Crystallographic Data Centre as supplementary publication nos. CCDC-102586 and CCDC-102587 (**1a** and **1e**, respectively). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: (+44) 1223-336-033; E-mail: deposit@ccdc.cam.ac.uk).

[17] a) M. Fujita, O. Sasaki, T. Mitsuhashi, T. Fujita, J. Yazaki, K. Yamaguchi, K. Ogura, *Chem. Commun.* **1996**, 1535; b) P. J. Stang, D. H. Cao, S. Saito, A. M. Arif, *J. Am. Chem. Soc.* **1995**, *117*, 6273; c) R. V. Slone, D. I. Yoon, R. M. Calhoun, J. T. Hupp, *J. Am. Chem. Soc.* **1995**, *117*, 11813.

[18] L. R. MacGillivray, J. L. Atwood, *Nature* **1997,** *389*, 469 – 472.

[19] R. Hoss, O. Konig, V. Kramer-Ross, U. Berger, P. Rogin, J. Hulliger, *Angew. Chem.* **1996**, *108*, 1774; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1664.

[20] M. E. Brown, M. D. Hollingsworth, *Nature* **1995,** *376*, 323 – 326.

[21] M. Sakamoto, *Chem. Eur. J.* **1997,** *3*, 684 – 689.

Conformationally Flexible Biphenylphosphane Ligands for Ru-Catalyzed Enantioselective Hydrogenation**

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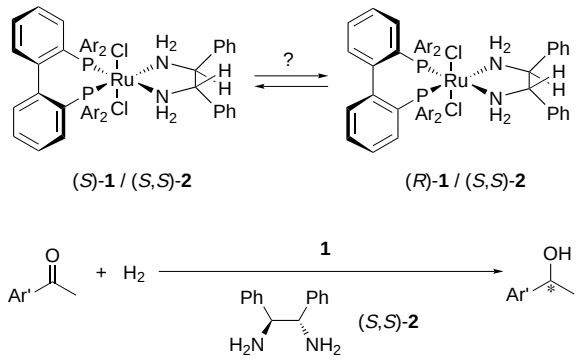
In asymmetric catalytic reactions,[1] racemic catalysts inherently give only racemic products, whereas nonracemic catalysts generate nonracemic products with or without a nonlinear relationship.[2] Conversely, we reported a conceptually new strategy for asymmetric catalysis using racemic catalysts wherein a chiral additive selectively activates,[3] rather than deactivates,[4] one enantiomer of the racemic catalyst. We here describe an advanced strategy that uses conformationally flexible bis(phosphanyl)biphenyl ligands (BIPHEP)[5] for a Ru catalyst which, following activation by a chiral diamine,[3d, 6] achieves high enantioselectivity in the hydrogenation of carbonyl compounds (see Scheme 1). Combination of a racemic BINAP/$RuCl_2$ species (BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) with an equimolar amount of an enantiomerically pure diamine gives a 1:1 mixture of two diastereomeric diphosphane/diamine complexes.[3d] When the BINAP ligand is replaced by the flexible and proatropisomeric BIPHEP, diastereomeric complexes are formed, in principle, in unequal amounts. Here, if the major diastereomer shows higher chiral efficiency than does the minor isomer, this strategy becomes more beneficial than the use of structurally similar BINAP analogues.

The hydrogenation of a carbonyl compound by the complex formed from [$RuCl_2$(dm-biphep)$(dmf)_n$] (**1**; DM-BIPHEP = 2,2′-[(3,5-dimethylphenyl)phosphanyl]biphenyl) and enantiopure (*S*,*S*)-1,2-diphenylethylenediamine ((*S*,*S*)-DPEN; (*S*,*S*)-**2**)[7] is shown in Scheme 1. Conformational flexibility of the



Scheme 1. Enantioselective hydrogenation of carbonyl compounds to optically active alcohols catalyzed by Ru complexes containing conformationally flexible BIPHEP ligands. In each case, (*S*)-**1** and (*R*)-**1** (Ar = 3,5-dimethylphenyl) is fixed in the respective configuration. The chiral amine (*S*,*S*)-**2** is added as activator to complex **1** prior to the hydrogenation.

