BINAP: An Efficient Chiral Element for Asymmetric Catalysis

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Until the early 1970s, chemical access to enantiomerically pure substances from prochiral precursors remained extremely difficult. Recent dramatic advances in man-made catalysts, however, are converting the chemists' dream into reality. Particularly, homogeneous asymmetric catalysis using chiral metal complexes provides an ideal way to multiply chirality, beginning a new era where production of large amounts of chiral compounds of either absolute configuration is possible with a very small quantity of chiral source. This methodology based on accumulated chemical knowledge is highly rational and flexible, and the opportunities it affords are practically unlimited. Reported examples of the highly enantioselective catalyses include hydrogenation, hydrosilylation, and hydroboration of unsaturated compounds, epoxidation of allylic alcohols, vicinal hydroxylation, hydrovinylation, hydroformylation, cyclopropanation, and isomerization of olefins, propylene polymerization, organometallic addition to aldehydes, allylic alkylation, organic halide–organometallic coupling, aldol type reactions, and Diels–Alder and ene reactions.[1,2]

Proper combination of selected central metals and well-designed chiral ligands is the most important requirement for high efficiency. Many metal complexes have diastereotopic reaction sites and, in solution, are thermodynamically or kinetically labile. Such tendencies often result in competing reactions which lead to products of opposite configuration at different rates. As such, intellectual and technical efforts should be made to achieve a singular catalytic species in order to obtain a high degree of stereoselection, although, in some special cases, highly enantioselective reactions may be accomplished by using even partially resolved chiral auxiliaries;[3] where apparently plural catalysts (precursors) are operating.

BINAP and Its Metal Complexes

The ligands or ancillaries of metals must be endowed with suitable functionality, configuration, and conformational rigidity or pliancy,[4] depending on the case, all of which contribute to the desired stereoselectivity. In view of the general utility of phosphine ligands in transition-metal-catalyzed asymmetric reactions, we had a keen interest in 2,2′-bis(diarylphosphino)-1,1′-binaphthyl (BINAP, **1**),[5] which possesses only an axial element of chirality. After many trials to obtain (*R*)-BINAP (**1**, Ar = C_6H_5) by stereospecific conversion of optically pure (*R*)-2,2′-diamino-1,1′-binaphthyl,[6,7] we were first able to report a reliable synthesis of (*R*)- and (*S*)-BINAP (Ar = C_6H_5), in 1980, based on the resolution of the racemate by an optically active amine–Pd(II) complex.[5] A more convenient approach to BINAP is the resolution of the racemic diphosphine dioxide, BINAPO, by camphorsulfonic acid or 2,3-*O*-dibenzoyltartaric acid, followed by reduction with trichlorosilane.[8] This method is very practical and allows the synthesis of various analogues on a large scale.[9]

BINAP has numerous unique features. Firstly, this diphosphine is characterized by full aromatic substitution which exerts paramount steric influence, provides polarizability, and enhances the Lewis acidity of the metal complexes. The aromatic compound has higher chemical stability than aliphatic phosphines. Axially dissymmetric BINAP possesses C_2 symmetry,[10] the significance of which was first shown by Kagan's DIOP in conjunction with the Rh-catalyzed asymmetric hydrogenation,[11] while the binaphthyl skeleton is known to have superior chirality recognition and induction abilities.[12] The BINAP ligand is conformationally

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(1) For the present state of this subject, see: (a) Noyori, R. *Science* **1990**, *248*, 1194. (b) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods 1989*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1989; p 115. (c) Blystone, S. L. *Chem. Rev.* **1989**, *89*, 1663. (d) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901. (e) Brunner, H. *Top. Stereochem.* **1988**, *18*, 129.

(2) Accomplishments up to the early 1980s: (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5. (b) Kagan, H. B. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: London, 1982; Vol. 8, p 463. (c) *Asymmetric Catalysis*; Bosnich, B., Ed.; NATO ASI Series; Martinus Nijhoff Publishers: Dordrecht, 1986.

(3) (a) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597. (b) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (c) Oguni, N.; Matsuda, Y.; Kaneko, T. *Ibid.* **1988**, *110*, 7877. (d) Noyori, R.; Kitamura, M. *Angew. Chem.*, in press.

(4) Noyori, R.; Takaya, H. *Chem. Scr.* **1985**, *25*, 83.

(5) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

(6) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.

(7) Brown, K. J.; Berry, M. S.; Waterman, K. C.; Lingenfelter, D.; Murdoch, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 4717.

