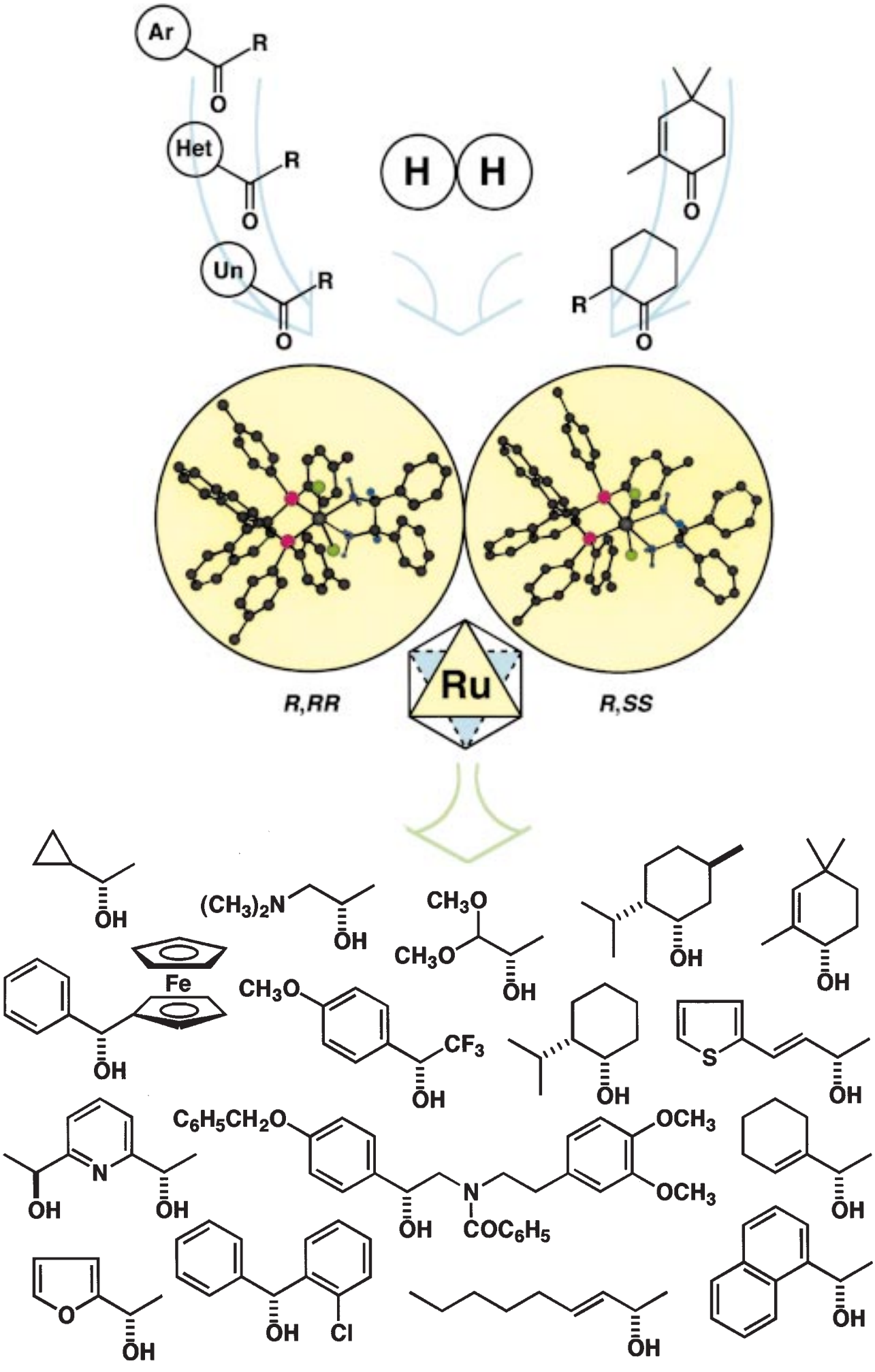


Asymmetric Catalysis by Architectural and Functional Molecular Engineering: Practical Chemo- and Stereoselective Hydrogenation of Ketones

Ryoji Noyori* and Takeshi Ohkuma

Hydrogenation is a core technology in chemical synthesis. High rates and selectivities are attainable only by the coordination of structurally well-designed catalysts and suitable reaction conditions. The newly devised [$RuCl_2$-(phosphane)$_2$(1,2-diamine)] complexes are excellent precatalysts for homogeneous hydrogenation of simple ketones which lack any functionality capable of interacting with the metal center. This catalyst system allows for the preferential reduction of a C=O function over a coexisting C=C linkage in a 2-propanol solution containing an alkaline base. The hydrogenation tolerates many substituents including F, Cl, Br, I, CF_3, OCH_3, $OCH_2C_6H_5$, $COOCH(CH_3)_2$, NO_2, NH_2, and NRCOR as well as various electron-rich and -deficient heterocycles. Furthermore, stereoselectivity is easily controlled by the electronic and steric properties (bulkiness and chirality) of the ligands as well as the reaction conditions. Diastereoselectivities observed in the catalytic hydrogenation of cyclic and acyclic ketones with the standard triphenylphosphane/ethylenediamine combination compare well with the best conventional hydride reductions. The use of appropriate chiral diphosphanes, particularly BINAP compounds, and chiral diamines results in rapid and productive asymmetric hydrogenation of a range of aromatic and heteroaromatic ketones and gives a consistently high enantioselectivity. Certain amino and alkoxy ketones can be used as substrates. Cyclic and acyclic α,β-unsaturated ketones can be converted into chiral allyl alcohols of high enantiomeric purity. Hydrogenation of configurationally labile ketones allows for the dynamic kinetic discrimination of diastereomers, epimers, and enantiomers. This new method shows promise in the practical synthesis of a wide variety of chiral alcohols from achiral and chiral ketone substrates. Its versatility is manifested by the asymmetric synthesis of some biologically significant chiral compounds. The high rate and carbonyl selectivity are based on nonclassical metal–ligand bifunctional catalysis involving an 18-electron amino ruthenium hydride complex and a 16-electron amido ruthenium species.

Keywords: asymmetric hydrogenation · carbonyl hydrogenation · P ligands · ruthenium · synthetic methods

1. Introduction

Catalysis plays a vital role in chemical synthesis. In particular, efficient molecular organometallic catalysis[1] provides a logical basis for molecular science and related technologies. Although selectivity, particularly in the control of absolute stereochemistry,[2, 3] is a major concern in modern organic synthesis, reactivity and productivity are also important in making reactions efficient and practical.[4, 5]

A useful catalysis must show a high turnover number (TON), defined as mols of product per mol of catalyst, and a high turnover frequency (TOF), defined as TON per h or s. In addition, reactions should be operationally simple, safe, and environmentally friendly. These important attributes can be obtained only by designing suitable molecular catalysts and reaction conditions through a deep understanding of, or a unique insight into, the catalytic cycle. In fact, to a large extent the discovery of efficient catalytic reactions still relies on serendipity but originates from sound, comprehensive chemical knowledge.

Combinatorial approaches coupled with high-throughput screening techniques obviously facilitate the discovery process[6] but their powers are still that not evident in the field of molecular catalysis. Most excellent new catalysts are optimized forms of existing catalysts rather than being truly novel. Neither current sophisticated quantum theory nor elaborate force field methods or combinations thereof can yet predict the best catalyst.

Hydrogen (H_2) is the simplest molecule and its properties are fully understood. Because this clean resource is available in abundance at a very low cost, catalytic hydrogenation is a core technology in both research and industry.[4, 5, 7, 8] Never-

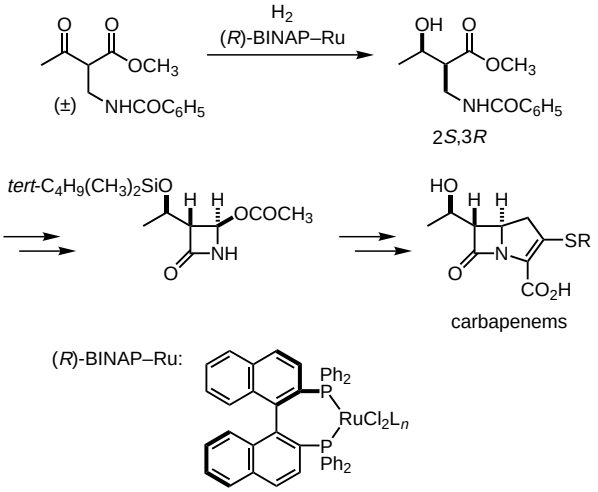
[*] Prof. Dr. R. Noyori, Assoc. Prof. Dr. T. Ohkuma
Department of Chemistry and Research Center for Materials Science
Nagoya University
Chikusa, Nagoya 464-8602 (Japan)
Fax: (+81) 52-783-4177
E-mail: noyori@chem3.chem.nagoya-u.ac.jp

  1433-7851/01/4001-0041 $ 17.50+.50/0

theless, the ways to manipulate H_2 chemically have remained limited. During our studies on homogeneous hydrogenation over two decades,[2, 9–11] our approaches and our choices, particularly chiral multiplication,[2] have been solely intuitive. Herein we describe the discovery and development of an uncommonly practical homogeneous hydrogenation process. The relative and absolute stereochemistry can be controlled efficiently and flexibly by molecular engineering. Prior to this, no general catalysts that effect selective ketone hydrogenation have existed.[10–13]

1.1. Research Background

Asymmetric catalysis is having a revolutionary impact on the chemical synthesis of chiral compounds.[2, 3, 5, 14, 15] Scheme 1 illustrates the situation of our research project on asymmetric hydrogenation in the early 1990s.[9–11] The BINAP – Ru^{II} complexes[16] effect highly enantioselective hydrogenation of various β-keto esters to chiral β-hydroxy esters.[17] By combining this asymmetric reaction with dynamic kinetic resolution,[18, 19] an important industrial process was realized. Thus, asymmetric hydrogenation of methyl α-(benzamidomethyl)acetoacetate utilizing in situ stereochemical inversion of the configurationally labile substrate leads selectively to the 2*S*,3*R*-configured *erythro* isomer of the four possible stereoisomers.[20–23] Takasago International Co. commercialized this enantio- and diastereoselective hydrogenation method for the production of a chiral intermediate for the synthesis of carbapenem antibiotics (Scheme 1).[4d, 5a, 9–11] However, this significant reaction is merely one of the applications of the BINAP – Ru-catalyzed asymmetric hydrogenation of functionalized ketones which are generalized in Scheme 2.[9–11] The



Scheme 1. Industrial application of BINAP – Ru catalyzed hydrogenation to the asymmetric synthesis of carbapenem antibiotics.

reaction is optimized in alcoholic solvents. In a similar manner, a large range of functionalized olefins can be hydrogenated with a high level of enantioselectivity.[9, 10, 11c] A wide variety of in situ prepared and preformed BINAP – Ru^{II} complexes can be used for these reactions.[11, 12i, 22, 24]

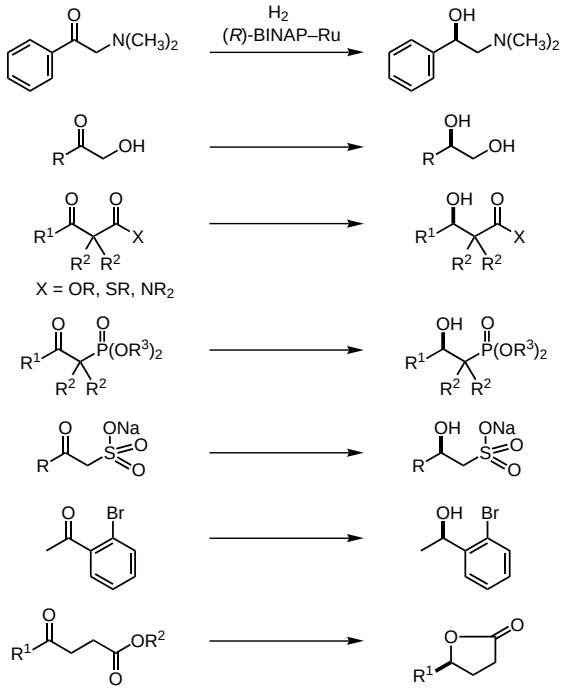
Scheme 3 presents our proposed mechanism for the asymmetric reaction of β-keto esters.[10c] The hydrogenation probably proceeds via a Ru^{II} monohydride **2** formed by the heterolysis of a hydrogen molecule by the ruthenium dichloride **1**. The Ru hydride **2** interacts reversibly with the keto ester to form the chelating complex **3**. Protonation of the keto oxygen changes the geometry of **3** from the σ to the π complex and, at the same time, increases the electrophilicity of the

R. Noyori

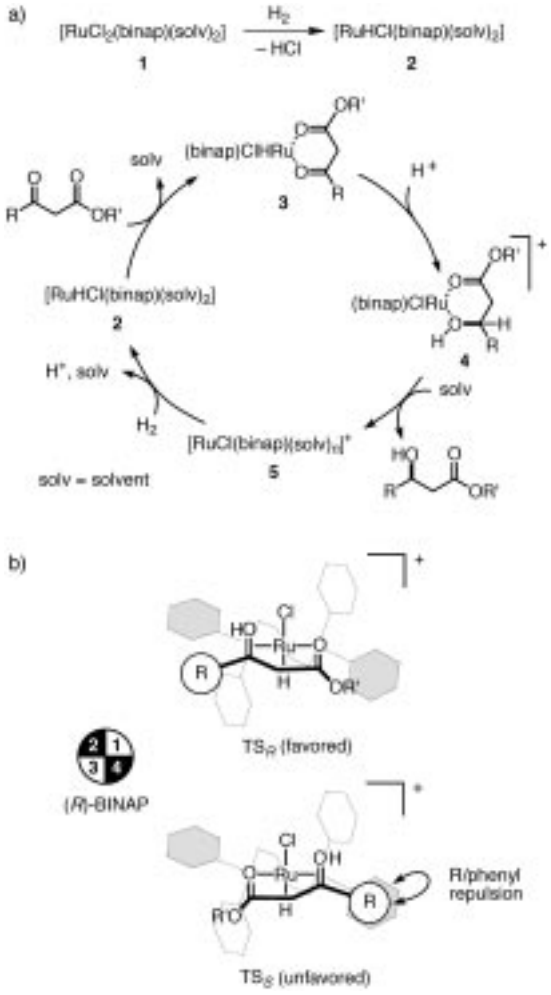
T. Ohkuma

Ryoji Noyori obtained his M.Sc. degree in 1963 at Kyoto University and became a Research Associate (Instructor) with Professor H. Nozaki at the same university. He received his Ph.D. in 1967 and in the following year he was appointed Associate Professor at Nagoya University. In 1969 – 1970, he spent a postdoctoral year at Harvard University with Professor E. J. Corey, and shortly after returning to Nagoya, he was promoted to Professor in 1972. His major research has focused on the fundamentals and applications of molecular catalysis based on organometallic chemistry. His scientific contributions have been recognized with many international awards including The Tetrahedron Prize (1993), The Arthur C. Cope Award (1997), The King Faisal International Prize (1999), and the Roger Adams Award (2001). He was honored to receive The Order of Culture in 2000 from the Japanese emperor.

Takeshi Ohkuma, born in Gunma, Japan, in 1962, studied chemistry at Keio University, and completed his M.Sc. under the supervision of the late Professor Gen-ichi Tsuchihashi. He moved to Nagoya University to join the Professor Noyori's research group and worked in the field of molecular catalysis. After obtaining his Ph.D. in 1991, he worked with Professor Paul A. Wender at Stanford University until 1992. In the same year he joined the ERATO Noyori Molecular Catalysis Project. In 1996 he became an Associate Professor at the Department of Chemistry, Nagoya University. His research interests encompass the development of new catalytic reactions with high reactivity and selectivity. He received The Progress Award in Synthetic Organic Chemistry, Japan, in 1997.



Scheme 2. General BINAP–Ru catalyzed asymmetric hydrogenation of functionalized ketones.



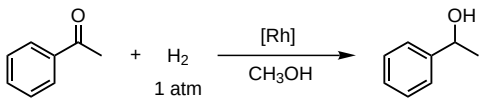
Scheme 3. Mechanism of (*R*)-BINAP–Ru catalyzed hydrogenation of β-keto esters; a) catalytic cycle and b) enantio-determining transition states.

carbonyl carbon, facilitating intramolecular hydride transfer.[25, 26] The resulting Ru–hydroxy ester complex **4** readily releases the chiral product by the action of solvent molecules. The cationic ruthenium species **5** reacts with hydrogen to revert back to **2**, completing the catalytic cycle. When an (*R*)-BINAP–Ru complex is used, the *R* product is obtained in $>99\,\%$ *ee*. Structures TS_R and TS_S illustrated in Scheme 3b show the diastereomeric transition states that provide a distinct bias for the stereo-determining hydride-transfer step.[9g, 10c, 18, 26] The C_2 symmetry of (*R*)-BINAP binding to the Ru^{II} center provides a chiral backbone with a fixed λ-oriented seven-membered chelate ring.[27] In TS_R leading to the *R* product, the chiral template accommodates the keto ester in such a way as to minimize the nonbonded interaction with the equatorial phenyl rings, while diastereomeric TS_S undergoes a significant nonbonded repulsion between the R group and the phenyl ring.[9g, 10c, 18, 26] The presence of an additional substituent at C-2 induces further *erythro*/*threo* diastereoselection,[23] enabling the asymmetric synthesis shown in Scheme 1. The coordination of the ester carbonyl oxygen to the ruthenium center not only accelerates the reaction but also makes a highly organized, stereo-differentiating transition state.

Noteworthy is that methyl 3-oxobutyrate is hydrogenated even *in aqueous acetone* containing $[RuCl_2\{(R)\text{-binap}\}(dmf)_n]$ to give (*R*)-methyl-3-hydroxybutyrate in 97 % *ee*.[28] Acetone, the simplest, unfunctionalized ketone, is almost inert under such reaction conditions. This is a pivotal feature of our earlier BINAP–Ru chemistry.

1.2. Historical Aspects of Ketone Hydrogenation

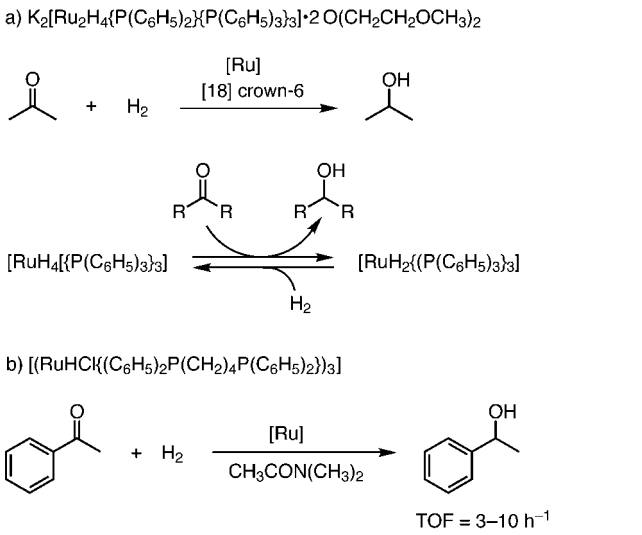
Ketones are the most common unsaturated substrates. In spite of extensive studies, only a limited number of transition metal catalysts were known to exhibit satisfactory activity in hydrogenation of simple ketones that have no functionality close to the carbonyl group.[7, 8, 11] Schrock and Osborn found that $[RhH_2\{P(C_6H_5)(CH_3)_2\}_2L_2]X$ (L = solvent, X = PF_6 or ClO_4) effectively reduces acetone under 1 atm of H_2 in the presence of a small amount of water.[29] Tani and Otsuka achieved hydrogenation of ketonic substrates using a cationic rhodium complex with a fully alkylated bidentate diphosphane (Scheme 4).[30] In these cases, the high basicity of the ligands[31] increases the electron density of the rhodium center so that the oxidative addition of H_2 might be accelerated.[30, 32] A bipyridine-based rhodium complex showed high catalytic



[Rh]	TOF [h^{-1}]
$[Rh(dipb)(nbd)]ClO_4$	569
$[RhCl_2(bpy)_2]Cl{\bullet}2H_2O$ + NaOH	372

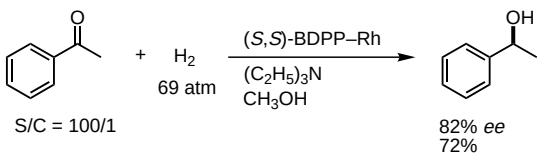
Scheme 4. Hydrogenation of acetophenone catalyzed by rhodium complexes. NBD = norbornadiene, DIPB = 1,4-bis(diisopropylphosphino)butane, bpy = bipyridine.

activity in the presence of methanolic NaOH (Scheme 4),[33] where the $[Rh(bpy)_2]^+$ species (bpy = bipyridine) was proposed as a catalyst.[34] $[Rh_2Cl_2(OCOH)_2(bpy)_2]$[35] and a $[RhClP(C_6H_5)_3(cod)]/NaBH_4$ combined system[36] (cod = cycloocta-1,5-diene) also effected hydrogenation under basic conditions. Some phosphane–ruthenium complexes were known to hydrogenate simple ketones,[37, 38] but their activities were normally lower than those of the rhodium complexes. Grey, Pez, and Wallo claimed that $K_2[Ru_2H_4\{P(C_6H_5)_2\}\{P(C_6H_5)_3\}_3]\cdot 2\,O(CH_2CH_2OCH_3)_2$, an anionic ruthenium complex, coupled with [18]crown-6 acts as a catalyst in the hydrogenation of acetone in toluene at 7 atm and 85 °C (Scheme 5).[39] Later Halpern and Linn concluded that the actual active species is neutral $[RuH_4\{P(C_6H_5)_3\}_3]$ complex.[40] A trinuclear ruthenium complex, $[\{RuHCl(dppb)\}_3]$ (dppb = 1,1′-bis(diphenylphosphanyl)butane) as reported by James et al., slowly catalyzes hydrogenation of acetophenone under 1 atm of H_2 at 50 °C in *N*,*N*-dimethylacetamide (Scheme 5b).[41] Thus, synthetically versatile catalyst systems remained unknown.



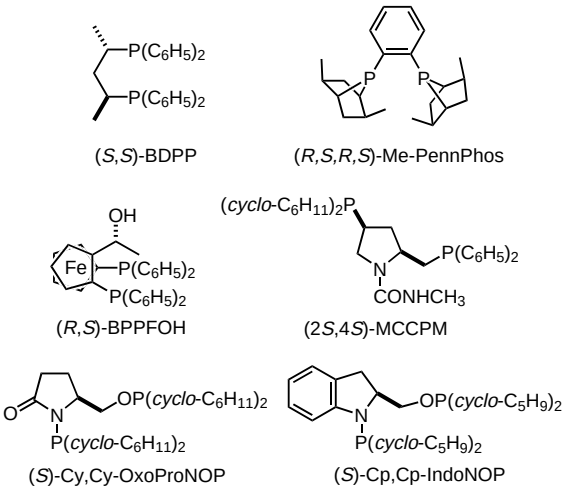
Scheme 5. Ruthenium complexes for the hydrogenation of simple ketones.

