# Axial chirality control of *tropos* BIPHEP–Rh complexes by chiral dienes: synergy effect in catalytic asymmetric hydrogenation†‡

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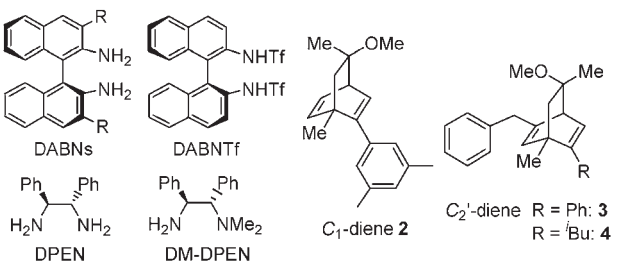
**Diastereopure *tropos* Rh complexes bearing not only BIPHEP but also chiral dienes can be employed as highly enantioselective hydrogenation catalysts for an olefinic substrate.**

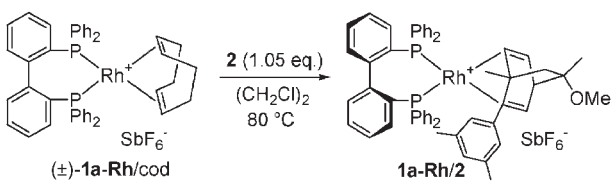
In new frontiers of asymmetric catalysis, various chiral ligands have been designed and synthesized.[1] Especially, atropisomeric (originating from *atropos*: "*a*" meaning "not" and "*tropos*" meaning "turn" in Greek[2]) ligands such as BINAP[3] derivatives with a high rotation barrier are widely utilized because of their rigid and effective asymmetric environments. On the other hand, the use of *tropos*[2] (chirally flexible) ligands with a low rotation barrier is attractive as a powerful and practical strategy for asymmetric catalysis. *tropos* BIPHEP (2,2′-bis(diphenylphosphino)-1,1′-biphenyl)[4] **1a** is not resolvable at room temperature for the fast racemization. However, the chirality of racemic BIPHEP–metal complexes can be controlled by chiral diamines DABNs,[5c,6–8] DPEN,[5] DM-DPEN,[5b] and their triflate derivatives such as DABNTf[7c,8b] to lead to the single BIPHEP–metal enantiomer. We have thus succeeded in axial chirality control of BIPHEP–Ru,[5] Rh,[6] Pd,[7] and Pt[8] complexes for catalytic asymmetric reactions.[9] Herein, we report the first example of complete chirality control of *tropos* BIPHEP–Rh complexes by chiral dienes[10–12] rather than chiral diamines and the synergy effect of chirally controlled BIPHEP and chiral dienes in catalytic asymmetric hydrogenation of an olefinic substrate.




Thermodynamic axial chirality control was first attempted (Scheme 1). BIPHEP–Rh/diene (**1a-Rh**/**2**) complex was synthesized by treatment of racemic **1a-Rh**/cod complex and $C_1$-symmetric diene **2**[11] in $(CH_2Cl)_2$ at 80 °C. The isomerization of **1a-Rh** proceeded to give a 72 : 28 ((*S*)-**1a-Rh**/**2** : (*R*)-**1a-Rh**/**2**) mixture of diastereomers after 24 h. Heating for 48 h afforded the single diastereomer through complete ligand exchange between cod and chiral diene **2**, along with a by-product (18%). The employment of racemic **1a-Rh**/cod bearing $BAr_F^-$ instead of $SbF_6^-$ anion also led to the single diastereomer under the same conditions, but the remaining **1a-Rh**/cod and by-product were obtained in significant amounts. No ligand exchange was observed at 80 °C using *pseudo*-$C_2$-symmetric diene **3**[12] due to more severe steric repulsion than in the $C_1$-symmetric diene **2**.[13]

Kinetic chirality control without heating was also examined using cationic Rh–diene dimer as a starting material (Scheme 2).[14] In contrast to the thermodynamic control, the combination of [RhCl(**2**)]$_2$ and silver salt followed by the addition of BIPHEP led to the complex (**1a-Rh**/**2**) without formation of a by-product. Unfortunately, irrespective of silver salt, the axial chirality control of the BIPHEP moiety was unsuccessful ((*S*)-**1a-Rh**/**2** : (*R*)-**1a-Rh**/**2** = 64 : 36 to 59 : 41). The thermodynamic chirality control of the complex (**1a-Rh**/**2**) was then attempted to convert the less favorable diastereomer subsequently to the favorable one. The isomerization was observed to give solely (*S*)-**1a-Rh**/**2** at 50 °C for 62 h, though with a by-product (20%).