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

(9) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1988**, *67*, 20.

(10) Review: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(11) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

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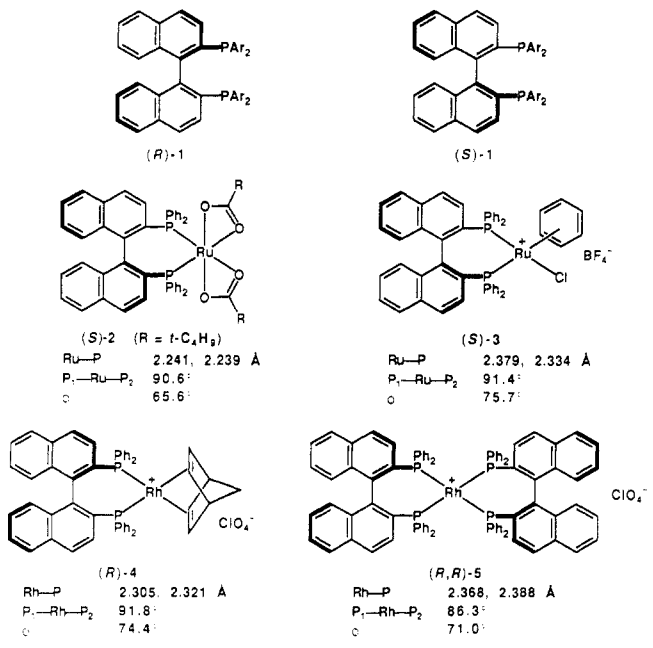
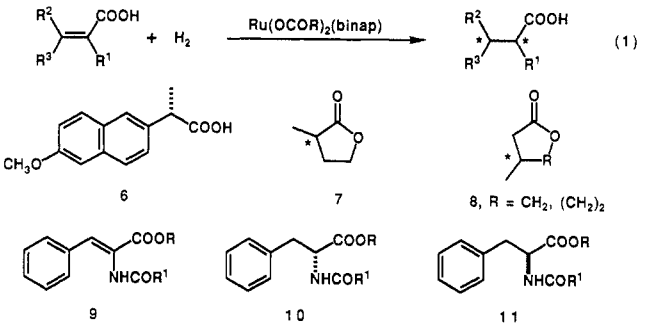
flexible and can accommodate a wide variety of transition metals by rotation about the binaphthyl C(1)–C(1′) pivot and C(2 or 2′)–P bonds without a serious increase of torsional strain. The resulting seven-membered rings containing only sp^2-hybridized carbon atoms are in turn skeletally unambiguous and are skewed to a greater extent than analogous structures containing sp^3 carbons. This feature, providing distinct differentiation of the quadrant space sectors, is indicated by the single-crystal X-ray analysis of the octahedral Ru(II) complexes, **2**[13] and **3**,[14] and the square-planar Rh(I) complexes, **4**[5,15] and **5**[16] (ϕ = dihedral angle between the naphthalene rings). Notably, the bidentate ligation of the pivalate moieties in (*S*)-**2** occurs stereoselectively to form the Λ diastereomer. Furthermore, the double bonds in the coordinated norbornadiene in **4** are not perpendicular to the P–Rh–P plane but tilted by ca. 15°. Thus the chirality which originally issued by the binaphthyl skeleton is transmitted to the other metal coordination sites through phosphorus–metal interaction, where the phenyl rings attached to the phosphorus atoms exert a significant role. The complexes **2**–**5** serve as excellent catalyst precursors in various enantioselective reactions. Some other catalytically active BINAP metal complexes can be generated by modification of these complexes or in independent ways.



Asymmetric Hydrogenation of Olefins

Homogeneous asymmetric hydrogenation of olefins using chiral phosphine–Rh complexes, first found in 1968,[17] has presented a variety of impressive chemistries. A number of natural and unnatural amino acids are now available in >90% ee from (*Z*)-α-(acylamino)acrylic acids or esters, and this methodology is gaining practical significance in industry.[18] A cationic BINAP–Rh complex also effects enantioselective (up to 100%) hydrogenation.[5,6] Unfortunately, the scope of the Rh-catalyzed reaction is not very wide. On the other hand, the BINAP–Ru chemistry has unprecedentedly broad utility.[19,20]