BIPHEP/$RuCl_2$/diamine complexes was proven by ^{1}H NMR spectroscopic analysis. A mixture of **1** and **2** in $CDCl_3$ at room temperature showed a ^{1}H NMR spectrum that is quite similar to that of the racemic DM-BINAP/$RuCl_2$/(*S*,*S*)-DPEN complex.[8, 9] This indicated the initial formation of an equimolar mixture of *S*- and *R*-fixed DM-BIPHEP/$RuCl_2$/(*S*,*S*)-DPEN diastereomers in this solvent (^{1}H NMR ($CDCl_3$): (*S*)-DM-BIPHEP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta = 3.42$, 3.43, 4.33; (*R*)-DM-BIPHEP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta = 3.28$, 4.06, 4.59). However, when this mixture was diluted with [D_8]2-propanol ($CDCl_3$/$(CD_3)_2CDOD$ 1/2) and allowed to stand at room temperature for 3 h or at 80 °C for 30 min, a 3:1 mixture of the *S*/*S*,*S* and *R*/*S*,*S* diastereomers was formed (Figure 1, Scheme 2; ^{1}H NMR

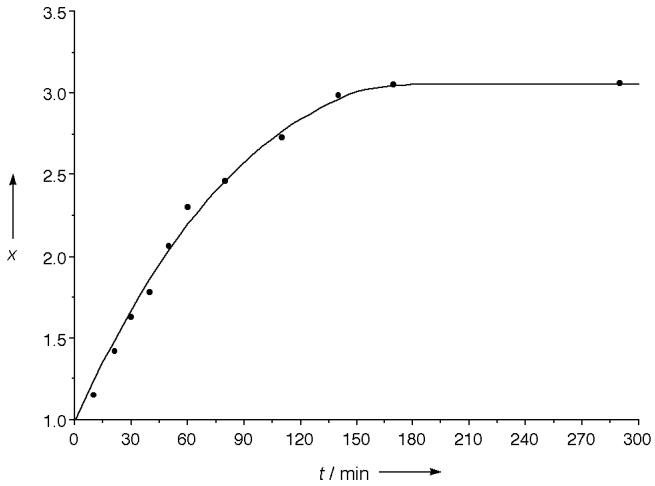


Figure 1. Stereomutation of DM-BIPHEP/$RuCl_2$/(*S*,*S*)-DPEN diastereomers in $CDCl_3$/$(CD_3)_2CDOD$ (1/2) at 25 °C. x = ratio of (*S*)-DM-BIPHEP/$RuCl_2$/DPEN to (*R*)-DM-BIPHEP/$RuCl_2$/DPEN.

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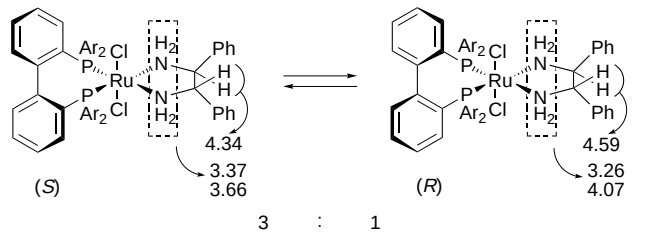
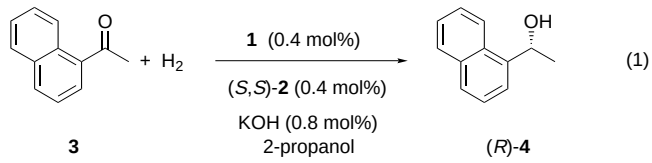
($CDCl_3$/$(CD_3)_2CDOD$ 1/2): (*S*)-DM-BIPHEP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta = 3.37$, 3.66, 4.34; (*R*)-DM-BIPHEP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta = 3.26$, 4.07, 4.59). Stereomutation of the DM-BIPHEP/$RuCl_2$/DPEN complex could occur through rupture of a Ru–P bond, rotation about the C1–C1′ bond to invert the



Scheme 2. Assignment of ^{1}H NMR signals for DM-BIPHEP/$RuCl_2$/(*S*,*S*)-DPEN diastereomers in $CDCl_3$/$(CD_3)_2CDOD$ (1/2). In each case, the *R* and *S* configuration is fixed. Ar = 3,5-dimethylphenyl.

