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Racemic but *Tropos* (Chirally Flexible) BIPHEP Ligands for Rh(I)-Complexes: Highly Enantioselective Ene-Type Cyclization of 1,6-Enynes

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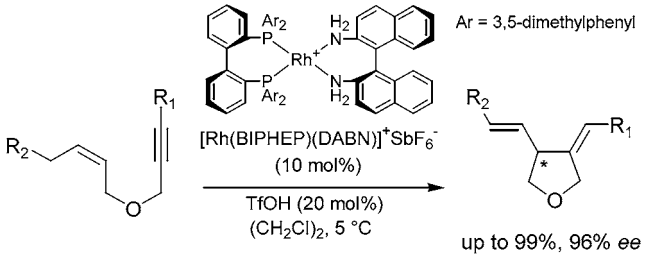
ABSTRACT



The *tropos* (chirally flexible) or *atropos* (chirally rigid) nature of BIPHEP–Rh complexes at room temperature critically depends on the amines complexed. The aliphatic DPEN complex is *atropos*, whereas the aromatic DABN complex is *tropos*. BIPHEP–Rh chirality can thus be controlled by DABN at room temperature. The amine-free BIPHEP–Rh complex is *tropos*. At 5 °C, even amine-free BIPHEP–Rh complexes are *atropos* and hence can be used as enantiopure catalysts to give high enantioselectivity in ene-type cyclization of 1,6-enynes.

Despite enantioresolution and synthetic transformation, many enantiopure atropisomeric (*atropos* in Greek; *a* = not, *tropos* = turn)[1] ligands are synthesized and used in catalytic asymmetric reactions.[2] In sharp contrast, we have succeeded in asymmetric catalysis using racemic but chirally flexible (*tropos*)[1] bis(phosphanyl)biphenyl (BIPHEP) ligand,[3,4a] of which the axial chirality can be controlled by a chiral controller. Thus, the BIPHEPs−Ru and −Pd complexes afford high enantioselectivity in asymmetric hydrogenation and Diels−Alder reactions, respectively.[4] The complexes bearing BIPHEPs are inherently *tropos*, but high levels of enantioselectivity can be achieved under appropriate conditions depending on the central metals employed. Ru complexes are *tropos*, but Pd complexes are, by contrast, *atropos* at room temperature. Thus, the question arises with BIPHEP-complexes of Rh in the same row between Ru and Pd: *tropos* or *atropos* at room temperature?[5]

Herein, we report chiral control of *tropos* BIPHEPs−Rh complexes at room temperature (25 °C) and their application as *atropos* catalysts for highly enantioselective ene-type cyclization of 1,6-enynes at 5 °C.

(1) Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, *10*, 1561−1578.

(2) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vols. 1−3.

(3) The activation barrier to axial torsion in selectivity deuterated BIPHEP is measured to be only (22 ± 1) kcal, which suggests that axial rotation takes place at room temperature or above: Desponds, O.; Schlosser, M. *Tetradedron Lett*. **1996**, *37*, 47−48.

(4) For the BIPHEP−Ru complex: (a) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495−497. For the BIPHEP−Pd complex: (b) Mikami, K.; Aikawa, K.; Yusa, Y.; Hatano, M. *Org. Lett*. **2002**, *4*, 91−94. (c) Mikami, K.; Aikawa, K.; Yusa, Y. *Org. Lett*. **2002**, *4*, 95−97. For the BIPHEP−Pt complex: (d) Tudor, M. D.; Becker, J. J.; White, P. S.; Gagné, M. R. *Organometallics* **2000**, *19*, 4376−4484. (e) Becker, J. J.; White, P. S.; Gagné, M. R. *J. Am. Chem. Soc*. **2001**, *123*, 9478−9479.

(5) A half-life of 1000 s (16.7 min) is considered as the minimum requirement for *atropos* molecules; cf. Oki, M. *Top. Stereochem.* **1983**, *14*, 1−81.