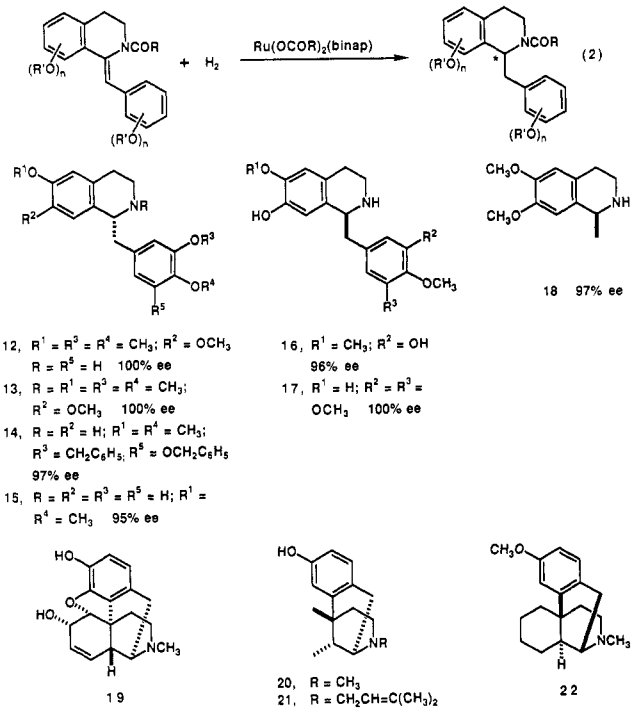
First, the BINAP–Ru dicarboxylate complexes of type **2** hydrogenate prochiral α,β- or β,γ-unsaturated carboxylic acids to give optically active saturated carboxylic acids (eq 1).[21] Chelate complexes in which carboxylate and olefinic double bond coordinate to a Ru metal center are considered to be reactive intermediates, and under optimized conditions, ee's as high as 85–97% are accessible. The sense and extent of the asymmetric induction are highly dependent on the substitution pattern and reaction conditions, particularly the hydrogen pressure.[22] Antiinflammatory (*S*)-naproxen (**6**) is obtainable in 97% ee by the high-pressure reaction in methanol. Hydrogenation of certain hydroxylated or acetoxylated unsaturated acids leads to optically active lactones such as **7** or **8**. Itaconic acid and butadiene-2,3-dicarboxylic acid are saturated in an enantioselective manner by hydrogenation with $Ru_2Cl_4(binap)_2{\cdot}N(C_2H_5)_3$.[23]



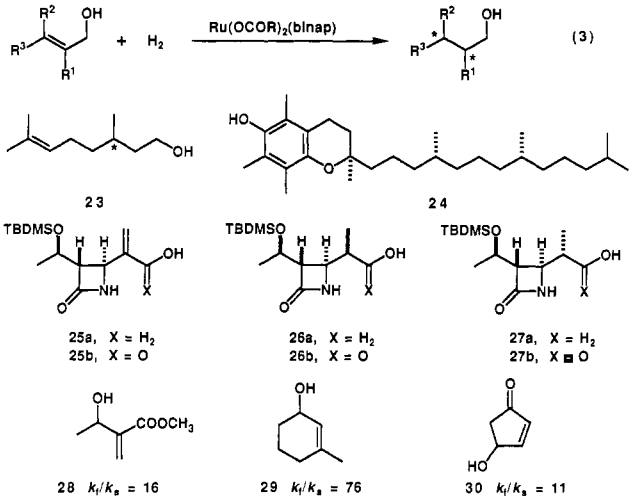
Neutral functionalities also exert a directing effect through heteroatom coordination to the Ru atom in the enantioface differentiation.[24] In the presence of (*R*)-BINAP–Ru(II) complexes, the enamide **9** is hydrogenated to **10** in 79–92% ee.[23a,25] Notably, with $[Rh((R)\text{-binap})(CH_3OH)_2]ClO_4$ as catalyst,[5,6] the opposite asymmetric orientation is seen, giving enantiomeric **11** in 92–100% ee. Here the amide group is directing the reactivity and selectivity. The BINAP–Ru dicarboxylate complexes (**2**) catalyze highly enantioselective hydrogenation of *N*-acyl-(*Z*)-1-alkylidene-