Asymmetric hydrogenation of simple achiral ketones was even more difficult.[11] Although it appears to be simple, in fact, it is a serious challenge for synthetic chemists. In 1985, Markó et al. reported that a BDPP–Rh^I complex in methanol and triethylamine at a substrate to catalyst ratio (S/C) of 100/1 catalyzes hydrogenation of acetophenone under 69 atm H_2 and 50 °C to afford 1-phenylethanol in 82 % *ee* (Scheme 6).[42] Based on this observation, various chiral phosphane–rhodium,[43, 44] –iridium,[45] and –ruthenium complexes[46, 47] were



Scheme 6. Asymmetric hydrogenation of acetophenone with a BDPP–Rh catalyst. Conditions: (*S*,*S*)-BDPP–Rh = 1/2[RhCl(nbd)]$_2$+(*S*,*S*)-BDPP (Scheme 7), ketone:Rh:amine = 100:1:5, 50 °C, 24 h.

devised for asymmetric hydrogenation (Scheme 7), however, the number of substrates giving reasonable enantioselectivity was limited and the reactivity and selectivity remained unsatisfactory. Therefore, asymmetric hydroboration[48–53] and



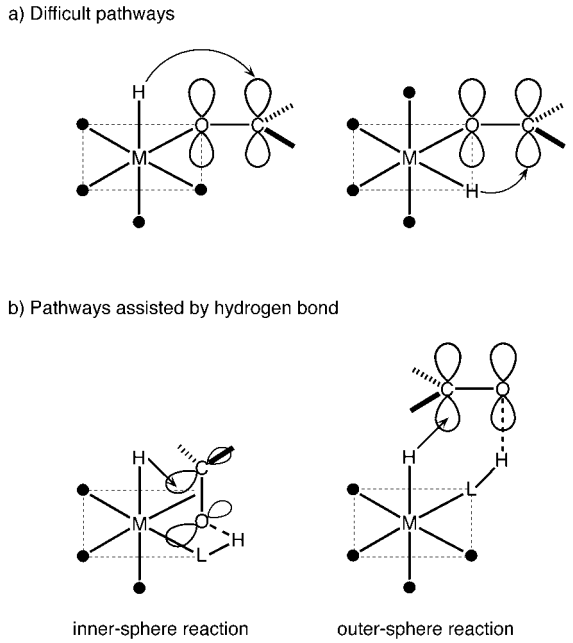
Scheme 7. Structures of some chiral P ligands that can be employed in hydrogenation catalysts.

hydrosilylation[54, 55] as well as transfer hydrogenation[11b,c, 56–58] using organic hydrogen donors have been utilized as the major tools for catalytic conversion of ketones into chiral secondary alcohols.[59, 60] Obviously a direct and practical hydrogenation method was needed.

1.3. Early Attempts

Conventional diphosphane–ruthenium(II) complexes were mostly useless for the hydrogenation of simple ketones. Since the hydrogen molecule is readily activated by ruthenium complexes regardless of the substrate structures (Scheme 2 and 3), the lack of reactivity of simple ketones is merely because of the absence of coordinating heteroatoms near the carbonyl group. A new way to *catalytically* activate the carbonyl group was needed. Despite insufficient mechanistic information about ketone hydrogenation, our initial attempts were directed toward designing new ruthenium catalysts.

Since electrophilic metals tend to form σ complexes rather than π complexes with carbonyl compounds,[61, 62] the relative locations of the nucleophile and carbonyl carbon are inappropriate for reaction. This may also be the case in catalytic hydrogenation which involves metal hydride species MH. As illustrated in Scheme 8a, the delivery of hydride from the metal center to the carbonyl carbon is difficult for geometric reasons. The requisite interaction between the M–H bond and π face of the C=O group is achieved only through drastic geometric changes of the ground-state σ structures. The ground-state π complexation is achieved only with electropositive transition metals and carbonyl compounds with a low-lying LUMO, which facilitate the metal to substrate backbonding.[63] Furthermore, the resulting metal alkoxide

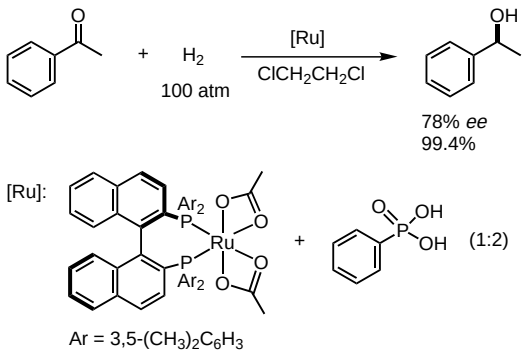


Scheme 8. Hydride transfer from the metal center M to the carbonyl carbon. LH = protic neutral ligand.

intermediate may undergo reverse β-elimination,[64] unless some subsequent process rapidly cleaves the O–M bond.

Although most textbooks state that reactions between carbonyl compounds and metal alkyls or hydrides occur with a 1:1 C=O:metal stoichiometry, the simple $[\pi 2+\sigma 2]$ process may be kinetically unfavorable.[65] Instead, many organometallic reactions are now considered to involve *two* metal centers in the transition states, in which one metal carries a nucleophile and the other interacts with the carbonyl oxygen atom enhancing the nucleophilicity of the carbon atom.[48, 65–67] Protonation or hydrogen bonding to the carbonyl oxygen atom would also facilitate the π-face attack of a nucleophile on the metal center. In fact, unlike in the reaction of a functionalized ketone (Scheme 2),[25, 26] addition of strong acids does not assist hydrogenation of acetophenone in the presence of $[RuCl_2\{(R)\text{-binap}\}(dmf)_n]$, because the bimolecular reaction between a RuH intermediate and the protonated ketone, both present in low concentrations in a catalytic reaction system, is unfavorable. However, if the anionic ligand on the metal center, for example, X in $[RuHX(binap)(solv)_2]$, is protic, then it might facilitate the hydride delivery with the aid of ligand/substrate hydrogen bonding (Scheme 8b). Furthermore, unlike the pathway involving metal alkoxide intermediates, such a process would produce alcohol products directly without a subsequent reaction.

In this context, we anticipated that the requisite BINAP–Ru complexes could form by ligand-exchange reactions between the BINAP–Ru diacetate complex and hydroxy carboxylic acid, amino acids, phosphoric acid, hydroxy phosphonic acids, etc. Reaction of the BINAP–Ru dichloride and sodium or potassium salts of weak acids would also lead to the corresponding ligand-exchange products under thermodynamic control. Thus, various (pre)catalysts were prepared in situ and tested in the asymmetric hydrogenation of acetophenone. Of more than 200 such experiments the best results were with a catalyst prepared in situ from $[Ru(OCOCH_3)_2\{(R)\text{-xylbinap}\}]$[16] and phenylphosphonic acid in a 1:2 ratio (Scheme 9).[68] This catalyst system effected hydrogenation of acetophenone with an S/C ratio of 700/1 in 1,2-dichloroethane under 100 atm H_2 at 100 °C for 18 h to afford



Scheme 9. Asymmetric hydrogenation of acetophenone catalyzed by a XylBINAP–Ru diacetate complex aided by phenylphosphonic acid. Conditions: 100 °C, 18 h.

(*S*)-1-phenylethanol in 78% *ee* and in 99.4% yield. The phosphonic acid appeared to activate the chiral diphosphane–ruthenium complex probably by the formation of a RuH–phosphonate complex in which the anionic ligand has an additional OH group which interacts with the carbonyl oxygen. Although this was a positive result, the enantioselectivity was moderate and the reaction was rather slow. Despite the sustained efforts of our able young collaborators for many years, the efficiency did not meet the standards required by modern organic synthesis.[2, 14, 15]

2. Hydrogenation of Simple Ketones

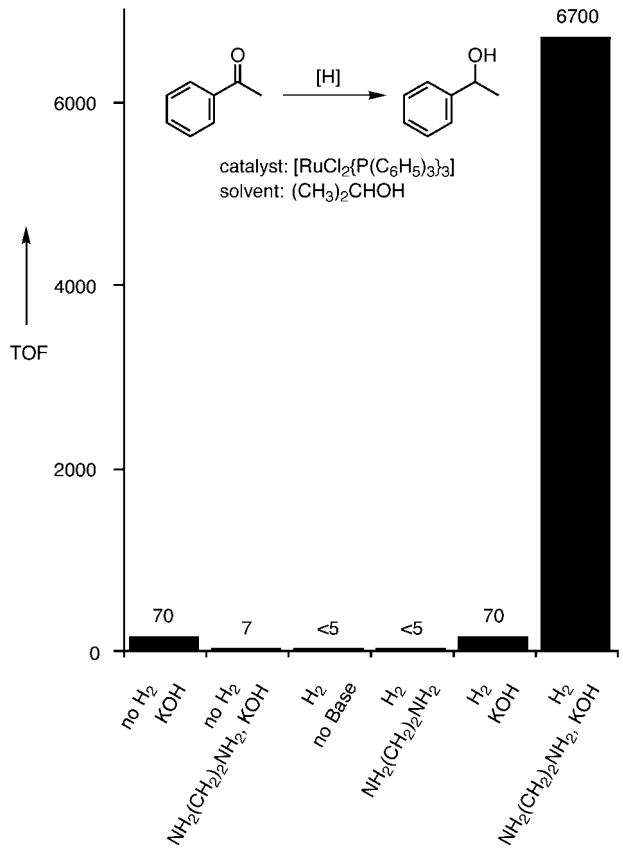
2.1. Conceptual Turning Point: Metal–Ligand Cooperation in Molecular Functions

Although the early efforts to achieve efficient asymmetric hydrogenation of acetophenone were not fruitful, the failure provided us with the opportunity for a new discovery. We set a more ambitious goal for ourselves, namely replacing a range of metal hydride reductions by catalytic hydrogenation. For over half a century the selective reduction of carbonyl compounds to alcohols has relied heavily on the use of the hydrides of boron, aluminum, and silicon,[48–55, 59, 60] however, for scientific, technical, and economic reasons, particularly for large-scale reactions, homogeneous hydrogenation is obviously more desirable than stoichiometric hydride reduction. Heterogeneous hydrogenation[8, 13, 69] is technically advantageous but often nonselective and/or the reaction course is less predictable.

The mechanism of homogeneous hydrogenation is known. Our first task was to generate high reactivity by designing molecular catalysts, we concentrated on the use of protic, neutral ligands. Most hydrogenation catalysts that have been developed utilize aprotic neutral ligands (L) such as tertiary phosphanes, phosphites, tertiary amines, ethers and dienes, or

anionic ligands (X) including halides, alkoxides, and carboxylates.[3d, 15i, 70] On the other hand, the use of protic neutral ligands (LH) such as alcohols had been largely unexplored. The LH ligands were considered as mere spectators or weak donors, often indicated as solvent molecules (solv), whose liberation from metals forms catalytically active, coordinatively unsaturated complexes. We were intrigued to see if the characteristics of LH could be utilized in a more positive fashion.

Hydrogen bonding is an ubiquitous electrostatic interaction that is very important in chemistry. If strength of hydrogen bonding is greater in the transition state than in the ground-state molecules, then hydrogen bonding must contribute to the acceleration of chemical reactions. Scheme 8b illustrates a possible hydrogen-bond-assisted hydride transfer from M to a carbonyl carbon atom. The alcohol product may form in either the inner or outer coordination sphere of the MH species. The presence of the LH···OC hydrogen bond facilitates the interaction between the M–H linkage and the π face of the C=O unit.[71] This is an extension of the idea given in Section 1.3 but is more concrete.[72] In this context, we were impressed by the origin of the anticancer activity of cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, and its analogues which utilize ammonia or primary or secondary amines as ligands, but not tertiary amines.[73] A free NH proton is not a strong hydrogen-bond donor, however, when the nitrogen atom interacts with the Pt center, the NH group has increased acidity allowing for interaction with a phosphate moiety in DNA. As a consequence, the DNA double-stranded structure is perturbed and the Pt center forms a complex with a guanine moiety. Thus, the Pt metal and protic neutral ligand cooperate in developing antitumor activity. We anticipated that this chemical principle based on an NH function could be utilized for homogeneous hydrogenation by metal–ligand difunctional catalysis.



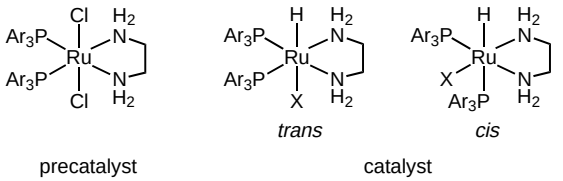
Scheme 10. Reduction of acetophenone catalyzed by a ruthenium complex. TOF = moles of product/mole of Ru × h. Conditions: Ketone:$[RuCl_2\{P(C_6H_5)_3\}_3]$ = 5000:1, [ketone] = 1.4 M, 28 °C, common (but not always utilized) reagents: 20 equivalents of KOH, 1 equivalent of $NH_2(CH_2)_2NH_2$, 3 atm H_2.

2.2. Discovery of a Highly Reactive Catalyst System

Based on the above concept, we pursued the catalytic saturation of C=O bonds by using both hydrogen gas (hydrogenation) and stable organic compounds, including 2-propanol (transfer hydrogenation),[11b,c, 58a] with the aid of Ru^{II} complexes. In our search for a reactive catalyst system, we used a standard system of 1.4 M acetophenone solution in 2-propanol containing $[RuCl_2\{P(C_6H_5)_3\}_3]$ and KOH (ketone:Ru:base = 5000:1:20).[74]

A combined system of a transition metal complex and an alkaline base in 2-propanol has frequently been used for the transfer hydrogenation of ketones.[11b,c, 56–58] In fact, under such conditions even in the absence of hydrogen gas, the reduction of acetophenone proceeded with a TOF of 70 h^{-1} at 28 °C (Scheme 10). However, the addition of one equivalent of ethylenediamine retarded the transfer hydrogenation, the TOF being only 7 h^{-1} under otherwise identical conditions. This was surprising because other experiments showed that structurally similar compounds, ethanolamine and *N*-tosylethylenediamine, significantly accelerate the transfer hydrogenation of simple ketones catalyzed by $[\{RuCl_2(\eta^6\text{-arene})\}_2]$ and KOH or other strong bases.[58, 75] More significantly, however, ethylenediamine enormously accelerated *hydrogenation with molecular hydrogen* giving a TOF number of 6700 h^{-1} at 3 atm (Scheme 10).[76] This is a net hydrogenation; the absence of transfer hydrogenation was confirmed by a deuterium-labeling experiment using [2-D]2-propanol which yielded no deuterated 1-phenylethanol or acetone.[74] However, formation of a reactive ruthenium hydride species from the ruthenium chloride precatalyst in the induction step might be facilitated by the 2-propanol solvent.[58, 77, 78] It should be noted that $[RuCl_2\{P(C_6H_5)_3\}_3]$ is a poor catalyst for ketone hydrogenation; without ethylenediamine or KOH, the TOF remained less than 5 h^{-1}. The TOF of 70 h^{-1} obtained with KOH but without the diamine is probably a result of background transfer hydrogenation with 2-propanol.[78] Thus, both the organic and inorganic bases are necessary for the catalytic hydrogenation. A minimum of 2 equivalents of a strong base is required to generate sufficient activity. As to the chelating diamine auxiliary, at least one primary or secondary amine end is necessary; *N*,*N*,*N*′*N*′-tetramethylethylenediamine (TMEDA), for example, is totally ineffective. 2-Propanol is the solvent of choice, although various alcohols and DMF can also be used. The rate is highly sensitive to the pressure of hydrogen, and hydrogenation with an S/C of 500/1 at 1 atm gave a TOF of only 880 h^{-1} but a TOF of 23000 h^{-1} was obtained with an S/C of 10000/1 at 50 atm.

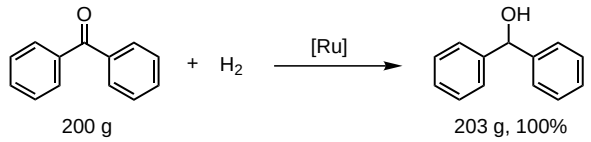
Subsequently we found that the preformed *trans*-[$RuCl_2$(phosphane)$_2$(1,2-diamine)] complexes (Scheme 11) serve as stable precatalysts and effect the even more rapid and productive hydrogenation of ketones.[79–81] For example, when



Scheme 11. Structures of a catalyst precursor and possible calalytic (reducing) species. Ar = 4-$CH_3C_6H_4$, X = H, OR.

a 2.1M solution of cyclohexanone in 2-propanol containing *trans*-[$RuCl_2${$P(C_6H_4$-4-$CH_3)_3$}$_2${$NH_2(CH_2)_2NH_2$}] and $(CH_3)_3COK$ (ketone:Ru:base = 100000:1:450) was stirred under 10 atm of hydrogen at 60 °C for 2 h, cyclohexanol was produced in 96% yield. The reaction rate and productivity are some two orders of magnitude higher than those obtained with the ruthenium complexes generated in situ; the reaction took place with an initial TOF of 563000 h^{-1} or 156 s^{-1}.[79, 82] Thus, the phosphane/diamine ruthenium complexes are among the most reactive (pre)catalysts for the homogeneous hydrogenation of ketones (compare the TOF with the values in Scheme 10).

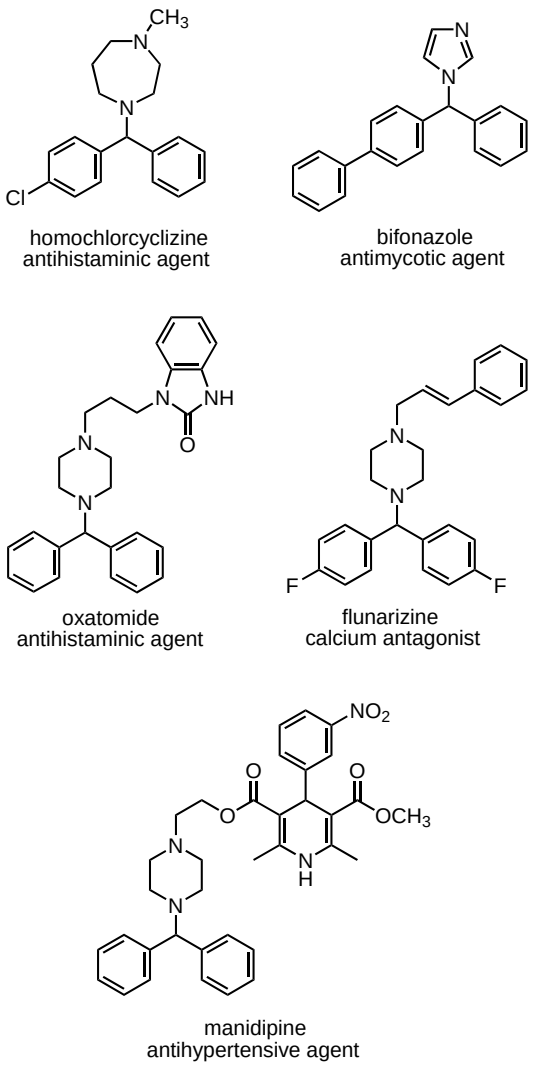
This hydrogenation of ketones does not proceed via their enol forms. In the presence of *trans*-[$RuCl_2${$P(C_6H_4$-4-$CH_3)_3$}$_2${$NH_2(CH_2)_2NH_2$}] and $(CH_3)_3COK$ with an S/C ratio as high as 20000/1 various benzophenone derivatives are cleanly converted into benzhydrols under 8 atm H_2 and 23–35 °C.[83] Scheme 12 illustrates the corresponding reaction of



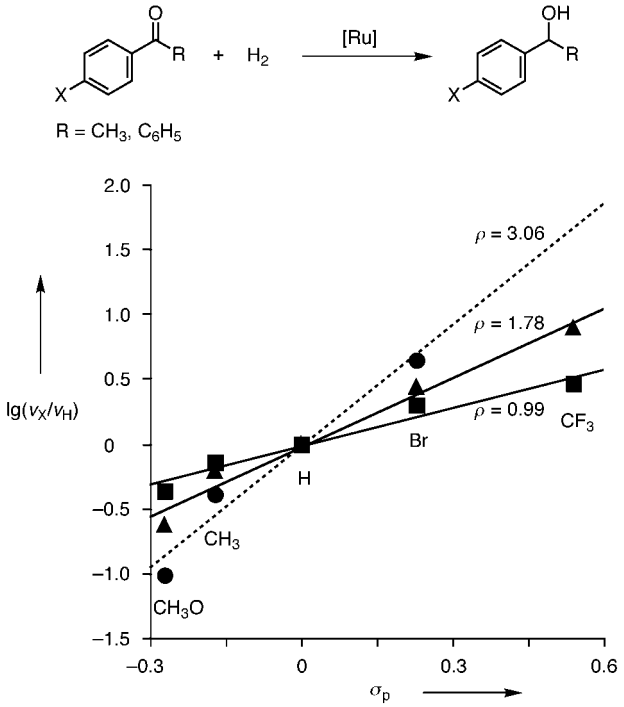
Scheme 12. Hydrogenation of benzophenone with a phosphane/diamine–ruthenium catalyst. Conditions: [Ru] = *trans*-[$RuCl_2${$P(C_6H_4$-4-$CH_3)_3$}$_2${$NH_2(CH_2)_2NH_2$}] (46 mg), $(CH_3)_3COK$ (0.49 g), ketone:Ru:base = 20000:1:80, [ketone] = 2.7 M, $(CH_3)_2CHOH$ (200 mL), 8 atm H_2, 35 °C, 48 h.

parent benzophenone; also sterically hindered *ortho*-substituted benzophenones can be employed as substrates. Unlike many other hydrogenation methods, this reaction did not produce any diphenylmethane products. The reaction does not require a homogeneous 2-propanol solution of ketonic substrates, sparingly soluble solid benzophenones can be subjected to the reaction as a slurry whereby a high reaction rate is maintained. Benzhydrols are used widely as intermediates for the commercial synthesis of pharmaceuticals as illustrated in Scheme 13.[84] This method is particularly useful for the large-scale synthesis of benzhydrols.

Substrates possessing an electron-withdrawing group are more reactive than those with an electron-donating substituent; *p*-trifluoromethylbenzophenone was hydrogenated 11 times faster than the *p*-methoxy ketone at 5 atm and 28 °C, but this is unimportant from a synthetic point of view. Competition experiments using an equimolar mixture of benzophenone and a series of *para*-substituted derivatives and *trans*-[$RuCl_2${$P(C_6H_4$-4-$CH_3)_3$}$_2${$NH_2(CH_2)_2NH_2$}] showed a linear relationship between the relative rate and σ_p constant with a ρvalue of +1.78 (Scheme 14).[83] Similarly, hydrogenation of acetophenone derivatives gave a ρvalue of +0.99. The electron influence is smaller than that observed with the $NaBH_4$ reduction of acetophenones, $\rho = +3.1$.[85] Although the actual catalyst formed under the hydrogenation conditions remains to be elucidated, we consider that the reducing species is a ruthenium hydride or dihydride formulated as *trans*- or *cis*-[RuHX(phosphane)$_2$(diamine)] (X = H or OR) (Scheme 11). Since the isolated phosphane/diamine ruthenium complexes and in situ formed complexes exhibit very similar selectivity (see Section 3.5), the same reactive species would be generated during the hydrogenation reaction. *trans*-[$RuHCl${$P(C_6H_5)_3$}$_2${$NH_2(CH_2)_2NH_2$}] showed no catalytic activity for the hydrogenation of acetophenone in the absence of a strong base.[28]



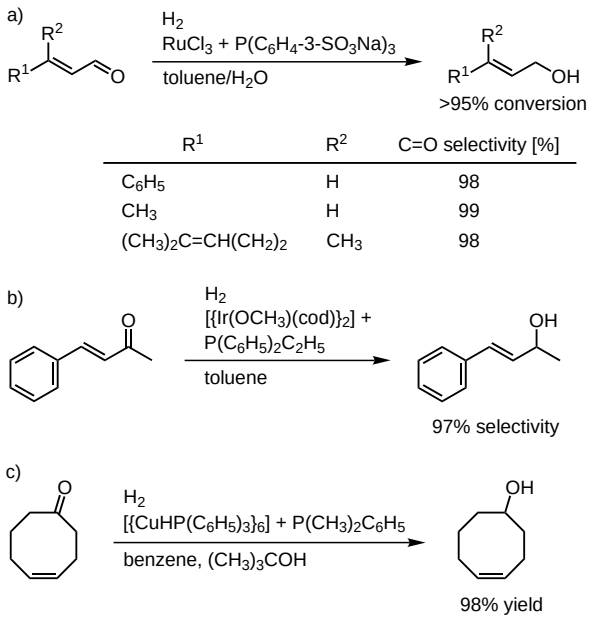
Scheme 13. Pharmaceutically important benzhydryl compounds.