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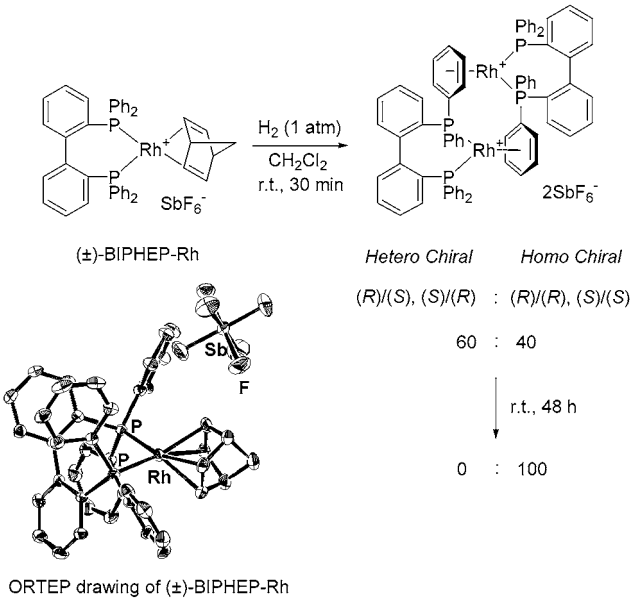
Scheme 1



The reaction of racemic BIPHEP−Rh complex[6] in nonpolar solvents such as dichloromethane under hydrogen (1 atm) gave a dimeric BIPHEP−Rh complex (Scheme 1). The dimer complexes[7] consisted of homo- and hetero-chiral ones in a 40:60 ratio, but the hetero-chiral complex isomerized slowly to the homo-chiral one at room temperature over 48 h.[8]

The complexation of the BIPHEP−Rh complex and an equimolar amount of (*R*,*R*)-DPEN (1,2-diphenylethylenediamine) as a chiral controller was examined to give a mixture of diastereomers in a 50:50 ratio (eq 1). Unfortunately, no change was observed in the diastereomeric ratio at room temperature regardless of solvents.

Next, an equimolar amount of (*R*)-DABN (2,2′-diamino-1,1′-binaphthyl) was added under a similar condition, to give a mixture of diastereomers in a *R*,*R*/*S*,*R* 46:54 ratio (eq 2). However, the isomerization proceeded slowly in dichloromethane at room temperature, leading eventually to the single *R*,*R* diastereomer after 17 days (Figure 1). As a solvent effect, the complexation in polar solvents such as methanol gave a different diastereomer ratio *R*,*R*/*S*,*R* 56:44, and the isomerization was found to be faster to afford the single *R*,*R* diastereomer within 72 h. The single *R*,*R* diastereomer could also be obtained at 80 °C in dichloroethane within 5 h. However, isomerization was not observed at 5 °C in either solvent.

