A New Planar Chiral Bisphosphine Ligand for Asymmetric Catalysis: Highly Enantioselective Hydrogenations under Mild Conditions

Philip J. Pye,* Kai Rossen,* Robert A. Reamer, Nancy N. Tsou,† R. P. Volante, and Paul J. Reider

Department of Process Research
Merck Research Laboratories, P.O. Box 2000
Rahway, New Jersey 07065

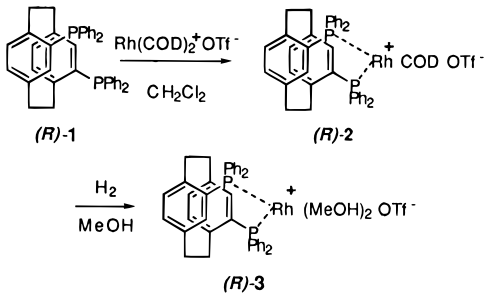
Received March 3, 1997

The introduction of chiral bisphosphine ligands and especially the C_2 symmetric 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) has provided synthetic chemists with highly enantioselective catalysts for a multitude of asymmetric transformations.[1] BINAP is designed so that the axially chiral backbone of the binaphthyl system is used as a scaffold for the placement of the diphenylphosphino groups. Recently, planar chiral molecular systems based on ferrocenes have been applied to catalytic systems with impressive results.[2] Described here is the use of a paracyclophane backbone[3] for the placement of two diphenylphosphino groups to give a planar chiral C_2 symmetric bisphosphine **1** (4,12-bis(diphenylphosphino)-[2.2]-paracyclophane abbreviated as [2.2]PHANEPHOS). Application of this ligand in Rh-catalyzed hydrogenations[4] has led to an exceptionally active and highly enantioselective catalytic system.

Preparation of the active catalyst [[2.2]PHANEPHOS Rh]$^+$OTf$^-$ **3** was achieved by treatment of **1** with bis(1,5-cyclooctadiene)rhodium(I) triflate to form the bright orange-colored complex **2**[5] (Scheme 1). Subsequent hydrogenation of this precatalyst **2** in MeOH led to the loss of the COD (cyclooctadiene) ligand and generated **3** as a single species.[6]

[[2.2]PHANEPHOS Rh]$^+$OTf$^-$ **3** is a highly enantioselective catalyst for the hydrogenation of dehydroamino acid methyl esters under very mild conditions. For example, **4a**, **4b**, and **4e** were all completely reduced in less than 10 min by simply passing a stream of H_2 through a solution of precatalyst **2** (1 to 2 mol %) and the substrate in MeOH at 23 °C. While the unsubstituted dehydroamino acid **4a** gave (*R*)-Ac-Ala-OMe in excellent 99.6% enantiomeric excess (ee),[7] substrates **4b** and **4e** gave disappointingly low ee values of 83% and 78%, respectively. Remarkably, formation of catalyst **3** prior to substrate addition made it possible to perform the hydrogenation at reduced temperatures—*complete conversions in less than 60 min were obtained by passing H_2 through the reaction mixture at −45 °C*! The high activity of **3** even made it possible to run the hydrogenations routinely at −45 °C,[8] and superb enantioselectivity was obtained for a variety of substrate substitution patterns (Table 1). Amide-protected aminoacrylic acid methyl esters gave >94% ee under these conditions; however, geminal substitution at the acrylic acid formed the opposite enantiomer in up to 51% ee. The use of the free acid or the carbobenzoxycarbonyl protecting group led to a decline in the observed enantioselectivities.