configuration of the diphosphane,[5a] and recoordination of P to Ru.[10] Alternatively, the configuration of the diphosphane-chelated seven-membered ring might be directly inverted. The dichloro complexes may further be converted into active mono- or dihydrido Ru species under hydrogenation conditions.[11]

The enantioselective hydrogenation was performed after addition of KOH and a ketone (e.g. **3**) to a mixture of **1** and **2** with or without preheating at 80 °C for 30 min [Eq. (1), Table 1]. The advantage of the conformationally flexible



(1)

Table 1. Results of the enantioselective hydrogenation of ketone **3** to alcohol **4**. Equation (1) shows the reaction catalyzed by the complex formed from [$RuCl_2$(dm-biphep)$(dmf)_n$] (**1**) and (*S*,*S*)-1,2-diphenylethylenediamine ((*S*,*S*)-**2**).[a]

Run	Phosphane	*S*/*S*,*S*:*R*/*S*,*S*[b]	$p(H_2)$ [atm]	*T* [°C]	*t* [h]	*ee* [%]	Yield [%]
1	DM-BIPHEP	1:1	8	28	4	63	> 99
2	DM-BIPHEP	2:1	8	28	4	73	> 99
3[c]	DM-BIPHEP	3:1	8	28	4	84	> 99
4	(±)-DM-BINAP		8	28	4	80	> 99
5[c]	DM-BIPHEP	3:1	40	−35	12	92	> 99
6	(±)-DM-BINAP		40	−35	7	89	> 99

[a] Hydrogenation performed as described in the text without preheating, unless otherwise noted. [b] The ratio of (*S*)-**1**/(*S*,*S*)-**2** to (*R*)-**1**/(*S*,*S*)-**2** was determined by ^{1}H NMR spectroscopy. [c] **1**/(*S*,*S*)-**2** in 2-propanol was preheated at 80 °C for 30 min.

BIPHEP/$RuCl_2$/diamine complexes is clear in the ratio-dependent enantioselectivity of hydrogenation of 1′-acetonaphthone (**3**) in comparison with the enantioselectivity obtained using the (±)-DM-BINAP/$RuCl_2$/(*S*,*S*)-diamine pair (Table 1, runs 1–3 versus run 4). The lower enantioselectivity of the 1:1 BIPHEP chelate complex pair compared with the 1:1 BINAP chelate pair (runs 1 versus 4) indicates the differences in steric demand of the two types of ligands. Even so, a higher enantioselectivity with a 3:1 BIPHEP-chelate equilibrium (run 3) clearly indicated the advantage of conformationally flexible BIPHEP compared with that of a 1:1 BINAP pair (run 4).

Further increase in enantioselectivity was attained at a lower reaction temperature (−35 °C, run 5). The enantioselectivity by **1**/(*S*,*S*)-**2** was higher than that by the (±)-DM-BINAP/$RuCl_2$/(*S*,*S*)-diamine complex at the same low temperature and high pressure (run 6). Thus, (*R*)-1-(1-naphthyl)ethanol (**4**)[12] was obtained with 92 % *ee* in quantitative yield. DM-BIPHEP/$RuCl_2$/DPEN was also employable in the reduction of *o*-methylacetophenone with H_2 (8 atm). The reaction was carried out with KOH and 2-propanol at 0 °C for 4 h to provide 1-*o*-methylphenylethanol quantitatively and with 88 % *ee* (for comparison, the analogous reaction with (±)-DM-BINAP/$RuCl_2$/(*S*,*S*)-DPEN proceeds with 86 % *ee*).

In summary, we have presented an enantioselective hydrogenation by a conformationally flexible BIPHEP-Ru catalyst containing a chiral diamine ligand. The asymmetric activation will provide a general strategy for the use of not only racemic but also conformationally flexible ligands.

