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Asymmetric Hydrogenation

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Ruthenium(II) complexes possessing an atropisomeric BINAP ligand display spectacular efficiency in enantioselective hydrogenation of prochiral α,β- and β,γ-unsaturated carboxylic acids, allylic and homoallylic alcohols, enamides, etc. In addition, a wide range of functionalized ketones can be hydrogenated with a high degree of enantiofacial selectivity and in a predictable sense. The use of chiral substrates, coupled with dynamic kinetic resolution, further enhances the synthetic utility. A long-sought asymmetric hydrogenation of simple aromatic or olefinic ketones has been realized by use of a combination of BINAP and a chiral 1,2-diamine as co-modifiers of the ruthenium(II) species. The BINAP-based organometallic molecular catalysts can generate a diverse array of natural and unnatural chiral compounds, simply depending on the structures of the unsaturated substrates. Some industrial applications of BINAP–ruthenium are illustrated.

Well designed chiral metal complexes can discriminate precisely between enantiotopic atoms, groups, or faces in achiral molecules and catalyze the formation of a wide range of natural and unnatural substances with high enantiomeric purity.[1,2] Certain racemates can also be resolved by reaction with chiral molecular catalysts.

This strategy has been applied to a variety of homogeneous catalyses, providing an ideal way of multiplying molecular chirality.[3] The efficiency of the chemical means, now rivals, or in certain cases exceeds, that of biological processes, converting the chemists' dream into reality.

Appropriate combination of metals and chiral ligands, as well as selection of reaction conditions, is very important in obtaining a high degree of stereoselectivity. BINAP [2,2′-bis(diarylphosphino)-1,1′-binaphthyl] given in Fig. 1 is an axially dissymmetric C_2 chiral diphosphine.[4] The fully aromatic substitution exerts a strong steric influence and provides high polarizability. This conformationally flexible diphosphine can accommodate a wide range of transition metals by rotating about the binaphthyl C(1)–C(1′) pivot and C(2 or 2′)–P bonds without a serious increase in torsional strain, while the resulting seven-membered chelate rings containing only sp^2 carbon atoms are in turn skeletally unambiguous.[5] Figure 2 illustrates the chiral template created by the (*R*)-BINAP ligand and a transition metal element, M.[6,7] The chirality of the binaphthyl skeleton is transmitted spatially via the *P*-phenyl rings to the in-plane and out-of-plane coordination sites, shown by □ and ■, respectively. The in-plane coordination sites are sterically affected by the 'equatorial' phenyl rings, while the out-of-plane sites are influenced by the 'axial' phenyl substituents. Consequently, the two sets of quadrants of the chiral template (first and third vs. second and fourth) are clearly differentiated spatially. In the catalytic reaction, □ and ■ are occupied by a reactant, substrate, spectator ligand, or solvent. Bond-forming and -breaking reactions that occur in such a dissymmetric environment display excellent chiral discrimination. BINAP–transition metal complexes actually exhibit an extremely high chiral recognition ability in various catalytic reactions, providing a major breakthrough in stereoselective organic synthesis.[1,2] We here summarize the current stage of the asymmetric hydrogenation catalyzed by BINAP–Ru^{II} complexes.

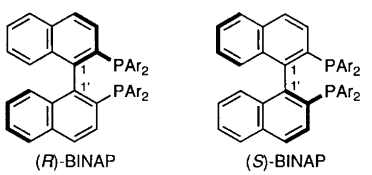


Fig. 1. The structure of BINAP. In most cases, Ar = phenyl.

* Contribution presented at the Nobel Symposium on *Catalytic Asymmetric Synthesis*, September 3–7, 1995 at Tammsvik, Bro, Sweden.

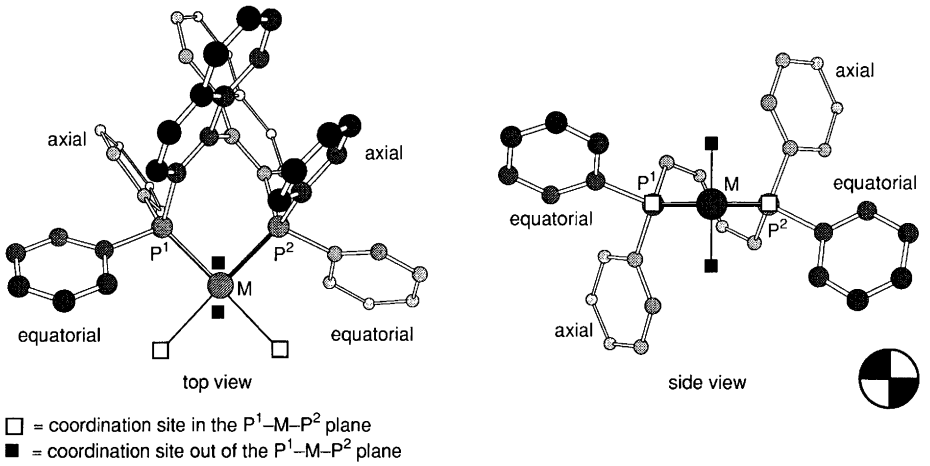


Fig. 2. Chiral environment of an (*R*)-BINAP–transition metal complex. The naphthalene rings are omitted in the side view.

Asymmetric hydrogenation of olefins

Enantio- and diastereo-selective hydrogenation. BINAP–Ru^{II} dicarboxylates[7,8] act as excellent catalysts for the hydrogenation of various functionalized olefins as summarized in Fig. 3. Hydrogenation of α,β-and β,γ-unsaturated carboxylic acids is effected in alcoholic media to give the corresponding saturated products, where the sense and degree of the enantioselection are highly dependent on the substitution pattern as well as the reaction conditions, particularly hydrogen pressure.[9] Use of certain hydroxylated substrates gives optically active γ- and δ-lactones. The carboxy group in the substrate serves as a binding tether to the catalytic Ru center. Notably, the mechanism of the Ru^{II}-catalyzed hydrogenation has proved entirely different from that of the Rh^{I}-catalyzed reaction; the Ru center remains in the +2 oxidation state throughout the catalytic cycle.[10] The presence of a non-ionic, neutral functionality in the substrate also facilitates the C=C bond saturation. Thus, allylic and homoallylic alcohols are also hydrogenated in methanol with a high enantioselection.[11] Certain racemic allylic alcohols can be resolved by BINAP–Ru catalyzed hydrogenation.[12] The chiral Ru complexes effect enantioselective hydrogenation of (*Z*)-2-acyl-1-benzylidene-1,2,3,4-tetrahydroisoquinolines.[13] In a similar manner, optically active α- and β-amino acids are also obtainable from suitably amido-substituted olefins.[2d,14] Interestingly, the Ru^{II} and Rh^{I} complexes, which have the same BINAP chirality, form antipodal amino acids as the predominant products.[2d,13c]