(12) For example: (a) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8. (b) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709. (c) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *Ibid.* **1984**, *106*, 6717.
(13) Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566.
(14) Mashima, K.; Kusano, K.; Ohta, T.; Noyori, R.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1208.
(15) Toriumi, K.; Ito, T.; Takaya, H.; Souchi, T.; Noyori, R. *Acta Crystallogr., Sect. B* **1982**, *B38*, 807.
(16) Tani, K.; Yamagata, T.; Tatsuno, Y.; Yamagata, Y.; Tomita, K.; Akutagawa, S.; Kumobayashi, H.; Otsuka, S. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 217.
(17) (a) Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942. (b) Knowles, W. S.; Sabacky, M. J. *J. Chem. Soc., Chem. Commun.* **1968**, 1445.
(18) (a) Knowles, W. S. *J. Chem. Educ.* **1986**, *63*, 222. (b) Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 2. (c) Koenig, K. E. *Ibid.* Chapter 3. (d) Kagan, H. B. *Bull. Soc. Chim. Fr.* **1988**, 846.
(19) Noyori, R. *Chimia* **1988**, *42*, 215.
(20) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187.
(21) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174.
(22) Unpublished result.
(23) (a) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *J. Chem. Soc., Perkin Trans.* **1989**, 1571. (b) Muramatsu, H.; Kawano, H.; Ishii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 769.
(24) Review on functional group directed hydrogenation: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.
(25) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.

1,2,3,4-tetrahydroisoquinolines as depicted by eq 2.[26] The reaction under 1–4 atm of hydrogen in methanol with the (*R*)-BINAP complexes generally gives the 1*R* products in 95–100% ee, while the *S* catalysts predominantly afford the 1*S* antipodes. This versatility has been demonstrated with the enantioselective preparation of tetrahydropapaverine (**12**), laudanosine (**13**), norreticurine (**16**), tretoquinol (**17**), salsolidine (**18**), etc. The Ru complex catalysts are superior to the Rh complexes giving opposite enantioselection in lower ee's (for example, **12** in 70% ee). This enantioselective hydrogenation coupled with Grewe type annulation has provided a new route to optically active morphine (**19**) and its analogues.[27] Thus the Beyerman and Rice intermediates, **14** and **15**, for the synthesis of **19** are readily obtainable.[22] In addition, this procedure is applicable to the synthesis of benzomorphan derivatives such as metazocine (**20**) or pentazocine (**21**) and morphinan analogues including dextromethorphan (**22**), an anticough agent. This invention has thus realized a general asymmetric synthesis of isoquinoline alkaloids.



Allylic alcohols are another class of substrates that can be hydrogenated with a high degree of enantioselection (eq 3).[28] The substitution pattern and hydrogen pressure profoundly affect the sense and extent of the asymmetric induction.[22] For instance, the high-pressure hydrogenation of geraniol catalyzed by the (*R*)-BINAP complex affords (*S*)-citronellol (**23**) in 96–99% ee, leaving the C(6)–C(7) double bond intact. Either antipodal **23** is accessible by choosing the handedness of the BINAP ligand or by changing the olefin geometry. The hydrogenation can be run in alcoholic media with high (50%) substrate concentration, and the substrate/catalyst mole ratio approaches even 50 000. Satisfactory results were not obtained with cationic or neutral BINAP–Rh complexes.[29] Homogeraniol is hydrogenated also in high (92%) enantioselectivity, but the bis-homo analogue is inert to the hydrogenation. The regio- and enantiocontrolled hydrogenation has been used to prepare dolichols.[22,30] This procedure is applicable to the synthesis of stereodefined side chains of vitamin E (**24**) and K_1.[28]



