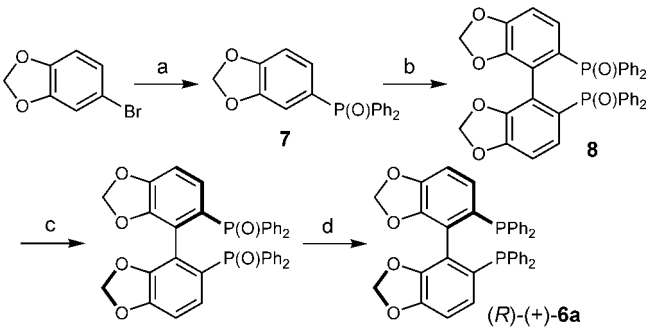


Figure 3. Ketone substrates **2** and hydrogenation products **3**.



Scheme 1. Synthesis of the (*R*)-(+)-SEGPHOS ligand.

The application of the present ligands to Ru-catalyzed hydrogenations has led to an exceptionally active and highly enantioselective catalytic system. These SEGPHOS–Ru(II) complex catalysts are widely applicable for the hydrogenation of a wide range of ketonic substrates as shown in Figure 3 and Table 1.

Table 1. Hydrogenation of ketone compounds **2** using the (*R*)-SEGPHOS-Ru(II) complex as catalyst.[a]

Compound	S/C	H_2 (kg/cm^2)	Solvent	Temperature (°C)	Time (h)	Conversion (%)	% ee
2a	3,000	30	methanol	65	7	100	99.5
2a	10,000	30	methanol	65	7	100	98.5
2b	1,500	50	ethanol	50	17	100	93.7
2c	1,000	50	ethanol	70	17	99	98.6
2d	10,000	30	methanol	80	6	100	97.6
2e	2,500	30	ethanol	90	2	100	98.5
2f	10,000	10	ethanol	95	8	100	99.4
2g	1,000	50	ethanol	50	20	100	99.0

[a] $[NH_2Me_2][\{RuCl[(R)\text{-segphos}]\}_2(\mu\text{-}Cl)_3]$ was used as a catalyst.

Firstly, the excellent chiral recognition ability of a (*R*)-SEGPHOS–Ru(II) complex catalyst can be demonstrated by the hydrogenation of **2a** to afford (2*R*)-**3a** in 98.5% ee and with a substrate-to-catalyst ratio of up to 10,000. Using the (*R*)-Tol-BINAP–Ru(II) complex catalyst, this process is now industrially operating at 89% ee and with a 3,000 to 1 substrate-to-catalyst ratio.[6] Hydrogenation of α-keto esters catalyzed by a SEGPHOS–Ru(II) complex was also achieved with a high enantioselectivity. The hydrogenation of α-keto ester **2b** in the presence of the (*R*)-SEGPHOS–Ru(II) complex catalyst gives (2*R*)-ethyl 4-phenyl-2-hydroxybutanoate (**3b**) in 93.7% ee. When the (*R*)-BINAP–Ru(II) complex catalyst was used for this hydrogenation, the enantioselectivity decreased to 90.0% ee. Since BINAP–Ru(II) complexes have been recognized to be generally efficient catalysts for the hydrogenation of the β-keto esters, the enantioselectivity in the hydrogenation of methyl 3-oxo-3-phenylpropionate (**2d**) with the BINAP–Ru(II) complex was disappointingly low, giving (3*R*)-methyl 3-hydroxy-3-phenylpropionate (**3d**) with 87.0% ee (cf., MeO-BIPHEP, 93.5% ee).[7] When the (*R*)-SEGPHOS–Ru(II) complex catalyst was employed for this hydrogenation, the enantioselectivity rose to 97.6% ee. In the case of the hydrogenation of a β-keto ester containing a heteroatom at the γ-position, the enantioselectivity is not sufficient with BINAP because the coordination abilities of the heteroatom and the carbonyl group of the ester are competitive. The pronounced selectivity and activity of the (*R*)-SEGPHOS–Ru(II) complex catalyst can be shown by the hydrogenation of ethyl 4-chloro-3-oxobutanoate (**2e**) to afford (3*R*)-ethyl 4-chloro-3-hydroxybutanoate (**3e**) in 98.5% ee at 90 °C and 30 kg/cm^2 in only 2 h with 100% conversion (cf., BINAP, 95.9% ee).[8] Furthermore, in the case of the hydrogenation of ethyl 4-benzyloxy-3-oxobutanoate (**2f**), the enantioselectivity of (*R*)-**3f** (99.4% ee) with the (*R*)-SEGPHOS–Ru(II) catalyst is higher than that obtained with the (*R*)-Tol-BINAP–Ru(II) catalyst (97.4% ee). In order to investigate the efficiency and further applicability of the SEGPHOS ligand, we attempted to hydrogenate γ-keto esters. Hydrogenation of ethyl levulinate (**2g**) can be performed with the (*R*)-SEGPHOS–Ru(II) catalyst to give (*R*)-ethyl 4-hydroxypentanoate (**3g**) with up to 99% ee.[9]

Next, a dramatic improvement in diastereoselection was observed in the hydrogenation of α-substituted β-keto esters along with a high enantioselectivity by employing the (–)-DTBM-SEGPHOS **6c**–Ru(II) complex catalyst. Thus, the hydrogenation of methyl 2-benzamidomethyl-3-oxobutanoate (**9**) with a (–)-DTBM-SEGPHOS–Ru(II) complex catalyst gave (2*S*,3*R*)-methyl 2-benzamidomethyl-3-hydroxybutanoate (**10**) almost quantitatively in 98.6% de and 99.4% ee (cf., Tol-BINAP, 86.0% de and 99.0% ee);[10] this compound can be transformed to a key intermediate **11** of carbapenem antibiotics (Figure 4).[11] The previous diastereo- and enantioselective hydrogenation of **9** using the BINAP–Ru(II) complex catalyst proceeded with 86% de. Two *tert*-butyl groups at the *meta*-position of a phenyl ring of the ligand are essential for the diastereoselectivity (SEGPHOS **6a**; 79.6% de, DM-SEGPHOS **6b**; 93.5% de).