Scheme 14. Hammett plots for hydrogenation of *para*-substituted acetophenones (■) and benzophenones (▲) with *trans*-$[RuCl_2\{P(C_6H_4\text{-}4\text{-}CH_3)_3\}_2\{NH_2(CH_2)_2NH_2\}]$ and $(CH_3)_3COK$ in $(CH_3)_2CHOH$ (5 atm H_2, 28 °C). Reduction of *para*-substituted acetophenones with $NaBH_4$[85] is shown by ●.

3. Chemoselective Hydrogenation

Many kinds of ketonic substrates exist. We first raised the very simple question of how to reduce the carbonyl group in olefinic ketones such as $C_6H_5COCH_2CH_2CH{=}CH_2$. Various metal hydride reagents, including $NaBH_4$ and $LiAlH_4$, saturate the C=O linkage selectively.[86] On the other hand, despite a century of extensive efforts in hydrogenation chemistry, there are no general catalysts effecting selective hydrogenation of a carbonyl function in the presence of an olefinic linkage.[11a, 58] Currently available catalyst systems, either homogeneous or heterogeneous, are mostly selective for C=C bonds.[7, 8, 87] A notable exception is the two-phase hydrogenation of α,β-unsaturated aldehydes to allyl alcohols catalyzed by a water-soluble $P(C_6H_4\text{-}3\text{-}SO_3Na)_3$–Ru catalyst which is used in industrial processes.[88–91] Scheme 15 gives some examples of aldehyde-selective hydrogenations. However, keto groups in α,β-enones are much less reactive. An iridium catalyst with a sterically demanding phosphane ligand effects a carbonyl-selective hydrogenation of benzalacetone (Scheme 15b).[92, 93] Some unconjugated enals and enones are converted preferentially into the unsaturated alcohols with Cu,[94] Ir,[95] and Rh[33b] catalysts.[96] However, the scope of these reactions is unclear. Thus, this selectivity problem has received only fragmentary attention in spite of its significance. Development of general and reliable hydrogenation catalysts with excellent carbonyl selectivity is highly desirable particularly for practical reasons. A system comprising *trans*-$[RuCl_2(phosphane)_2(1,2\text{-diamine})]$ and an alkaline base or a

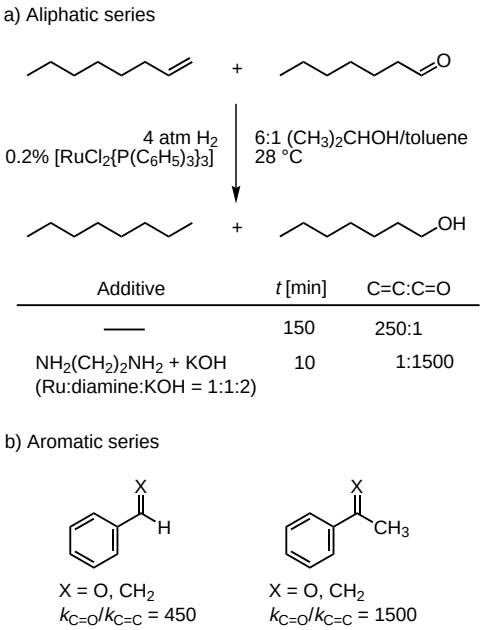


R^1	R^2	C=O selectivity [%]
C_6H_5	H	98
CH_3	H	99
$(CH_3)_2C{=}CH(CH_2)_2$	CH_3	98

Scheme 15. Selected examples of carbonyl-selective hydrogenation of olefinic aldehydes and ketones.

ternary system consisting of $[RuCl_2(phosphane)_3]$, 1,2-diamine, and a strong base was a major breakthrough.

First, we compared the reactivity of 1-octene and heptanal.[97] $[RuCl_2\{P(C_6H_5)_3\}_3]$ is an excellent catalyst for hydrogenation of terminal olefins[7, 37, 98] but very inactive for reaction of carbonyl compounds. An intermolecular competition experiment using an equimolar mixture of 1-octene and heptanal with $[RuCl_2\{P(C_6H_5)_3\}_3]$ in a 2-propanol/toluene mixture under 4 atm of H_2 and 28 °C showed that 1-octene is 250 times more reactive than heptanal (Scheme 16a). However, when one equivalent of ethylenediamine and two equivalents of KOH with respect to ruthenium (not sub-

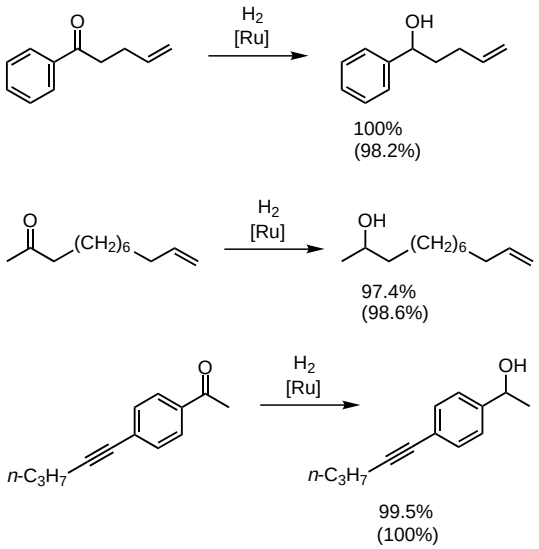


Additive	*t* [min]	C=C:C=O
——	150	250:1
$NH_2(CH_2)_2NH_2$ + KOH (Ru:diamine:KOH = 1:1:2)	10	1:1500

Scheme 16. The diamine effect on the relative reactivities of olefins and carbonyl compounds in ruthenium catalyzed hydrogenation.

strates) were added, the selectivity was reversed dramatically, hydrogenating the aldehyde 1500 times faster than the olefin. Thus, the combined effects of the diamine and KOH has been proven to decelerate olefin hydrogenation catalyzed by $[RuCl_2\{P(C_6H_5)_3\}_3]$ and in turn accelerate aldehyde hydrogenation. Very small quantities of the diamine and inorganic base change the C=O/C=C selectivity profile by a factor of 375000. This marked effect reflects differences in the mechanism in the presence or absence of the basic agents. In a similar manner, the hydrogenation of a mixture of styrene and benzaldehyde proceeded with a C=O/C=C selectivity of 450/1 to give mostly benzyl alcohol (Scheme 16b). Acetophenone was hydrogenated 1500 times faster than α-methylstyrene.[28]

This selective hydrogenation is applicable to a variety of carbonyl compounds having an unsaturated carbon–carbon bond.[97] Scheme 17 illustrates examples of intramolecular

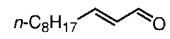
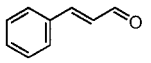
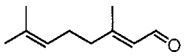
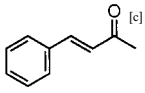
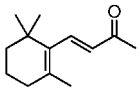


Scheme 17. Carbonyl-selective hydrogenation of unsaturated ketones. Conditions: $[Ru] = [RuCl_2\{P(C_6H_5)_3\}_3]$, $NH_2(CH_2)_2NH_2$, KOH, ketone:Ru:diamine:KOH = 500:1:1:2, $(CH_3)_2CHOH$ or a 6:1 $(CH_3)_2CHOH$/toluene mixture, 4 atm H_2, 28 °C. The selectivity is given in parentheses.

C=O/C=C competition effecting selective conversion of unsaturated ketones into unsaturated alcohols. The hydrogenation with S/C ratios of 500/1 to 10000/1 took place smoothly at 1–8 atm, and very rapidly at 50 atm, giving a near quantitative yield. Aliphatic and aromatic ketones with an unconjugated terminal olefinic bond were hydrogenated preferentially at the carbonyl site and the products were 98–100% pure. Although $[RuCl_2\{P(C_6H_5)_3\}_3]$ is known to isomerize terminal olefins to internal olefins during hydrogenation,[37] no migration of C=C bonds took place under the conditions employed. Internal acetylenic bonds are also tolerated, while terminal acetylenes and α,β-acetylenic ketones diminish the catalytic activity of the ruthenium complexes.[99] The excellent C=O selectivity is reminiscent of that attained by the stoichiometric $NaBH_4$ reduction. The chemoselectivity arises mainly from the electrophilic reactivity of carbonyl carbon versus the nucleophilic reactivity of an olefinic bond.

In contrast in α,β-unsaturated aldehydes and ketones the carbonyl carbon reacts only with nucleophiles, while the olefinic part reacts with both nucleophiles and electrophiles. As shown in Table 1, conjugated enals including 2-undecenal,

Table 1. Carbonyl-selective hydrogenation of α,β-unsaturated carbonyl compounds.[a]

Substrate	Conversion [%]	C=O selectivity [%][b]
	100	100
	99.7	99.8
	100	100
	100	> 99.9
	> 99	100
	98.2	99.6
	100	70
	9.8	> 99.9

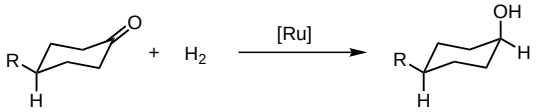
[a] Reactions were conducted at 4 or 8 atm of H_2 and at 28 °C in 2-propanol or a 6:1 2-propanol/toluene mixture containing $[RuCl_2\{P(C_6H_5)_3\}_3]$, $NH_2(CH_2)_2NH_2$, and KOH. Ketone:Ru:diamine:KOH = 500:1:1:2. [b] A percent distribution of the unsaturated alcohol relative to all the hydrogenated products. [c] Ketone:Ru:diamine:KOH = 10000:1:1:2.

cinnamaldehyde, and citral were hydrogenated to the corresponding allyl alcohols with excellent chemoselectivity.[97] Benzalacetone (30.0 g), an open-chain α,β-enone, was hydrogenated under 4 atm H_2 (28 °C, 18 h) in 2-propanol (100 mL) containing $[RuCl_2\{P(C_6H_5)_3\}_3]$ (19.7 mg), ethylenediamine (1.2 mg), and KOH (2.3 mg) with an S/C ratio of 10000/1 to the corresponding allyl alcohol (29.4 g) with a 97% isolated yield. Hydrogenation of 1-acetylcyclohexene, another type of α,β-enone, also showed a very high C=O selectivity (Table 1 entry 6). β-Ionone, a dienone, exhibited perfect selectivity, forming only β-ionol (Table 1 entry 5). There are some problems with this hydrogenation of 2-cyclohexenones; as with $NaBH_4$, simple 2-cyclohexenone (entry 7) underwent 1,2- and 1,4-reduction competitively to give a 7:3 mixture of unsaturated and saturated alcohols. However, a perfect keto selectivity was obtained by introducing a methyl group at the β position, the hydrogenation of 3-methyl-2-cyclohexenone gave solely the allyl alcohol (entry 8).

4. Diastereoselective Hydrogenation

Diastereoselective conversion of ketones into secondary alcohols is a major subject in organic synthesis. This desired stereoselectivity was accomplished by stoichiometric reactions with boron-based hydride reagents.[86, 100–103] Although various hydride reagents are available, each one has a limited scope of reaction linked to its inherent chemical properties and the difficulties in modifying its structure.

The new hydrogenation reaction using a phosphane/diamine–ruthenium catalyst system is a beneficial tool for the diastereoselective reduction of simple ketones. First, when 4-*tert*-butylcyclohexanone (30 g) was hydrogenated with the standard $[RuCl_2\{P(C_6H_5)_3\}_3]/NH_2(CH_2)_2NH_2/KOH$ system (S/C = 10000/1) under 4 atm H_2 and 28 °C, a 98.4:1.6 mixture of *cis*-4-*tert*-butylcyclohexanol and its *trans* isomer was obtained (Scheme 18).[104, 105] Thus, in the conformationally



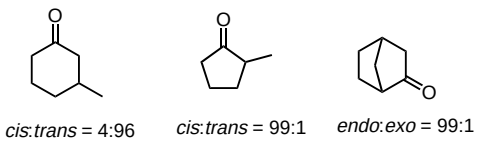
ketone		Alcohol	
R	eq:ax	yield [%]	*cis*:*trans*
$(CH_3)_3C$	100:0	>99	98.4:1.6
C_6H_5	99:1	>99	96:4
CH_3	95:5	97	92:8
OH	—	>99	83:17

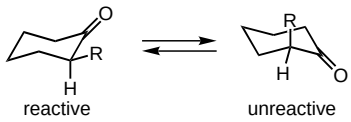
Scheme 18. Diastereoselective hydrogenation of 4-substituted cyclohexanones. Conditions: [Ru] = $[RuCl_2\{P(C_6H_5)_3\}_3]$, $NH_2(CH_2)_2NH_2$, KOH, ketone:Ru:diamine:KOH = 10 000:1:1:2, $(CH_3)_2CHOH$, 4 atm H_2, 28 °C.

anchored substrate the ruthenium hydride species appeared to approach the carbonyl carbon atom preferentially from the less-crowded equatorial side.[106] Use of preformed *trans*-$[RuCl_2\{P(C_6H_4\text{-}4\text{-}CH_3)_3\}_2\{NH_2(CH_2)_2NH_2\}]$ effected rapid hydrogenation in 2-propanol containing $(CH_3)_3COK$ (ketone:Ru:base = 50000:1:250, 10 atm H_2, 60 °C) with a *cis*:*trans* selectivity of 97:3. The TOF was 178000 h^{-1} or 49 s^{-1}.[79] Similar *cis* selectivity was attained earlier by heterogeneous Rh[107] and PtO_2[108] catalysts.[8, 69a] Homogeneous hydrogenation with certain Rh[29, 30a, 32a] or Cu catalysts[94, 109] tends to result in *trans* selectivity.

Scheme 18 shows the diastereoselectivity of reactions of various 4-substituted cyclohexanones.[104] With conformationally flexible substrates, the extent of stereoselection is essentially controlled by the relative populations of the equatorial and axial conformers,[110] resulting in a predominance of the *cis* alcohols. Reaction of 4-phenylcyclohexanone with either the in situ catalyst or the preformed catalyst gave a 96:4 mixture of the *cis* and *trans* alcohols.

In a similar manner, some other cyclic ketones are hydrogenated with a high diastereoselectivity (Scheme 19).[104] Reaction of 3-methylcyclohexanone gave *trans*-3-methylcyclohexanol and the *cis* isomer with a 96:4 selectivity and a 100% yield. There is a conformational reason for this *trans*

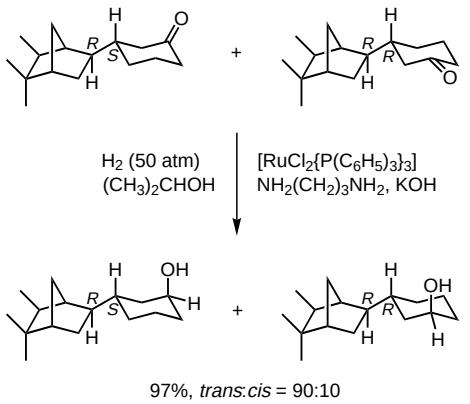




R	Ketone eq:ax	Alcohol *cis*:*trans*
$(CH_3)_2CH$	74:26	>99.8:0.2
CH_3	97:3	98:2

Scheme 19. Diastereoselective hydrogenation of cyclic ketones. Conditions: $[RuCl_2\{P(C_6H_5)_3\}_3]$, $NH_2(CH_2)_2NH_2$, KOH, $(CH_3)_2CHOH$, 4 atm, 28 °C.

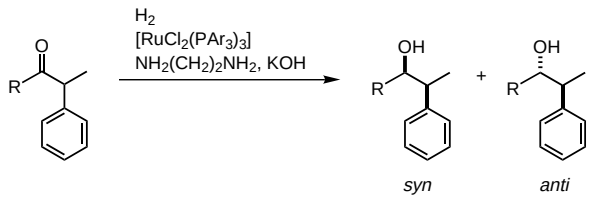
preference. Cyclohexanones alkylated in the 2-position were hydrogenated to give predominantly the *cis* alcohol. Notably, hydrogenation of 2-isopropylcyclohexanone gave the *cis* and *trans* alcohols in a >99.8:0.2 ratio. The selectivity is much higher than the equatorial:axial equilibrium ratio of 74:26,[111, 112] and this is probably a result of the repulsive interaction between the axial 2-isopropyl substituent and incoming ruthenium hydride species which prevents the *trans* alcohol formation. 2-Methylcyclopentanone afforded the *cis* alcohol with a diastereoselectivity of 99:1 and bicyclo[2.2.1]-heptan-2-one showed a 99:1 *endo*:*exo* selectivity. Scheme 20 illustrates the stereoselective synthesis of a substitute for



Scheme 20. Fragrance synthesis by ruthenium-catalyzed diastereoselective hydrogenation. The products shown are substitutes for α and β-santarol.

α- and β-santarol, an expensive fragrance from sandalwood oil, by hydrogenation of a 3-substituted cyclohexanone.[113] The substrate is a diastereomeric mixture, because the isocamphyl group is derived from a natural source, while the product alcohols have a 1,3-*trans* relationship regardless of the chirality of the C-3 substituent.

A high degree of Cram selectivity[23, 114–117] was seen in the hydrogenation of open-chain chiral ketones.[28, 104] As shown in Scheme 21, in the reactions of conformationally flexible 1-phenylethyl ketones, the *syn* alcohols predominate. This

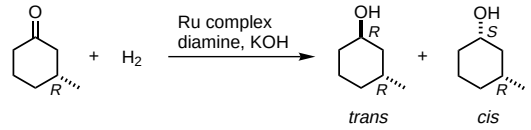


R	PAr$_3$ Ar	ν [cm^{-1}][a]	Alcohol *syn*:*anti*
C_6H_5	C_6H_5		98:2
(*E*)-C_6H_5CH=CH	C_6H_5		75:25
cyclo-C_6H_{11}	C_6H_5		96:4
n-C_4H_9	C_6H_5		93:7
CH_3	C_6H_4-4-OCH_3	2066.1	96:4
CH_3	C_6H_4-4-CH_3	2066.7	95:5
CH_3	C_6H_5	2068.9	86:14
CH_3	C_6H_4-4-F	2071.3	78:22

Scheme 21. Diastereoselective hydrogenation of acyclic ketones of type 1-phenylethylketone. Conditions: S/C = 500/1, $(CH_3)_2CHOH$, 4 atm H_2, 28 °C. [a] $\nu_{CO}(A_1)$ for $[Ni(CO)_3(PAr_3)]$ in CH_2Cl_2 (Tolman, 1977[31]).

and the foregoing stereoselective reactions indicate that the reactive species generated in this hydrogenation behave as "bulky hydrides". The levels of the diastereoface selectivity attained with the standard triphenylphosphane/ethylenediamine–ruthenium catalyst compare well with those of stoichiometric reduction using L-Selectride reagents.[101] A major beneficial characteristic of this catalyst system is the high tunability of its stereochemical and electronic properties through structural modifications of the phosphane and diamine ligands. The stereoselectivity was subtly influenced by the electronic properties of the phosphane ligands.[31] Thus, although the Cram selectivity in the reaction of 3-phenyl-2-butanone (R = CH_3, Scheme 21) with the standard catalyst remained 86:14, it was improved simply by using electron-donating triarylphosphane ligands in tandem with ethylenediamine and reached 96:4 (see Scheme 21).[104]

Diastereoselectivity in the hydrogenation of a chiral ketonic substrate is affected profoundly by the chirality of the phosphane and diamine ligands.[118] A typical example is given in Scheme 22. Thus hydrogenation of (*R*)-3-methylcyclohexanone with a ruthenium complex modified by (*S*)-BINAP and (*S*,*S*)-DPEN[16, 119] formed a 97:3 mixture of the *trans* (1*R*,3*R*) and *cis* (1*S*,3*R*) alcohols, respectively.[104] When the diphosphane and diamine were replaced by (*R*)-BINAP and (*S*)-DAIPEN,[16, 120] a slightly *cis*-enriched (44:56) product mixture was obtained.

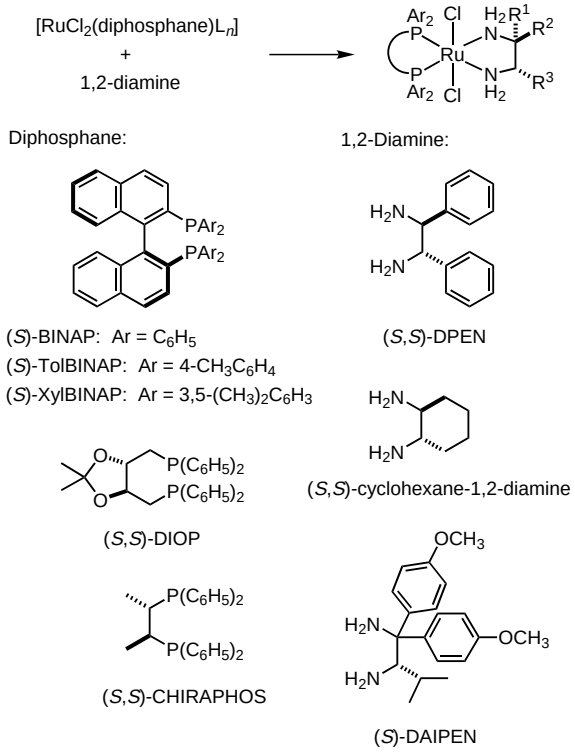


Ru complex	Diamine	*trans*:*cis*
[$RuCl_2${(*S*)-binap}(dmf)$_n$]	(*S*,*S*)-DPEN	97:3
[$RuCl_2${(*R*)-binap}(dmf)$_n$]	(*S*)-DAIPEN	44:56

Scheme 22. Multiple stereodifferentiation in hydrogenation of a chiral ketone. Conditions: S/C = 500/1, $(CH_3)_2CHOH$, 4 atm H_2, 28 °C.

