Atropisomerism

Atropos but Achiral Tris(phosphanyl)biphenyl Ligands for Ru-Catalyzed Asymmetric Hydrogenation**

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In modern synthetic and pharmaceutical chemistry, the advance of asymmetric catalysts is of central importance.[1] The design of chiral ligands is the key to attaining high asymmetric induction and to increasing catalytic activity from an achiral precatalyst ("ligand-accelerated catalysis").[2] How-

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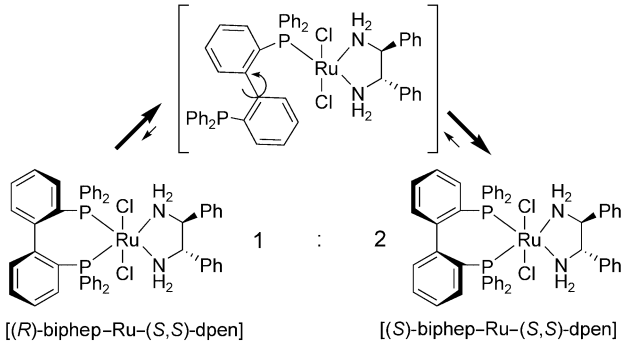
[**] K. Aikawa is grateful to the Japan Society for the Promotion of Science for Young Scientists for a research fellowship.

 DOI: 10.1002/anie.200352277

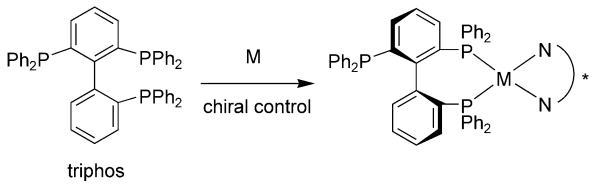
ever, to obtain enantiopure forms of atropisomeric (from Greek *atropos*; *a* = not, *tropos* = turn) ligands,[3] asymmetric synthesis or resolution is requisite. In contrast, we reported a new strategy for asymmetric catalysis with chirally flexible (*tropos*) 2,2′-bis(diphenylphosphanyl)biphenyl (biphep) ligands.[3,4] The chirality of the biphep–Ru complex can be controlled through isomerization by (*S,S*)-1,2-diphenylethylenediamine ((*S,S*)-dpen) as a chiral controller. As a result, a 2:1 mixture of *S,S,S* and *R,S,S* diastereomers was formed at room temperature (Scheme 1).[4c,5] The isomerization of the [biphep–Ru–dpen] complex could take place through disconnection of a Ru–P bond followed by the rotation of the biphenyl rings, and then recoordination of the Ru–P bond (Scheme 1).[4c,6]

Herein we report a novel strategy that employs *atropos* but achiral triphos (2,6,2′-tris(diphenylphosphanyl)biphenyl) ligands for Ru catalysts through chiral control by chiral diamines (Scheme 2). The three *ortho* substituents of the biphenyl compound prevent rotation about the single bond,[7] but axial chirality is created upon complexation with a metal.

A racemic and *atropos* binap–Ru complex gives a 1:1 mixture of two diastereomers when combined



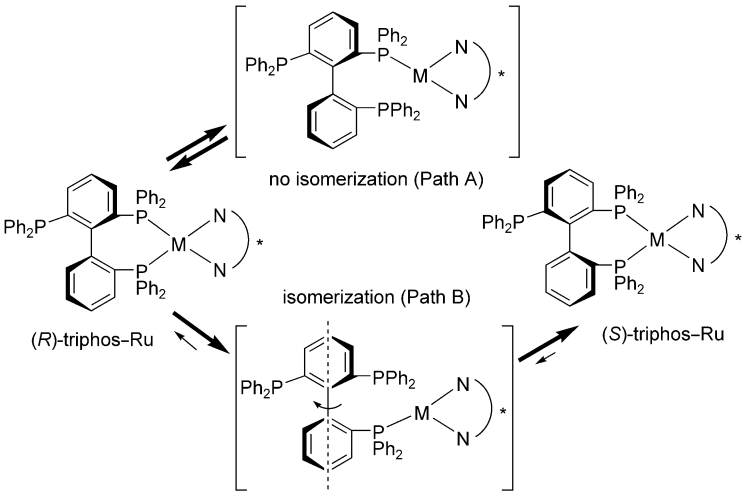
Scheme 1. Isomerization of the *tropos* biphep–Ru complex at room temperature.