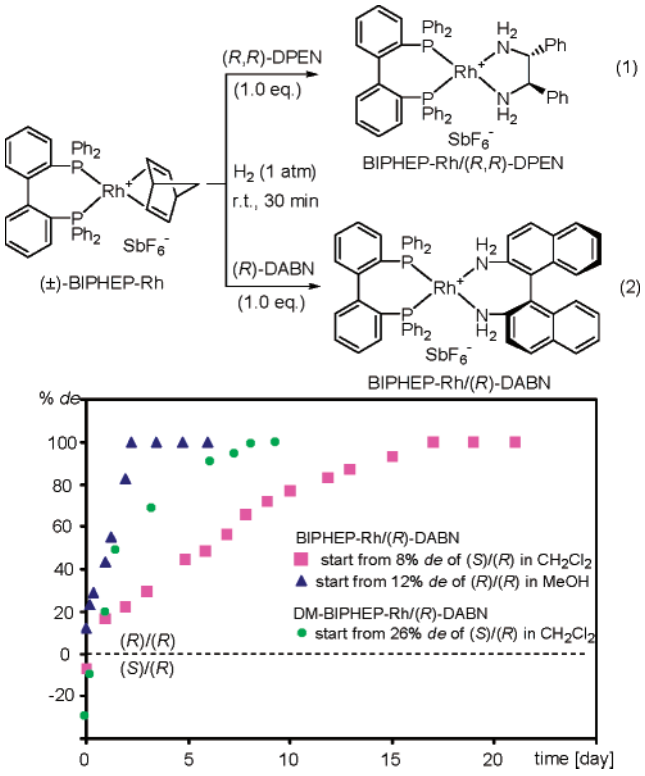


Figure 1. Solvent effect on chiral control of BIPHEP−Rh/DABN complex. The diastereomeric ratios were determined by ^{31}P and ^{1}H NMR at room temperature.

It is thus clarified that the *tropos* or *atropos* nature of BIPHEP−Rh complexes at room temperature critically depend on the amines complexed. The aliphatic DPEN complex is *atropos*, whereas the aromatic DABN complex is *tropos*. Furthermore, the amine-free BIPHEP−Rh complexes are *tropos*, as proven after amine complexation. However, at 5 °C or below, even amine-free BIPHEP−Rh complexes are *atropos* and hence can be used as chiral catalysts.

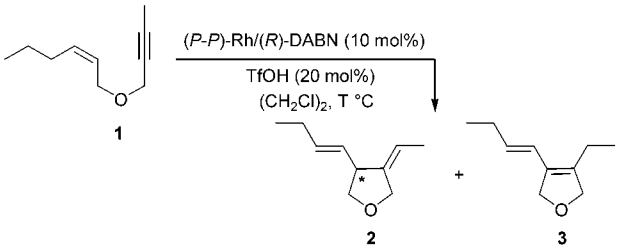
The enantiopure Rh-complexes obtained via heat pretreatment (80 °C in dichloroethane for 5 h) could be used as asymmetric catalysts for ene-type cyclization[9] of 1,6-enyne substrate **1** by addition of TfOH to protonate diamines off the Rh metal center (Table 1). BIPHEP−Rh gave the desired cyclic product **2** in good yield but in moderate enantioselectivity at room temperature (entry 1). Without TfOH, the reaction was very slow (12.5 h) (entry 2). Using DM-BIPHEP (DM = 3,5-dimethy-phenyl) instead of BIPHEP,

(6) Crystal data for BIPHEP−Rh complex in X-ray analysis: formula $C_{46}H_{44}F_6P_2RhSbCl_2$, monoclinic, space group $P2_1/n$ (No. 14), a = 14.065(4) Å, b = 13.737(4) Å, c = 21.407(56) Å, β = 89.5260(1)°, V = 4097.9(21) Å^3, Z = 4, and D = 1.732 g cm^{-3}. X-ray diffraction data were collected on a Rigaku Saturn 70 CCD system with graphite-monochromated Mo Kα (λ = 0.71070 Å) at −100 °C and the structure was solved by direct methods (SIR92). The final cycle of full-matrix least-squares refinement on F^2 was based on 12097 observed reflections and 542 variable parameters and converged to R = 0.076 and Rw = 0.179. Goodness of fit = 1.084, shift/error = 0.006. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-241306. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. Fax: (+44)1223-336-033; E-mail: deposit@ccdc.cam.ac.uk.

(7) For the BINAP−Rh complex: Takaya, H.; Miyashita, A.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245−1253. For the X-ray analysis of DPPE-Rh complex: Halpern, J.; Rily, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc.* **1977**, 8055−8057.

(8) ^{31}P NMR (162 MHz, CD_2Cl_2): heterochiral δ 39.8 (dd, J = 193.3, 49.6 Hz), 43.3 (dd, J = 209.5, 49.6 Hz); homochiral δ 40.8 (dd, J = 192.3, 48.8 Hz), 44.6 (dd, J = 209.5, 48.8 Hz). For the homochiral dimer (*R*)-BINAP−Rh complex: ^{31}P NMR (162 MHz, CD_2Cl_2) δ 42.7 (dd, J = 195.5, 43.6 Hz), 46.4 (dd, J = 211.4, 43.6 Hz).