Experimental Section

4: A 100-mL autoclave was charged with solid **1** (11.4 mg, 0.012 mmol) and **2** (2.6 mg, 0.012 mmol). 2-Propanol (3.3 mL) was added to the autoclave under a stream of argon. The solution was preheated at 80 °C for 30 min, and KOH/2-propanol (0.5 M, 48 μL, 0.024 mmol) was added with stirring at room temperature over 30 min. 1′-Acetonaphthone (**3**; 0.46 mL, 3.00 mmol) was added to the autoclave at room temperature under a stream of argon, and then hydrogen (40 atm) was introduced. After the mixture was vigorously stirred for 12 h at −35 °C, the solution was concentrated under reduced pressure. The resulting residue was filtered through a short column of silica gel. The chemical yield and enantiomeric ratio of **4** were calculated by chiral GC (> 99 %, (*R*)-**4**:(*S*)-**4** = 96.0:4.0). Product **4** can also be isolated (510 mg, 99 %) by column chromatography on silica gel (eluent: hexane/EtOAc 5/1). $[\alpha]_D^{28} = +69.0$ ($c = 1.0$, $CHCl_3$; lit. value:[12] $[\alpha]_D^{25} = +78.9$ ($c = 1$, $CHCl_3$), *R* isomer); GC (column: CP-Cyclodextrin-β-2,3,6-M-19, inner diameter: 0.25 mm × 25 m, CHROMPACK, carrier gas: nitrogen (75 kPa), column temperature: 160 °C, injection temperature: 190 °C, split ratio: 100:1), retention time t_R = 32.7 min ((*R*)-(+)-**4**, 96.0 %), 31.6 min ((*S*)-(−)-**4**, 4.0 %), 21.3 min (**3**, 0 %).

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[1] a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; b) H. Brunner, W. Zettlmeier, *Handbook of Enantioselective Catalysis*, VCH, Weinheim, **1993**; c) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**; d) H. B. Kagan, *Comprehensive Organic Chemistry, Vol. 8,*, Pergamon, Oxford, **1992**.

[2] Reviews: R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 34–55; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49–69; H. B. Kagan, D. Guillaneux, D. Rainford, O. Samuel, S.-H. Zhao, *Acta Chem. Scand.* **1996**, *50*, 345–352; M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Tetrahedron Asymm.* **1997**, *8*, 2997–3017; C. Girard, H. B. Kagen, *Angew. Chem.* **1998**, *110*, 3088–3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959; examples: a) D. Guillaneux, S.-H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430–9439; C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353–2357; b) M.

  1433-7851/99/3804-0496 $ 17.50+.50/0

Kitamura, S. Suga, M. Niwa, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 4832 – 4842; c) N. Oguni, Y. Matsuda, T. Kaneko, *J. Am. Chem. Soc.* **1988**, *110*, 7877 – 7877; d) K. Mikami, Y. Motoyama, M. Terada, *J. Am. Chem. Soc.* **1994**, *116*, 2812 – 2820; K. Mikami, M. Terada, *Tetrahedron* **1992**, *48*, 5671 – 5680; M. Terada, K. Mikami, T. Nakai, *J. Chem. Soc. Chem. Commun.* **1990**, 1623 – 1624.

[3] a) K. Mikami, S. Matsukawa, *Nature* **1997**, *385*, 613 – 615; b) S. Matsukawa, K. Mikami, *Tetrahedron Asymm.* **1997**, *8*, 815 – 816; c) *Enantiomer* **1996**, *1*, 69 – 73; d) T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 1086 – 1087.

[4] For an opposite strategy of deactivation, see N. W. Alcock, J. M. Brown, P. J. Maddox, *J. Chem. Soc. Chem. Commun*. **1986**, 1532 – 1534; J. M. Brown, P. J. Maddox, *Chirality* **1991**, *3*, 345 – 354; K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 789 – 790; J. W. Faller, J. Parr, *J. Am. Chem. Soc.* **1993**, *115*, 804 – 805.

[5] a) The activation barrier to axial torsion in selectively deuterated BIPHEP is measured to be only (22 ± 1) kcal, which suggests that axial rotation takes place at room temperature or above: O. Desponds, M. Schlosser, *Tetrahedron Lett*. **1996**, *37*, 47 – 48, and references therein; b) see also 6,6′-substituted analogues: G. Trabesinger, A. Albinati, N. Feiken, R. W. Kunz, P. S. Pregosin, M. Tschoerner, *J. Am. Chem. Soc.* **1997**, *119*, 6315 – 6323, and references therein.