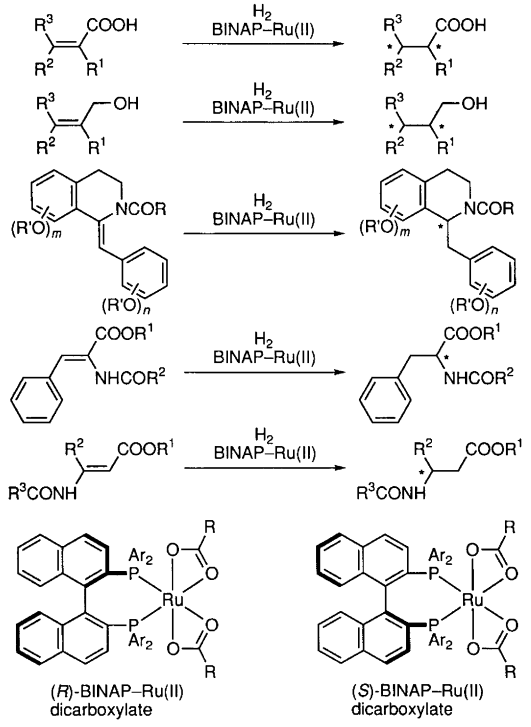


Fig. 3. Asymmetric hydrogenation of olefins catalyzed by BINAP–Ru^{II} complexes.

Synthetic utility. An important application of this method is the synthesis of the anti-inflammatory drug Naproxen (Fig. 4).[9,15] As shown in Fig. 5, in the presence of a very small amount of the Ru catalyst [substrate/catalyst mole ratio (S/C) = 50 000], geraniol and nerol are convertible into natural or unnatural citronellol with up to 99% ee without saturation of the C(6)–C(7) double bond.[11] The hydrogenation of (*R*,*E*)-6,7,10,11-tetrahydrofarnesol produces (3*R*,7*R*)-hexahydrofarnesol, a C_{15} side chain of α-tocopherol (vitamin E) and a part of vitamin K_1. The hydrogenation of an allylic alcohol possessing a chiral azetidinone unit gives diastereoselectively a 1β-methylcarbapenem synthetic intermediate.[16]

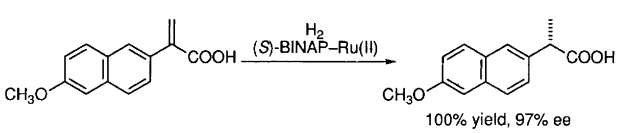


Fig. 4. Asymmetric synthesis of Naproxen.

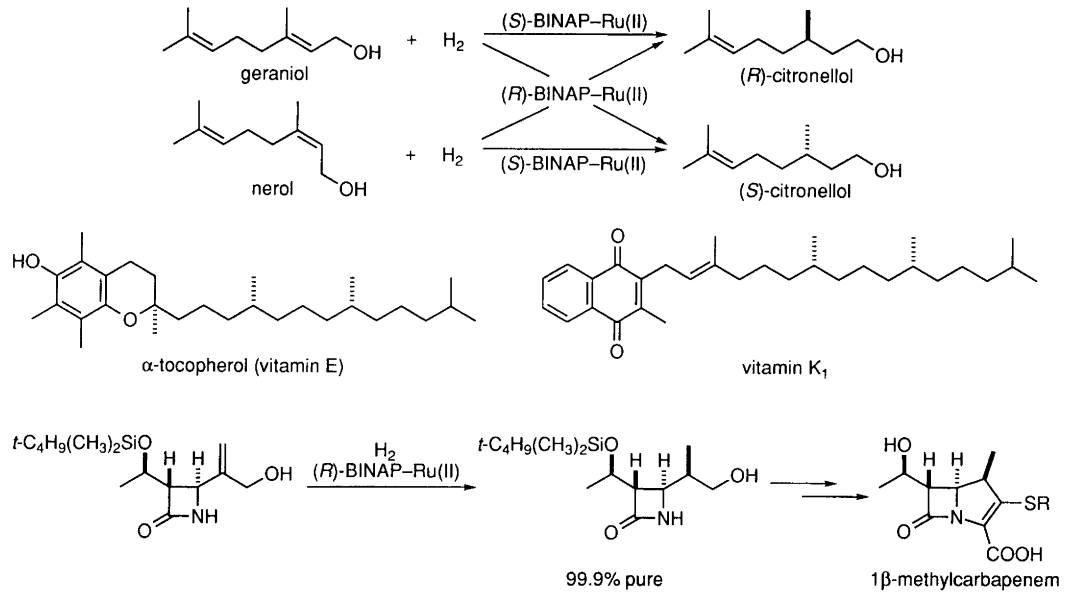


Fig. 5. Asymmetric hydrogenation of allylic alcohols.

Furthermore, the discovery of the new hydrogenation method realized a general asymmetric synthesis of isoquinoline alkaloids including morphine, benzomorphans, and morphinans such as the antitussive Dextromethorphan (Fig. 6).[13] This method has also been used for the asymmetric synthesis of Clozilacon (an excellent fungicide),[17a] α-aminoadipic acid,[17b] and a core component of HIV protease[17c] (Fig. 7).

