# Asymmetric Activation of Racemic Ruthenium(II) Complexes for Enantioselective Hydrogenation

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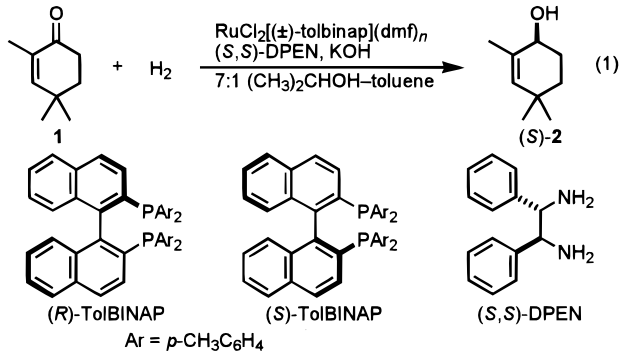
The stereoselectivity and turnover frequency (rate) of asymmetric catalysis with chiral metal complexes are significantly affected by the nature of the donor compounds present in the reaction mixture, resulting in various nonlinear phenomena.[1−3] Certain racemic metal complexes can catalyze an enantioselective transformation in the presence of a nonracemic auxiliary, when one of the catalyst enantiomers is selectively activated[4] or deactivated.[5] The recently developed $RuCl_2$(diphosphine)$S_n$/1,2-diamine/alkaline base ternary catalyst system effects practical hydrogenation of a diverse array of nonfunctionalized ketones.[6] The reaction with mild conditions (1 to 8 atm) exhibits high C═O/C═C selectivity and excellent diastereo- and enantioselectivity. Here if one can use a racemic diphosphine ligand for asymmetric hydrogenation, the synthetic utility will be further increased. We now have realized asymmetric activation of racemic diphosphine−Ru(II) complexes using a nonracemic 1,2-diamine.

$RuCl_2$(tolbinap)$(dmf)_n$,[7,8] either racemic or enantio-pure, is a feeble catalyst for hydrogenation of simple ketones. However, when 2,4,4-trimethyl-2-cyclohexenone (**1**) was hydrogenated in the presence of racemic $RuCl_2$(tolbinap)$(dmf)_n$, (*S*,*S*)-1,2-diphenylethylenediamine [(*S*,*S*)-DPEN],[9] and KOH in a 7:1 mixture of 2-propanol and toluene ([**1**] = 0.6 M, ketone:Ru:diamine:KOH molar ratio = 500:1:1:2, 8 atm, 0 °C, 6 h), the allylic alcohol (*S*)-**2** was produced in 95% ee in 100% yield (eq 1).[10,11] The




enantiomeric purity was very close to the 96% ee attainable with a combination employing enantiomerically pure (*R*)-TolBINAP and (*S*,*S*)-DPEN. The (*R*)-diphosphine/(*R*,*R*)-diamine combination (1:1 molar ratio) catalyzed the reaction slowly to give (*S*)-**2** in only 26% ee. As illustrated in Figure 1, the rate of hydrogenation with the (±)-TolBINAP−Ru complex was enhanced with an increase in the amount of (*S*,*S*)-DPEN, reaching a near maximum value with the addition of a 1.0 molar amount of the diamine. On the other hand, the ee value of the product was consistently high (>90%) from the beginning (diamine/Ru > 0.25). Thus, (*S*,*S*)-DPEN was shown to more effectively activate the (*R*)-TolBINAP−Ru isomer of the racemate under the hydrogenation conditions employed.

A mixed-ligand catalyst was prepared from equimolar amounts of the (±)-TolBINAP−Ru complex and (*S*,*S*)-DPEN, and this was followed by the addition of an equimolar amount of (*R*,*R*)-DPEN. The system contains equal amounts of enantiomers for both diphosphine and diamine (diphosphine:diamine = 1:2). Nevertheless, this mixture catalyzed hydrogenation of **1** in a 2-propanol−toluene solution containing KOH (8 atm, 14 h) affording (*S*)-**2** in 91% ee and 100% yield, in which the inherent stereoselectivity of the (*R*)-TolBINAP/(*S*,*S*)-DPEN combination was preserved. This result indicates that the interaction of the $RuCl_2$(diphosphine) complex and DPEN is virtually irreversible. In fact, a complex prepared from $RuCl_2$[(*R*)-tolbinap]$(dmf)_n$ and (*S*,*S*)-DPEN (1:1) in a 1:7 $(CD_3)_2CDOD-C_6D_5CD_3$ mixture gave a single $^{31}$P-NMR signal at $\delta$ 45.8 ppm (10% $H_3PO_4$ as external standard), while the *S*/*S*,*S* ligand combination gave a signal at $\delta$ 46.2 ppm. A 1:0.5 to 1:2 mixture of $RuCl_2$[(±)-tolbinap]$(dmf)_n$ and (*S*,*S*)-DPEN showed these signals with equal intensities.