Scheme 2. Chiral control of the *atropos* triphos–M complex.

with an equimolar amount of an enantiopure diamine controller. However, if biphep is used as a ligand instead of binap, the diastereomer ratio can be increased up to 2:1, even at room temperature, by virtue of the *tropos* nature.[4c]

In spite of the *atropos* nature, the diastereomer ratio of the triphos–Ru complex can, in principle, be increased by a chiral controller (Scheme 3). However, the isomerization process is different from that of the biphep–Ru complex. At low temperatures, the monophosphane part might dissociate easily, but should re-form the identical enantiomer upon recomplexation with the metal (Scheme 3, Path A). At higher

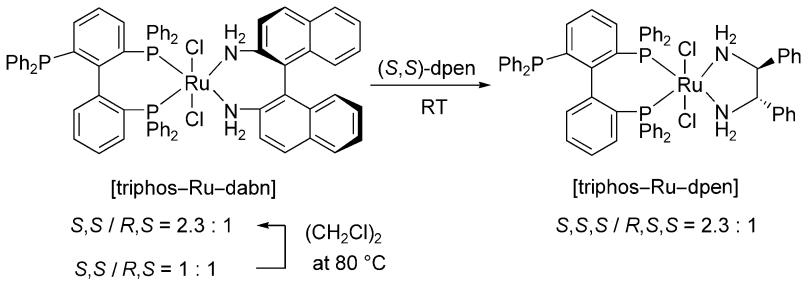


Scheme 3. Mechanism of isomerization of the triphos–Ru complex.

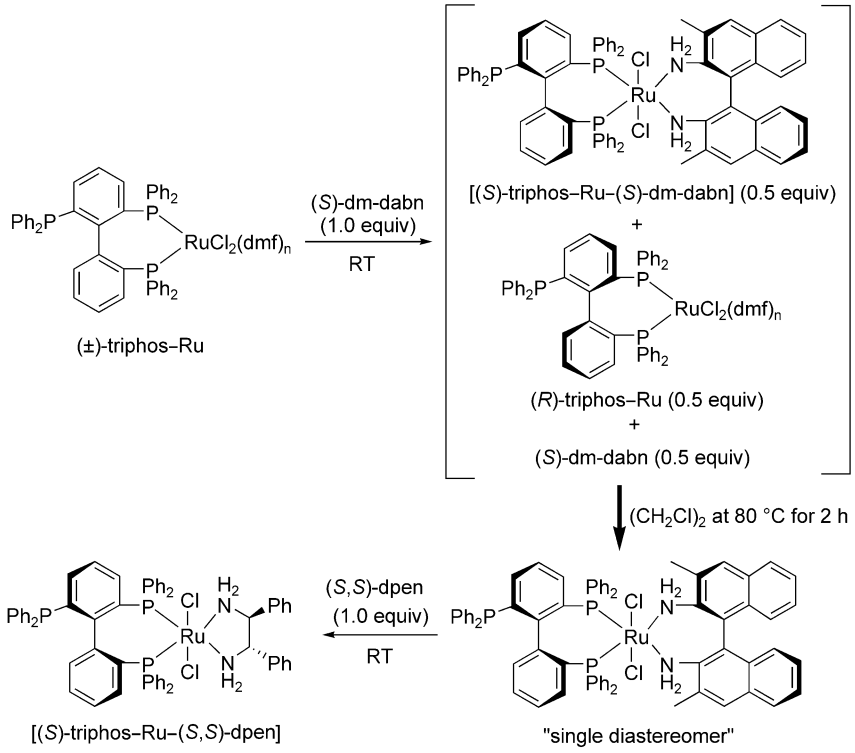
temperatures, the bisphosphane portion can dissociate to give the opposite enantiomer (Scheme 3, Path B).

First, the complexation of the triphos–Ru complex and enantiopure (*S,S*)-dpen was examined to give a mixture of diastereomers in a kinetic (1:1) ratio (see below).[8] Next, isomerization was attempted to convert the diastereomeric mixture of [(*S*)-triphos–Ru–(*S,S*)-dpen] and [(*R*)-triphos–Ru–(*S,S*)-dpen] (1:1) into a single diastereomer. Unfortunately, no change was observed in the diastereomeric ratio at room temperature or even at 80 °C. Similarly, the 1:1 diastereomeric mixture of [triphos–Ru–dabn] (dabn = 2,2′-diamino-1,1′-binaphthyl) did not isomerize at room temperature.[9] However, the isomerization did proceed at 80 °C over 2 hours to the favorable [(*S*)-triphos–Ru–(*S*)-dabn] (*S,S*/*R,S* 2.3:1) (Scheme 4). Upon addition of an equimolar amount of (*S,S*)-dpen to the diastereomer mixture, the aliphatic diamine dpen exchanged with the aromatic diamine dabn without racemization at room temperature (Scheme 4). In sharp contrast to [biphep–Ru–dpen], which readily isomerizes, the triphos ligand of [triphos–Ru–dpen] retained its configuration under the same conditions. Additionally, heating at 80 °C for 24 h did not change the 2.3:1 diastereomeric ratio (see above).