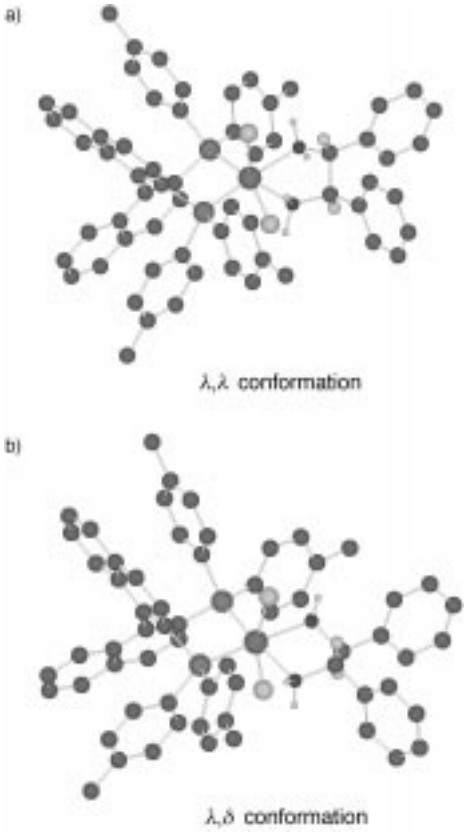
5. Enantioselective Hydrogenation

A major goal of our endeavor is the development of an asymmetric hydrogenation with a wide scope of application.[121] Over the last 15 years a variety of chiral catalysts have been developed,[2, 3, 9–14] in particular BINAP-based catalysts have displayed excellent stereoinductive properties. No single catalyst, however, can be universal because of the structurally diverse array of unsaturated substrates. To obtain a highly enantioselecive reaction, the correct catalyst as well as appropriate reaction conditions must be selected, depending on the structures and properties of the ketonic substrates. This new hydrogenation system has the flexibility to cope with such diverse situations through modification of catalyst structures and reaction parameters. A wide range of chiral ruthenium catalysts can be prepared by different combinations of chiral phosphane and diamine ligands (Scheme 23). Both in situ generated complexes[74] and preformed complexes[79, 80, 122] are



Scheme 23. Synthesis of shelf-stable *trans*-[$RuCl_2$(diphosphane)(1,2-diamine)] complexes. For the abbreviation of the ligands, see ref [16].

usable, although the latter exhibit a higher TON. An X-ray analysis of the isolated (*R*)-TolBINAP/(*R*,*R*)-DPEN–ruthenium complex shows a distorted octahedral coordination geometry of the ruthenium center, to which both the diphosphane and diamine ligands are coordinated in a λ fashion (Scheme 24a).[79, 123] In the *R*/*S*,*S* diastereomer (Scheme 24b), the TolBINAP ligand forms a λ seven-membered structure, while the DPEN ligand assumes a δ five-membered ring. ^1H and ^{31}P NMR spectral analyses of these compounds showed that they exist as a single conformer in [D_6]benzene. Although all the isolated complexes possess a *trans*-dichloro *OC-6-13* geometry, this does not secure the

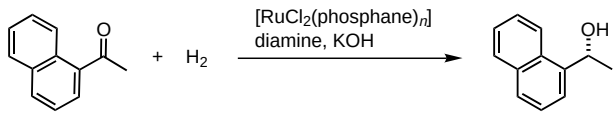


Scheme 24. Molecular structures of a) *trans*-[$RuCl_2${(*R*)-tolbinap}{(*R*,*R*)-dpen}] and b) *trans*-[$RuCl_2${(*R*)-tolbinap}{(*S*,*S*)-dpen}]. All the hydrogen atoms except for the amino and methine groups of DPEN are omitted for clarity.

stereochemistry of the reactive hydride species (see Scheme 11). Depending on the structures of the phosphane and diamine ligands as well as the properties of the anionic ligands, several diastereomers are possible.

5.1. Aromatic Ketones

The pioneering work of Markó et al.[42, 124] spurred research on the asymmetric hydrogenation of simple aromatic ketones but without significant success (Schemes 6 and 9). The enantioselectivity and/or reactivity was insufficient in most cases. We found that hydrogenation of 1′-acetonaphthone with a catalyst system consisting of [$RuCl_2${(*S*)-binap}$(dmf)_n$], (*S*,*S*)-DPEN, and KOH (1:1:2 mol ratio) in 2-propanol under 4 atm H_2 and 28 °C afforded the *R* alcohol in 97 % *ee* in quantitative yield.[74] The high degree of enantioselectivity is a result of the synergistic effects of the chiral diphosphane and diamine,[118] as illustrated in Scheme 25. Replacement of the *S*,*S* diamine by the *R*,*R* enantiomer led to the *R* alcohol in only 14 % *ee*. A combination of the (*S*)-BINAP–Ru complex and achiral ethylenediamine or achiral [$RuCl_2${$P(C_6H_5)_3$}$_3$] and (*S*,*S*)-DPEN formed the *R* alcohol with a moderate *ee* value. The (*R*)-1-(1-naphthyl)ethanol product has been utilized for desymmetrization of prochiral 3-substituted glutaric anhydrides giving chiral building blocks for the synthesis of

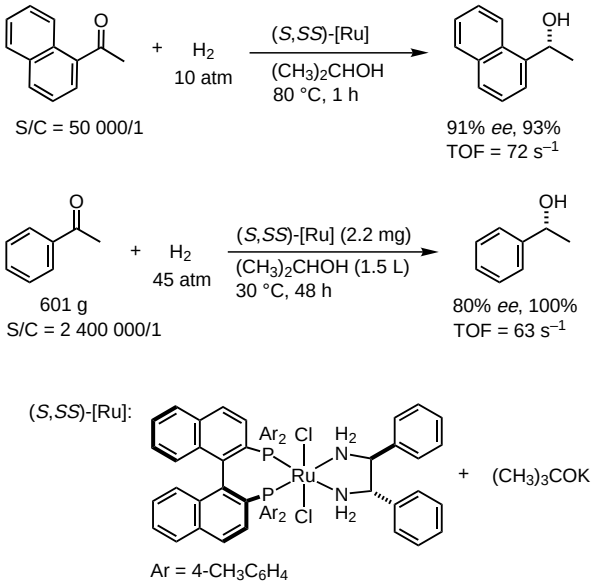


(Di)phosphane	Diamine	*ee* [%]
(*S*)-BINAP	(*S*,*S*)-DPEN	97
(*S*)-BINAP	(*R*,*R*)-DPEN	14
(*S*)-BINAP	$NH_2(CH_2)_2NH_2$	57
$P(C_6H_5)_3$	(*S*,*S*)-DPEN	75

Scheme 25. Double stereodifferentiation in the asymmetric hydrogenation of 1′-acetonaphthone catalyzed by chiral phosphane/diamine–ruthenium complexes. Conditions: ketone:Ru:KOH = 500:1:1:2, $(CH_3)_2CHOH$, 4 atm H_2, 28 °C.

(+)-compactin, an HMG-CoA-reductase inhibitor, and 1233A, a hypocholesterolemic agent.[125]

Rapid, highly productive asymmetric hydrogenation is achievable with a preformed diphosphane/diamine–ruthenium complex (Scheme 26).[79] Thus, reaction using a 2.1 M 2-propanol solution of the same ketone with *trans*-[$RuCl_2${(*S*)-tolbinap}{(*S*,*S*)-dpen}] and $(CH_3)_3COK$ (S/C = 50 000/1) under 10 atm H_2 and 80 °C proceeded with an initial

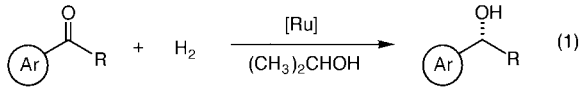


Scheme 26. Rapid, productive, and enantioselective hydrogenation of aromatic ketones.

TOF of 259 000 h^{-1} or 72 s^{-1}, and after 1 h afforded the *R* alcohol in 91 % *ee* and a 93 % yield.[126] In a similar manner, when a mixture of acetophenone (601 g), the (*S*)-TolBINAP/(*S*,*S*)-DPEN–ruthenium complex (2.2 mg), and $(CH_3)_3COK$ (5.6 g) in 2-propanol (1.5 L) was stirred under 45 atm H_2 at 30 °C for 48 h, the *R* alcohol is obtained with 80 % *ee* and a 100 % yield.[127] The substrate concentration was as high as 30 % (w/v). Under such conditions, the TON is at least 2 400 000, while the TOF at 30 % conversion is 228 000 h^{-1} or 63 s^{-1}.[79] In contrast, β-keto esters, the best substrates for the standard BINAP–Ru catalyzed hydrogenation (see

Schemes 1 and 3), are not hydrogenated under these new catalytic conditions.

Although the extent of enantioselectivity obtained with the TolBINAP/DPEN system was unsatisfactory, it was improved greatly by combining (*S*)-XylBINAP and (*S*)-DAIPEN (or *R* and *R*).[16] The latter C_1 symmetric diamine is obtained readily from leucine.[120] The utility of the XylBINAP/DAIPEN complex in reactions of type ilustrated in Eq. (1) is shown in Table 2 and



(1)

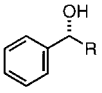
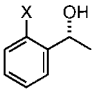
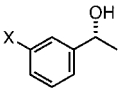
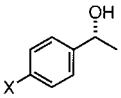
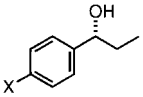
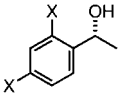
Table 3.[28, 74, 79, 126] This combination very often gave the best result;[128] for example, by this simple method reactions with an S/C ratio of 100000/1 gave various ring-substituted 1-phenylethanols with high *ee* values. Thus, hydrogenation of acetophenone with *trans*-[$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}] and $(CH_3)_3COK$ with an S/C of 100000/1 under 8 atm H_2 afforded the *R* alcohol in 99% *ee*.[128] Although the catalyst possesses bulky diphosphane and diamine ligands, the reaction of acetophenone is only 1.3 times slower than that with the sterically less demanding TolBINAP/DPEN – ruthenium complex under otherwise identical reaction conditions.

With the use of the XylBINAP/DAIPEN – ruthenium complex, various *ortho*-, *meta*-, and *para*-substituted acetophenones have been hydrogenated with consistently high enantioselectivity (Table 2).[128] This hydrogenation tolerates many ring substituents including F, Cl, Br, I, CF_3, OCH_3, $COOCH(CH_3)_2$, NO_2, NH_2, $N(CH_3)_2$, and $NHCOCH_3$. Esters can also be used, although they undergo transesterification with the 2-propanol solvent. The acid-sensitive compound 1-(3,4,5-trimethoxyphenyl)ethanol was obtained in 99% *ee* (Table 3). The electronic effects of *para* and *meta* substituents on the *ee* values are relatively small and steric hindrance resulting from bulky *ortho*-substitutents is not significant either. Higher analogues of acetophenone are also hydrogenated with high enantioselectivity, the one exception being pivalophenone which was almost inert under the standard reaction conditions. Hydrogenation of 3-butenyl phenyl ketone, an unsaturated aromatic ketone, gives a chiral alcohol selectively leaving the olefinic bond intact (Table 3).[97] The reaction is also applicable to 2,2,2-trifluoroacetophenone and its derivatives (Scheme 27)[128] and unlike the reaction with many boron-based reducing agents,[48, 129, 130] the asymmetric sence is identical to that observed with nonfluorinated acetophenones.

The Horeau effect is sometimes applicable to increase enantioselectivity (Scheme 28).[131, 132] Hydrogenation of acetophenone and its *para*-substituted derivatives with an (*S*)-TolBINAP/(*S*)-DAIPEN (not XylBINAP/DAIPEN) combined system gave the *R* alcohols normally with less than 90% *ee*. However, reaction of 1,4-diacetylbenzene afforded enantiomerically pure *R*,*R* diol in 85% yield at the expense of the minor *S* alcohol formed initially in the second hydrogenation (Scheme 28).[74] In a similar manner, triple hydrogenation of 1,3,5-triacetylbenzene with (*S*)-BINAP/(*S*,*S*)-DPEN gave the enantiomerically pure *R*,*R*,*R* triol in 67% yield.[133]

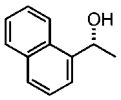
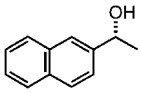
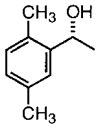
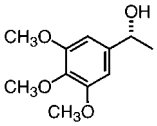
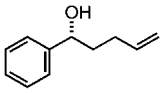
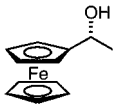
This asymmetric reaction is normally achieved by the tandem use of a chiral diphosphane and chiral 1,2-diamine but some chiral P,N ligands may also be used. Thus, a ruthenium complex generated in situ from a [{$RuCl_2(\eta^6$-arene)}$_2$] and

Table 2. ee Values for the asymmetric hydrogenation of aromatic ketones catalyzed by diphosphane/diamine – ruthenium complexes as in Eq (1).The abbreviations for the ligands are given in ref [16].

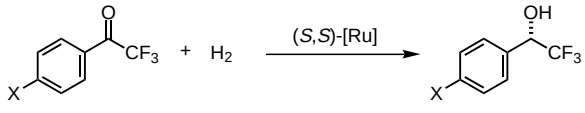
Alcohol	R or X	(*S*)-XylBINAP/ (*S*)-DAIPEN	(*S*)-TolBINAP/ (*S*)-DAIPEN	(*S*)-BINAP/ (*S*,*S*)-DPEN
	CH_3	99	91	87[a]
	C_2H_5	99	92	
	n-C_3H_7		94	
	n-C_4H_9			90[b]
	$C_6H_5CH_2$		98	
	$(CH_3)_2CH$	99		
	Cyclopropyl	96	92	
	$(CH_3)_3C$			61[c]
	CH_3	99	99	95
	F	97	82	
	Cl	98	94	
	Br	96	98	
	CF_3	99	99	
	CH_3O	92	82	
	CH_3CONH	98	86	
	CH_3	100	87	
	F	98	88	
	Br	99.5	77	
	CF_3	99	83	
	CH_3O	99	88	88[a]
	CH_3	98	84	94[a]
	C_2H_5		97	89[a]
	n-C_4H_9	98	93	
	$(CH_3)_2CHCH_2$		96[d]	
	$cyclo$-C_6H_{11}		95	
	$(CH_3)_3C$		96	
	C_6H_5	97	87	
	F	97		73
	Br	99.6		84[a]
	I	99	83	71[a]
	CF_3	99.6	78	
	CH_3O	100	86	92[a]
	$(CH_3)_2CHOCO$	99		
	$(CH_3)_2NCO$		88	
	NO_2	99.8		83[a]
	NH_2	99		
	CH_3CONH		95	
	$(CH_3)_2N$			94[a]
	CH_3		95	
	F	99[e]	92	
	Cl	99[e]	86[d]	87[a]
	CH_3O		95	
	CH_3	99[e]	99	
	F	97	77	
	Cl	96[e]	94	
	CF_3	99.5		

[a] With (*S*)-BINAP/(*S*)-DAIPEN. [b] With (*S*)-BINAP/(*S*)-DAMEN. [c] Under 50 atm H_2, 6% yield. Absolute configuration undetermined. [d] With(*S*)-TolBINAP/(*S*,*S*)-DPEN. [e] With (*S*)-XylBINAP/(*S*,*S*)-DPEN.

Table 3. *ee* Values for the asymmetric hydrogenation of aromatic ketones catalyzed by diphosphane/diamine–ruthenium complexes as in Eq (1).The abbreviations for the ligands are given in ref [16].

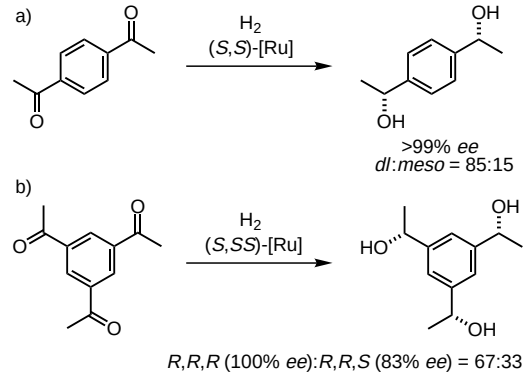
Product alcohol	Ligand combination	*ee* [%]	Product alcohol	Ligand combination	*ee* [%]
	(*S*)-TolBINAP/(*S*,*S*)-DPEN	98		(*S*)-TolBINAP/(*S*)-DAIPEN	98
	(*S*)-BINAP/(*S*,*S*)-DPEN	97		(*S*)-XylBINAP/(*S*)-DAIPEN	98
	(*S*)-XylBINAP/(*S*,*S*)-DPEN	99			
	(*S*)-TolBINAP/(*S*)-DAIPEN	99		(*S*)-XylBINAP/(*S*)-DAIPEN	99
	(*S*)-BINAP/(*S*)-DAIPEN	90[a]		(*S*)-TolBINAP/(*S*)-DAIPEN	87

[a] The C=O selectivity was 98.9%.



X	*ee* [%]
H	96
Cl	94
Br	94
CH_3O	96

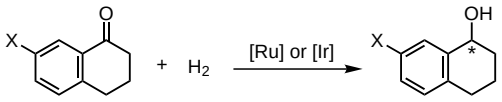
Scheme 27. Asymmetric hydrogenation of 2,2,2-trifluoroacetophenones. Conditions: (*S*,*S*)-[Ru] = *trans*-[$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}], $(CH_3)_3COK$, $(CH_3)_2CHOH$, 8–10 atm H_2, 28 °C.



Scheme 28. The Horeau effect in asymmetric hydrogenation of a) 1,4-diacetylbenzene and b) 1,3,5-triacetylbenzene. Conditions: a) (*S*,*S*)-[Ru] = [$RuCl_2${(*S*)-tolbinap}$(dmf)_n$], (*S*)-DAIPEN, KOH, $(CH_3)_2CHOH$, 4 atm H_2, 28 °C; b) (*S*,*SS*)-[Ru] = [$RuCl_2${(*S*)-binap}$(dmf)_n$], (*S*,*S*)-DPEN, KOH, $(CH_3)_2CHOH$, 8 atm H_2, 28 °C.

(*S*)-1-(2-(diphenylphosphano)phenyl)ethylamine (Ru:P,N ligand in a 1:2 mol ratio) had activity similar to the BINAP/DPEN–ruthenium complex in the hydrogenation of acetophenone, although the *ee* value of the *S* product was only 35%.[28] Further structural elaboration is necessary for developing an efficient asymmetric reaction. It is relevant that a PennPhos/rhodium catalyst developed by Zhang et al. promotes hydrogenation of several aromatic ketones with up to 96% *ee* (S/C = 100/1, 30 atm H_2).[43]

α-Tetralone is a difficult substrate, its hydrogenation using an (*R*)-XylBINAP/(*S*,*S*)-DPEN/KOH combined catalyst (S/C = 1000/1, 15 atm H_2, 30 °C, 6 h) gave the *S* alcohol in only 82% *ee* (Scheme 29).[28] For the asymmetric hydrogenation of 1,2-benzocycloalken-3-ones, better enantioselectivity

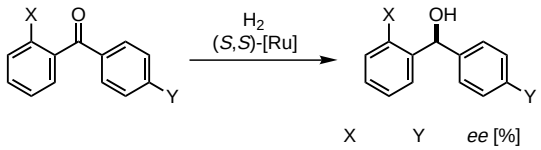


X	Catalyst (S/C)	Alcohol yield [%]	Alcohol *ee* [%]
H	[$RuCl_2${(*R*)-xylbinap}{(*S*,*S*)-dpen}] + KOH (1000/1)	81	82 (*S*)
H	[Ir{(*R*)-binap}(cod)]BF_4 + P[C_6H_4-2-N$(CH_3)_2]_2C_6H_5$ (190/1–230/1)	88	95 (*R*)
CH_3O	[Ir{(*R*)-binap}(cod)]BF_4 + P[C_6H_4-2-N$(CH_3)_2]_2C_6H_5$ (190/1–230/1)	74	95 (—)
NO_2	[Ir{(*R*)-binap}(cod)]BF_4 + P[C_6H_4-2-N$(CH_3)_2]_2C_6H_5$ (190/1–230/1)	64	94 (—)

Scheme 29. Asymmetric hydrogenation of α-tetralones.

was obtained by the [Ir{(*R*)-binap}(cod)]BF_4/P[C_6H_4-2-N$(CH_3)_2]_2C_6H_5$ mixed system of Takaya et al. (S/C ~ 200/1), although the reaction requires a hydrogen pressure of > 50 atm and a temperature as high as 90 °C.[45] This catalyst system, however, is not appropriate for the asymmetric hydrogenation of simple aryl alkyl ketones, for example acetophenone and valerophenone gave the alcohols in only 54 and 3% *ee*, respectively.[134] Benzo-fused cyclic ketones are converted enantioselectively into the chiral alcohols by various methods: our Ru-catalyzed transfer hydrogenation with 2-propanol or formic acid (S/C = 200/1),[58a, 135] Corey hydroboration (S/C = 4/1–100/1),[48, 136, 137] Mukaiyama cobalt-aided $NaBH_4$ reduction (S/C = 20/1),[49] and Rh-catalyzed hydrosilylation (S/C = 100/1)[55b,e,g] as well as stoichiometric aluminum hydride or organoboron reduction.[138, 139]

Use of *trans*-[$RuCl_2${(*S*)-xylbinap}][{(*S*)-daipen}] allows for asymmetric hydrogenation of *ortho*-substituted benzophenones with an S/C ratio of up to 20000/1.[83, 140, 141] Some examples are given in Scheme 30.[126] The (*S*)-2-methyl-

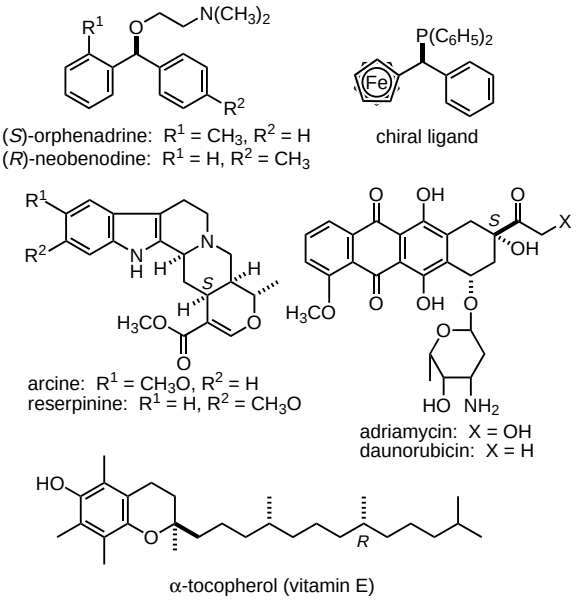


X	Y	*ee* [%]
CH_3	H	93[a]
F	H	97
Cl	H	97
Br	H	96
Br	CH_3	98[b]
CH_3O	H	99.4

Scheme 30. Asymmetric hydrogenation of *ortho*-substituted benzophenones. Conditions: (*S*,*S*)-[Ru] = *trans*-[$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}], $(CH_3)_3COK$, $(CH_3)_2CHOH$, 8 atm H_2, 28–35 °C. [a] A precursor of (*S*)-orphenadrine, see Scheme 31. [b] A precursor of (*R*)-neobenodine, see Scheme 31.

benzhydrol thus obtained is a precursor of (*S*)-orphenadrine which has potent antihistaminic and anticholinergic activity (see Scheme 31).[142] The methyl, fluoro, chloro, and bromo derivatives exhibit the same sense of asymmetric induction, which indicates that the possible ruthenium/heteroatom interaction is not the origin of the enantioselection.

As might be expected, simple *meta*- and *para*-substituted benzophenones were hydrogenated with low or only moderate enantioselectivity. The highest *ee* value was 47%, obtained with *p*-trifluoromethylbenzophenone. However, the antihistaminic (*R*)-neobenodine (Scheme 31)[142] has been synthesized using asymmetric hydrogenation of *o*-bromo-*p*′-methylbenzophenone as a key step.[83]

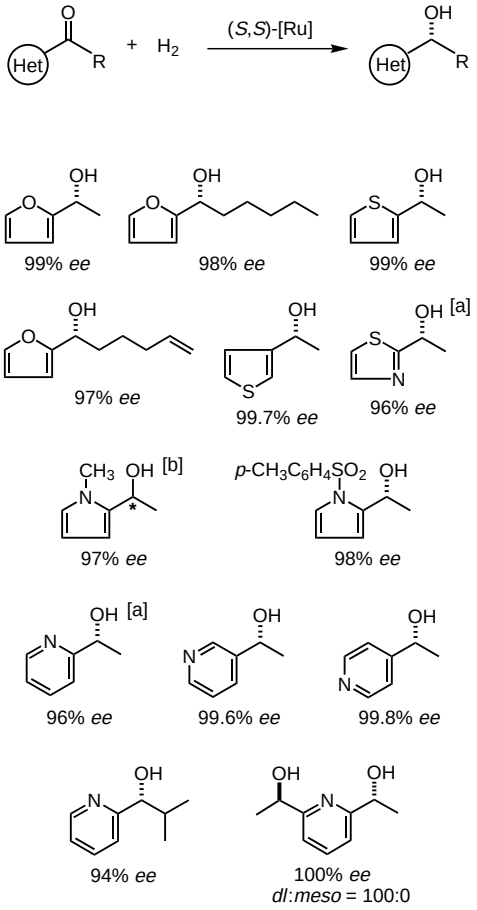


Scheme 31. Products obtained by routes involving asymmetric hydrogenation catalyzed by chiral diphosphane/diamine–ruthenium complexes.