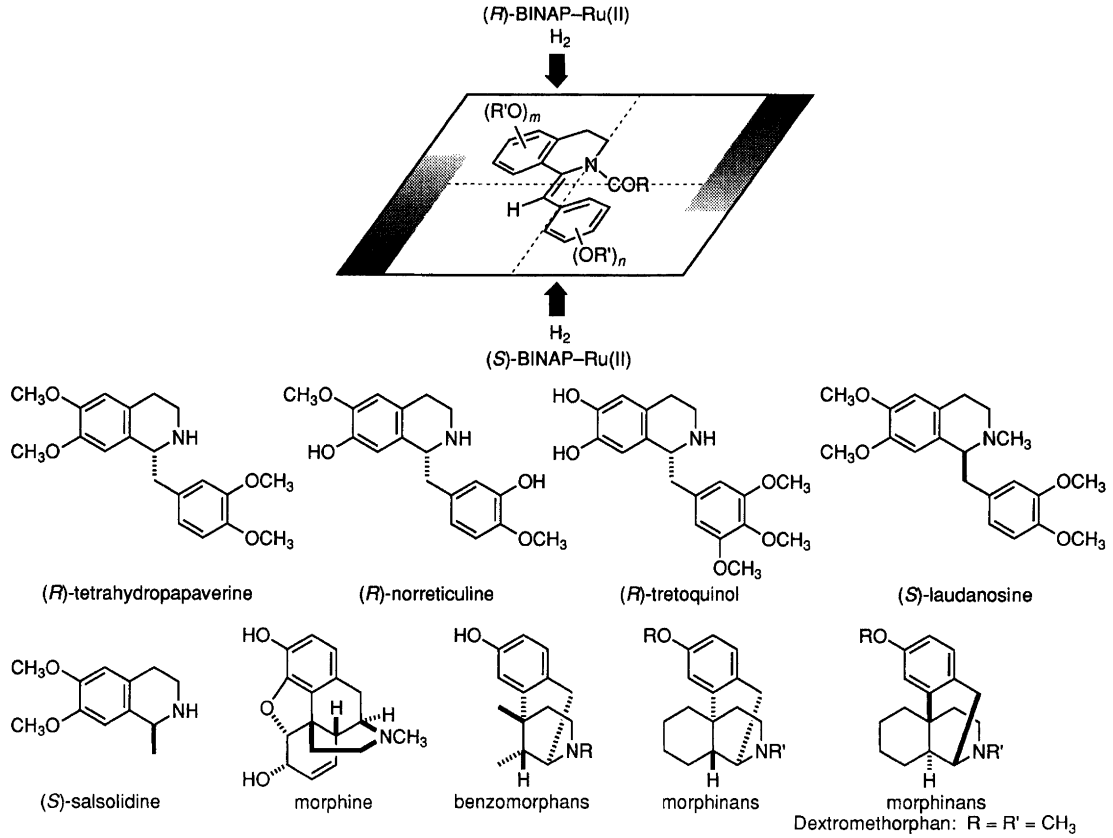


Fig. 6. Asymmetric synthesis of isoquinoline alkaloids. The general sense of the asymmetric induction and examples.

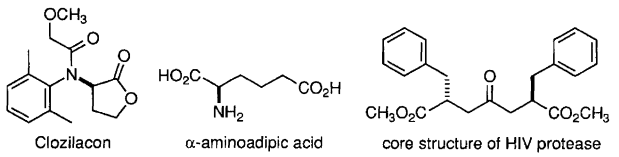


Fig. 7. Applications of BINAP–Ru catalyzed asymmetric hydrogenation of olefins.

Asymmetric hydrogenation of functionalized ketones

Enantioselective hydrogenation. Halogen-containing BINAP–Ru^{II} complexes[18] serve as efficient catalysts for the enantioselective hydrogenation of a series of functionalized ketones, wherein nitrogen, oxygen, and halogen atoms near carbonyl functions direct the reactivity and steric course.[19] Figure 8 shows the general sense and examples of the asymmetric reaction. A wide variety of prochiral ketones can be hydrogenated in a predictable manner. The reaction is believed to occur via a Ru monohydride formed by heterolytic cleavage of hydrogen by the catalyst.[20]

The asymmetric hydrogenation of β-keto esters, leading to chiral β-hydroxy esters, finds a remarkably wide generality and great chiral flexibility.[21] The reaction using the (*R*)-BINAP catalyst consistently gives the *R* hydroxy ester in >98% ee, while the use of the *S* catalyst affords the *S* product. Fig. 9 illustrates the stereo-determining step in the (*R*)-BINAP–Ru catalyzed hydrogenation, where hydrogen on Ru moves to the carbonyl carbon.[20] The substrate occupies the in-plane coordination sites, □, in the stucture of Fig. 2 (side view). The sterically demanding 'equatorial' *P*-phenyl rings are shaded. The *S*-generating diastereomer is obviously disfavored because of the phenyl/R′ non-bonded interaction.

The reaction can be performed in organic media, normally alcohols, with up to 50% substrate concentration under 4–100 atm of hydrogen at room temperature with S/C up to 10 000 on any scale using <100 mg to >100 kg of the substrate. The reaction is applicable to the synthesis of many biologically significant compounds, such as carnitine, γ-amino-β-hydroxybutyric acid (GABOB), and compactin (Fig. 10).[22] Figure 11 exemplifies some natural and unnatural chiral compounds that can be prepared using BINAP–Ru catalyzed asymmetric hydrogenation.[17a,23]

Furthermore, the BINAP–Ru complexes catalyze the enantioselective hydrogenation of β-ketophosphonic esters in alcoholic media to give the corresponding hydroxyphosphonic esters in >94% ee (Fig. 12).[24] The sense is identical with that observed in the reaction of β-ketocarboxylates.