The use of 3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl (dm-dabn), which can readily discriminate between enantiomers owing to its sterically demanding methyl substituents,[4b,10] resulted in isomerization to give the diastereopure triphos–Ru complex (Scheme 5). The combination of racemic (±)-triphos–Ru and an equimolar amount of (*S*)-dm-dabn gave the single diastereomer by isomerization of the (*R*)-triphos–Ru complex in dichloroethane at 80 °C.[11] Significantly, an equimolar amount of (*S,S*)-dpen did exchange with dm-dabn upon addition to the enantiopure complex, to give enantiopure [(*S*)-triphos–Ru–(*S,S*)-dpen] without racemiza-

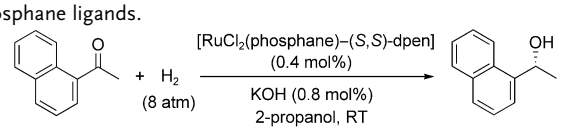


Scheme 4. Isomerization and chiral stability of the triphos–Ru–diamine complexes.



Scheme 5. Resolution and subsequent isomerization by (*S*)-dm-dabn, and *atropos* nature of the triphos–Ru complex.

Table 1: Enantioselective hydrogenation by Ru catalysts with different phosphane ligands.



Entry	Phosphane	*S,S,S*/*R,S,S*[a]	*t* [h]	*ee* [%]	Yield [%]
1	(±)-binap	1:1	4	71	>99
2	biphep	1:1	4	54	>99
3[b]	biphep	2:1	4	69	>99
4	triphos	1:1	6	66	>99
5	triphos	100:0	6	85	>99

[a] The *S,S,S*/*R,S,S* ratio was determined by ^{1}H and ^{31}P NMR spectroscopic analysis. [b] [biphep–Ru–(*S,S*)-dpen] in 2-propanol was prestirred at room temperature for 3 h.

tion of the triphos–Ru moiety at room temperature (Scheme 5).

The enantiopure [triphos–Ru–dpen] was used in the enantioselective hydrogenation of a simple ketone in the presence of KOH (Table 1).[12] The enantioselectivity observed with [(±)-binap–Ru–(*S,S*)-dpen][13] was higher than that found with chirally flexible [biphep–Ru–(*S,S*)-dpen], even after isomerization (Table 1, entries 1–3).[14] The [triphos–Ru–(*S,S*)-dpen] complex (d.r. 1:1) also resulted in lower enantioselectivity (Table 1, entry 4). However, the enantioselectivity exhibited by enantiopure [(*S*)-triphos–Ru–(*S,S*)-dpen] was much higher than that by [(±)-binap–Ru–(*S,S*)-dpen] under the same conditions (Table 1, entries 1 and 5).

In summary, we have demonstrated that the axial chirality of a Ru complex with an *atropos* but achiral triphos ligand can be controlled perfectly and retained at room temperature, in contrast to the *tropos* biphep–Ru complex. The enantiopure [triphos–Ru–dm-dabn] complex underwent exchange with dpen without racemization of the triphos–Ru moiety at room temperature, and the enantiopure [triphos–Ru–dpen] complex led to higher enantioselectivity than that attained with (±)-binap–Ru and biphep–Ru complexes in the asymmetric hydrogenation of a ketone.

Experimental Section

[(*S*)-triphos–Ru–(*S*)-dm-dabn]: Degassed *N,N*-dimethylformamide (3.5 mL) was added to a mixture of [{$RuCl_2$(benzene)}$_2$] (25.0 mg, 0.05 mmol) and triphos (70.7 mg, 0.10 mmol) under an argon atmosphere in a Schlenk tube. After stirring for 3 h at 100 °C, the clear reddish-brown solution was concentrated at 50 °C under reduced pressure. Degassed dichloroethane (5.0 mL) was added to the mixture of the triphos–Ru complex and (*S*)-dm-dabn (31.2 mg, 0.10 mmol) under an argon atmosphere in a Schlenk tube. The solution was stirred for 2 h at 80 °C and then concentrated under reduced pressure to give [(*S*)-triphos–Ru–(*S*)-dm-dabn] quantitatively. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.82$ (s, 3H), 1.85 (s, 3H), 3.94–3.99 (m, 2H; NH_2), 4.69 (d, $J = 6.6$ Hz, 1H; NH_2), 4.74 (d, $J = 6.6$ Hz, 1H; NH_2), 5.45–5.47 (m, 1H), 6.19 (t, $J = 5.7$ Hz, 1H), 6.77–8.18 ppm (m, 45H); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = -11.3$ (d, $J_{P\text{-}P} = 6.2$ Hz, 1P), 44.6 (d, $J_{P\text{-}P} = 39.7$ Hz, 1P), 47.7 ppm (dd, $J_{P\text{-}P} = 6.2$, 39.7 Hz, 1P).