In the presence of the (*S*)-TolBINAP/(*S*)-DAIPEN catalyst, ferrocenyl phenyl ketone was hydrogenated to give the *S* alcohol in 95% *ee*.[83] This alcohol can be converted into a chiral ferrocenylphosphane with retention of configuration (Scheme 31).[143, 83]

5.2. Heteroaromatic Ketones

Various ketones possessing an electron-rich or -deficient heterocycle substituent can be used as substrates (Scheme 32).[144] When a 5 M solution of 2-acetylfuran



Scheme 32. Asymmetric hydrogenation of heteroaromatic ketones. Usually yields of >96% are obtained. Conditions: (*S*,*S*)-[Ru] = *trans*-[$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}], $(CH_3)_3COK$, $(CH_3)_2CHOH$, 8 atm H_2, 25–30 °C. [a] $B[OCH(CH_3)_2]_3$ was added (ketone:Ru:borate = 2000:1:20). [b] 61% yield. Absolute configuration undetermined. Het = heteroaryl.

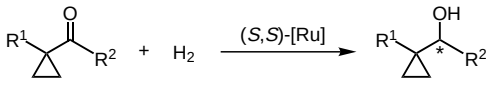
(110 g) in 2-propanol was hydrogenated with an (*S*)-XylBINAP/(*S*)-DAIPEN–ruthenium catalyst at an S/C of 40000/1, (*R*)-1-(2-furyl)ethanol was obtained in 99% *ee* without reduction of the furan ring.[126, 145] Hydrogenation of 2- and 3-acetylthiophenes gave the chiral alcohols in >99% *ee*, the sulfur-containing heterocycles did not disturb the catalytic activity. Although hydrogenation of 2-acetylthiazole and 2-acetylpyridine was sluggish under the standard conditions, in the presence of $B[OCH(CH_3)_2]_3$ (ketone:Ru:borate = 2000:1:20)[53, 139] the reaction gave the corresponding chiral alcohols quantitatively. The reactions of 3- and 4-acetylpyridines gave the chiral alcohols in high yield and *ee* values without $B[OCH(CH_3)_2]_3$. Double hydrogenation of 2,6-diacethylpyridine gave the enantiomerically pure *R*,*R* diol.[144, 146] In all cases, the sense of asymmetric induction was identical to that observed with aromatic ketones. This method, like asymmetric hydroboration, is very general.[48, 51c, 139, 141i, 147] A

combination of BICP (a chiral 1,4-diphosphane) and DPEN also gives enantioselective hydrogenation of acetylthiophenes.[47] 2-Acetylfuran is reduced enantioselectively by asymmetric hydrogenation using a PennPhos/rhodium complex[43] or by transfer hydrogenation with formic acid, catalyzed by a chiral ruthenium complex.[135b]

Chiral 1-(3-pyridyl)- and 1-(4-pyridyl)ethanols have been used for stereoselective condensation with racemic α-arylcarboxylic anhydrides to give the diastereomerically enriched esters.[148] (*R*)-1-(3-Pyridyl)ethanol is an intermediate in the synthesis of heteroyohimbine alkaloids such as arcin and reserpinin (Scheme 31),[149] the (*S*,*S*)- or (*R*,*R*)-2,6-di(1-hydroxyethyl)pyridines serve as a key precursor of C_2 symmetric P,N,P-tridentate ligands,[150] and the alkyl(2-thiazolyl)methanol products can be converted into synthetically useful chiral α-hydroxy aldehydes.[151]

5.3. Cyclopropyl Ketones

Hydrogenation of cyclopropyl methyl ketone in the presence of the (*S*)-XylBINAP/(*S*)-DAIPEN catalyst and $(CH_3)_3COK$ proceeded without cleavage of the cyclopropane ring, forming the *R* alcohol in 95% *ee* (Scheme 33).[128] The cyclopropyl group exerts an electronic effect in the transition state thus generating the stereochemical bias.[141f] Cyclopropyl phenyl ketone gave the alcohol in 96% *ee* with an opposite sense of asymmetric induction.[128] Hydrogenation of 1-acetyl-1-methylcyclopropane gave the alcohol (with an unknown absolute configuration) in 98% *ee*.[28] The structurally similar pinacolone was inert under these conditions.

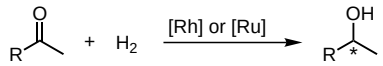


R^1	R^2	*ee* [%]
H	CH_3	95 (*R*)
H	C_6H_5	96 (*R*)
CH_3	CH_3	98 (—)

Scheme 33. Asymmetric hydrogenation of cyclopropyl ketones. Conditions: (*S*,*S*)-[Ru] = *trans*-[$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}], $(CH_3)_3COK$, $(CH_3)_2CHOH$, 8 or 10 atm H_2, 28 °C.

5.4. Dialkyl Ketones

Asymmetric hydrogenation of simple dialkyl ketones is still difficult. Hydrogenation of cyclohexyl methyl ketone catalyzed by the (*R*)-XylBINAP/(*R*)-DAIPEN complex and $(CH_3)_3COK$ (S/C = 10000/1) gave an *S* alcohol in 85% *ee* (Scheme 34), while 2-nonanone gave nearly racemic 2-nonanol.[128] Hydrogenation of 4-phenyl-2-butanone with (*R*)-XylBINAP/(*S*,*S*)-DPEN catalyst gave 4-phenyl-2-butanol in 51% *ee*.[28] Currently, the best catalyst for this purpose is a PennPhos–rhodium complex, although an improvement in catalytic activity (S/C = 100/1) is desirable.[43] A DEGUPHOS–rhodium complex hydrogenates pinacolone to give the alcohol in 84% *ee*.[44] Heterogeneous hydrogenation of 2-alkanones in the presence of a tartaric acid modified Raney



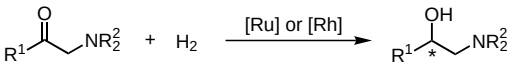
R	Catalyst (S/C)	Alcohol yield [%]	Alcohol *ee* [%]
n-C_4H_9	(*R*,*S*,*R*,*S*)-Me-PennPhos–Rh (100/1)	96	75 (*S*)
n-C_7H_{15}	(*R*)-XylBINAP/(*R*)-DAIPEN Ru (2000/1)	100	1
$C_6H_5(CH_2)_2$	(*R*,*S*,*R*,*S*)-Me-PennPhos–Rh (100/1)	99	73 (*S*)
$C_6H_5(CH_2)_2$	(*R*)-XylBINAP/(*S*,*S*)-DPEN Ru (1000/1)	100	51
$(CH_3)_2CH$	(*R*,*S*,*R*,*S*)-Me-PennPhos–Rh (100/1)	99	84 (*S*)
cyclo-C_6H_{11}	(*R*,*S*,*R*,*S*)-Me-PennPhos–Rh (100/1)	90	92 (*S*)
cyclo-C_6H_{11}	(*R*)-XylBINAP/(*R*)-DAIPEN Ru (10 000/1)	99	85 (*S*)
$(CH_3)_3C$	(*R*,*S*,*R*,*S*)-Me-PennPhos–Rh (100/1)	51	94 (*S*)

Scheme 34. Asymmetric hydrogenation of dialkyl ketones. For the structures of the chiral ligands, see Schemes 7 and 23.

Ni and an excess amount of pivalic acid gives 2-alkanols in up to 85% *ee*.[152] 2,5-Dimethylborolane is known to reduce a variety of alkanones to afford the chiral alkanols with a high optical purity.[53]

5.5. Amino Ketones

Kumada and co-workers pioneered the development of asymmetric hydrogenation of 2-(alkylamino)acetophenone derivatives catalyzed by chiral ferrocenylphosphane-based rhodium complexes.[153] In this regard, Achiwa's MCCPM-rhodium complex catalyzed hydrogenation of 2-(diethylamino)acetophenone hydrochloride in methanol (S/C of 100000/1 20 atm of H_2, 50 °C, 20 h) in a 96% optical yield.[154] Some related examples are given in Scheme 35.[153–155] BINAP–Ru

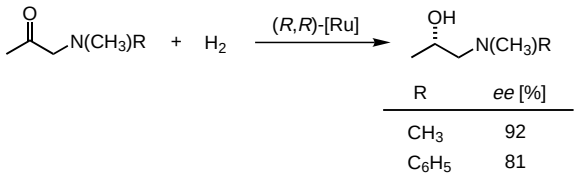


R	NR_2	Catalyst	Alcohol *ee* [%]
CH_3	$N(CH_3)_2$	(*S*)-BINAP–Ru	99 (*S*)
CH_3	$N(CH_3)_2$•HCl	(*S*)-Cy,Cy-oxoProNOP–Rh	97 (*S*)
C_6H_5	NH_2•HCl	(*R*)-MOC-BIMOP–Rh	93 (*R*)
C_6H_5	NH_2•HCl	(*S*)-Cy,Cy-oxoProNOP–Rh	93 (*S*)
C_6H_5	$NHCH_2C_6H_5$•HCl	(2*S*,4*S*)-MCCPM–Rh	93 (*S*)
C_6H_5	$N(CH_3)_2$	(*S*)-BINAP–Ru	95 (*S*)
C_6H_5	$N(CH_3)_2$HCl	(*S*)-Cp,Cp-IndoNOP–Rh	>99 (*S*)
C_6H_5	$N(C_2H_5)_2$•HCl	(2*S*,4*S*)-MCCPM–Rh	97 (*S*)
3,4-$(OH)_2$-C_6H_3	$NHCH_3$•HCl	(*R*)-(*S*)-BPPFOH–Rh	95 (*R*)
2-naphthyl	$N(C_2H_5)_2$	(*S*,*S*)-DIOP–Rh	95 (+)

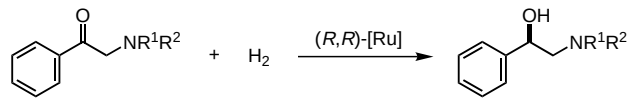
Scheme 35. Asymmetric hydrogenation of α-amino ketones with chiral ruthenium and rhodium catalysts. For the structures of the chiral ligands, see Schemes 7 and 23.

catalysts also gave highly enantioselective hydrogenation of α-dialkylamino ketones (S/C = 1000/1) (see Scheme 2),[22, 156] but the catalytic activity was modest requiring a hydrogen pressure as high as 100 atm. The XylBINAP/DAIPEN–ruthenium complex appears to be an efficient catalyst for this

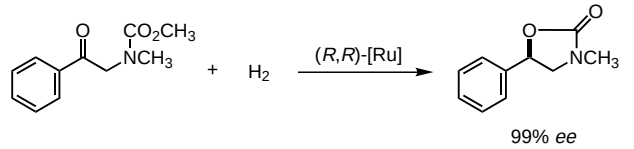
purpose. For example, hydrogenation of α-(dimethylamino)-acetone with the *R*,*R* catalyst and with an S/C of 2000/1 under 8 atm of H_2 gave the *S* alcohol in 92% *ee* (Scheme 36).[157] The reaction does not involve the coordination of the amino group to the ruthenium center; thus, the sense of enantioselection is opposite to that of the reaction with the diamine-free BINAP–Ru catalysts which is triggered by nitrogen/ruthenium interaction as seen with β-keto ester substrates (see Scheme 3).[9–11] 2-(Dimethylamino)acetophenone was hydrogenated under 8 atm of H_2 with the *R*,*R* catalyst to give the *R* alcohol in 93% *ee* (Scheme 36). The hydrogenation using an



R	*ee* [%]
CH_3	92
C_6H_5	81



R^1	R^2	*ee* [%]	R^1	R^2	*ee* [%]
CH_3	CH_3	93	COC_6H_5	CH_3	99.8
$COCH_3$	CH_3	99	$CO_2C(CH_3)_3$	CH_3	99
COC_6H_5	H	95			

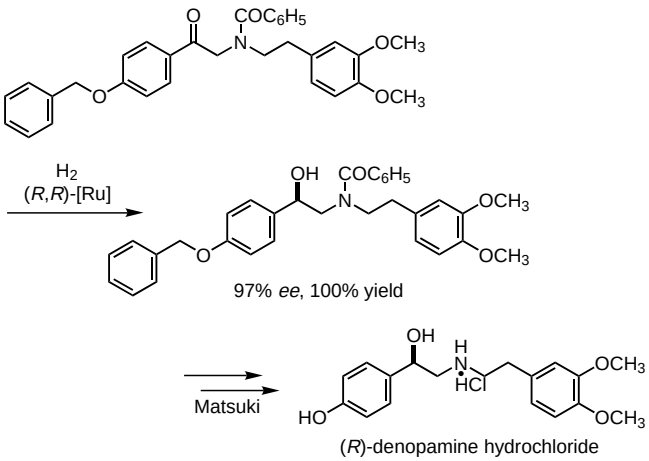


99% *ee*

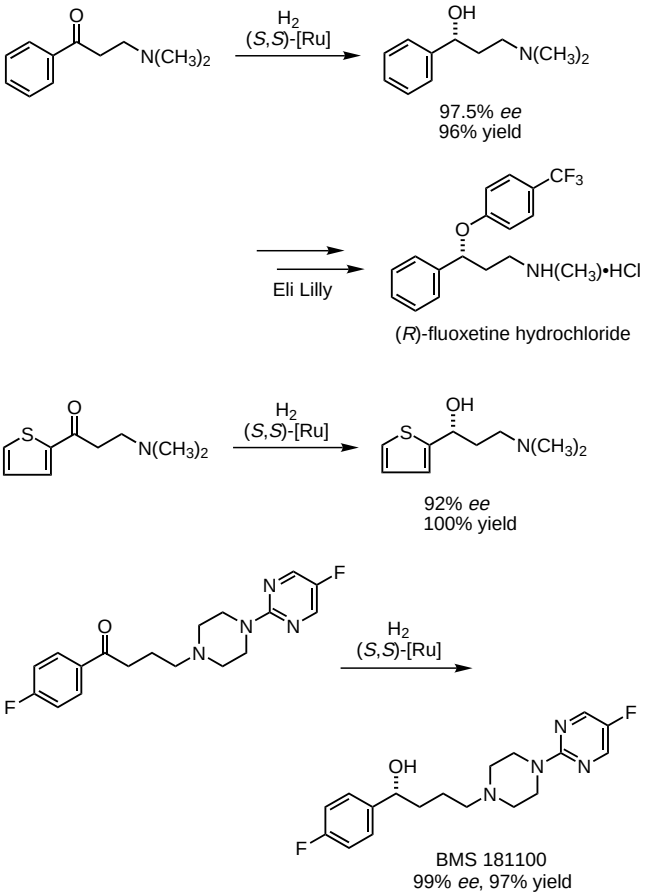
Scheme 36. Asymmetric hydrogenation of α-amino ketones. Conditions: (*R*,*R*)-[Ru] = *trans*-[$RuCl_2${(*R*)-xylbinap}{(*R*)-daipen}], $(CH_3)_3COK$, $(CH_3)_2CHOH$, S/C = 2000/1, 8 atm H_2, 25 °C.

α-amido ketone was applied to the enantioselective synthesis of (*R*)-denopamine, a β_1-receptor agonist used for treating congestive heart failure (Scheme 37).[157–159] Again, in this hydrogenation the protected 2-aminoacetophenone behaves as a simple aromatic ketone and the amide group does not exert any directive influence.

The XylBINAP/DAIPEN–ruthenium complex was utilized successfully for the asymmetric hydrogenation of certain β- or γ-amino ketones. Hydrogenation of 3-(dimethylamino)-propiophenone with an (*S*)-XylBINAP/(*S*)-DAIPEN ruthenium complex with an S/C ratio of 10000/1 gave the corresponding *R* amino alcohol in 97.5% *ee* (Scheme 38),[157] which is a synthetic intermediate of (*R*)-fluoxetine, a selective serotonin-uptake inhibitor.[160] Eli Lilly sells racemic fluoxetine hydrochloride as the antidepressant Prozac with a market value of $2.6 billion (1997).[161] However, the *R* enantiomer is more potent. Furthermore, as illustrated in Scheme 38, asymmetric hydrogenation of a γ-amino ketone (S/C = 10000/1) allows for the direct asymmetric synthesis of the potent antipsychotic BMS 181100.[157, 162] This approach



Scheme 37. Asymmetric synthesis of (*R*)-denopamine. Conditions of hydrogenation: (*R*,*R*)-[Ru] = *trans*-[$RuCl_2${(*R*)-xylbinap}{(*R*)-daipen}], $(CH_3)_3COK$, $(CH_3)_2CHOH$, S/C = 2000/1, 8 atm H_2, 25 °C.



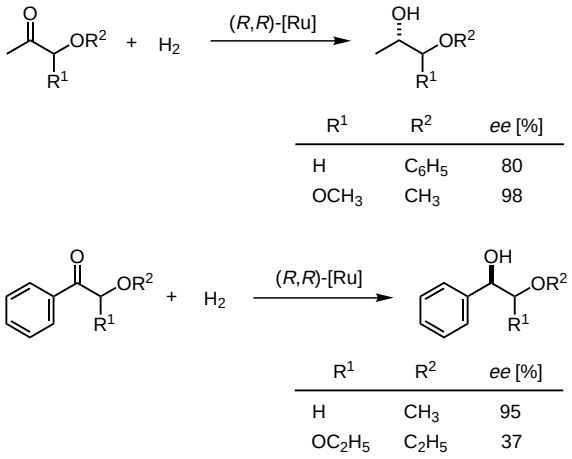
Scheme 38. Asymmetric hydrogenation of β- and γ-amino ketones including application to the synthesis of fluoxetine and BMS 181100. Conditions of hydrogenation: (*S*,*S*)-[Ru] = *trans*-[$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}], $(CH_3)_3COK$, $(CH_3)_2CHOH$, S/C = 2000/1 or 10000/1, 8 atm H_2, 25 °C.

is superior to the reaction using chiral rhodium complexes that requires a high catalyst loading (S/C = 200/1–1000/1) and relatively high H_2 pressure (30–50 atm).[155d, 163]

Thus, this asymmetric hydrogenation is applicable to the synthesis of a wide variety of important pharmaceutical chiral amino alcohols and their derivatives.

5.6. α-Alkoxy Ketones

α-Phenoxyacetone and 2-methoxyacetophenone were hydrogenated under 8 atm of H_2 in the presence of the (*R*)-XylBINAP/(*R*)-DAIPEN complex to give the corresponding *S* and *R* alcohols in 80 and 95% *ee*, respectively (Scheme 39).[28] Hydrogenation of pyruvic aldehyde dimethylacetal gave the *S* alcohol in 98% *ee*,[28] while the reduction of



R^1	R^2	*ee* [%]
H	C_6H_5	80
OCH_3	CH_3	98

R^1	R^2	*ee* [%]
H	CH_3	95
OC_2H_5	C_2H_5	37

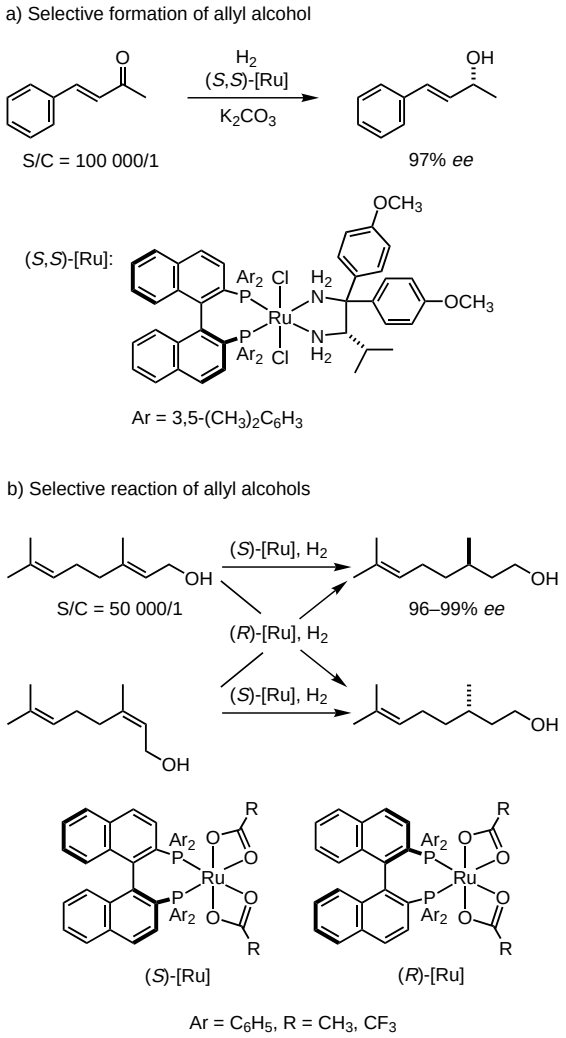
Scheme 39. Asymmetric hydrogenation of α-alkoxy ketones. Conditions: (*R*,*R*)-[Ru] = *trans*-[$RuCl_2${(*R*)-xylbinap}{(*R*)-daipen}], $(CH_3)_3COK$, $(CH_3)_2CHOH$, S/C = 2000/1, 8 atm H_2, 25–28 °C.

2,2-diethoxyacetophenone gave the *R* alcohol in only 37% *ee*.[28] Thus, the alkoxy or phenoxy group possesses a significant strereo-directing ability but its function is not coordinative in nature. The effect of a phenyl group is overwhelming. It is relevant that certain chiral rhodium complexes are known to hydrogenate pyruvic aldehyde dimethylacetal in up to 75% *ee*.[164] Cinchona modified Pt/Al_2O_3 catalysts provide the chiral alcohol in up to 97% *ee*.[165]

5.7. Olefinic Ketones

Efficient asymmetric hydrogenation of α,β-unsaturated ketones is an enduring problem in organic chemistry and has been our cardinal focus. Chiral allyl alcohol products are important not only for their own sake but also in connection with Claisen technology and various S_N2' substitution reactions.[166–168] This transformation has been achieved only by stoichiometric use of metal hydride reagents.[51a, 55d,e,h, 130a, 136, 138, 141f, 169–171] Alternatively, chiral allyl alcohols are obtained by the Sharpless kinetic resolution (acyclic compounds)[172] or our ruthenium-catalyzed hydrogenation[173] or our transfer hydrogenation (cyclic substrates).[174] The ideal stereoselective hydrogenation of alkenyl ketones, however, was difficult because of the conformational flexibility and the presence of two kinds of unsaturated groups, C=C and C=O, the former having higher reactivity in conventional hydrogenation. A BINAP–Ir complex is known to hydrogenate benzalacetone in 65% optical yield and 97% keto selectivity.[93] Earlier we found that hydrogenation of the same ketone with an in situ generated BINAP/DPEN–ruthenium catalyst in 2-propanol containing KOH showed perfect keto selectivity but with only 70% optical yield.[97] In addition, some simple enones are highly sensitive to basic conditions, hampering the utility of our original procedure.