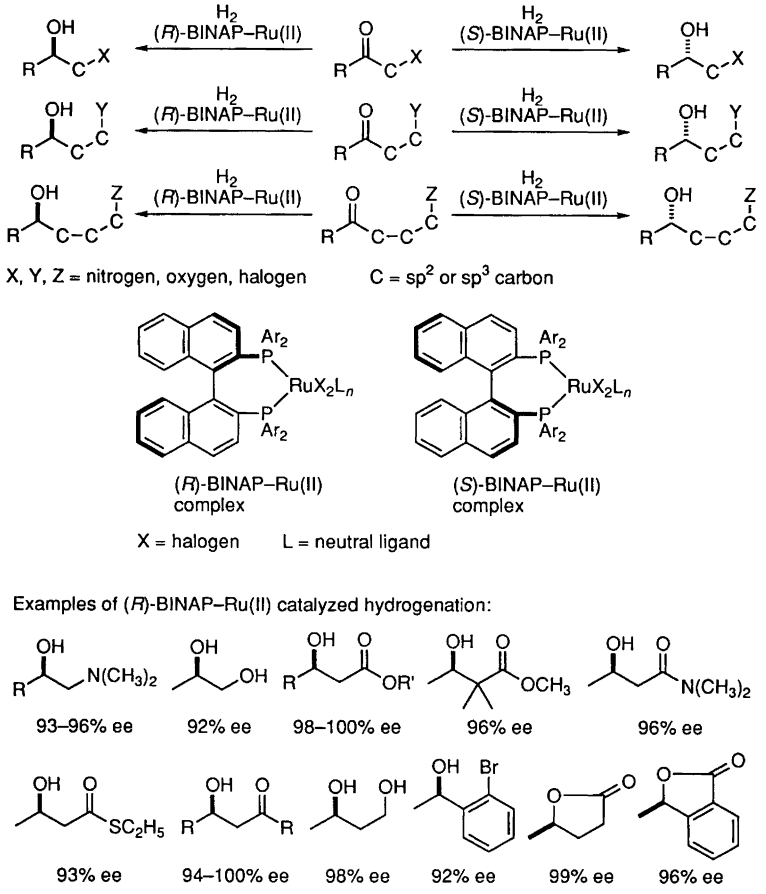


Fig. 8. Enantioselective hydrogenation of functionalized ketones.

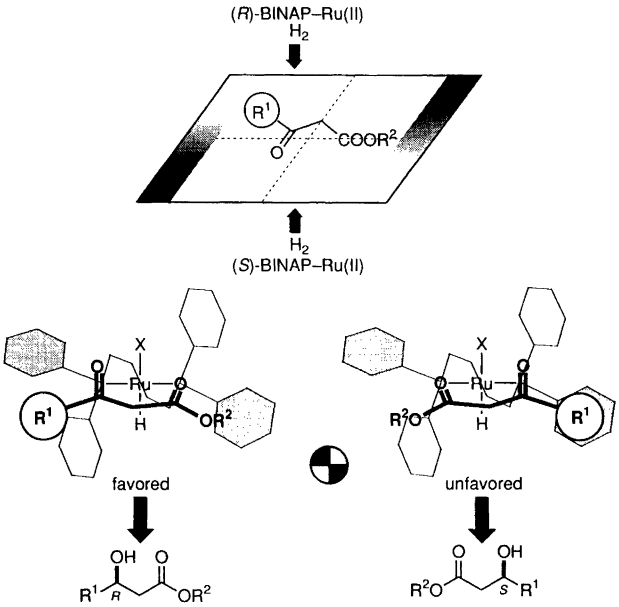


Fig. 9. General sense of the asymmetric hydrogenation of β-keto esters and the origin of the enantioselection in the (*R*)-BINAP–Ru catalyzed reaction. X = halogen, H_2, solvent, etc.

Diastereoselective hydrogenation. The pre-existing stereocenter in the ketonic substrate strongly influences the steric course of the asymmetric hydrogenation. Figure 13 shows some examples. The reaction of protected (*S*)-γ-amino β-keto esters in the presence of an (*R*)-BINAP–Ru catalyst leads efficiently to a statine series with an *S,S threo* configuration in virtually 100% ee.[25] The products are essential components of the aspartic proteinase inhibitor pepstatin and its analogues. The double hydrogenation of 1,3-diones via chiral hydroxy ketones leads to the *anti* 1,3-diols of a very high enantiomeric purity.[19a]

As illustrated at the bottom of Fig. 13, certain racemic ketones can be resolved by Ru-catalyzed asymmetric hydrogenation, where the maximum yield of the chiral product or recovered starting material remains 50%. However, racemic compounds with a configurationally labile stereogenic center undergoing *in-situ* stereoinversion can, in principle, be transformed into enantiomerically pure products in 100% yield.[20] As illustrated in Fig. 14, the BINAP–Ru catalyzed hydrogenation of racemic α-substituted β-keto esters can produce a single isomer out of the four possible stereoisomers with high enantio- and diastereoselectivity.[26] A highly stereoselective reaction with such a dynamic kinetic resolution can be accomplished only when the reaction proceeds with high k_{fast}/k_{slow} (k_R/k_S) and k_{inv}/k_{slow} (k_{inv}/k_S) values as well as efficient catalyst- and substrate-based asymmetric induction (C_{cat} and C_{sub}, respectively). The situation can be visualized in the 3D representation in Fig. 15.[20,27] Thus, the overall stereoselectivity is profoundly affected by the reaction conditions.

The absolute configuration of the hydroxy-bearing β position is determined by the chirality of the BINAP ligand, whereas the configuration of the α stereogenic center is affected by the structures of the keto substrates.[26] Figure 16 exhibits contrasting stereochemistries observed with certain cyclic substrates. As shown in Fig. 17, hydrogenation of racemic α-(acylamino) acetoacetate in dichloromethane, rather than ordinary alcoholic media, affords the hydroxy ester products in high enantio- and diastereo-selectivity. A variety of threonine-type compounds including L-DOPS are accessible by this method. This dynamic kinetic resolution has been extended to the stereoselective synthesis of certain α-substituted β-hydroxyphosphonates, opening a new, practical route to phosphothreonine derivatives[28] and fosfomycin,[24] a clinically used antibiotic. Figure 18 lists some other biologically active compounds which can be conveniently synthesized using this stereoselective method in the key step.[26b,29]

The (*R*)-BINAP–Ru catalyzed reaction of racemic methyl α-(benzamidomethyl)acetoacetate in dichloromethane proceeds with 94 : 6 *threo* : *erythro* diastereoselec-