The *pseudo*-$C_2$-symmetric diene (**3**) was used instead of the $C_1$-symmetric diene (**2**) for more efficient enantiomer discrimination (Scheme 3). Under the same conditions, the complex (**1b-Rh**/**3**) was prepared by treatment of DM-BIPHEP **1b** (DM = 3,5-dimethylphenyl) to afford a single diastereomer (*S*)-**1b-Rh**/**3** without formation of a by-product, except for the $AgSbF_6$ case.§ The unfavorable diastereomer (*R*)-**1b-Rh**/**3** was not observed by $^{31}$P NMR analysis. The use of **4** (R = $^t$Bu) instead of **3** (R = Ph) for the chirality control also led to a similar result.




**Scheme 1** Thermodynamic chirality control by $C_1$-symmetric diene **2**.

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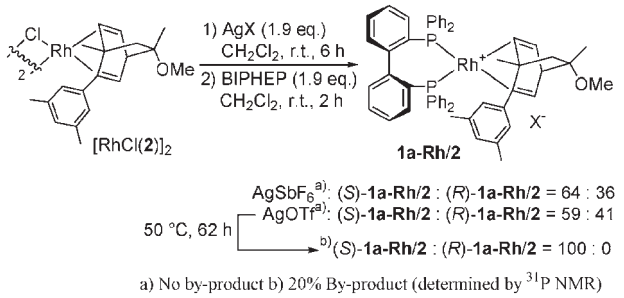
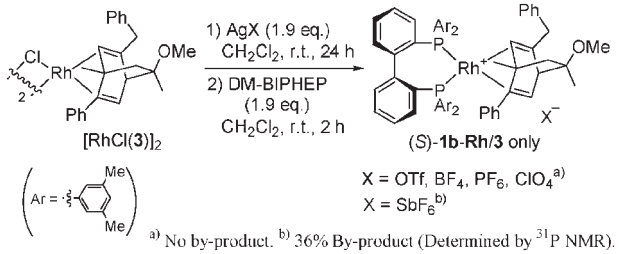



**Scheme 2** Kinetic chirality control by $C_1$-symmetric diene **2**.




**Scheme 3** Kinetic chirality control by *pseudo*-$C_2$-symmetric diene **3**.

We have already determined the structure of racemic **1a-Rh**/**nbd** complex[6] by X-ray analysis.[14] The orientation of axial and equatorial phenyl groups in the BIPHEP moiety is quite similar to that of BIPHEP–Ru, Pd, and Pt complexes.[5–8] In the present enantiomer discrimination of (*R*)-**1b-Rh** complex by *pseudo*-$C_2$-symmetric diene **3′**, there is strong steric repulsion between equatorial aryl groups of BIPHEP and the Ph and Bn groups of chiral diene **3′** (Fig. 1: DFT calculations; see ESI‡). In sharp contrast, there is essentially no steric repulsion in the diastereomeric complex (*S*)-**1a-Rh**/**3′**. The (*S*)-**1a-Rh**/**3′** complex is thermodynamically more stable than the diastereomer (*R*)-**1a-Rh**/**3′** complex by 4.9 kcal mol$^{-1}$. As a result, (*S*)-enantiomeric BIPHEPs could selectively complex with the cationic Rh/**3** complex after isomerization from the opposite (*R*)-enantiomeric BIPHEPs.

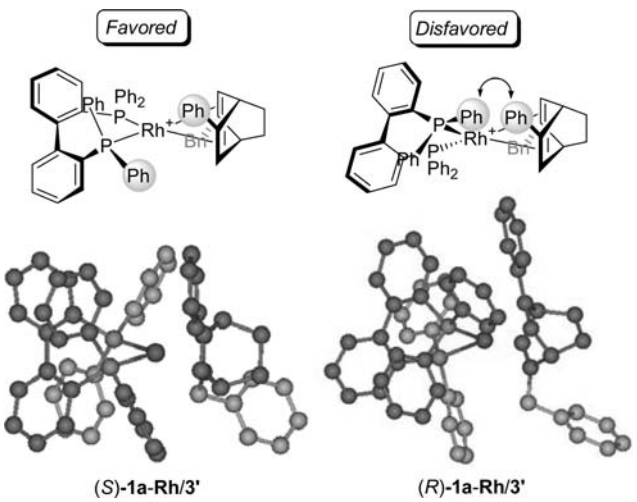
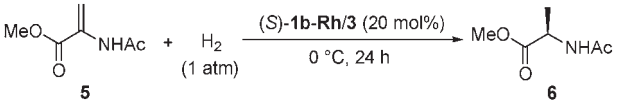