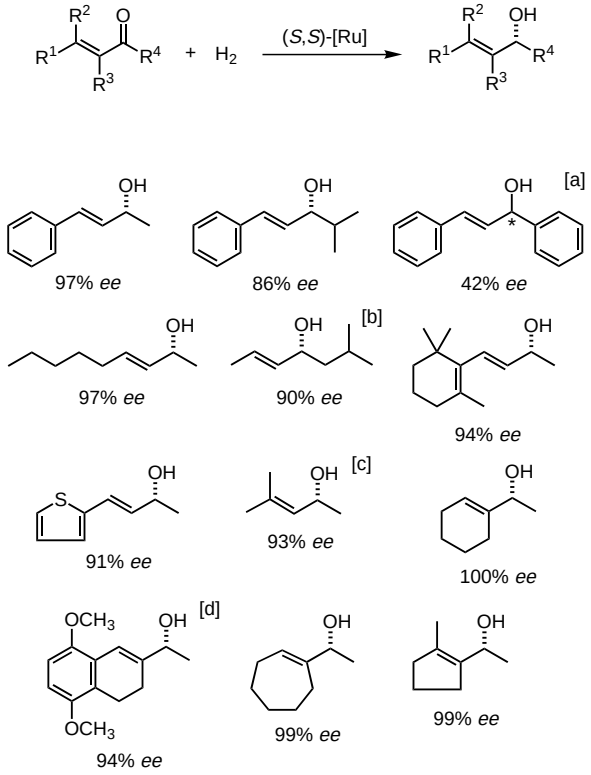
Fortunately, this long-standing problem has now been solved by the development of the XylBINAP/DAIPEN–ruthenium catalyst and by the use of K_2CO_3, a weak base cocatalyst, in place of conventional KOH or $(CH_3)_3COK$.[128] Thus, reaction of benzalacetone (100 g) in 2-propanol (150 mL) containing the (*S*)-XylBINAP/(*S*)-DAIPEN–ruthenium catalyst (8.3 mg) and K_2CO_3 (9.4 g) under 80 atm of H_2 (S/C = 100000/1, 2.7 M solution) gave the *R* alcohol in 97% *ee* (Scheme 40a). With an S/C of 10000/1 hydrogenation



Scheme 40. ruthenium-catalyzed asymmetric hydrogenation of a) benzalacetone ($(CH_3)_2CHOH$, 80 atm H_2, 30 °C, 100% yield) and b) geraniol and nerol (CH_3OH, 30 atm H_2, 18–20 °C, 97–100% yield).

was accomplished smoothly under 10 atm of H_2. The absence of any trace of C=C reduction products is noteworthy, because the related diamine-free BINAP–Ru complexes, developed in our laboratories, exhibit eminent catalytic activity for the hydrogenation of the C=C unit of allyl alcohols such as geraniol and nerol (Scheme 40b).[175] The chemistries of both systems are thus entirely different.

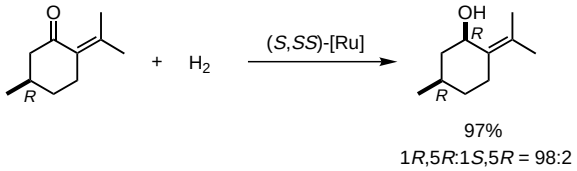
Scheme 41 illustrates asymmetric hydrogenation of structurally flexible enones with various substitution patterns to the corresponding chiral allyl alcohols.[126, 128] Highly base-sensitive 3-nonen-2-one is convertible to the allyl alcohol in 97% *ee* by using a dilute (0.1M) 2-propanol solution to minimize undesired polymerization. Hydrogenation of (*E*)-6-methyl-2-hepten-4-one catalyzed with an (*R*)-XylBINAP/(*R*)-DAIPEN – ruthenium catalyst afforded the *S* allyl alcohol with 90% *ee*, which serves as a key building block for the preparation of the side chain of α-tocopherol (vitamin E; see Scheme 31).[128, 176] More substituted, less base-sensitive



Scheme 41. Asymmetric hydrogenation of α,β-olefinic ketones. The yields are >96%. Conditions: (*S*,*S*)-[Ru] = *trans*-[$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}], K_2CO_3 or $(CH_3)_3COK$, $(CH_3)_2CHOH$, 8–10 atm H_2 (S/C = 2000/1–13000/1) or 80 atm H_2 (S/C = 100000/1), 25–30 °C. [a] Absolute configuration undetermined. [b] A precursor of α-tocopherol side chain, see Scheme 31. [c] Reduction with an (*S*)-XylBINAP/(*S*,*S*)-DPEN – ruthenium catalyst. [d] The *S* enantiomer obtained with an (*R*)-BINAP/(*R*)-DAIPEN – ruthenium catalyst is a precursor of anthracycline antibiotics, see Scheme 31.

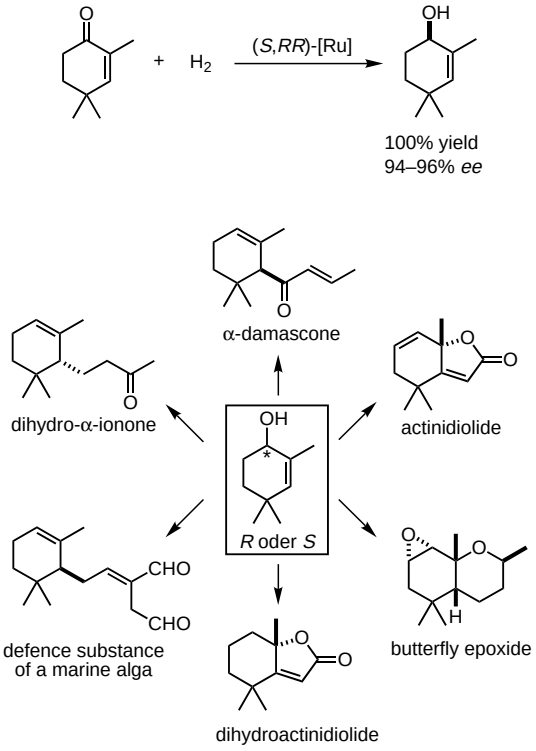
enones can be hydrogenated more rapidly and conveniently by using a strong-base cocatalyst. 1-Acetylcycloalkenes were hydrogenated to 1-hydroxyethylcycloalkenes with high *ee*-values. This method allows asymmetric synthesis of a key intermediate for anthracycline antibiotics (adriamycin and daunorubicin in Scheme 31).[97, 177] β-Ionone, a dienone, is converted into β-ionol in 94% *ee* and the hydrogenation of (*E*)-4-(2-thienyl)-3-buten-2-one gave the chiral allyl alcohol without saturation of the olefinic bond or the thiophene ring.[28] Here the combination of the *S* diphosphane and *S* diamine (or *R* and *R*) is crucial for obtaining a high level of enantioselection, as has been observed in the reactions of aromatic ketones. Differentiation between aromatic and vinyl groups is difficult. Chalcone was hydrogenated to the allyl alcohol in only 42% *ee*.[28] Simple vinyl ketones undergo both 1,2- and 1,4-hydrogenation competitively. For example, the reaction of 2-methyl-1-decen-3-one under 8 atm H_2 with an (*S*)-XylBINAP/(*S*)-DAIPEN catalyst gave a mixture of the expected *R* allyl alcohol (99% *ee*), saturated ketone, and saturated alcohol in a 59:40.5:0.5 ratio.[28]

(*R*)-Pulegone, a chiral *s-cis* enone, was hydrogenated smoothly under 8 atm H_2 by using a simple (*S*)-BINAP/(*S*,*S*)-DPEN catalyst system to give a 98:2 mixture of the 1*R*,5*R* and 1*S*,5*R* alcohols in 97% yield together with 1.8% of other minor products (Scheme 42).[178] Use of an (*R*)-BINAP/(*R*,*R*)-DPEN system led to somewhat lower diastereoselectivity (1*R*,5*R*:1*S*,5*R* = 95:5) with concomitant formation of (1*S*,2*S*,5*R*)-2-isopropenyl-5-methylcyclohexanol (9.7%).



Scheme 42. Diastereoselective hydrogenation of pulegone. Conditions: (*S*,*SS*)-[Ru] = [$RuCl_2${(*S*)-binap}$(dmf)_n$], (*S*,*S*)-DPEN, KOH, $(CH_3)_2CHOH$, S/C = 250/1, 8 atm H_2, 28 °C.

Certain cyclic enones can also be hydrogenated with high enantioselection. Scheme 43 shows the useful application of this method to Mori chemistry.[179] When 2,4,4-trimethyl-2-

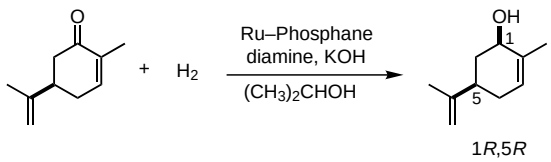


Scheme 43. Combination of the ruthenium-catalyzed asymmetric hydrogenation and Mori chemistry. Conditions of hydrogenation: (*S*,*RR*)-[Ru] = *trans*-[$RuCl_2${(*S*)-tolbinap}{(*R*,*R*)-dpen}], $(CH_3)_3COK$, $(CH_3)_2CHOH$, S/C = 10000/1 at 10 atm H_2 and 28 °C or S/C = 500/1 at 8 atm H_2 and 0 °C.

cyclohexenonewas hydrogenated by using the (*S*)-TolBINAP/(*R*,*R*)-DPEN–ruthenium catalyst in 2-propanol containing $(CH_3)_3COK$ with an S/C of 10000/1 under 10 atm H_2 at room temperature, the C=O group was selectively saturated to give (*R*)-2,4,4-trimethyl-2-cyclohexenol with 94% *ee* and in 100% yield.[79, 178] No conjugate reduction product was detected. The *ee* value was increased to 96% by lowering the temperature to 0°C.[180] The *R* and *S* alcohols, coupled with the Claisen reaction, can be converted into a series of carotenoid-derived odorants and other bioactive terpenes.[179, 181] The selectivity of this catalytic reaction appears to depend on the synergistic effects of the chiral diphosphane and diamine ligands as well as the structures of ketones. In this case, unlike the asymmetric reactions described above, the combined use of the (*S*)-BINAP and (*R*,*R*)-DPEN (or *R* and *S*,*S*) is necessary for the high stereoselection. A reaction using the *R* diphosphane and the *R*,*R* diamine gave the *S* alcohol in only 26% *ee*.[79, 178] In addition, the *ee* value obtained with the BINAP/DPEN catalyst was superior to the 80% *ee* obtained with the (*S*)-XylBINAP/(*R*,*R*)-DPEN system.[28]

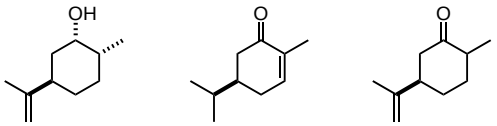
The presence of the methyl substituent at the C-2 position is crucial for efficient generation of the C-1 stereogenic center. Hydrogenation of simple 2-cyclohexenone under 4 atm H_2 with an (*R*)-BINAP/(*R*,*R*)-DPEN system gave a mixture of (*R*)-2-cyclohexenol in 58% *ee* (65% yield), cyclohexanol (2%), and polymeric material (30%).[178, 182] In the presence of the same catalyst, 3-methyl-2-cyclohexenol gave (*R*)-3-methyl-2-cyclohexenol with 45% *ee* in 99% yield. Reaction of 4,4-dimethyl-2-cyclohexenone with an (*S*)-BINAP/(*R*,*R*)-DPEN system produced (*S*)-4,4-dimethyl-2-cyclohexenol in only 47% *ee* in 100% yield. Thus, more suitable catalysts and conditions need to be developed for these enone substrates. Currently, efficient catalytic access to 2-unsubstituted 2-cyclohexenols with high enantiomeric purity is limited to kinetic resolution by asymmetric hydrogenation[173] or transfer hydrogenation catalyzed by chiral ruthenium catalysts.[174]

(*R*)-Carvone a compound which possesses three unsaturated bonds and a C-5 stereogenic center poses many selectivity problems: 1) 1,2 versus 1,4 selectivity in the α,β-enone moiety, 2) chemoselectivity between the conjugated and isolated C=C linkage, and 3) *cis* versus *trans* diastereoselectivity with respect to the C-5 substituent in the C=O saturation. With no control over selectivity, 17 different hydrogenation products are possible! In fact, hydrogenation of the dienone under 4 atm H_2 with an (*S*)-BINAP/(*R*,*R*)-DPEN combined system resulted in perfect chemo- and diastereoselectivity, giving solely (1*R*,5*R*)-carveol in 100% yield (Scheme 44).[178] The 5*R* configuration of the chiral ketone significantly affects the rate and stereoselectivity. Thus, in the presence of the (*R*)-BINAP/(*S*,*S*)-DPEN combined system, the *R* dienone was hydrogenated rather slowly, giving a 34:66 mixture of the 1*R*,5*R* (*cis*) and 1*S*,5*R* (*trans*) alcohols. Use of the achiral $P(C_6H_5)_3/NH_2(CH_2)_2NH_2$ system gives the allyl alcohol in 93% yield (*cis*:*trans* = 81:19) in addition to 7% of the 2,3-saturated 1*S*,2*R*,5*R* product arising from 1,4-addition followed by diastereoselective C=O hydrogenation. Notably, hydrogenation of carvone with $[RhCl\{P(C_6H_5)_3\}_3]$ in toluene takes place selectively at the nonconjugated C=C bond to give (*R*)-5-isopropyl-2-methyl-2-



1*R*,5*R*

Phosphane	Diamine	Alcohol yield [%]	Alcohol *cis*:*trans*
(*S*)-BINAP	(*R*,*R*)-DPEN	100	100:0
(*S*)-BINAP	(*S*,*S*)-DPEN	93	87:13
(*R*)-BINAP	(*R*,*R*)-DPEN	98	88:12
(*R*)-BINAP	(*S*,*S*)-DPEN	98	34:66
$P(C_6H_5)_3$	(*R*,*R*)-DPEN	97	95:5
$P(C_6H_5)_3$	$NH_2(CH_2)_2NH_2$	93	81:19



1*S*,2*R*,5*R* dihydrocarvone

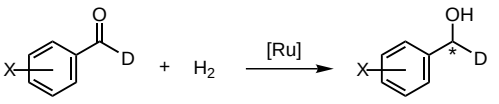
Scheme 44. Stereoselective hydrogenation of (*R*)-carvone.

cyclohexenone((*R*)-dihydrocarvone).[183] Stoichiometric reduction of carvone with L-Selectride in THF at −78°C is known to give the 1,4-reduction product, (*R*)-isopropenyl-2-methylcyclohexanone (*trans*:*cis* = 81:19) exclusively,[178, 184] whereas the use of an equimolar mixture of $NaBH_4$ and $CeCl_3$ in methanol gives a 97:3 mixture of (1*R*,5*R*)-carveol and the 1*S*,5*R* isomer quantitatively.[178, 185]

Asymmetric methods for hydrogenating α,β-acetylenic ketones to chiral propargyl alcohols are still unavailable.[99] Enantioselective reduction requires ruthenium-catalyzed transfer hydrogenation employing 2-propanol[186] or the use of metal hydride reagents.[169c, 187–190]

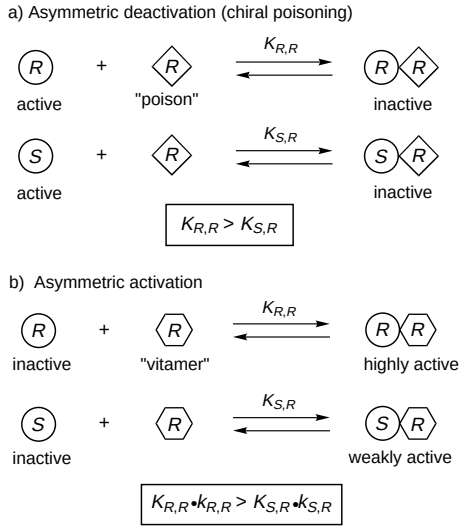
5.8. 1-Deuteriobenzaldehydes

Chiral 1-deuterio alcohols are useful for mechanistic studies of various chemical and biochemical reactions.[191] Hydrogenation of 1-deuterio-*o*-methylbenzaldehyde with an (*S*)-TolBINAP/(*S*)-DAIPEN ruthenium complex in the presence of base at 28°C and 8 atm H_2 gave the (*S*)-alcohol in 89% *ee* (Scheme 45).[28] The asymmetric sense was opposite to that in the hydrogenation of *o*-methylacetophenone with the same catalyst system (*R* alcohol in 99% *ee*, see Table 2).[79] The XylBINAP/DAIPEN system showed lower selectivity. Simple 1-deuteriobenzaldehyde was hydrogenated in only 46% *ee*.[28] In comparison, hydrogenation of 1-deuteriobenzaldehydes with $[Ru(OCOCH_3)_2\{(R)\text{-binap}\}]$ in the presence of a strong acid gave (*S*)-1-deuterio alcohols in up to 89% *ee* (Scheme 45).[192] At present, transfer hydrogenation using a chiral arene–ruthenium complex and 2-propanol or formic acid is better than hydrogenation.[193] The Corey, Bakshi, Shibata (CBS) reduction of aldehydes[48] using a deuterated catecholborane gives the chiral deuterated primary alcohols in up to 95% *ee*.[136c]



X	Catalyst	Alcohol *ee* [%]
H	*trans*-[$RuCl_2${(*S*)-tolbinap}{(*S*)-daipen}] + $(CH_3)_3COK$	46 (*S*)
H	[$Ru(OCOCH_3)_2${(*R*)-binap}] + HCl	65 (*S*)
2-CH_3	*trans*-[$RuCl_2${(*S*)-tolbinap}{(*S*)-daipen}] + $(CH_3)_3COK$	89 (*S*)
2-Br	[$Ru(OCOCH_3)_2${(*R*)-binap}] + HCl	89 (*S*)
3-Cl	[$Ru(OCOCH_3)_2${(*R*)-binap}] + HCl	73 (—)
4-Cl	[$Ru(OCOCH_3)_2${(*R*)-binap}] + HCl	70 (—)

Scheme 45. Asymmetric hydrogenation of 1-deuteriobenzaldehydes with chiral ruthenium complexes.

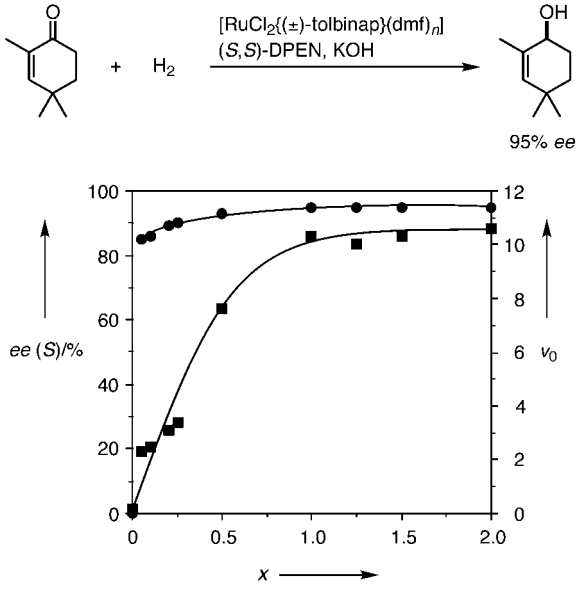


Scheme 46. Strategies for asymmetric catalysis using racemic metal complexes. a) Asymmetric deactivation and b) asymmetric activation by nonracemic compounds.

6. Asymmetric Activation

Racemic catalysts normally give racemic products. However, sometimes the chemical attributes of enantiomeric molecules can be affected strongly by a surrounding nonracemic compound.[132] Diastereomeric interactions lead to unequal stabilities (K_{R^*,R^*} vs K_{S^*,R^*}) and reactivities (k_{R^*,R^*} vs k_{S^*,R^*}) of the associates, resulting in unique chemical consequences. As schematically illustrated in Scheme 46, when one of the enantiomeric catalysts can be selectively deactivated by a nonracemic compound acting as a "poison", asymmetric catalysis can be achieved by the remaining enantiomer.[194] Another useful strategy employing racemic compounds is the asymmetric activation of an inactive racemic metal complex by a nonracemic compound,[76, 195] which we call a "vitamer" (Scheme 46b). Thus, a diastereomeric catalyst, formed by enantioselective activation of racemic metal complexes, if its architecture is suitable, can promote a highly selective asymmetric reaction. This has been realized by the activation of racemic diphosphane–ruthenium complexes with an enantiomerically pure 1,2-diamine as a vitamer.

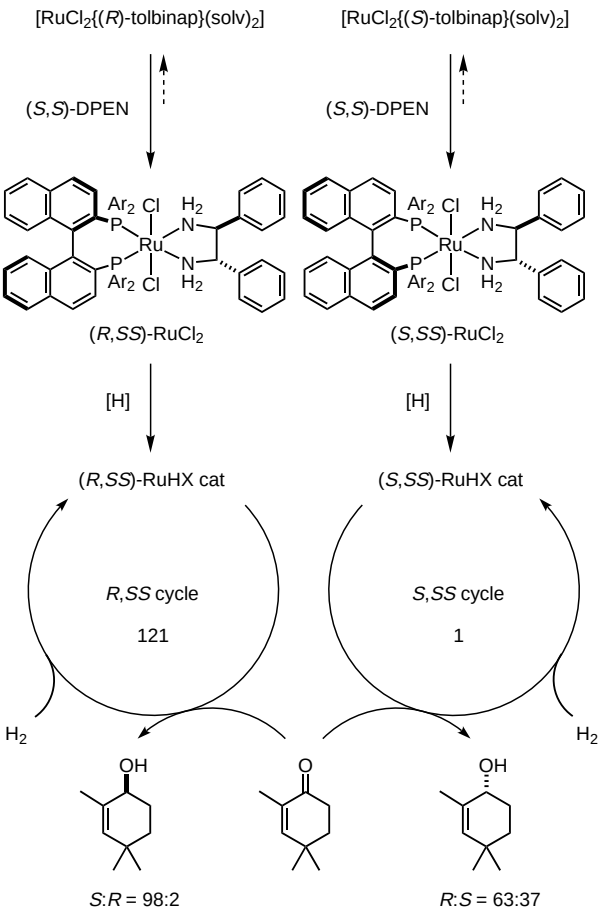
The target was the challenging allyl alcohol, (*R*)- or (*S*)-2,4,4-trimethyl-2-cyclohexenol. As described in Section 1.1, racemic [$RuCl_2$(tolbinap)$(dmf)_n$][24a,b] is a feeble catalyst for hydrogenation of unfunctionalized ketones. However, when 2,4,4-trimethyl-2-cyclohexenone was hydrogenated in the presence of (*S*,*S*)-DPEN (diamine/ruthenium = 1/1), and KOH under 8 atm H_2 and 0 °C, the *S* allyl alcohol was obtained in 95% *ee* in 100% yield (Scheme 47).[180] The *ee* value is close to the 96% attained with the enantiomerically pure (*R*)-TolBINAP/(*S*,*S*)-DPEN system. The reaction using the diastereomeric *R*/*R*,*R* phosphane–diamine combination occurred rather slowly to give the *S* alcohol in only 26% *ee*. As illustrated in Scheme 47, increasing the amount of added (*S*,*S*)-DPEN enhanced the rate of hydrogenation, reaching a near maximum value with a molar ratio of diamine:ruthenium of 1:1.[180] The *ee* value of the *S* alcohol, on the other hand, was consistently high from the beginning (diamine/ruthenium > 0.25). Thus, under this hydrogenation



Scheme 47. Asymmetric hydrogenation of a cyclohexenone using a racemic TolBINAP–Ru complex and an enantiomerically pure diamine. v_0 (■) = Initial rate in moles of product/mol of Ru × min. x = Mol diamine per mol Ru. ● = *ee* Value. Conditions: 7/1 $(CH_3)_2CHOH$/toluene, S/C = 500/1, 8 atm H_2, 0 °C.

condition the (*S*,*S*)-DPEN vitamer effectively activated the (*R*)-TolBINAP–ruthenium enantiomer of the racemate. A mixed-ligand complex prepared from equimolar amounts of the racemic TolBINAP–ruthenium complex and (*S*,*S*)-DPEN resulted in enantioselective hydrogenation even in the presence of an equimolar amount of (*R*,*R*)-DPEN. This result indicates that the initial interaction of the [$RuCl_2$(diphosphane)] complex with DPEN is virtually irreversible, as was also demonstrated by a ^{31}P NMR study.