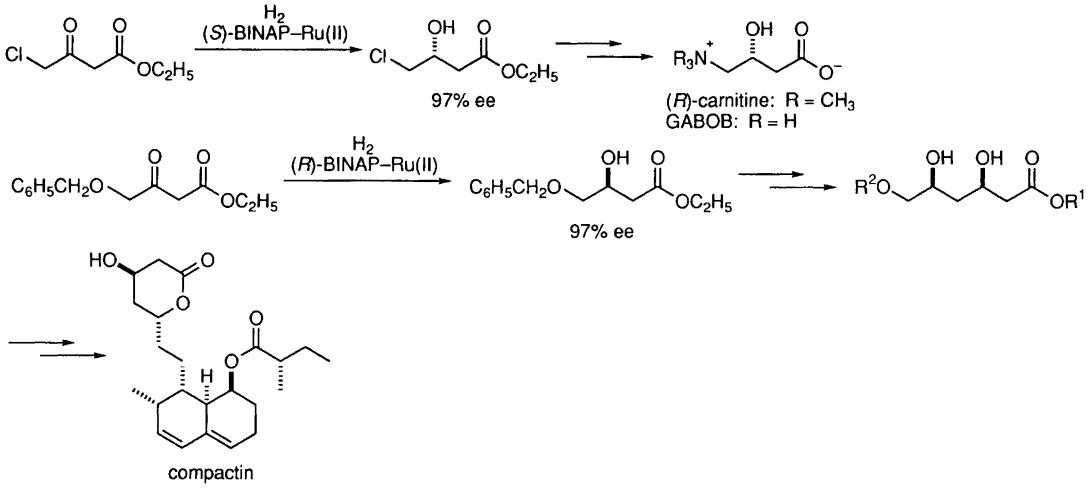


Fig. 10. Applications of asymmetric hydrogenation of β-keto esters.

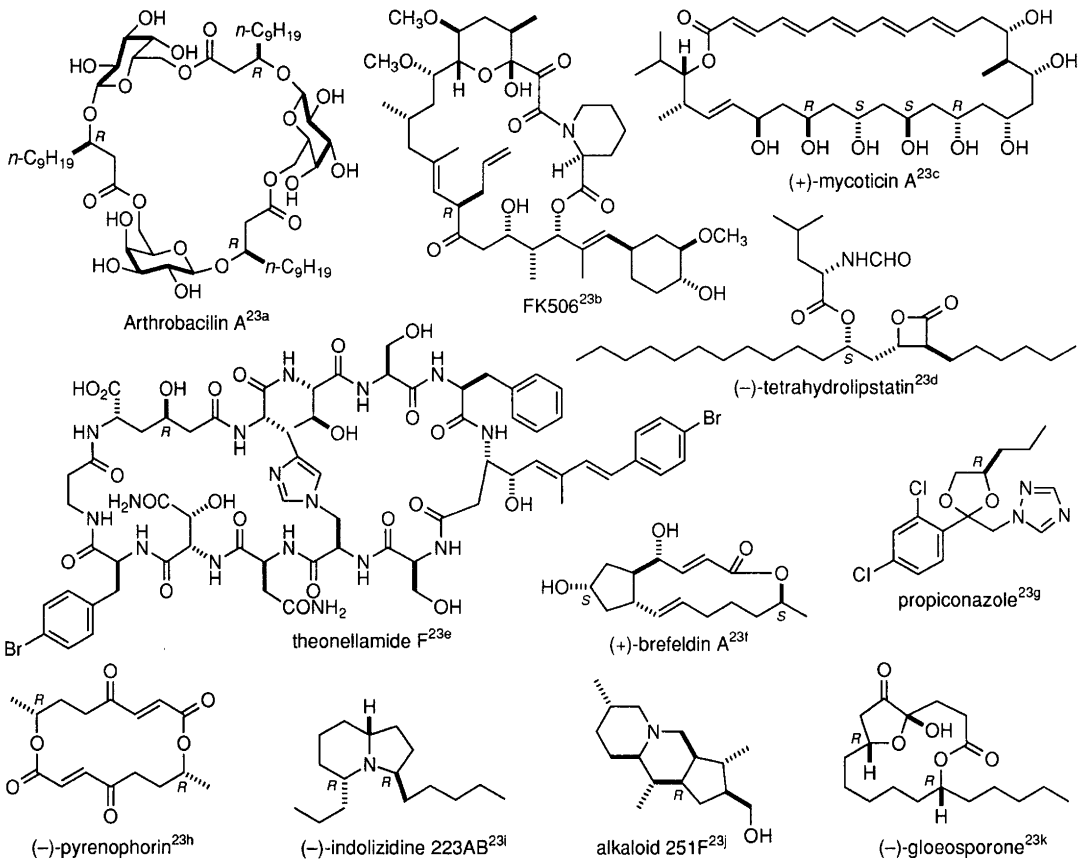


Fig. 11. Examples of biologically active compounds obtainable by BINAP–Ru catalyzed asymmetric hydrogenation. The asymmetric reaction determines the stereocenter labeled by *R* and *S*.

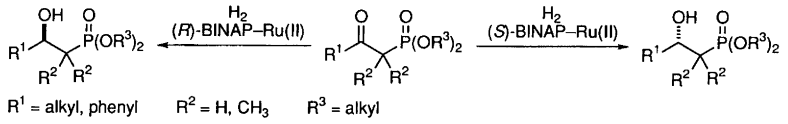


Fig. 12. General sense of asymmetric hydrogenation of β-keto phosphonates.

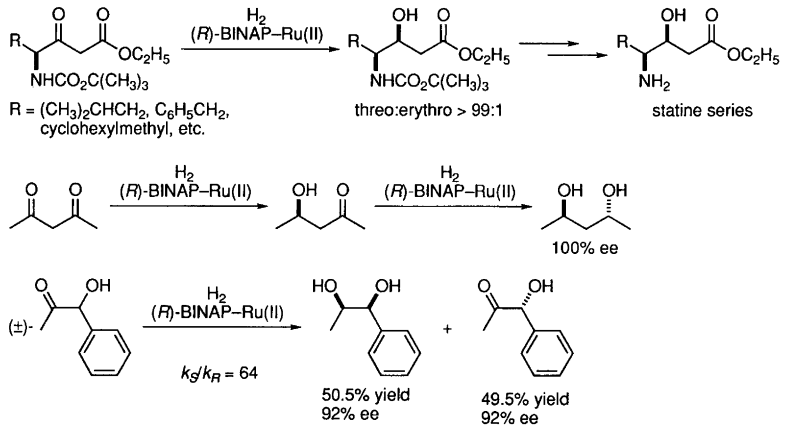


Fig. 13. Diastereoselective hydrogenation of ketonic substrates.