**Fig. 1** Enantiomer discrimination by chiral diene **3**: DFT calculation of **1a-Rh**/**3′** diastereomer.

**Table 1** Asymmetric hydrogenation catalyzed by the single diastereomer (*S*)-**1b-Rh**/**3**




| Entry | Solvent | Counter anion | Conv. (%) | *ee* (%)[a] |
|---|---|---|---|---|
| 1 | MeOH | OTf | 21 | 55 |
| 2 | $CH_2Cl_2$ | OTf | 69 | 14 |
| 3 | THF | OTf | 100 | 89 |
| 4 | THF | $BF_4$ | 100 | 91 |
| 5 | THF | $PF_6$ | 47 | 51 |
| 6 | THF | $ClO_4$ | 97 | 60 |
| 7 | THF | $SbF_6$ | 97 | 78 |
| 8[b] | THF | $SbF_6$ | 31 | 40 |
| 9[c] | THF | $SbF_6$ | 0 | — |
| Ref. 16 | $Rh(cod)_2(OTf)$ + (*S*)-BINAP | | 100 | 21 |

[a] Enantiopurity was determined by chiral GC analysis on a CP Chirasil Dex CB column. [b] Chiral diene **4** was used instead of chiral diene **3**. [c] $[RhCl(\mathbf{3})_2]$ with 2 equiv. of $AgSbF_6$ was used as an asymmetric catalyst without DM-BIPHEP **1b**.

With complete chirality control, the asymmetric hydrogenation[15] of the olefinic substrate (**5**) was investigated (Table 1),§ for which the *atropos* BINAP ligand[16] gave only a low level of enantioselectivity (21% *ee*). Furthermore, the cationic Rh–diene dimer without diphosphine ($[RhCl(\mathbf{3})]_2/2AgSbF_6$) was totally inactive (entry 9).

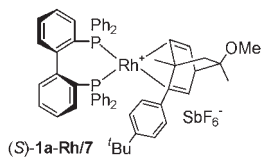
The synergy effect[17] of chirally controlled BIPHEP and the chiral dienes (**3** and **4**) was thus examined in catalytic asymmetric hydrogenation (entries 1–8). The use of THF increased both the catalytic activity and enantioselectivity up to 89% *ee* (entries 1, 2 *vs.* 3). The remarkable effect of counter anions was observed; under similar reaction conditions, the $BF_4$ anion was found to be the most effective, affording **6** with 91% *ee* in 100% conversion (entry 4). On the other hand, the use of the isobutyl diene (**4**) instead of the phenyl diene (**3**) gave lower enantioselectivity to indicate the synergy effect of chiral dienes with chirally controlled DM-BIPHEP (entries 7 *vs.* 8). Significantly, it was confirmed by $^{31}$P NMR analysis that racemization of the DM-BIPHEP moiety and decomposition of the complex were not observed even after the hydrogenation reaction.‡

In conclusion, we have succeeded in the complete chirality control of *tropos* BIPHEP–Rh complexes by chiral dienes and in the highly enantioselective hydrogenation of an olefinic substrate catalyzed by diastereopure Rh complexes bearing not only *tropos* diphosphines but also chiral dienes. While the use of chiral dienes instead of achiral cod or nbd decreased the catalytic activity (hence, not asymmetric activation[18]), the synergy effect by chirally controlled *tropos* BIPHEP and chiral dienes led to higher enantioselectivity than that by *atropos* BINAP itself without chiral diene. Significantly, the hydrogenation of chiral dienes and racemization of the DM-BIPHEP moiety have not been observed even under the hydrogenation conditions. Further applications of the enantiopure *tropos* diphosphine–Rh–diene complexes in asymmetric catalysis are now under investigation.