Hydrogenation of 9-acetylanthracene with the (±)-TolBINAP/(*S*,*S*)-DPEN combined system (0.9 M, ketone:Ru:diamine:KOH = 250:1:1:2, 8 atm, 80 °C, 10 h) gave (*R*)-1-(9-anthryl)ethanol

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(1) (a) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357. (b) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430−9439.

(2) Review: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. See also: (b) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877−7878. (c) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767−768. (d) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997−3017.

(3) For selected examples, see: (a) Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623−1624. (b) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205−1215. (c) Tanaka, K.; Matsui, J.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 153−157. (d) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529−4533. (e) Evans, D. A.; Nelson, S. G.; Gagné, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800−9801. (f) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543−6544. (g) Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467−4478. (h) Terada, M.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1994**, 833−834. (i) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812−2820.

(4) (a) Matsukawa, S.; Mikami, K. *Enantiomer* **1996**, *1*, 69−73. (b) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613−615.

(5) (a) Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 789−790. (b) Faller, J. W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804−805. (c) Faller, J. W.; Tokunaga, M. *Tetrahedron Lett.* **1993**, *34*, 7359−7362. (d) Faller, J. W.; Sams, D. W. I.; Liu, X. *J. Am. Chem. Soc.* **1996**, *118*, 1217−1218. (e) Sablong, R.; Osborn, J. A.; Faller, J. W. *J. Organomet. Chem.* **1997**, *527*, 65−70. (f) Alcock, N. W.; Brown, J. M.; Maddox, P. J. *J. Chem. Soc., Chem. Commun.* **1986**, 1532−1534. (g) Brown, J. M.; Maddox, P. J. *Chirality* **1991**, *3*, 345−354.

(6) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675−2676. (b) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417−10418. (c) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872−4873. (d) Ohkuma, T.; Ikehira, H.; Ikariya, T.; Noyori, R. *Synlett* **1997**, 467−468.

(7) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629−635.

(8) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1−13.

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

(10) A mixture of $RuCl_2$[(±)-tolbinap]$(dmf)_n$[8] (9.4 mg, 0.01 mmol), (*S*,*S*)-DPEN[9] (2.1 mg, 0.01 mmol), 2-propanol (3 mL), toluene (1 mL), and a 0.5 M KOH solution in 2-propanol (40 $\mu$L, 0.02 mmol) placed in a glass autoclave was degassed and sonicated for 15 min. 2-Propanol (4 mL) and **1** (691 mg, 5.0 mmol) were added to the autoclave and hydrogen was introduced to a pressure of 8 atm. The reaction mixture was vigorously stirred for 6 h at 0 °C. Workup and chromatography with a short silica gel column gave (*S*)-**2** in 95% ee (684 mg, 98% yield), $[\alpha]^{24}_D$ −88.3° (*c* 1.03, $CH_3OH$).

(11) (*R*)- and (*S*)-**2** are the key intermediates in the synthesis of carotenoid-derived odorants and other bioactive compounds. See: (a) Mori, K.; Puapoomchareon, P. *Liebigs Ann. Chem.* **1991**, 1053−1056. (b) Croteau, R.; Karp, F. In *Perfumes: Art, Science and Technology*; Müller, P. M., Lamparsky, D., Eds.; Blackie Academic & Professional: London, 1991; Chapter 4.

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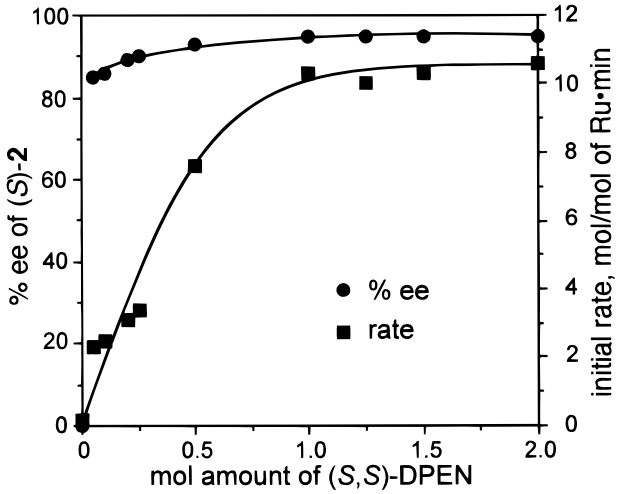
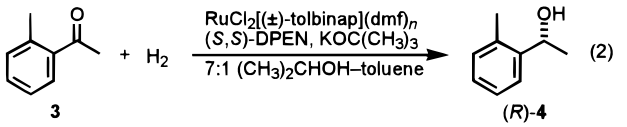



**Figure 1.** Asymmetric activation of a racemic TolBINAP−Ru complex with (*S*,*S*)-DPEN in the hydrogenation of **1** (**1**:Ru:KOH = 500:1:10, 8 atm, 28 °C).

in 80% ee in 99% yield. The ee value was comparable with the 82% accessible with the pure *R*/*S*,*S* combination.