[6] a) T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2675 – 2676; b) T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 10417 – 10418; c) H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem.* **1998**, *110*, 1792 – 1796; *Angew. Chem. Int. Ed.* **1998**, *37*, 1703 – 1707.

[7] a) P. Mangeney, T. Tejero, A. Alexakis, F. Grosjean, J. Normant, *Synthesis* **1988**, 255 – 257; b) S. Pikul, E. J. Corey, *Org. Synth*. **1993**, *71*, 22 – 29.

[8] 3,5-Dimethylphenyl-BINAP: K. Mashima, Y. Matsumura, K. Kusano, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Chem. Soc. Chem. Commun*. **1991**, 609 – 610.

[9] ^{1}H NMR ($CDCl_3$): (*S*)-DM-BINAP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta = 3.02$, 3.16, 4.19; (*R*)-DM-BINAP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta = 2.62$, 3.86, 4.43. ^{1}H NMR ($CDCl_3$/$(CD_3)_2CDOD$ 1/2): (*S*)-DM-BINAP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta = 2.98$, 3.36, 4.21; (*R*)-DM-BINAP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta =$ 2.60, 3.87, 4.42.

[10] Although the DM-BIPHEP/$RuCl_2$/DPEN complex was treated with DM-BINAP in 2-propanol, it was not observed by ^{1}H NMR spectroscopy.

[11] R. L. Chowdhury, J.-E. Bäckvall, *J. Chem. Soc. Chem. Commun*. **1991**, 1063 – 1064; K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem*. **1997**, *109*, 297 – 300; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 285 – 288; R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97 – 102.

[12] P. D. Theisen, C. H. Heathcock, *J. Org. Chem.* **1988**, *53*, 2374 – 2378; W. H. Pirkle, S. D. Beare, *J. Am. Chem. Soc.* **1967**, *89*, 5485 – 5487.

Super High Throughput Screening (SHTS) of Chiral Ligands and Activators: Asymmetric Activation of Chiral Diol – Zinc Catalysts by Chiral Nitrogen Activators for the Enantioselective Addition of Diethylzinc to Aldehydes**

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Combinatorial chemistry has been well recognized as a useful strategy for the discovery and optimization of bioactive drugs, coordination complexes, and solid-state materials.[1] Of the split-and-mix and parallel-matrix strategies, the latter is more employable for lead optimization, and high-throughput screening (HTS) is essential for tuning a variety of modifications.[2] However, only a limited number of investigations has so far been reported on the optimization of chiral ligands for metal complexes.[3] With HPLC or gas chromatography (GC) on chiral columns, it takes a tediously long time to separate enantiomeric products and then to determine the enantioselectivity of the reactions. The application of a detection system based on circular dichroism (CD) to HPLC on nonchiral stationary phases allows the simultaneous monitoring of the CD signal $\Delta\varepsilon$, the absorption ε, and their ratio $g = \Delta\varepsilon/\varepsilon$. The dissymmetry factor g is independent of concentration and is linearly related to the enantiomeric excess.[4] With this technique, the enantiomeric excess of the product could be determined within minutes without separation of the enantiomeric products. Therefore, combined application of the combinatorial chemistry (CC) factory (Dainippon Seiki, DNC) for reactions and HPLC-CD provide a highly efficient screening system, which we refer to as the super high throughput screening (SHTS) system, for finding the most effective catalyst through asymmetric activation.

Asymmetric activation of a chiral catalyst with a chiral additive may enhance the levels of catalyst efficiency and enantioselectivity.[5] The advantage of this approach over the deactivation strategy[6] is that the activated catalyst can produce a greater enantiomeric excess in the products than can the enantiomerically pure catalyst on its own. Sharpless et al. emphasized the importance of "chiral ligand accelation" through the construction of an asymmetric catalyst from an achiral precatalyst by ligand exchange with a chiral ligand.[7] Chiral catalysts thus obtained with chiral ligands (L1*, L2*,…) may be further evolved with chiral activators (A1*, A2*,…) into the most catalytically active and enantioselective chiral catalysts (Scheme 1).

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