## Notes and references

§ *Kinetic chirality control*: To a mixture of $[RhCl(\mathbf{3})]_2$ (9.4 mg, 0.01 mmol) and $AgBF_4$ (3.7 mg, 0.019 mmol) was added dry dichloromethane (1.0 mL) under argon atmosphere, and the mixture was stirred for 6 h at room temperature. A solution of DM-BIPHEP **1b** (12.1 mg, 0.019 mmol) in dry dichloromethane (1.0 mL), prepared in another Schlenk tube, was then added to the reaction mixture *via* cannula. After stirring for 2 h at room temperature, the AgCl precipitate was removed by filtration under argon atmosphere through a bed of Celite®. Diastereopure (*S*)-**1b-Rh**/**3** was isolated quantitatively by concentration of the mixture *in vacuo*, addition of a few mL of $Et_2O$, removal of supernatant liquid *via* syringe, washing with $Et_2O$, and drying *in vacuo*.
$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.60 (d, $J$ = 13.2 Hz, 1H), 0.66 (d, $J$ = 13.2 Hz, 1H), 0.91 (s, 3H), 1.69 (s, 3H), 2.17 (s, 6H), 2.20 (s, 3H), 2.31 (s, 6H), 2.34 (s, 6H), 2.46 (s, 6H), 2.82 (d, $J$ = 14.1 Hz, 1H), 3.52 (d, $J$ = 15.9 Hz, 1H), 3.71 (d, $J$ = 15.9 Hz, 1H), 4.28 (m, 1H), 4.62 (d, $J$ = 6.3 Hz, 1H), 5.86–5.89 (m, 1H), 6.00–6.03 (m, 1H), 6.66–7.55 (m, 27H), 7.87–7.93 (m, 1H). $^{31}$P NMR (121 MHz, $CDCl_3$) $\delta$ 21.7 (dd, $J_{Rh-P}$, $J_{P-P}$ = 157.9, 46.0 Hz), 27.4 (dd, $J_{Rh-P}$, $J_{P-P}$ = 161.8, 46.0 Hz). Anal. Calcd for $C_{68}H_{70}BF_4OP_2Rh{\cdot}2CH_2Cl_2$: C, 63.46; H, 5.63%. Found: C, 63.71; H, 5.58%. $[\alpha]_D^{27}$ = +34.0 ($c$ = 0.08 in $CHCl_3$).
*Asymmetric hydrogenation*: To a mixture of (*S*)-**1b-Rh**/**3** (11.5 mg, 0.01 mmol), prepared by kinetic chirality control as described above, and 2-acetamidoacrylic acid methyl ester **5** (7.2 mg, 0.05 mmol) in a 10 mL Schlenk tube was added dry dichloromethane (0.5 mL) under argon atmosphere. The mixture was charged with hydrogen gas using a balloon (1 atm), then stirred for 24 h at 0 °C. The solvent was concentrated under reduced pressure. The product **6** was isolated quantitatively by flash chromatography using dichloromethane–MeOH (19 : 1). *Ee* values were determined by chiral GC analysis; GC (column: CP Chirasil Dex CB, i.d. 0.32 mm × 25 m, CHROMPACK; carrier gas: nitrogen 75 kPa; column temperature: 100 °C; injection and detection temperature: 130 °C), $t_R$ (*S* isomer) = 10.9 min, $t_R$ (*R* isomer) = 11.7 min.