tivity and with 99.5 : 0.5 enantioselectivity to give the *S,R* isomer in 93% yield (Fig. 19).[26a] The quantitative analysis indicates that the *S* substrate is hydrogenated, giving the *S,R* product, 15 times faster than the *R* enantiomer, and that the slow-reacting *R* isomer also forms the same product because it is inverted to the *S* enantiomer 92

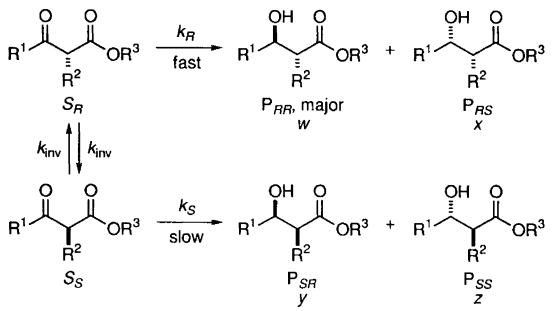


Fig. 14. Hydrogenation of α-substituted β-keto esters. The values, *w–z*, are partition coefficients of the isomers ($w+x+y+z=1$), where S_R and S_S are assumed to be present in equal amounts.

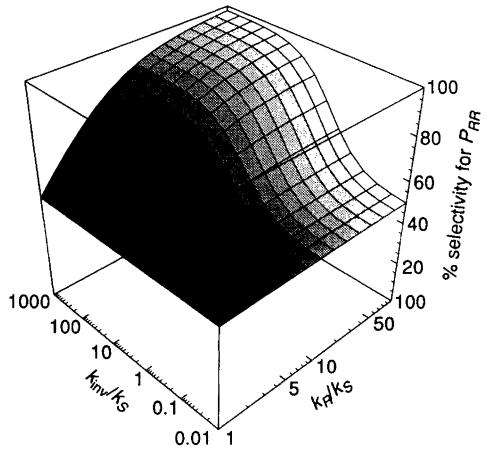


Fig. 15. 3D-graphic demonstration of relationship of k_{inv}/k_S, k_R/k_S, and % selectivity of the most abundant isomer with C_{cat} $[(wy/xz)^{1/2}]=10$ and C_{sub} $[(wz/xy)^{1/2}]=10$.

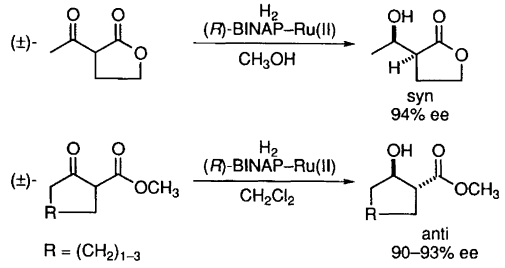


Fig. 16. Stereoselective hydrogenation of racemic keto esters.

times faster than it is hydrogenated.[20,27a] The extent of the catalyst-based asymmetric induction (C_{cat}) is calculated to be 104 (*R*/S**), while the substrate-based asymmetric induction (C_{sub}) is 9 (*threo/erythro*).

Asymmetric hydrogenation of simple ketones

The catalyst systems described above, though displaying a very wide scope, are unable to hydrogenate simple ketones that lack heteroatoms capable of interacting with the Ru^{II} atom. A newly invented ternary catalyst system consisting of $RuCl_2[P(C_6H_5)_3]_3$, $NH_2(CH_2)_2NH_2$, and KOH in a 1 : 1 : 2 molar ratio (S/C = 500 to 10 000) effects facile hydrogenation of unfunctionalized ketones in 2-propanol at room temperature at 1–8 atm to give secondary alcohols in near-quantitative yield.[30] The hydrogenation is very rapid. For example, in the reaction of acetophenone (Fig. 20), the turnover frequency, defined as the moles of product per mole of Ru catalyst per hour, approaches 6700 at 3 atm and 28°C and even 23 000 at 50 atm, also at 28°C.

Most significantly, the discovery of this catalyst system realized a long-sought synthetic operation, namely, preferential hydrogenation of a carbonyl function over olefinic and acetylenic bonds.[31] As shown by the reaction using an equimolar mixture of heptanal and 1-octene (Fig. 21), $RuCl_2[P(C_6H_5)_3]_3$ itself is an excellent catalyst for olefin hydrogenation but very poor for carbonyl hydrogenation ($k_{C=C}/k_{C=O}=250$). However, the combined effects of the 1,2-diamine and KOH decelerate olefin hydrogenation catalyzed by $RuCl_2[P(C_6H_5)_3]_3$, and in turn accelerate carbonyl saturation, displaying a carbonyl/olefin selectivity as high as 1500. Thus, the amine additive, in an amount of only 1 equiv. to the catalyst (0.0014 M in a 6 : 1 2-propanol–toluene mixture), together with KOH changes the selectivity profile by a factor of 375 000. Furthermore, a wide range of ketones and aldehydes possessing a carbon–carbon multiple bond are hydrogenated at the carbonyl group, leading to unsaturated alcohols with high selectivity. Both conjugated and unconjugated enals or enones can be used. The excellent C=O vs. C=C chemoselectivity is reminiscent of that attained by stoichiometric $NaBH_4$ reduction.

Highly enantioselective hydrogenation of aromatic ketones is achievable when BINAP is combined with certain chiral 1,2-diamines such as 1-alkyl-2,2-bis(*p*-methoxyphenyl)ethylenediamine and 1,2-diphenylethylenediamine.[30] Fig. 22 contains some examples. The high degree of enantioface differentiation is a result of the synergetic effects of the chiral diphosphine and diamine. A combination of (*S*)-BINAP and an *S* diamine (or *R* and *R*) is important to achieve a satisfactory enantioselection.[30]

Olefinic or acetylenic ketones are also convertible into optically active unsaturated alcohols, as exemplified in Fig. 23.[31] This method allows easy access to a key intermediate in the synthesis of anthracycline antibiotics.