Scheme 1



The pronounced activity of [[2.2]PHANEPHOS Rh]$^+$OTf$^-$ **3** can be demonstrated by the reduction of tetrahydropyrazine **6** to afford the HIV protease inhibitor Crixivan intermediate precursor **7** in 86% ee at −40 °C and 1.5 bar in only 6 h (100% conversion, Scheme 2). Previous reductions of **6** using known bisphosphine rhodium catalysts required forcing conditions (70 bar/40 °C/24 h) and proceeded with only moderate enantioselectivities and incomplete conversions (e.g., BINAP, 56% ee; Et-DuPHOS, 50% ee).[9]

Synthesis of [2.2]PHANEPHOS (**1**) began with the iron-catalyzed bisbromination of [2.2]paracyclophane (**8**) (Scheme 3).[10] The tedious chromatographic isolation of the desired pseudo ortho isomer *rac*-**9** from the complex reaction mixture was avoided by crystallization of the highly insoluble pseudo para isomer **10**. Subsequent thermal isomerization (triglyme, 230 °C, 3 h) of the pure pseudo para isomer led to a 50:50 mixture of *rac*-**9** and **10**. The pseudo para isomer **10** crystallized on cooling to leave the desired *rac*-**9** in the mother liquors in >90% purity.

Lithiation (4 equiv of *tert*-butyllithium) of *rac*-**9**, followed by transmetallation ($MgBr_2 \cdot Et_2O$) and reaction with diphenylphosphinic chloride afforded *rac*-**11** in 76% yield from *rac*-**9** (Scheme 4). Resolution of *rac*-**11** was performed with dibenzoyl-D-tartaric acid to give the complex **12** in high optical purity. After the resolving agent was removed, the phosphine oxide (*R*)-**11** (>99.5% ee) was reduced to the enantiomerically pure bisphosphine ligand (*R*)-**1** ([2.2]PHANEPHOS) with $SiHCl_3$.[11]

* Authors to whom correspondence should be addressed at the following: e-mail, philip_pye@merck.com and kai_rossen@merck.com.
† Department of Molecular Design and Diversity. Please direct questions concerning the X-ray analysis to this author.

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1994. (b) Ojima, I. *Catalytic Asymmetric Synthesis*, VCH: New York, 1994.

(2) (a) Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 7995. (b) Burk, M. J.; Gross, M. F. *Tetrahedron Lett.* **1994**, *35*, 9363. (c) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475 and references cited therein.

(3) (a) Sergeeva, E. V.; Rozenberg, V. I.; Vorontsov, E. V.; Danilova, T. I.; Strikova, Z. A.; Yanovsky, A. I.; Belokon, Y. N.; Hopf, H. *Tetrahedron: Asymmetry* **1996**, *7*, 3445. (b) Bodwell, G. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2085 and references cited therein. (c) Diederich, F. *Cyclophanes*; The Royal Society of Chemistry: Cambridge, 1991. (d) Keehn, P. M.; Rosenfeld, S. M. *Cyclophanes*; Academic Press: New York, 1983.

(4) (a) Kagan, H. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 5, Chapter 1. (b) Koenig, K. E. In *Catalysis of Organic Reactions*; Kosak, J. R., Ed.; Dekker: New York, 1984; Chapter 3. (c) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.

(5) ^{1}H NMR (399.87 MHz, $CDCl_3$) δ 8.58 (m, 2 H), 7.85 (m, 1 H), 7.31 (m, 2 H), 7.59 (m, 1 H), 7.43 (m, 1 H), 7.36 (m, 2 H), 7.19 (m, 2 H), 6.55 (br d, J = 8.0, 1 H), 6.43 (dd, J = 8.0, 4.0, 1 H), 4.50 (br s, 2 H), 2.77 (m, 1 H), 2.67 (m, 1 H), 2.54 (m, 1 H), 2.48 (m, 1 H), 2.20 (o m, 3 H), 2.03 (m, 1 H); ^{13}C NMR (100.55 MHz, $CDCl_3$) (due to the magnetic nonequivalence of the phosphorus atoms, some carbon signals are second-order multiplets; these patterns are noted as multiplets) δ 142.2, 139.9 (m), 139.3 (m), 139.0 (t, J = 4.0), 138.3 (m), 134.6, 133.7, 132.2 (t, J = 4.0), 131.2 (m), 130.8 (m), 130.59, 130.58 (m), 129.2 (t, J = 4.2), 128.9 (t, J = 4.4), 100.5 (dt, J = 8.8, 3.2), 91.6 (dt, J = 8.0, 7.0), 35.1, 34.5, 32.5, 28.8; ^{31}P NMR (161.87 MHz, $CDCl_3$) δ 32.7 (d, J_{PRh} = 146.1 Hz).