1 (*a*) *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, New York, 1993, vol. I; *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, New York, 2000, vol. III; (*b*) *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, VCH, Weinheim, 1998; (*c*) *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Berlin, 1999, vols. 1–3; (*d*) *New Frontiers in Asymmetric Catalysis*, ed. K. Mikami and M. Lautens, Wiley, New York, 2007.
2 (*a*) *Stereochemie*, ed. K. Freudenberg and W. Kuhn, Franz Deuticke, Leipzig, 1933, pp. 803–824; (*b*) K. Mikami, K. Aikawa, Y. Yusa, J. J. Jodry and M. Yamanaka, *Synlett*, 2002, **10**, 1561.
3 (*a*) A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi and R. Noyori, *J. Am. Chem. Soc.*, 1980, **102**, 7932; (*b*) R. Noyori and H. Takaya, *Acc. Chem. Res.*, 1990, **23**, 345.
4 The activation barrier to axial torsion in selectively deuterated BIPHEP is measured to be only (22 ± 1) kcal mol$^{-1}$, which suggests that axial rotation takes place at temperatures around or above 25 °C: O. Desponds and M. Schlosser, *Tetrahedron Lett.*, 1996, **37**, 47.
5 BIPHEP–Ru: (*a*) K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham and R. Noyori, *Angew. Chem., Int. Ed.*, 1999, **38**, 495; (*b*) T. Korenaga, K. Aikawa, M. Terada, S. Kawauchi and K. Mikami, *Adv. Synth. Catal.*, 2001, **3**, 284; (*c*) K. Mikami, K. Aikawa and T. Korenaga, *Org. Lett.*, 2001, **3**, 243; (*d*) Y. Liang, Z. Wang and K. Ding, *Adv. Synth. Catal.*, 2006, **348**, 1533; DPBP–Ru/DPEN: (*e*) K. Mikami, K. Wakabayashi and K. Aikawa, *Org. Lett.*, 2006, **8**, 1517; (*f*) Q. Jing, C. A. Sandoval, Z. Wang and K. Ding, *Eur. J. Org. Chem.*, 2006, 3606.
6 BIPHEP–Rh: K. Mikami, S. Kataoka, Y. Yusa and K. Aikawa, *Org. Lett.*, 2004, **6**, 3699.
7 BIPHEP–Pd: (*a*) K. Mikami, K. Aikawa, Y. Yusa and M. Hatano, *Org. Lett.*, 2002, **4**, 91; (*b*) K. Mikami, K. Aikawa and Y. Yusa, *Org. Lett.*, 2002, **4**, 95; (*c*) K. Mikami, Y. Yusa, K. Aikawa and M. Hatano, *Chirality*, 2003, **15**, 105.
8 BIPHEP–Pt: (*a*) J. J. Becker, P. S. White and M. R. Gagné, *J. Am. Chem. Soc.*, 2001, **123**, 9478; (*b*) K. Mikami, H. Kakuno and K. Aikawa, *Angew. Chem., Int. Ed.*, 2005, **44**, 7257; (*c*) S. Doherty, J. G. Knight, C. H. Smyth, R. W. Harrington and W. Clegg, *Org. Lett.*, 2007, **9**, 4925.
9 Chirality control by chiral anions: (*a*) J. Lacour and V. Hebbe-Viton, *Chem. Soc. Rev.*, 2003, **32**, 373. Chirality control of *tropos* NUPHOS ligands: ; (*b*) S. Doherty, C. R. Newman, R. K. Rath, H. Luo, M. Nieuwenhuyzen and J. G. Knight, *Org. Lett.*, 2003, **5**, 3863.
10 (*a*) T. Hayashi, K. Ueyama, N. Tokunaga and K. Yoshida, *J. Am. Chem. Soc.*, 2003, **125**, 11508; (*b*) N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani and T. Hayashi, *J. Am. Chem. Soc.*, 2004, **126**, 13584.
11 C. Fischer, C. Defieber, T. Suzuki and E. M. Carreira, *J. Am. Chem. Soc.*, 2004, **126**, 1628.
12 J. Paquin, C. Defieber, C. R. J. Stephenson and E. M. Carreira, *J. Am. Chem. Soc.*, 2005, **127**, 10850.
13 (*a*) C. Defieber, H. Grützmacher and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2008, **47**, 4482; (*b*) F. R. Hartley, *Chem. Rev.*, 1973, **73**, 163.
14 Recently, Faller *et al.* reported the resolution of diastereopure (*S*)-**1a-Rh**/**7** by recrystallization from the diastereomeric mixture ((*S*)-**1a-Rh**/**7** : (*R*)-**1a-Rh**/**7** = 3 : 1) after the kinetic chirality control. The structure was proved by X-ray analysis: J. W. Faller and J. C. Wilt, *J. Organomet. Chem.*, 2006, **691**, 2207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15 (*a*) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029; (*b*) S. Mori, T. Vreven and K. Morokuma, *Chem.–Asian J.*, 2006, **1**, 391.
16 J. M. Hopkins, S. A. Dalrymple, M. Parvez and B. A. Keay, *Org. Lett.*, 2005, **7**, 3765.
17 K. Aikawa, S. Akutagawa and K. Mkami, *J. Am. Chem. Soc.*, 2006, **128**, 12648. Asymmetric catalysts are prepared by a suitable combination of chiral ligands and metals. The asymmetric catalysts thus prepared can be further evolved into more activated catalysts with higher catalytic activity and enantioselectivity by ligation of chiral activators (''Asymmetric Activation'', see ref. 18). However, the additional ligation does not necessarily lead to higher catalytic activity, for which we have proposed the term ''asymmetric synergy (effect)'' leading to higher enantioselectivity without an increase in the catalytic activity (even with a decrease).
18 (*a*) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki and R. Angelaud, *Angew. Chem., Int. Ed.*, 2000, **39**, 9000; (*b*) S. Matsukawa and K. Mikami, *Enantiomer*, 1996, **1**, 69; (*c*) K. Mikami and S. Matsukawa, *Nature*, 1997, **385**, 613.