Asymmetric hydrogenation: An autoclave (100 mL) was charged with solid [(*S*)-triphos–Ru–(*S*)-dm-dabn] (14.3 mg, 0.012 mmol) and (*S*)-dpen (2.5 mg, 0.012 mmol). After replacing the air in the

autoclave with argon, degassed CH_2Cl_2 (2.0 mL) was added. The solution was stirred for 24 h at room temperature, and then concentrated under reduced pressure. The autoclave was again charged with an argon atmosphere, and 2-propanol (3.3 mL) and KOH/2-propanol (0.5 M; 48 μL, 0.024 mmol) was added under a stream of argon. The mixture was stirred for 30 min at room temperature. 1′-Acetonaphthone (0.46 mL, 3.0 mmol) was added under a stream of argon, and hydrogen was then introduced at a pressure of 8 atm. The reaction mixture was vigorously stirred for 6 h at room temperature. After concentration under reduced pressure, the residue was filtered through a short column of silica gel. The yield and *ee* values were determined by chiral GC analysis. The product was isolated by column chromatography on silica gel (hexane/EtOAc 3:1) in 99% yield; GC (column: CP-Cyclodextrin-β-2,3,6-M-19, i.d. 0.25 mm × 25 m, CHROMPACK; carrier gas: nitrogen 75 kPa; column temperature: 160 °C; injection and detection temperature: 190 °C; split ratio: 100:1): t_R (*S* isomer) = 31.6 min, t_R (*R* isomer) = 32.5 min.

Received: July 3, 2003 [Z52277]

Keywords: atropisomerism · chirality · hydrogenation · phosphane ligands · ruthenium

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[8] [(±)-triphos–Ru–(*S,S*)-dpen]: ^{31}P NMR (162 MHz, $CDCl_3$): *R,S,S*: $\delta = -11.1$ (d, $J_{P\text{-}P} = 6.2$ Hz, 1P), 46.7 (d, $J_{P\text{-}P} = 36.6$ Hz, 1P), 48.0 ppm (dd, $J_{P\text{-}P} = 6.2$, 36.6 Hz, 1P); *S,S,S*: $\delta = -10.8$ (d, $J_{P\text{-}P} = 5.3$ Hz, 1P), 46.2 (d, $J_{P\text{-}P} = 36.6$ Hz, 1P), 47.4 ppm (dd, $J_{P\text{-}P} = 5.3$, 36.6 Hz, 1P).

[9] [(±)-triphos–Ru–(*S*)-dabn]: ^{31}P NMR (162 MHz, $CDCl_3$): *R,S*: $\delta = -12.5$ (d, $J_{P\text{-}P} = 5.3$ Hz, 1P), 50.9 (d, $J_{P\text{-}P} = 45.0$ Hz, 1P), 53.5 ppm (dd, $J_{P\text{-}P} = 5.3$, 45.0 Hz, 1P); *S,S*: $\delta = -11.5$ (d, $J_{P\text{-}P} = 5.3$ Hz, 1P), 50.3 (d, $J_{P\text{-}P} = 42.8$ Hz, 1P), 52.1 ppm (dd, $J_{P\text{-}P} = 5.3$, 42.8 Hz, 1P).

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[11] [(*S*)-triphos–Ru–(*S*)-dm-dabn]: ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = -11.3$ (d, $J_{P\text{-}P} = 6.2$ Hz, 1P), 44.6 (d, $J_{P\text{-}P} = 39.7$ Hz, 1P), 47.7 ppm (dd, $J_{P\text{-}P} = 6.2$, 39.7 Hz, 1P).

[12] Hydrogenation with enantiopure [binap–Ru–dpen]: a) for an excellent review, see: R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40 – 75; *Angew. Chem. Int. Ed.* **2001**, *40*, 40 – 73; see also: b) T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2675 – 2676; c) T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 10417 – 10418.

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[14] We have already reported that a Ru complex with a 3,3′-dimethyl-substituted biphep ligand (dm-biphep) can be controlled to a 3:1 diastereomeric ratio by enantiopure dpen. In asymmetric hydrogenation, the complex gave a higher enantioselectivity than the racemic dm-binap–Ru complex.[4a]