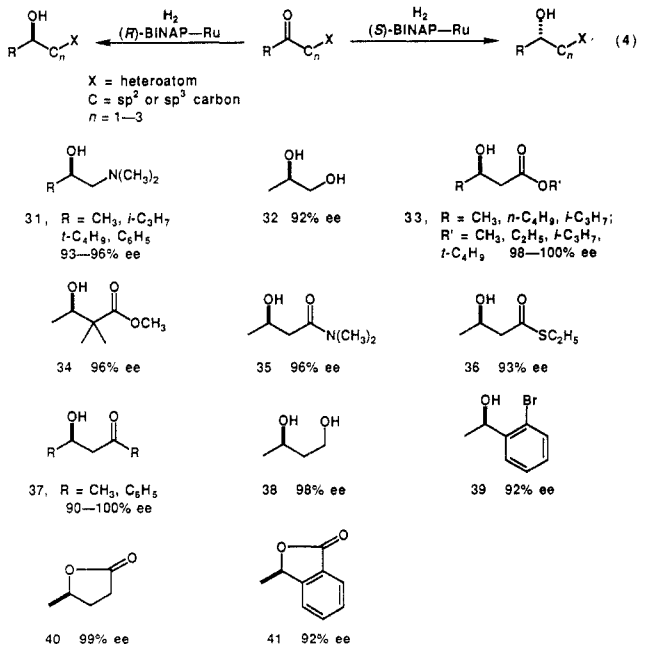
In the presence of an (*R*)-BINAP complex of type **2** (R = CH_3; *p*-$CH_3C_6H_4$ in place of C_6H_5), allylic alcohol **25a** (TBDMS = *t*-$C_4H_9(CH_3)_2Si$) with a chiral azetidinone moiety at C(2) is hydrogenated under atmospheric pressure of hydrogen to give **26a** and **27a** in a 99.9:0.1 ratio.[31] This method provides a simple solution to the 1β-methylcarbapenem problem.[32] Since use of the (*S*)-BINAP–Ru catalyst results in only moderate diastereoselectivity, **26a**:**27a** = 22:78, the above extremely high stereoselectivity is a consequence of the cooperation of the efficient chirality transfer from the BINAP catalyst to the olefinic face (catalyst control, *R**:*S** = 59:1) and the favorable intramolecular 1,2-asymmetric induction (substrate control, 17:1). By comparison, hydrogenation of the chiral α,β-unsaturated carboxylic acid **25b** catalyzed by (*S*)-**2** (R = CH_3) affords **26b** and **27b** in an 88:12 ratio.[21,33] Racemic allylic secondary alcohols can be resolved efficiently by BINAP–Ru-catalyzed hydrogenation.[34] Both cyclic and certain acyclic substrates may be used. The combined effects of intermolecular and intramolecular asymmetric induction give up to 76:1 differentiation between the enantiomers (k_f/k_s). In the presence of an (*S*)-BINAP catalyst **2** (R = CH_3), the *R* enantiomer of **28** is hydrogenated readily to give a threo aldol product. When racemic **29** is hydrogenated with the (*R*)-BINAP catalyst, at 46% conversion, (1*R*,3*R*)-*trans*-3-methylcyclohexanol is formed in 95% ee. At 54% conversion, the

(26) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117.
(27) Kitamura, M.; Hsiao, Y.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4829.
(28) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596, 4129.
(29) Inoue, S.; Osada, M.; Koyano, K.; Takaya, H.; Noyori, R. *Chem. Lett.* **1985**, 1007.
(30) Imperiali, B.; Zimmerman, J. W. *Tetrahedron Lett.* **1988**, *29*, 5343.
(31) Kitamura, M.; Nagai, K.; Hsiao, Y.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 549.
(32) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.
(33) BINAP–Rh-catalyzed hydrogenation of a chiral α,β-unsaturated carboxylic ester: Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005.
(34) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708.

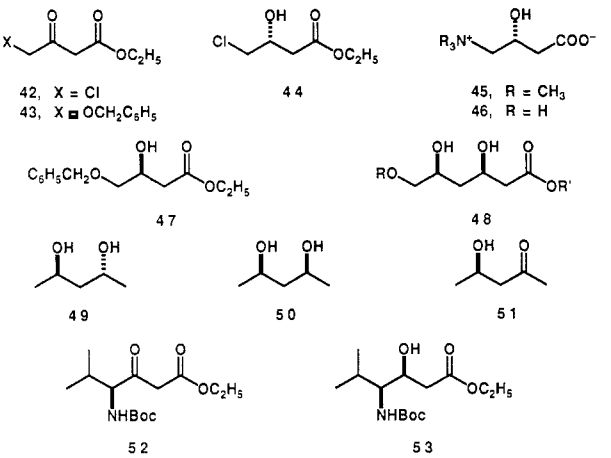
slow-reacting (*S*)-**29** is recovered in >99% ee. This procedure provides a practical route to (*R*)-**30**, an important building block for the three-component coupling prostaglandin synthesis.[35]