In conclusion, based on our working hypothesis, the series of SEGPHOS ligands has been shown to have high efficiency in asymmetric catalytic hydrogenations. The stereorecognition abilities of SEGPHOS–Ru complex catalysts in the hydrogenation of a wide variety of carbonyl compounds are superior to those observed with BINAP–Ru complex catalysts. Other potential applications of the SEGPHOS ligands in asymmetric reactions are being investigated.

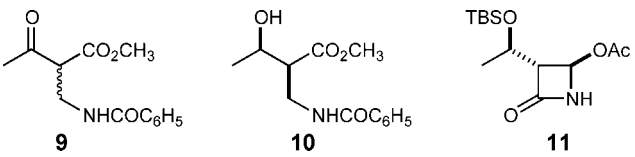


Figure 4. Structures of compounds **9**, **10**, and **11**.

Experimental Section

Asymmetric Hydrogenation of 2-Oxo-1-propanol (2a)

$[NH_2Me_2][\{RuCl((R)\text{-segphos})\}_2(\mu\text{-}Cl)_3]$ (111 mg, 0.067 mmol), 2-oxo-1-propanol (100.0 g, 1.35 mol) and methanol (200 mL) were charged to 1-L stainless steel autoclave under a nitrogen stream. Hydrogen (30 kg/cm^2) was introduced and the mixture was stirred for 7 h at 65 °C. The conversion and ee of (*R*)-1,2-propandiol (**3a**) were determined by GLC analysis (100% conversion, 98.5% ee).

(*R*)-(+)-(4,4′-Bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine oxide) (8)

Under a nitrogen atmosphere, 0.7 M LDA in THF (400 mL, 280 mmol) was added dropwise to a solution of 5-diphenylphosphinyl-1,3-benzodioxole (75.22 g, 233 mmol) in THF (300 mL) at –15 °C. The mixture was added to a suspension of $FeCl_3$ (45.79 g, 282 mmol) in THF (300 mL) at 0 °C. After evaporation of THF, the residue was dissolved in dichloromethane (500 mL) and washed with 10% hydrochloric acid, water, and then dried over Na_2SO_4. The solvent was evaporated and the residue was washed with hot ethyl acetate (200 mL) to give (±)-**8** (yield: 56.08 g, 75%).

A solution of (+)-DBT (11.68 g, 32.6 mmol) in methanol (30 mL) was added to a solution of (±)-(**8**) (20.73 g, 32.3 mmol) in methanol (60 mL). The mixture was stirred at reflux for 5 min. The precipitates were washed with methanol to give the complex (*R*)-(**8**)-(+)-DBT as colorless crystals. The complex was stirred in a mixture of dichloro-

methane (90 mL) and 1.5 N sodium hydroxide (50 mL) at room temperature for 30 min. The organic layer was washed with water, evaporated and dried under vacuum to give (*R*)-(+)-(**8**); yield: 9.12 g (>99% ee, 44%); mp: 158–159 °C, $[\alpha]_D^{24}$: +161.9 (*c* 0.063, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 5.26 (2 H, d, *J* = 1.5 Hz), 5.72 (2 H, d, *J* = 1.6 Hz), 6.65 (2 H, dd, *J* = 8.1, 2.1 Hz), 6.77 (2 H, dd, *J* = 14.1, 8.1 Hz), 7.28–7.72 (20 H, m); ^{31}P NMR ($CDCl_3$): δ = 29.6.

(*R*)-(+)-(4,4′-Bi-1,3-benzodioxiol)-5,5′-diylbis(diphenylphosphine) (6a)

The mixture of (*R*)-(+)-(**8**) (1.50 g, 2.34 mmol), *N*,*N*-dimethylaniline (3.11 g, 25.6 mmol), and trichlorosilane (3.22 g, 23.3 mmol) was stirred in toluene (25 mL) at 110 °C for 4 h. After the reaction mixture was cooled to 5 °C with an ice-water bath, 15% aqueous sodium hydroxide (30 mL) was added. The mixture was stirred at room temperature for 30 min, and then the aqueous layer was extracted with toluene (15 mL×2). The organic layers were washed with water, 1 N hydrochloric acid (30 mL×2) and water. Evaporation of the solvent, and purification by silica gel column chromatography gave (*R*)-(+)-(**6 a**); yield: 1.35 g (95% yield); mp: 215–217 °C, $[\alpha]_D^{24}$: +133.5 (*c* 0.502, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 5.03 (2H, d, *J* = 1.6 Hz), 5.66 (2 H, d, *J* = 1.6 Hz), 6.51 (2 H, dd, *J* = 7.9, 3.1 Hz), 6.66 (2 H, d, *J* = 8.1 Hz), 7.11–7.21 (20 H, m); ^{31}P NMR ($CDCl_3$): δ = –12.6.

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