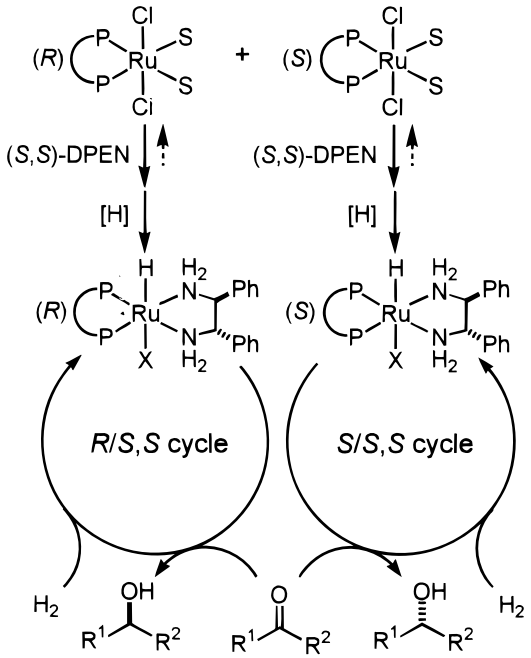
When *o*-methylacetophenone (**3**) was used as substrate, (*S*,*S*)-DPEN enhanced the activity of the (*S*)-TolBINAP−Ru complex more than that of the (*R*)-TolBINAP-based isomer. The hydrogenation in the presence of $RuCl_2[(\pm)\text{-tolbinap}](dmf)_n$, (*S*,*S*)-DPEN, and $KOC(CH_3)_3$ in a 7:1 mixture of 2-propanol and toluene (0.6 M, ketone:Ru:diamine:base = 500:1:1:2, 4 atm, 0 °C, 10 h) gave (*R*)-**4** quantitatively and in 90% ee (eq 2). Separate




experiments revealed that an enantiomerically pure complex, $RuCl_2[(S)\text{-tolbinap}](dmf)_n$, coupled with (*S*,*S*)-DPEN, catalyzes hydrogenation of **3** giving (*R*)-**4** in 97.5% ee and that the reaction with (*R*,*R*)-DPEN affords (*R*)-**4** in only 8% ee. Hydrogenation of 1′-acetonaphthone with the (±)-TolBINAP/(*S*,*S*)-DPEN system (0.6 M, ketone:Ru:diamine:KOH = 500:1:1:2, 4 atm, 0 °C, 6 h) gave (*R*)-1-(1-naphthyl)ethanol with 76% ee in 100% yield. The *R* alcohol is obtainable in 97% ee with the (*S*)-diphosphine/(*S*,*S*)-diamine combination.[6a]

Scheme 1 provides the simplest explanation for the observed asymmetric activation of the racemic Ru complex with (*S*,*S*)-DPEN. The enantioselectivity of hydrogenation reflects the relative turnover numbers of the competing *R*/*S*,*S* and *S*/*S*,*S* catalytic cycles, and the ratio is determined by the relative concentrations and reactivities of the coexisting diastereomeric diphosphine/diamine Ru catalysts.[1,12,13] The TolBINAP−Ru dichloride existing as aggregates[8] is feeble for hydrogenation of simple ketones. Under the reaction conditions, the labile ligands (S) are readily displaced by (*S*,*S*)-DPEN to form a monomeric

**Scheme 1.** Mechanism of Asymmetric Activation




diphosphine/diamine complex.[14] This equilibrium lies far to the mixed-ligand complex regardless of the chirality of the ligands. The real hydrogenation catalyst is probably the chiral Ru mono- or dihydride formed from the dichloride, alkaline base, and 2-propanol and/or hydrogen.[15,16] The rate and stereoselectivity including the sense of asymmetric induction achieved with these diastereomeric catalysts are highly dependent on the structures of ketonic substrates. During hydrogenation of the cyclohexenone **1** (eq 1), the *R*/*S*,*S* cycle with an *S*:*R* enantioselectivity of 98:2 occurs 121 times faster than the *S*/*S*,*S* cycle which has an *S*:*R* ratio of 37:63. On the other hand, with the aromatic ketone **3** as substrate (eq 2), the *S*/*S*,*S* cycle, which displays an *S*:*R* enantioselectivity of 1.3:98.7, turns over 13 times faster than does the diastereomeric *R*/*S*,*S* cycle with an *S*:*R* ratio of 54:46.

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**Supporting Information Available:** Experimental procedures for hydrogenation and GC, HPLC, and $^1$H-NMR data of the products (5 pages). See any current masthead page for ordering and Internet access instructions.

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(12) Review of double stereodifferentiation, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl*. **1985**, *24*, 1−30.

(13) Molecular association of the catalyst or its precursors may lead to further complicated nonlinear effects.[1, 2]

(14) Cenini, S.; Porta, F.; Pizzotti, M. *J. Mol. Catal*. **1982**, *15*, 297−308.

(15) (a) Chowdhury, R. L.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun*. **1991**, 1063−1064. (b) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 285−288. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res*. **1997**, *30*, 97−102.

(16) The geometry of the Ru complexes may be cis or trans or a mixture of both. The sensitivity of the catalytic complexes did not allow for structural elucidation.