Asymmetric Hydrogenation of Ketones

Homogeneous asymmetric hydrogenation using the BINAP–Ru complexes can be extended to ketonic substrates. As generalized by eq 4, a wide range of functionalized ketones are hydrogenated in a highly enantioselective and predictable manner.[36] In most cases, halogen-containing Ru complexes are superior to the dicarboxylate complexes of type **2**. Functionalities acting as the directing group include dialkylamino, hyrdoxyl, alkoxyl, siloxyl, keto, alkoxycarbonyl, alkylthiocarbonyl, (dialkylamino)carbonyl, and carboxyl. Neighboring halogen atoms also strongly affect the rate and stereochemical outcome. Structures **31**–**41** are examples of chiral hydrogenation products obtained with (*R*)-BINAP–Ru catalysts in alcoholic media. A wide variety of prochiral β-keto esters having flexible structures are hydrogenated in either asymmetric orientation in nearly 100% yield and with up to 100% ee.[37] Thus synthetic organic chemists no longer need envy bakers' yeast in this context.[38] Since the α,α-dialkylated product **34** is obtained in a high ee with consistent asymmetric orientation, the hydrogenation does not involve enol forms of β-keto esters.[25] γ-Keto esters can be hydrogenated in a similar manner, to give γ-substituted γ-lactones in high ee's.[22]



The general chiral tendency of eq 4 suggests that the key factor of the stereodifferentiation is the simultaneous coordination of the carbonyl oxygen and heteroatom X to the Ru atom making a five- to seven-membered chelate ring. Consequently, in the reaction of bifunctional keto substrates, only moderate selectivity is obtained owing to the competitive directing effects of the two heteroatoms present in the same molecule. Hydrogenation of the γ-chloro β-keto ester **42** catalyzed by (*S*)-BINAP complexes under standard conditions (100 atm of H_2, ethanol, room temperature, 10–40 h) gives **44** in <70% ee, but surprisingly, the reaction at 100 °C is completed within 5 min, affording the desired **44** in 97% ee.[39] This method allows a very practical chemical synthesis of carnitine (**45**) and GABOB (**46**). The high-temperature hydrogenation is applicable to the benzyloxy keto ester **43** to give **47** in 97% ee,[22] which is convertible to **48**, an important component of compactin, an HMG-CoA reductase inhibitor.

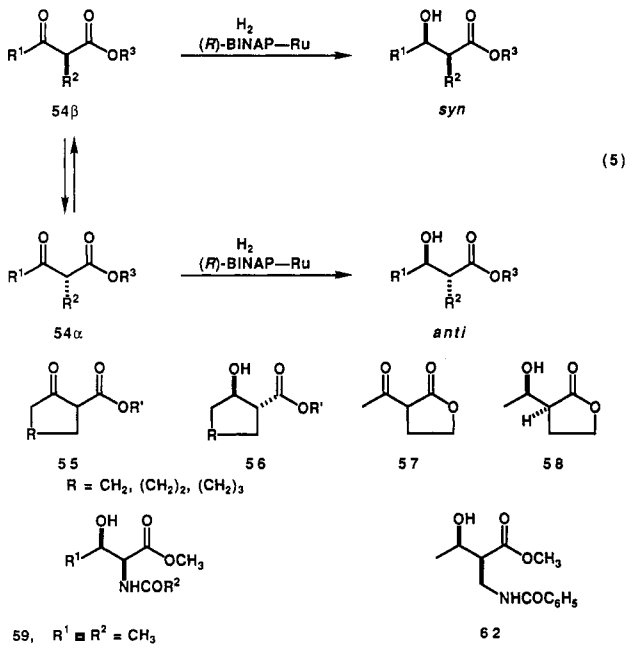


Stereogenic centers installed in the ketonic substrates cause unique asymmetric induction. When 2,4-pentanedione, a symmetrical β-diketone, is subjected to hydrogenation with an (*R*)-BINAP–Ru catalyst, almost enantiomerically pure (*R*,*R*)-1,3-diol **49** and the meso diol **50** are formed in a 99:1 ratio.[36,40] This reaction proceeds via *R* hydroxy ketone **51** in 98.5% ee, but most of the minor *S* enantiomer (0.75%) is removed by conversion to the meso diol **50**. Since the catalyst control (*R**/*S**) and substrate control (*dl*/meso) are estimated to be 33:1 and 6:1, respectively, on the basis of crossover experiments using enantiomerically pure **51**, the calculated *R*,*R*:*S*,*S* ratio in the *dl* type diol approaches ca. 900:1. Double asymmetric differentiation aided by intramolecular 1,2-chirality transfer allows a facile access to the statine series which serves as a key component of pepstatin and its analogues, potent aspartic proteinase inhibitors. Thus diastereoselective hydrogenation of chiral β-keto ester **52a** in the presence of an (*R*)-BINAP catalyst gives protected statine **53**, having a 3*S*,4*S* threo configuration, almost exclusively.[41]