(6) (a) ^{31}P NMR (161.87 MHz, CD_3OD) δ 65.1 (d, J_{PRh} = 219.7 Hz). (b) The hydrogenation of the analogous BINAP complex leads to the formation of two compounds that afford different enantioselectivities in the hydrogenation: Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.

(7) The DuPHOS ligand affords an equally high ee for this substrate: Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

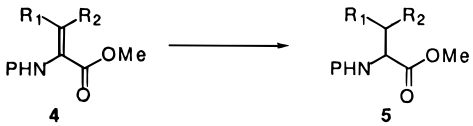
(8) (a) Reduction of **4b** with **3** between −45 and +50 °C showed an increase of ee with decreasing temperature and a good linear dependence of ln(ratio of enantiomers) on 1/T [ln(R/S) = 2440/T − 5.88 (T in K; R^2 = 0.9996)]. (b) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int., Ed. Engl.* **1991**, *30*, 477.

(9) Rossen, K.; Weissman, S. A.; Sager, J.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 6419.

(10) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3527.

S0002-7863(97)00654-9 CCC: $14.00

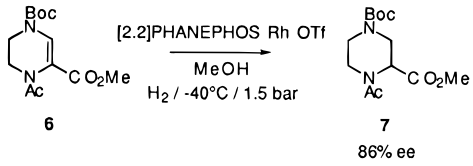
Table 1. Asymmetric Hydrogenation of **4** to **5**



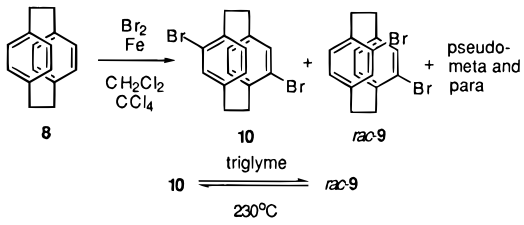
entry	R_1	R_2	P	ee (%)[a] of **5**[b]	config[g]
a	H	H	Ac	99.6[c]	*R*
b	Ph	H	Ac	98[d] (83[c])	*R*
c	Me	H	Ac	94[d]	*R*
d	Ph	H	Bz	97[d]	*R*
e	H	H	Cbz	91[d,e] (78[c])	*R*
f	Me	Me	Ac	51[f]	*S*

[a] Determination of the ee with a Hewlett Packard supercritical fluid chromatograph using two 25 cm Chiracel AD columns in tandem or on a Hewlett-Packard 5890 GC using a Chiracel Val III 25 m column. See the Supporting Information for separation conditions. [b] All reactions went to completion in 10 to 60 min by passing H_2 through the reaction mixture at the specified temperature in MeOH. Catalyst loading was 1−2 mol %, concentration of **4** was 0.1 M. [c] Precatalyst (*R*)-**2** was mixed with **4** prior to addition of H_2 at 23 °C. [d] Precatalyst (*R*)-**2** was reduced to (*R*)-**3** at 23 °C, prior to addition of substrate at −45 °C. [e] Conversion after 3 h: 50%. [f] Substrate added to (*R*)-**3** at −10 °C. [g] Absolute configuration determined by a comparison of the sign of the optical rotation with literature values.