This new hydrogenation method is particularly useful for large-scale reactions because of the low cost of the catalyst, the operational simplicity, and the minimal effect on the environment. The reaction pathway is obviously different from that of the hydrogenation of functionalized ketones, and may not involve substrate coordination to the Ru center.

Industrial applications

Standard BINAP–Ru catalyzed asymmetric hydrogenation is now utilized in many academic and industrial

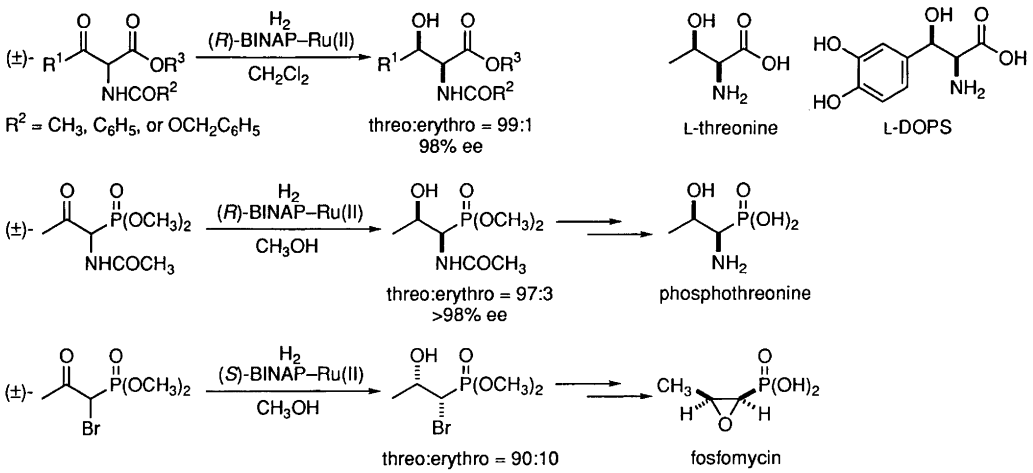


Fig. 17. Stereoselective synthesis of threonines, phosphothreonine, and fosfomycin by asymmetric hydrogenation via dynamic kinetic resolution.

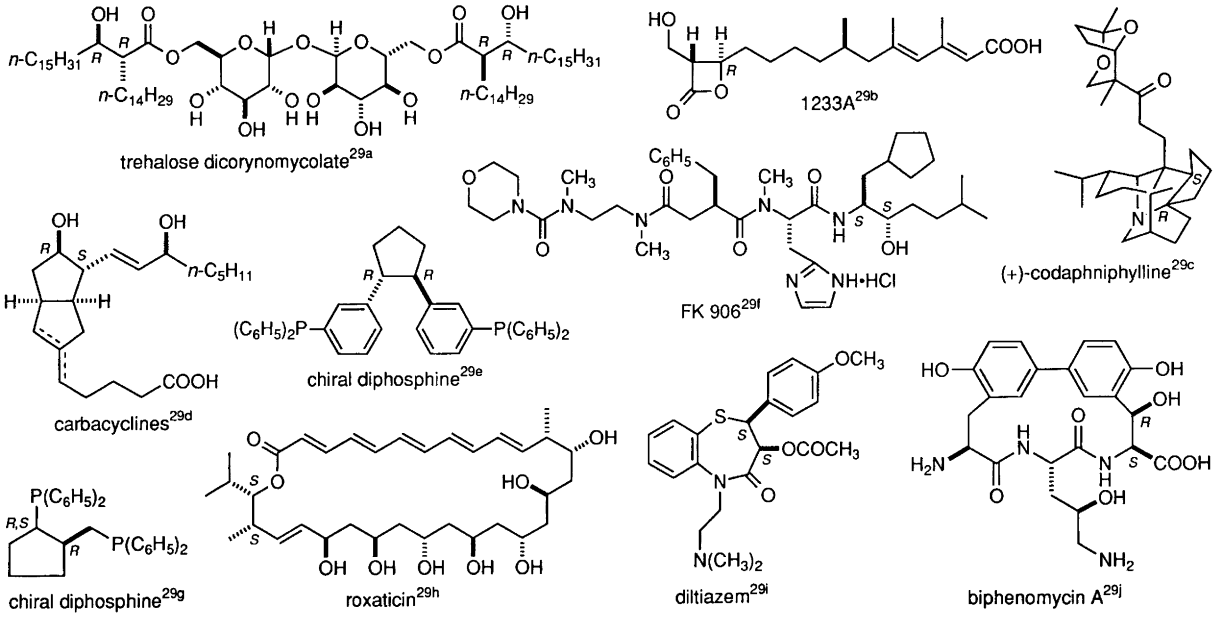


Fig. 18. Examples of biologically active compounds accessible by asymmetric hydrogenation via dynamic kinetic resolution. The stereocenters determined by BINAP chemistry (and subsequent inversion or asymmetric induction) are labeled *R* or *S*.

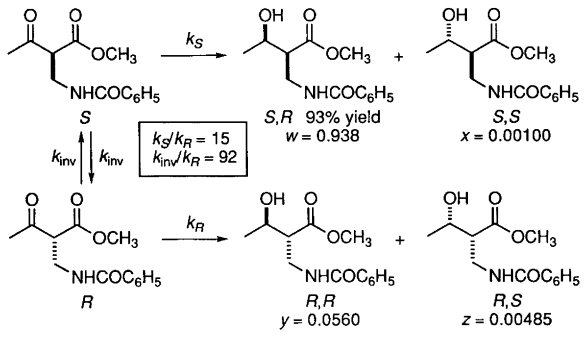
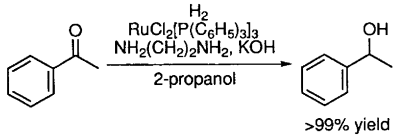


Fig. 19. Hydrogenation of methyl α-(benzamidomethyl)-acetoacetate (0.2 M) catalyzed by an (*R*)-BINAP–Ru complex (1.3 mM) in CH_2Cl_2 at 100 atm and 50 °C for 40 h.



H_2, atm	S/C	TOF, mol/Ru•h
1	500	880
3	5,000	6,700
50	10,000	23,000

Fig. 20. High-speed hydrogenation of acetophenone.