Particularly noteworthy is the dynamic kinetic resolution achieved by using the asymmetric hydrogenation. In ordinary kinetic resolution processes, the maximum yield of one enantiomer is 50%. However, the BINAP–Ru-catalyzed hydrogenation allows efficient resolution of certain chirally labile α-substituted β-keto esters (**54**) to afford in >95% yield one of the four possible stereoisomeric hydroxy esters in excellent enantiomeric and diastereomeric excess (eq 5). Achieve-

(35) Noyori, R. *Chem. Br.* **1989**, *25*, 883.
(36) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629.
(37) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.
(38) See also: Schreiber, S. L.; Kelly, S. E.; Porco, J. A., Jr.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210.
(39) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555.
(40) Kawano, H.; Ishii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 87.
(41) Nishi, T.; Kitamura, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 6327.

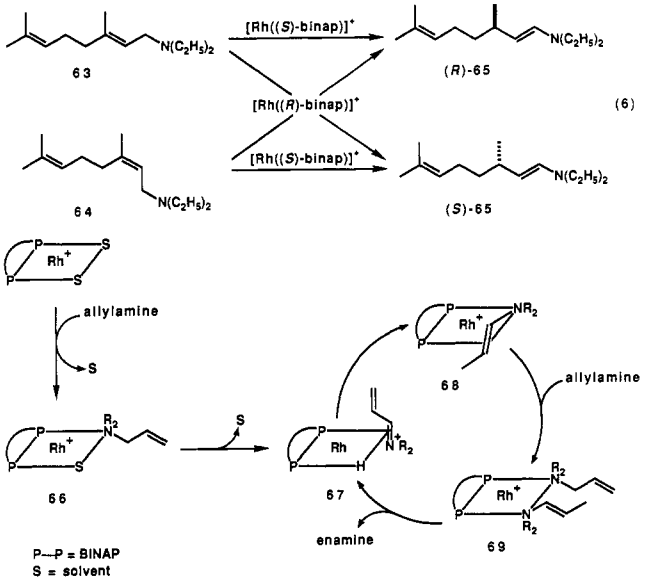
ment of such ideal second-order kinetic resolution relies on the facts that (1) racemization of the substrate **54** is sufficiently faster than hydrogenation, (2) facial discrimination by chiral BINAP–Ru catalysts is efficient, and (3) the structural or functional perturbation in **54** draws a clear distinction between stabilities of syn and anti transition states in the hydrogenation. Systematic examination has revealed that the absolute configuration at C(3) is controlled by the BINAP chirality while that at C(2) is highly dependent on substrate structures. Thus hydrogenation of cyclic substrates is uniquely stereoselective.[42] Annulation of the ketone moiety and lactonization of the directive trigger provide an equally effective, but opposite, diastereomeric bias. In dichloromethane containing [RuCl(C_6H_6)((*R*)-binap)]Cl, racemic cyclic ketones (**55**) are hydrogenated with consistently high anti selectivity (99:1 to 93:7) to give the trans products of type **56** in 90–95% ee. By contrast, hydrogenation of racemic lactonic ketone **57** by the same catalyst proceeds with 98:2 syn selectivity to form the *R* alcoholic compound **58** in 94% ee, in accord with eq 4 using prochiral substrates. An amide or carbamate group present in certain acyclic substrates exhibits remarkable syn directivity, leading to threonine type products in >90% ee's.[22] For instance, hydrogenation of **54** ($R^1 = R^3 = CH_3$; $R^2 = NHCOCH_3$) in dichloromethane containing a catalytic quantity of an (*R*)-BINAP–Ru catalyst produces a protected L-threonine **59** in 98% ee with 99:1 syn selectivity. This method is useful for the stereoselective synthesis of **60** (94% ee) and **61** (92% ee), which serve as intermediates of L-DOPS, an anti-Parkinsonian agent. Even the 2-amidomethyl substrate **54** ($R^1 = R^3 = CH_3$; $R^2 = CH_2NHCOC_6H_5$) is convertible to the syn product **62** in 98% ee.



Thus the scope of the BINAP–Ru-catalyzed hydrogenation is wider than that of reactions with any other chiral transition-metal complexes so far designed. The substrate:catalyst ratio is consistently high, which makes it a practical synthetic procedure. This chemical means is clean, operationally simple, economical, and hence suitable for large-scale reactions.