Scheme 48 provides the simplest explanation of the mechanism of asymmetric activation of the racemic TolBINAP–ruthenium complex, although molecular association of the catalysts or its precursors may lead to further complicated

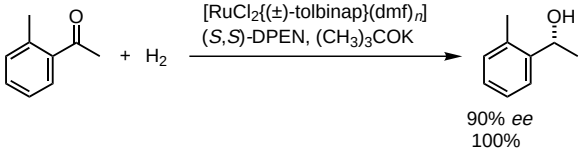


Ar = 4-$CH_3C_6H_4$; solv = DMF or other ligands
X = H, OR, etc.

Scheme 48. Mechanism of asymmetric activation.

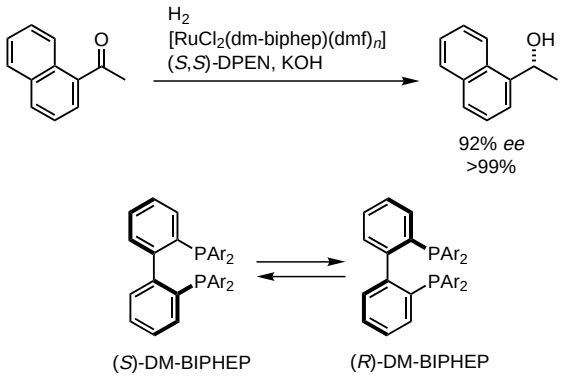
nonlinear effects.[132, 196] The observed enantioselectivity of hydrogenation reflects the relative TOFs of the competing *R*,*SS* and *S*,*SS* catalytic cycles, and the ratio is determined by the relative concentrations and reactivities of the coexisting diastereomeric diphosphane/diamine–ruthenium catalysts. The TolBINAP–Ru dichloride complex which exists as aggregates is almost inactive for the hydrogenation of ketones. Under the reaction conditions, the labile solvent ligands (solv) are displaced by (*S*,*S*)-DPEN to generate a monomeric TolBINAP/DPEN complex. The equilibrium lies far toward the mixed-ligand complex, regardless of the chirality of the ligands forming the diastereomeric (*R*,*SS*)- and (*S*,*SS*)-$RuCl_2$ complexes[197] with ^{31}P NMR chemical shifts (1/7 $(CD_3)_2CDOD/C_6D_5CD_3$) of $\delta = 45.8$ and 46.2, respectively. The real catalysts, ruthenium hydride or dihydride species (see Scheme 11) are formed from the dichloride under the basic reductive conditions. The *R*,*SS* cycle with an *S*:*R* enantioselectivity of 98:2 turns-over 121 times faster than the *S*,*SS* cycle having an *S*:*R* selectivity of 37:63.[180]

Noteworthy is that the relative significance of the diastereomeric cycles, *R*,*SS* and *S*,*SS*, as well as the direction and degree of asymmetric induction is highly dependent on the structures of the ketonic substrates. When *o*-methylacetophenone was used as the hydrogenation substrate, (*S*,*S*)-DPEN enhanced the activity of the (*S*)-TolBINAP–Ru complex more than the (*R*)-TolBINAP–Ru enantiomer. The hydrogenation catalyzed by racemic TolBINAP–Ru complex and (*S*,*S*)-DPEN gave the *R* alcohol in 90% *ee* and in 100% yield (Scheme 49).[180] In this case, unlike the above reaction, the *S*,*SS* cycle with an *S*:*R* enantioselectivity of 1.3:98.7 occurred 13 times faster than the *R*,*SS* cycle with an *S*:*R* selectivity of 54:46.



Scheme 49. Asymmetric hydrogenation of an aromatic ketone using a racemic TolBINAP–Ru complex and an enantiomerically pure diamine. Conditions: 7/1 $(CH_3)_2CHOH$/toluene, S/C = 500/1, 4 atm H_2, 0 °C.

2,2′-Bis(3,5-dimethylphenyl)phosphino-1,1′-biphenyl (DM-BIPHEP) is a conformationally flexible diphosphane (Scheme 50).[198] When it was combined with (*S*,*S*)-DPEN in the formation of the ruthenium complex, the diastereomeric DM-BIPHEP/(*S*,*S*)-DPEN–$RuCl_2$ complexes[197] were produced in a 3:1 ratio, in which the major *S*/*S*,*S* complex was more reactive in the hydrogenation of aromatic ketones.[199] Hydrogenation of 1′-acetonaphthone using a mixture of DM-BIPHEP–$RuCl_2$ complex, (*S*,*S*)-DPEN, and KOH gave the *R* alcohol in 92% *ee* and >99% yield.



Scheme 50. Asymmetric hydrogenation of an aromatic ketone using a racemic phosphane–ruthenium complex and a nonracemic diamine. Conditions: $(CH_3)_2CHOH$, Ru:DPEN:KOH = 1:1:2, S/C = 250/1, 40 atm H_2, −35 °C. Ar = 3,5-$(CH_3)_2C_6H_3$.

Thus, enantiomer-selective activation of racemic metal complexes by a chiral vitamer is becoming a viable approach for practical asymmetric catalysis when enantiomerically pure ligands are not readily available.

7. Dynamic Kinetic Discrimination of Stereoisomers

The greatest advantage of this hydrogenation method is the flexible molecular design of the mixed-ligand ruthenium catalysts. The stabilities of product-determining transition states are determined variably by stereo- and electro-complementary assemblies of the (di)phospanes, diamines, and other ligands on the ruthenium center and the ketonic substrate. In addition, the reaction conditions can be highly optimized. These attributes allow for systematic variation of

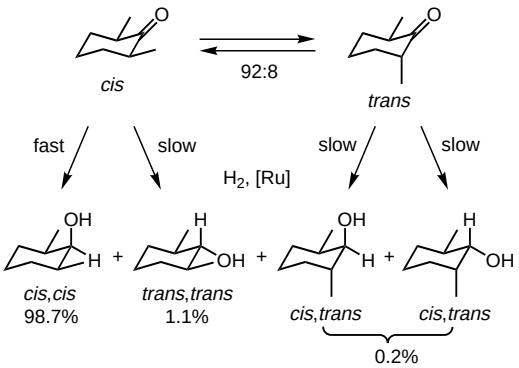
reactivity and selectivity. The described diastereo- and enantioselectivity, when coupled with appropriate kinetic parameters, leads to a new type of stereoselective hydrogenation of ketones. In general, stereoisomeric ketones react at different rates. Thus, when a configurationally labile α-substituted ketone is used, dynamic kinetic discrimination[18–22] of the stereoisomers is achievable by hydrogenation. The key is the facile configurational inversion of the ketonic substrate, which is facilitated by an alkaline base in a protic solvent.

7.1. Diastereomers

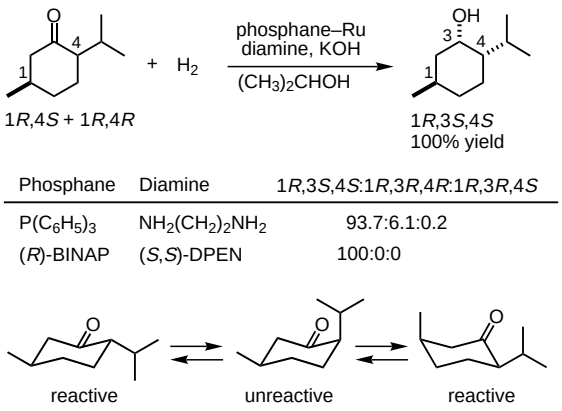
2,6-Dimethylcyclohexanone undergoes highly diastereoselective hydrogenation by kinetic discrimination of the diastereomers.[104] In 2-propanol containing KOH this ketone is in rapid equilibrium between the *cis* and *trans* isomers. The diequatorial:equatorial,axial:diaxial ratios are 92:8:0 (experiment) or 97:3:0 (ab initio MO calculation).[104, 111, 112] However, the *trans* isomer is rather unreactive because the equatorial approach of the ruthenium hydride species to the carbonyl carbon is blocked by the axially oriented methyl substituent at the α position, as shown in Scheme 19, while there is no such problem in the *cis* isomer with two equatorial methyl groups. Therefore, hydrogenation in the presence of a $[RuCl_2\{P(C_6H_5)_3\}_3]/NH_2(CH_2)_2NH_2$/KOH catalyst system (Ru:base 1:20 instead of the standard 1:2 ratio) in 2-propanol under 4 atm H_2 gave the *cis*,*cis* (98.7%), *trans*,*trans* (1.1%), and *cis*,*trans* alcohols (0.2%; Scheme 51). The distribution of the *cis*,*trans* isomer (0.2%) was much less than the equilibrium population of the *trans*-dimethyl ketone (8%).

7.2. Epimers

(−)-Menthone has a stable 1*R* stereogenic center and an unstable 4*S* center, in equilibrium with isomenthone, the 4*R* epimer. As illustrated in Scheme 52, when this ketone was subjected to hydrogenation with an achiral $[RuCl_2\{P(C_6H_5)_3\}_3]_3/NH_2(CH_2)_2NH_2$ catalyst, a 93.7:6.1:0.2 mixture of (+)-neomenthol with the 1*R*,3*S*,4*S* configuration, menthol (the 1*R*,3*R*,4*R* isomer), and neoisomenthol (the 1*R*,3*R*,4*S* isomer) was produced.[104] The high 1,2-*cis* stereoselectivity induced by the C-4 isopropyl group is not surprising (Scheme 19). Although the achiral catalyst showed a high stereodistinction, it became more evident when a chiral system was employed for the reaction of the chiral, nonracemic ketone. In fact, hydrogenation with a chiral (*R*)-BINAP/(*S*,*S*)-DPEN system led exclusively to (+)-neomenthol (Scheme 52). The overall stereochemical outcome is determined by the structural characteristics of the substrate and catalyst as well as the kinetic parameters affecting the epimerization and hydrogenation of the ketone.



Scheme 51. Dynamic kinetic discrimination of diastereomeric ketones by ruthenium-catalyzed hydrogenation. Conditions: [Ru] = $[RuCl_2\{P(C_6H_5)_3\}_3]$, $NH_2(CH_2)_2NH_2$, KOH (1:1:20), $(CH_3)_2CHOH$, S/C = 500/1, 4 atm H_2, 28 °C.

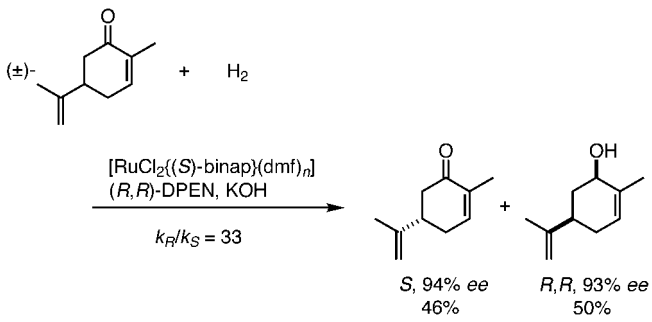


Scheme 52. Dynamic kinetic discrimination of epimeric ketones by ruthenium-catalyzed hydrogenation.

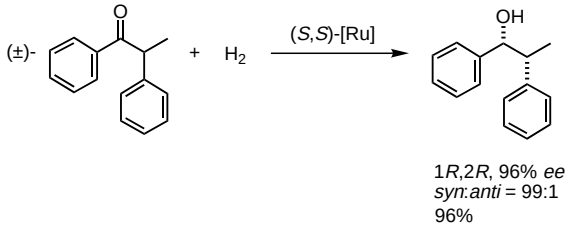
7.3. Enantiomers

As expected, certain racemic ketones can be resolved kinetically. For example, when racemic carvone was hydrogenated with an (*S*)-BINAP/(*R*,*R*)-DPEN–ruthenium catalyst in 2-propanol containing KOH, it gave, at 54% conversion, the starting (*S*)-carvone in 94% *ee* (46%) together with (1*R*,5*R*)-carveol in 93% *ee* (50%) and some other minor alcohols (3.7%) (Scheme 53).[178] The extent of the enantiomer differentiation, k_{fast}/k_{slow}, was calculated to be 33.[200]

Dynamic kinetic resolution provides a stereoselective method to convert racemic ketones with an α-stereogenic center into a single stereoisomer of the four possible isomers.[18–22] Thus, as shown in Scheme 54, racemic 2-phenylpropiophenone hydrogenated with an (*S*)-XylBINAP/(*S*)-DAIPEN–ruthenium catalyst under basic, protic conditions



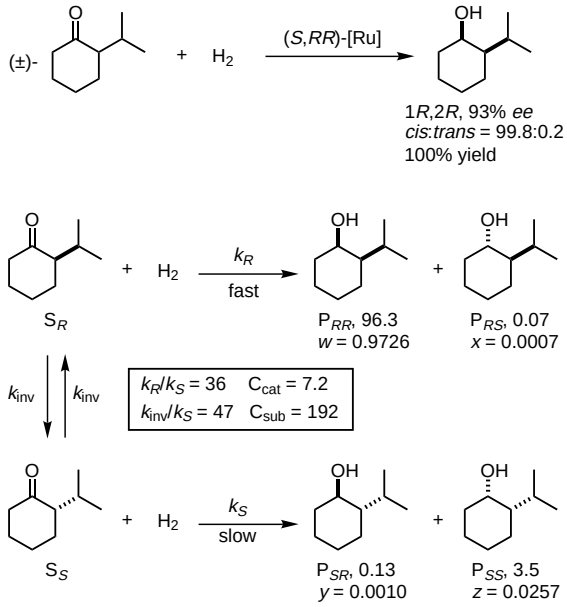
Scheme 53. Kinetic resolution of carvone by ruthenium-catalyzed hydrogenation. Conditions: $(CH_3)_2CHOH$, S/C = 1000/1, 4 atm H_2, 28 °C.



Scheme 54. Dynamic kinetic resolution of a racemic acyclic ketone. Conditions: (*S*,*S*)-[Ru] = *trans*-[$RuCl_2$\{(*S*)-xylbinap\}\{(*S*)-daipen\}], $(CH_3)_3COK$ (1:10), [ketone] = 0.2 M in $(CH_3)_2CHOH$, S/C = 1000/1, 4 atm H_2, 28 °C.

gave a 99:1 mixture of (1*R*,2*R*)-1,2-diphenyl-1-propanol (*syn*) in 96% *ee* and the 1*R*,2*S* isomer (*anti*) in 39% *ee*.[28] A very high Cram selectivity was seen, as with an achiral catalyst (Scheme 21). The degree and sense of enantioselectivity are consistent with those in reactions of simple aromatic ketones (Table 2).

Hydrogenation of racemic 2-isopropylcyclohexanone in the presence of an (*S*)-BINAP/(*R*,*R*)-DPEN – ruthenium catalyst under 4 atm of H_2 gave quantitatively a 99.8:0.2 mixture of the *cis* 1*R*,2*R* alcohol in 93% *ee*, and the *trans* 1*R*,2*S* isomer in 28% *ee* (Scheme 55).[104] The predominance of the *cis* product is in accord with the diastereoselectivity observed in the achiral hydrogenation of 2-substituted cyclohexanones (see Scheme 19). Scheme 55 explains why this hydrogenation

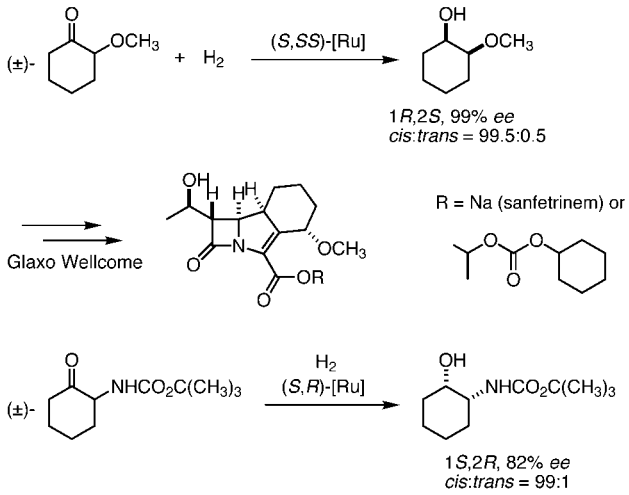


Scheme 55. Dynamic kinetic resolution of a racemic cyclic ketone. Conditions: (*S*,*RR*)-[Ru] = [$RuCl_2$\{(*S*)-binap\}$(dmf)_n$], (*R*,*R*)-DPEN, KOH (1:1:20), [ketone] = 0.8 M in $(CH_3)_2CHOH$, S/C = 500/1, 4 atm H_2, 28 °C.

proceeds with such a high stereoselectivity giving 96.3% of the 1*R*,2*R* alcohol of the four possible stereoisomers. Computer-aided analysis[18, 21] of the reaction revealed that 1) the inherent, highest 1*R*,2*R*:1*S*,2*S*:1*R*,2*S*:1*S*,2*R* selectivity at time $t = 0$ (*w*:*x*:*y*:*z* partition parameter, where the *R* and *S* enantiomers are assumed to exist in equal amounts) is 97.26:2.57:0.10:0.07; 2) under this reaction condition, the *R* ketone is hydrogenated 36 times faster than the *S* isomer; 3) the slow-reacting *S* substrate undergoes in situ stereochemical inversion 47 times faster than it is hydrogenated; 4) the extent of the substrate-based asymmetric induction (*cis*/*trans*) is 192 in favor of the *cis* isomer; and 5) the catalyst-controlled asymmetric induction (*R*/*S*) is 7.2/1. Thus, the kinetic and stereochemical factors are well coordinated to accomplish this diastereo- and enantioselective hydrogenation.[104]

This methodology was successfully applied to the asymmetric synthesis of sanfetrinem and its metabolically labile ester which has potent antibacterial activity (Scheme 56).[201, 202] The key step is the hydrogenation of racemic 2-methoxycyclohexanone with an (*S*)-XylBINAP/(*S*,*S*)-DPEN catalyst leading to (1*R*,2*S*)-2-methoxycyclohexanol with near-perfect stereoselectivity.

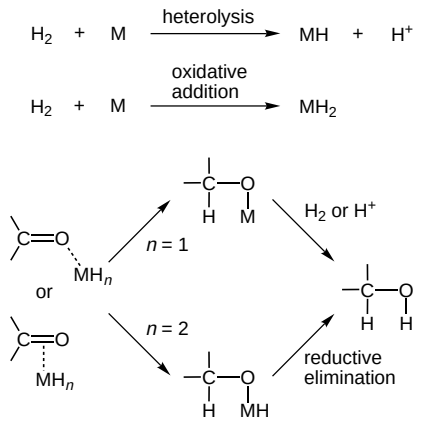
Thus, the synthetic utility of this hydrogenation is greatly enhanced by the application of dynamic kinetic resolution of configurationally labile diastereomeric, epimeric, and enantiomeric ketones.



Scheme 56. Dynamic kinetic resolution of racemic cyclic ketones and the application to the asymmetric synthesis of a carbapenem antibiotic. Conditions for reduction of 2-methoxycyclohexanone: (*S*,*SS*)-[Ru] = $[NH_2(C_2H_5)_2][\{RuCl[(S)\text{-xylbinap}]\}_2(\mu\text{-Cl})_3]$, (*S*,*S*)-DPEN, KOH, $(CH_3)_2CHOH$, 50 atm H_2, 5 °C. Conditions for reaction of the amino ketone: (*S*,*R*)-[Ru] = *trans*-[$RuCl_2$\{(*S*)-xylbinap\}\{(*R*)-daipen\}], KOH (1:200), [ketone] = 0.2 M in $(CH_3)_2CHOH$, S/C = 300/1, 8 atm H_2, 25 °C.

8. Metal-Ligand Difunctional Catalysis: Origin of the High Rate and Chemoselectivity

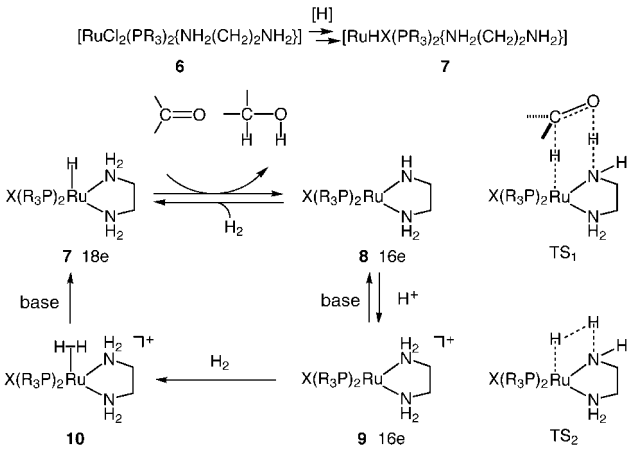
Homogeneous hydrogenation of simple ketones is generally conceived to occur by a [π2+σ2] pathway as depicted in Scheme 57,[29, 30, 39, 203] although there are some mechanistic constraints, as noted earlier in Scheme 8a. Certain transition metal complexes cleave molecular hydrogen to generate metal hydrides.[64, 77] The metal monohydride, MH, generated by heterolysis of H_2 first forms a σ or π complex with a ketonic substrate.[61–63] The conversion into a metal alkoxide intermediate[204] is followed by hydrogenolysis or protonolysis of the M–O bond to give an alcohol product. Alternatively, oxidative addition of H_2 to a metal catalyst generates a metal



Scheme 57. Putative pathways of homogeneous hydrogenation of ketones by transition metal monohydride and dihydride species.

dihydride, MH_2.[7a, 64] Subsequent reaction with a ketone, giving an alkoxy metal hydride, followed by reductive elimination, forms an alcohol product. In both cases, the ability of transition metals to form π complexes,[63] in the ground state and/or the transition state, their Lewis acidity, as well as their oxophilicity contributes to the carbonyl reduction.