Table 1. Enantioselective Ene-Type Cyclization of 1,6-Enyne **1**[a]



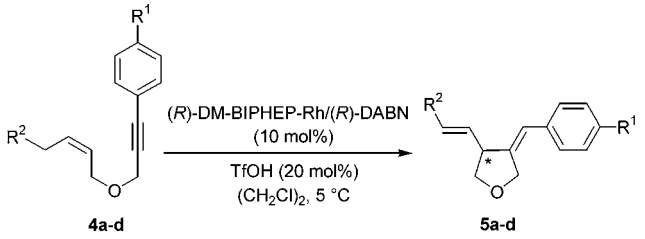
entry	P−P	T (°C)	time	yield[c] (%) 2	3	ee[d] (%)
1	(*R*)-BIPHEP	25	30 min	84		59 (−)
2[b]	(*R*)-BIPHEP	25	12.5 h	74		56 (−)
3	(*R*)-DM-BIPHEP	25	5 min	70	23	85 (−)
4	(*R*)-DM-BIPHEP	5	3 h	83	5	96 (−)

[a] All reactions were examined after preheating at 80 °C for 5 h. [b] The reaction was examined without TfOH. [c] Yield of isolated product. [d] Enantiopurity was determined by chiral GC analysis on a CP-Cyclodextrin-β-2,3,6-M-19 column.

both the activity and enantioselectivity of the Rh catalyst increased, however, along with the formation of *achiral* conjugated 1,3-diene **3** in 23% yield (entry 3). At lower temperature (5 °C), DM-BIPHEP−Rh complex exhibited high enantioselectivity and chemical yield of **2** (96% ee, 83%) with only 5% yield of undesired **3** (entry 4). After the ene-type reaction, the enantiopure form of the amine-free BIPHEP−Rh complex was confirmed by adding (*R*)-DABN.

Because racemization of the DM-BIPHEP−Rh complex might proceed during the reaction, the change in enantiomeric excess (% ee) was examined with progress of the reaction by choosing substrate **4a** not to give a 1,3-diene product.

Table 2. Enantioselective Ene-Type Cyclization of 1,6-Enynes[a]



entry	R_1	R_2	time (h)	yield[b] (%)	ee[d] (%)
1	H (**4a**)	Me	14	99 (**5a**)	94 (−)
2	OMe (**4b**)	Me	14	20[c] (**5b**)	94 (−)
3	Cl (**4c**)	Me	14	84 (**5c**)	88 (−)
4	H (**4d**)	Et	19	81 (**5d**)	89 (−)

[a] All reactions were examined after preheating at 80 °C for 5 h. [b] Yield of isolated product. [c] Most of 1,6-enyne substrate **4b** was decomposed. [d] Enantiopurity was determined by HPLC analysis.

As expected, at room temperature, enantioselectivity was decreased from 94% ee after 1 min to 86% ee after 1 h. However, at 5 °C, enantioselectivity (94% ee) did not change at all throughout the reaction time. Furthermore, the ene-product of 94% ee did not racemize under the reaction conditions even at room temperature.

Therefore, 1,6-enyne substrates **4a**−**d** with aromatic terminal substituents were examined at 5 °C (Table 2). All of the reactions were shown to be effective with both electron-withdrawing and -donating substituents except for low yield obtained with MeO-substrate (**4b**).

In conclusion, we have established the high levels of enantioselectivity in ene-type cyclization of 1,6-enynes catalyzed by BIPHEPs−Rh complexes despite the racemic and *tropos* ligands, through chiral control. Further applications of BIPHEPs-Rh complexes in asymmetric catalysis and chiral control of other metal complexes bearing BIPHEP ligands are now in progress.

Supporting Information Available: Typical experimental procedures and spectral data for BIPHEPs−Rh complexes and **1**−**5**, including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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