Scheme 2



Scheme 3



X-ray analysis of the dibenzoyltartaric acid complex **12**[12] allowed the determination of the absolute stereochemistry of the phosphine oxide and revealed the severe strain of the paracyclophane backbone (as in the unsubstituted [2.2]paracyclophane the phenyl rings are bent outward with the phenyl carbons connected to the bridges being pulled inward) (Figure 1). Additionally, the steric bulk of the diphenylphosphinyl groups of **12** tilts the two aromatic rings at a 5.7° angle. It is important to note that the P−P distance in **12** (and presumably a similar distance in **1**) is, at 4.8 Å, ideally suited to accommodate two P−Rh bond distances (2.2−2.4 Å range in similar complexes).[13]

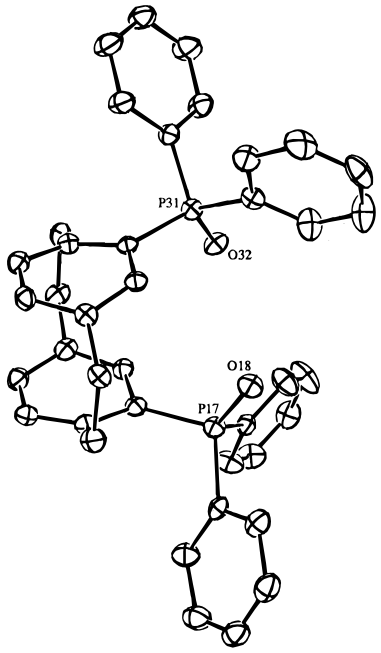
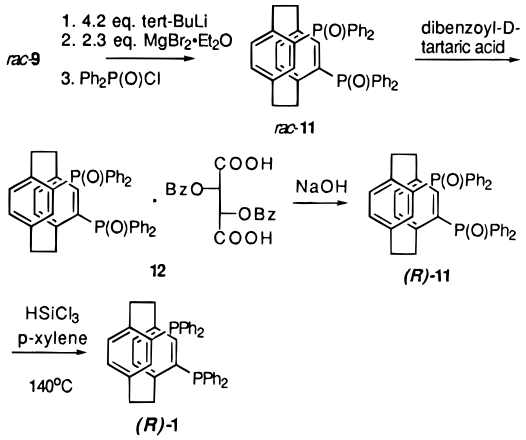


Figure 1. A drawing of the molecular structure of **12**. Ellipsoids are drawn at the 20% probability level. The dibenzoyltartaric acid and the hydrogen atoms are omitted for clarity.

Scheme 4



In summary, the 4,12-disubstituted [2.2]paracyclophane system provides an excellent chiral framework for the placement of catalytically active groups, such as the diphenylphosphino group in [2.2]PHANEPHOS. The resulting catalyst [[2.2]-PHANEPHOS Rh]$^+$OTf$^-$ **3** is highly active, facilitating the reduction of not only dehydroamino acid methyl esters but also of the otherwise difficult to reduce tetrahydropyrazine **6** in excellent enantioselectivity under very mild conditions. Further extensions of the use of cyclophanes in the generation of ligands for asymmetric catalytic reactions are currently being explored and will be reported separately.

Supporting Information Available: Full experimental details for all procedures (6 pages). See any current masthead page for ordering and Internet access instructions.

JA970654G

(11) (a) The preparation is in analogy to a synthesis of BINAP: Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1989**, *67*, 20. (b) The resolution was monitored on a 25 cm Chiracel AD column using an Hewlett-Packard SFC instrument with 15% MeOH/Supercritical-CO_2, 1.0 mL/min; *R* t_1 = 13.0 min, *S* t_2 = 17.8 min. (c) Reoxidation of **1** to **11** with H_2O_2 confirmed that no racemization took place during the reduction of **11** to **1**. (d) For a definition of the chiral descriptor, see: Cahn, R. S.; Ingold, I.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

(12) (a) A crystal suitable for single X-ray crystallography was obtained from the second crop of a resolution of *rac*-**11** with dibenzoyl-L-tartaric acid. Chiral SFC of the dissolved crystal showed that it corresponded to the peak eluting at 13.0 min. (b) Manuscript in preparation.

(13) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.