Enantioselective Allylic Hydrogen Shift

Olefin isomerization, in some cases, greatly increases the value of the organic substrates. Cationic Rh complexes that possess the BINAP ligand catalyze the asymmetric isomerization of *N*,*N*-diethylgeranylamine (**63**) or *N*,*N*-diethylnerylamine (**64**) to give the citronellal (*E*)-enamine **65** in >95% ee (eq 6).[43] The reaction proceeds smoothly in THF or acetone below 0 °C employing 1 mol % of the chiral complexes. With the bis-BINAP complex **5** (substrate:catalyst = 8000), a rather high temperature, 80–100 °C, is required to gain a reasonable reaction rate, but its high stability and crystallinity more than compensate for this.[16] This highly enantioselective catalysis, which is now working on a 7-ton scale (Takasago process), serves as a key step in the industrial production of (–)-menthol, providing an example of the most effective application of transition-metal-catalyzed asymmetric reactions in the homogeneous phase. This method may also be used for the synthesis of 7-hydroxydihydrocitronellal,[43b] vitamin E side chain,[44] etc.



In principle, any donor group such as an olefinic bond, heteroatom bases, carbanions, and heteroanions can activate its adjacent C–H bonds through coordination to appropriate unsaturated transition-metal centers. The metal hydride species formed by β-elimination undergo various unique chemical transformations, depending on the situation. The isomerization of allylic amines is believed to occur by a nitrogen-triggered mechanism.[45] The BINAP–Rh^+ complexes differentiate efficiently the enantiotopic C(1) hydrogens

(42) Kitamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron Asymmetry* **1990**, *1*, 1.

(43) (a) Tani, K.; Yamagata, T.; Otsuka, S.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1982**, 600. (b) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208.

(44) Takabe, K.; Uchiyama, Y.; Okisaka, K.; Yamada, T.; Katagiri, T.; Okazaki, T.; Oketa, T.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1985**, *26*, 5153.

(45) Inoue, S.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 4897.

of the allylamines through interaction with the adjacent nitrogen atoms. The initial complex **66** causes a four-centered hydride elimination via a dissociative mechanism to generate a transient iminium–RhH complex **67**. Subsequent hydride delivery from Rh to C(3) of the ligand forms the η^3-enamine complex **68**. The latter having an aza-allyl structure serves as the chain carrier in the actual catalytic cycle. Thus **69**, formed from **68** and the allylamine, undergoes enantioselective β-hydride elimination via dissociation of the enamine product, generating **67**, which goes back to **68**.

The BINAP complexes can kinetically resolve certain racemic allylic alcohols. When racemic hydroxy cyclopentenone **30** was exposed to a catalytic quantity of a cationic (*R*)-BINAP–Rh complex in THF at 0 °C, double-bond migration took place with 5:1 enantiomer discrimination to afford unreacted (*R*)-hydroxy enone **30** in 91% ee in 27% yield and 1,3-cyclopentanedione in 61% yield.[46]

Conclusion

The newly invented BINAP-based Ru(II) and Rh(I) complexes exhibit extremely high chiral recognition ability in catalytic reactions. Although the eminent utility has amply been demonstrated, the application is not limited to the above described reactions. A BINAP–Ru complex is known to catalyze hydrogenation of certain cyclic anhydrides, affording lactonic products in fair optical yields.[47] Further, highly enantioselective hydroboration of styrenes[48] and 1,4-disilylation of α,β-unsaturated ketones[49] are achievable by a BINAP-based Rh and Pd complex, respectively. Certain well-designed compact molecular catalysts consisting of metallic species and chiral organic ligands can precisely control the stereochemical outcome of reactions in a homogeneous phase. The efficiency of the chemical means rivals or, in some cases, even exceeds that of enzymatic processes exhibiting single-handed, lock-and-key specificity. This Account has presented a simple example showing the validity of this strategy.[50]

We are indebted to our collaborators who have made the sustained intellectual and experimental efforts to accomplish this highly efficient asymmetric catalysis. Names of the individuals are given in the references. We have particularly enjoyed collaboration with the research groups headed by Professor S. Otsuka (Osaka University) and Dr. S. Akutagawa (Takasago Research Institute).

(46) Kitamura, M.; Manabe, K.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4719.

(47) Ishii, Y.; Sasaki, T.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *Nippon Kagaku Kaishi* **1985**, 465.

(48) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426.

(49) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5579.

(50) **Note**: A limited, small quantity of $Ru(OCOCH_3)_2$[(*R*)- or (*S*)-binap][10] is available. Please contact R. Noyori at Nagoya University, indicating chirality of the complex and type of substrates.