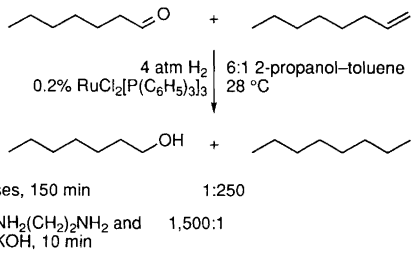


Fig. 21. Chemoselective hydrogenation.

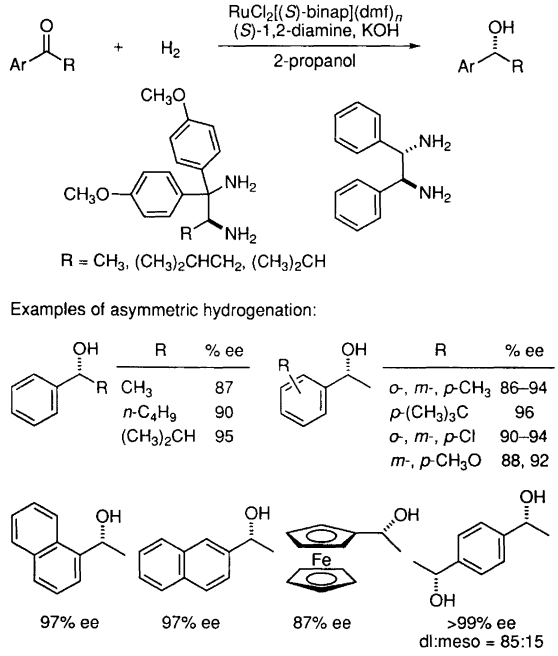


Fig. 22. Asymmetric hydrogenation of aromatic ketones.

institutes worldwide for the synthesis of optically active compounds.[1,2] The benefits of this chemistry include: (1) high yield and high stereoselectivity, (2) chiral flexibility giving both natural and unnatural chiral products, (3) low substrate specificity, (4) high volumetric yield, (5) capability of conducting a large-scale reaction, and (6) easy operation. Many examples described above are at a highly technical level, and some processes using this asymmetric method have already been industrialized. For example, kinetic resolution of racemic allylic alcohols by (*S*)-BINAP–Ru catalyzed hydrogenation[12, 32a,b] provides a very practical access to (*R*)-4-hydroxy-2-cyclopentenone on a multi-kilogram scale, a building block of the three-component prostaglandin synthesis (Fig. 24).[33] The requisite chiral lower side-chain unit can be obtained by the BINAL-H asymmetric reduction of the corresponding olefinic ketone.[34] (*R*)-1,2-Propanediol prepared by the asymmetric hydrogenation of acetol[18a,19a] is now being used for the commercial synthesis of the antibacterial Levofloxacin (Fig. 25).[32a,c] Most significantly, the hydrogenation of methyl α-(benzamidomethyl)acetoacetate via dynamic kinetic resolution,[26a] detailed in

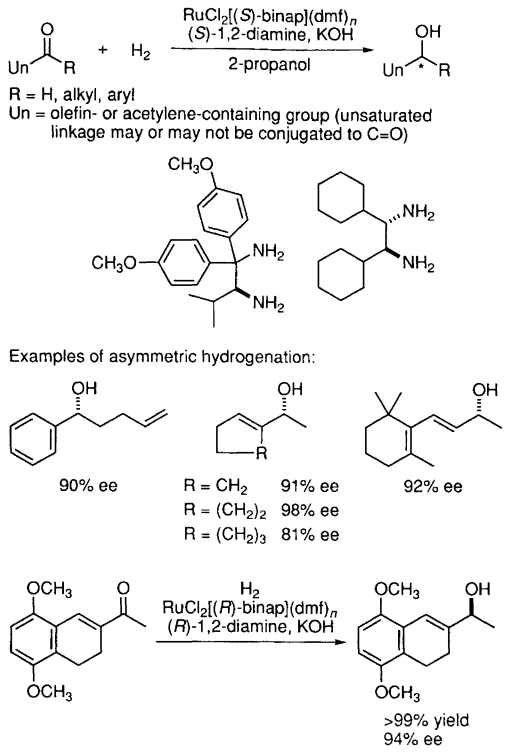


Fig. 23. Asymmetric hydrogenation of olefinic ketones.

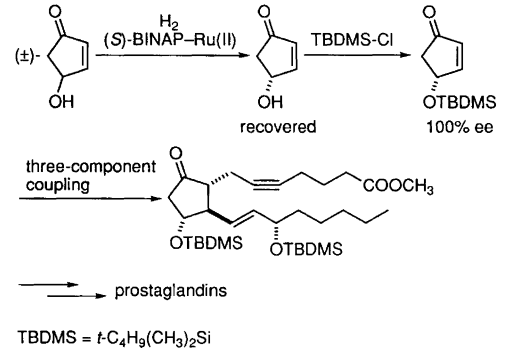


Fig. 24. Three-component synthesis of prostaglandins.

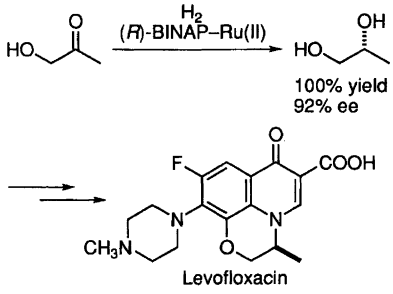


Fig. 25. Asymmetric synthesis of Levofloxacin.

Fig. 19, is used for the preparation of a chiral azetidinone derivative (120 ton $year^{-1}$). As illustrated in Fig. 26, it serves as a common intermediate for the synthesis of carbapenem antibiotics.[32a,35]

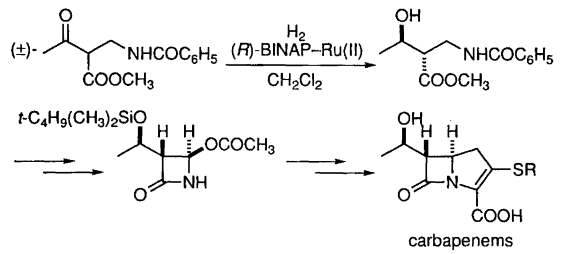


Fig. 26. Asymmetric synthesis of carbapenem antibiotics.

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