We believe, however, that the rapid hydrogenation occurs by an entirely different mechanism, that is catalysis with a metal-ligand difunctionality. Scheme 58 presents our current view of the mechanism. First, $[RuCl_2(PR_3)_2\{NH_2(CH_2)_2NH_2\}]$ (**6**) is converted into $[RuHX(PR_3)_2\{NH_2(CH_2)_2NH_2\}]$ (**7**; X = H or OR) in the presence of an alkaline base and a hydride source (H_2 and a trace of 2-propanol).[58, 77, 78] The major role of the strong base (2 equivalents relative to Ru) is to neutralize HCl formed in this process. The catalytic cycle involves two ground-state components, **7** and **8**, which are linked by transition states TS_1 and TS_2. The NH proton in **7** plays a key role in hydrogen delivery to ketones, while the amide nitrogen in **8** cleaves H_2. The high turnover efficiency relies on the universal functions of the complexes **7** and **8**, in which the metal centers and the ligands directly cooperate in the bond-breaking and -forming reactions. The operation of the metal-ligand difunctional mechanism has been substantiated experimentally (structures and kinetics[205]) and theoretically(ab initio MO and DFT[206]) in the closely related Ru^{II}-catalyzed transfer hydrogenation of ketones with 2-propanol. Although several diastereomers are possible for the reducing species **7** (see Scheme 11), the hydride and two nitrogen atoms must have a *fac* relationship in the octahedral geometry. The 18-electron ruthenium hydride **7** reacts with a ketonic substrate via a six-membered, pericyclic transition state TS_1, giving a product alcohol and the 16-electron complex **8**.[58, 205, 206] The hydrogenative reactivity of coordinatively saturated **7** originates from the charge-alternating $H^{\delta-}$-$Ru^{\delta+}$-$N^{\delta-}$-$H^{\delta+}$ arrangement. Thus, the hydride ligand at the ruthenium center possesses sufficient nucleophilicity, while the NH moiety exhibits a unique hydrogen-bonding ability[71, 73, 207] to activate the carbonyl substrate. The structure of the 1,4-dipole fits well with the carbonyl dipole, stabilizing the pericyclic transition state TS_1. The NH···O hydrogen bonding not only perturbs the electronic properties of the C=O bond but also creates a three-dimensional assembly appropriate for hydride transfer to the π face. The 16-electron complex **8** can form an the 18-electron complex with a Ru=N bond (resonance), since the amide nitrogen can donate its free electron pair (the nonbonding electrons) to the electron-deficient ruthenium center.[205, 208, 209] Because of this unique $Ru^{\delta+}$-$N^{\delta-}$ dipolar bond, **8** splits H_2 molecules in a heterolytic manner[210] via transition state TS_2 thus restoring the ruthenium hydride **7**. In view of the marked dependency of the rate on hydrogen pressure this H_2 cleavage would be the turnover-limiting step. Alternatively, **7** may be regenerated from **8** and H_2 by way of **9** and **10** by the action of a protic medium and base. Most notably, unlike in conventional metal hydride reactions (see Scheme 57), the carbonyl oxygen does not interact with the metal center. Neither a ketone/ruthenium complex nor a ruthenium alkoxide are involved in this reaction mechanism. The alcohol forms directly from the ketone. Alcohols may add across the polar Ru–N bond of **8** but in a reversible manner, where the resulting ruthenium alkoxides act merely as reservoirs for **8**. Therefore, the ketone reduction does not require any coordinative unsaturation at the ruthenium center but rather occurs in an outer coordination sphere of the 18-electron complex **7** (see Scheme 8b). This is the main origin of the high rate of this catalytic hydrogenation. Furthermore, this nonclassical mechanistic model also explains the uncommon functional selectivity in favor of the C=O group.



Scheme 58. Metal-ligand difunctional mechanism for hydrogenation of ketones. X = H, OR etc.

9. Conclusion

Homogeneous hydrogenation has remained underutilized in chemical synthesis largely a result of insufficient selectivity as well as low TON and TOF. However, we are now close to achieving the ambitious goal which was set some years ago. First, unlike classical hydrogenation catalysts, the phosphane/1,2-diamine–ruthenium complexes catalyze efficient hydrogenation of a large variety of simple ketones. In view of the existence of so many ketonic compounds, the full scope of the usefulness of the new homogeneous hydrogenation has not been defined. This catalysis can replace most of the current stoichiometric hydride reductions, particularly for large-scale

reactions.[4, 5] This method is general but also remarkably selective. The selectivities rival those of the best metal hydride reductions. The high C=O/C=C selectivity is similar to that of $NaBH_4$ reduction.[86] In addition, this hydrogenation tolerates various substituents including F, Cl, Br, I, CF_3, OCH_3, $OCH_2C_6H_5$, $COOCH(CH_3)_2$, NO_2, NH_2, NR_2, and NR^1COR^2 ($R^1 = H$, alkyl; $R^2 =$ alkyl, aryl), and various heterocyclic groups. The hydrogenation is also diastereoselective, to an extent which compares well with that of the reagent L-Selectride.[101] Furthermore, asymmetric hydrogenation is performed by using appropriate chiral diphosphanes and 1,2-diamines, where structural permutations are virtually unlimited. Also, the scope of the ketonic substrates showing high enantioselectivity is very wide. This catalytic reaction is rapid and productive and, therefore, is truly efficient. The reaction can normally be performed with < 8 atm of H_2 and at room temperature with a high S/C ratio (up to 2400000/1 under 45 atm of H_2) and a substrate concentration as high as 30% (w/v), leading to very high volumetric productivity.

Asymmetric catalysis is "four-dimensional chemistry".[2] The high efficiency can only be achieved through the coordination of both an ideal three-dimensional structure (x, y, z) and suitable kinetics (t). To achieve maximum chiral multiplication, efficient catalyst systems must be created that permit precise discrimination among the enantiotopic atoms, groups, or faces in achiral molecules with a very high turnover efficiency. Special molecular design to stabilize stereochemistry-determining transition states is of prime importance. Metal-ligand difunctional catalysis provides a new basis for developing efficient catalytic reactions. Furthermore, suitable kinetic parameters must be selected to facilitate the catalytic cycle. The BINAP–$RuCl_2$ complexes are effective for asymmetric hydrogenation of both functionalized ketones and simple ketones. Notably, however, the former reaction (see Scheme 2) is markedly accelerated by the addition of a strong acid,[25, 26] while the latter reaction requires the presence of a strong base.

New technologies must meet technical, economic, and environmental requirements. Because chemical products tend to be more dependent on catalytic synthesis, better catalytic efficiency leads directly to a number of scientific and economic benefits. In particular, enantioselective catalysis is rapidly becoming more important in the areas of pharmaceuticals, agrochemicals, flavors, and fragrances which require high degrees of chemical precision.[4, 5] In this regard, molecular catalysis is complementary to biotechnology.[211] Furthermore, creation of some chiral polymers, advanced materials with nonlinear optical properties, ferroelectric liquid crystals, etc. also relies on the availability of chiral building blocks. Therefore de novo development of efficient catalysts must have a significant impact on chemical research and industry. Although the art and science of asymmetric catalysis has reached a very sophisticated level, relatively few homogeneous enantioselective catalysts have been used on an industrial scale.[4, 5, 7] This practical asymmetric hydrogenation has a very wide scope and provides entry to a diverse array of significant chiral substances. Finally, hydrogenation is "green" chemistry that eliminates the use and generation of hazardous substances. In comparison to conventional stoichiometric hydride reductions, waste is greatly reduced by using this catalytic method.

We are especially indebted to our able collaborators for their sustained intellectual and experimental efforts. Their names are acknowledged in the publications cited from our laboratories at Nagoya University and in the ERATO Molecular Catalysis Project (Japan Science and Technology Corporation, 1991-1996). This work was also aided by grants from the Ministry of Education, Science, Sports, and Culture of Japan (Nos. 07CE2004 and 11440188).

Received: January 10, 2000 [A 386]

[1] a) J. P. Collman, L. S. Hegedus, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, **1980**; b) G. W. Parshall, *Homogeneous Catalysis: The Applications and Chemistry of Catalysis by Soluble Transition Metal Complexes*, Wiley, New York, **1980**; c) A. Nakamura, M. Tsutsui, *Principles and Applications of Homogeneous Catalysis*, Wiley, New York, **1980**; d) J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, **1987**; e) F. J. McQuillin, D. G. Parker, G. R. Stephenson, *Transition Metal Organometallics for Organic Synthesis*, Cambridge University Press, Cambridge, **1991**; f) *Metal Promoted Selectivity in Organic Synthesis* (Eds.: A. F. Noels, M. Graziani, A. J. Hubert), Kluwer, Dordrecht, **1991**; g) G. W. Parshall, S. D. Ittel, *Homogeneous Catalysis: The Applications and Chemistry of Catalysis by Soluble Transition Metal Complexes*, 2nd ed, Wiley, New York, **1992**; h) *Homogeneous Transition Metal Catalyzed Reactions* (Eds.: W. R. Moser, D. W. Slocum), American Chemical Society, Washington, **1992**; i) R. H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, 2nd ed., Wiley, New York, **1994**; j) *Comprehensive Organometallic Chemistry II*, *Vol. 12* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson, L. S. Hegedus), Elsevier, Oxford, **1995**; k) J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**; l) *Applied Homogeneous Catalysis with Organometallic Compounds*, *Vol. 1*, *2* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**; m) *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, *Vol. 1*, *2* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**; n) *Transition Metal Catalysed Reactions* (Eds.: S. Murahashi, S. G. Davies), Blackwell Science, Oxford, **1999**.

[2] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.

[3] a) Y. Izumi, A. Tai, *Stereo-Differentiating Reactions: The Nature of Asymmetric Reactions*, Academic Press, New York, **1977**; b) *Asymmetric Catalysis* (Ed.: B. Bosnich), Martinus Nijhoff, Dordrecht, **1986**; c) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**; d) H. Brunner, W. Zettlmeier, *Handbook of Enantioselective Catalysis*, VCH, Weinheim, **1993**; e) *Chiral Reactions in Heterogeneous Catalysis* (Eds.: G. Jannes, V. Dubois), Plenum, New York, **1995**; f) *Comprehensive Asymmetric Catalysis*, *Vol. 1–3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[4] a) G. M. R. Tombo, D. Bellus, *Angew. Chem.* **1991**, *103*, 1219–1241; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1193–1215; b) B. Cornils, W. A. Herrmann, M. Rasch, *Angew. Chem.* **1994**, *106*, 2219–2238; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2144–2163; c) H.-U. Blaser, B. Pugin in ref [3e], pp. 33–57; d) R. Noyori, S. Hashiguchi in ref [11], *Vol. 1*, pp. 552–571; e) H.-U. Blaser, B. Pugin, F. Spindler in ref [11], *Vol.* 2, pp. 992–1009; f) W. A. Herrmann, B. Cornils, *Angew. Chem.* **1997**, *109*, 1074–1095; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1048–1067; g) W. Keim in ref [1m], *Vol. 1*, pp. 14–22; h) R. Schmid, M. Scalone in ref [3f], *Vol. 3*, pp. 1439–1449; i) T. Aratani in ref [3f], *Vol. 3*, pp. 1451–1460; j) S. Akutagawa in ref [3f], *Vol. 3*, pp. 1461–1469.

[5] a) S. Akutagawa in *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds* (Eds.: A. N. Collins, G. N. Sheldrake, J. Crosby), Wiley, Chichester, **1992**, chap 17;

b) R. Schmid, *Chimia* **1996**, *50*, 110 – 113; c) R. Schmid, E. A. Broger, M. Cereghetti, Y. Crameri, J. Foricher, M. Lalonde, R. K. Müller, M. Scalone, G. Schoettel, U. Zutter, *Pure Appl. Chem*. **1996**, *68*, 131 – 138; d) H.-U. Blaser, F. Spindler in ref [3f], *Vol. 3*, pp. 1427 – 1437.

[6] Reviews: a) K. Burgess, A. M. Porte in *Advances in Catalytic Processes: Asymmetric Catalysis, Vol. 2* (Ed.: M. P. Doyle), JAI, Greenwich, **1997**, pp. 69 – 82; b) C. Gennari, H. P. Nestler, U. Piarulli, B. Salom, *Liebigs Ann. Chem.* **1997**, 637 – 647; c) H. B. Kagan, *J. Organomet. Chem*. **1998**, *567*, 3 – 6; d) M. B. Francis, T. F. Jamison, E. N. Jacobsen, *Curr. Opin. Chem. Biol*. **1998**, *2*, 422 – 428; e) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885 – 1889; f) T. Bein, *Angew. Chem*. **1999**, *111*, 335 – 338; *Angew. Chem. Int. Ed*. **1999**, *38*, 323 – 326; g) B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem*. **1999**, *111*, 2648 – 2689; *Angew. Chem. Int. Ed*. **1999**, *38*, 2494 – 2532; h) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda in ref [3f], *Vol. 3*, pp. 1389 – 1399; i) R. H. Crabtree, *Chem. Commun.* **1999**, 1611 – 1616, refs therein.

[7] a) B. R. James, *Homogeneous Hydrogenation*, Wiley, New York, **1973**; b) A. P. G. Kieboom, F. van Rantwijk, H. van Bekkum, *Hydrogenation and Hydrogenolysis in Synthetic Organic Chemistry*, Delft University Press, Rotterdam, **1977**; c) A. J. Birch, D. H. Williamson, *Org. React. (NY)* **1976**, *24*, 1 – 186; d) B. R. James, *Adv. Organomet. Chem*. **1979**, *17*, 319 – 405; e) H. Takaya, R. Noyori in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 443 – 469; f) P. A. Chaloner, M. A. Esteruelas, F. Joó, L. A. Oro, *Homogeneous Hydrogenation*, Kluwer, Dordrecht, **1994**; g) I. Ojima, M. Eguchi, M. Tzamarioudaki in ref [1j], chap 2.

[8] a) P. Rylander, *Catalytic Hydrogenation in Organic Syntheses*, Academic Press, New York, **1979**; b) P. N. Rylander, *Hydrogenation Methods*, Academic Press, London, **1985**; c) K. Harada, T. Munegumi in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 139 – 158; d) S. Siegel in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 417 – 442.

[9] a) R. Noyori, *Chem. Soc. Rev.* **1989**, *18*, 187 – 208; b) R. Noyori, *Science* **1990**, *248*, 1194 – 1199; c) R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345 – 350; d) R. Noyori, *CHEMTECH* **1992**, *22*, 360 – 367; e) R. Noyori, *Tetrahedron* **1994**, *50*, 4259 – 4274; f) R. Noyori in *Stereocontrolled Organic Synthesis* (Ed.: B. M. Trost), Blackwell Scientific Publications, Oxford, **1994**, pp. 1 – 15; g) R. Noyori, *Acta Chem. Scand*. **1996**, *50*, 380 – 390.

[10] a) R. Noyori, M. Kitamura in *Modern Synthetic Methods*, *Vol. 5* (Ed.: R. Scheffold), Springer, Berlin, **1989**, pp. 115 – 198; b) H. Takaya, T. Ohta, R. Noyori in ref [3c], chap 1; c) see ref [2], chap 2.

[11] a) T. Ohkuma, R. Noyori in ref [1m], *Vol. 2*, pp. 25 – 69; b) T. Ohkuma, R. Noyori in ref [3f], *Vol. 1*, pp. 199 – 246; c) T. Ohkuma, M. Kitamura, R. Noyori in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, Weinheim, in press.

[12] a) H. B. Kagan, J. C. Fiaud, *Top. Stereochem*. **1978**, *10*, 175 – 285; b) B. Bosnich, M. D. Fryzuk, *Top. Inorg. Organomet. Stereochem*. **1981**, *12*, 119 – 154; c) J. Halpern in *Asymmetric Synthesis*, *Vol. 5* (Ed.: J. D. Morrison), Academic Press, Orlando, **1985**, chap 2; d) K. E. Koenig in *Asymmetric Synthesis*, *Vol. 5* (Ed.: J. D. Morrison), Academic Press, Orlando, **1985**, chap 3; e) H. Brunner, *Top. Stereochem*. **1988**, *18*, 129 – 247; f) D. Arntz, A. Schäfer in ref [1f], pp. 161 – 189; g) H. Brunner in *Methoden Org. Chem. (Houben-Weyl)*, *4th ed.*, *Vol. E21d*, **1995**, pp. 3945 – 3966; h) M. Nógrádi, *Stereoselective Synthesis: A Practical Approach*, 2nd ed., VCH, Weinheim, **1995**, chap 2; i) J. P. Genêt in *Reductions in Organic Synthesis: Recent Advances and Practical Applications* (Ed.: A. F. Abdel-Magid), American Chemical Society, Washington, **1996**, chap 2 (*ACS Symp. Ser.* **1996**, *641*, 31 – 51); j) J. M. Brown in ref [3f], *Vol. 1*, pp. 121 – 182; k) R. L. Halterman in ref [3f], *Vol. 1*, pp. 183 – 195.

[13] Heterogeneous asymmetric hydrogenation of ketones see: a) Y. Izumi, *Adv. Catal*. **1983**, *32*, 215 – 271; b) K. Harada in *Asymmetric Synthesis*, *Vol. 5* (Ed.: J. D. Morrison), Academic Press, Orlando, **1985**, chap 10; c) A. Tai, T. Harada in *Tailored Metal Catalysts* (Ed.: Y. Iwasawa), Reidel, Dordrecht, **1986**, pp. 265 – 324; d) A. Baiker, H. U. Blaser in *Handbook of Heterogeneous Catalysis*, *Vol. 5* (Eds.: G. Ertl, H. Knözinger, J. Weitkamp), Wiley-VCH, Weinheim, **1997**, pp. 2422 – 2436.

[14] a) *Asymmetric Synthesis*, *Vol. 1 – 5* (Ed.: J. D. Morrison), Academic Press, New York, **1983 – 1985**; b) *Methoden Org. Chem. (Houben-Weyl)*, *4th ed.*, *Vol. E21a – f*, **1995**, **1996**.

[15] Current aspects of asymmetric synthesis: a) *Problems and Wonders of Chiral Molecules* (Ed.: M. Simonyi), Académiai Kiadó, Budapest, **1990**; b) *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds* (Eds.: A. N. Collins, G. N. Sheldrake, J. Crosby), Wiley, Chichester, **1992**; c) *Chirality in Industry II: Developments in the Commercial Manufacture and Applications of Optically Active Compounds* (Eds.: A. N. Collins, G. N. Sheldrake, J. Crosby), Wiley, Chichester, **1997**; d) *Asymmetric Synthesis* (Eds.: R. A. Aitken, S. N. Kilényi), Blackie Academic & Professional, London, **1992**; e) A. Koskinen, *Asymmetric Synthesis of Natural Products*, Wiley, Chichester, **1993**; f) *Stereocontrolled Organic Synthesis* (Ed.: B. M. Trost), Blackwell Scientific Publications, Oxford, **1994**; g) T.-L. Ho, *Symmetry: A Basis for Synthesis Design*, Wiley, New York, **1995**; h) M. Nógrádi, *Stereoselective Synthesis: A Practical Approach*, 2nd ed., VCH, Weinheim, **1995**; i) J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, **1995**; j) *Advances in Asymmetric Synthesis*, *Vol. 1* (Ed.: A. Hassner), JAI, Greenwich, **1995**; k) R. E. Gawley, J. Aubé, *Principles of Asymmetric Synthesis*, Elsevier, Oxford, **1996**; l) *Current Trends in Organic Synthesis* (Eds.: C. Scolastico, F. Nicotra), Kluwer Academic/Plenum Publishers, New York, **1998**; m) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets* (Ed.: V. A. Soloshonok), Wiley, Chichester, **1999**.

[16] Abbreviations: BINAP = 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. TolBINAP = 2,2′-Bis(di-4-tolylphosphino)-1,1′-binaphthyl. XylBINAP = 2,2′-Bis(di-3,5-xylylphosphino)-1,1′-binaphthyl. CHIRAPHOS = 2,3-Bis(diphenylphosphino)butane. DIOP = 2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. DPEN = 1,2-Diphenylethylenediamine. DAIBEN = 1,1-Di-4-anisyl-2-isobutyl-1,2-ethylenediamine. DAIPEN = 1,1-Di-4-anisyl-2-isopropyl-1,2-ethylenediamine. DAMEN = 1,1-Di-4-anisyl-2-methyl-1,2-ethylenediamine.

[17] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc*. **1987**, *109*, 5856 – 5858.

[18] R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36 – 55.

[19] R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475 – 1490.

[20] a) R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi, H. Kumobayashi, *J. Am. Chem. Soc*. **1989**, *111*, 9134 – 9135; b) M. Kitamura, T. Ohkuma, M. Tokunaga, R. Noyori, *Tetrahedron: Asymmetry* **1990**, *1*, 1 – 4; c) M. Kitamura, M. Tokunaga, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2931 – 2932.

[21] Computational analysis: a) M. Kitamura, M. Tokunaga, R. Noyori, *J. Am. Chem. Soc.* **1993**, *115*, 144 – 152; b) M. Kitamura, M. Tokunaga, R. Noyori, *Tetrahedron* **1993**, *49*, 1853 – 1860.

[22] K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Org. Chem*. **1994**, *59*, 3064 – 3076.

[23] a) M. N. Paddon-Row, N. G. Rondan, K. N. Houk, *J. Am. Chem. Soc.* **1982**, *104*, 7162 – 7166; b) K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y.-D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li, R. J. Loncharich, *Science* **1986**, *231*, 1108 – 1117.

[24] a) M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Tetrahedron Lett*. **1991**, *32*, 4163 – 4166; b) M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Org. Synth.* **1993**, *71*, 1 – 13; c) T. Ikariya, Y. Ishii, H. Kawano, T. Arai, M. Sabri, S. Yoshikawa, S. Akutagawa, *J. Chem. Soc. Chem. Commun*. **1985**, 922 – 924; d) B. Heiser, E. A. Broger, Y. Crameri, *Tetrahedron: Asymmetry* **1991**, *2*, 51 – 62; e) J. B. Hoke, L. S. Hollis, E. W. Stern, *J. Organomet. Chem*. **1993**, *455*, 193 – 196; f) S. A. King, L. DiMichele in *Catalysis of Organic Reactions* (Eds.: M. G. Scaros, M. L. Prunier), Marcel Dekker, New York, **1995**, pp. 157 – 166; g) T. Ohta, Y. Tonomura, K. Nozaki, H. Takaya, K. Mashima, *Organometallics* **1996**, *15*, 1521 – 1523.

[25] For the importance of an acid see: a) D. F. Taber, L. J. Silverberg, *Tetrahedron Lett*. **1991**, *32*, 4227 – 4230; b) S. A. King, A. S. Thompson, A. O. King, T. R. Verhoeven, *J. Org. Chem*. **1992**, *57*, 6689 – 6691;

c) J. P. Genêt, V. Ratovelomanana-Vidal, M. C. Cano de Andrade, X. Pfister, P. Guerreiro, J. Y. Lenoir, *Tetrahedron Lett*. **1995**, *36*, 4801 – 4804; d) P. J. Pye, K. Rossen, R. A. Reamer, R. P. Volante, P. J. Reider, *Tetrahedron Lett*. **1998**, *39*, 4441 – 4444.
[26] M. Kitamura, M. Yoshimura, N. Kanda, R. Noyori, *Tetrahedron* **1999**, *55*, 8769 – 8785; see also ref [17, 20].
[27] T. Ohta, H. Takaya, R. Noyori, *Inorg. Chem*. **1988**, *27*, 566 – 569.
[28] Unpubished results from our laboratory.
[29] R. R. Schrock, J. A. Osborn, *J. Chem. Soc. Chem. Commun*. **1970**, 567 – 568.
[30] a) K. Tani, K. Suwa, E. Tanigawa, T. Yoshida, T. Okano, S. Otsuka, *Chem. Lett*. **1982**, 261 – 264; b) K. Tani, E. Tanigawa, Y. Tatsuno, S. Otsuka, *J. Organomet. Chem*. **1985**, *279*, 87 – 101.
[31] C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313 – 348.
[32] a) M. J. Burk, T. G. P. Harper, J. R. Lee, C. Kalberg, *Tetrahedron Lett*. **1994**, *35*, 4963 – 4966; b) I. M. Lorkovic, R. R. Duff, Jr., M. S. Wrighton, *J. Am. Chem. Soc*. **1995**, *117*, 3617 – 3618.
[33] a) G. Mestroni, G. Zassinovich, A. Camus, *J. Organomet. Chem*. **1977**, *140*, 63 – 72; b) G. Mestroni, R. Spogliarich, A. Camus, F. Martinelli, G. Zassinovich, *J. Organomet. Chem*. **1978**, *157*, 345 – 352.
[34] J. D. Miller, F. D. Oliver, *J. Chem. Soc. Dalton Trans.* **1972**, 2473 – 2477.
[35] H. Pasternak, E. Lancman, F. Pruchnik, *J. Mol. Catal*. **1985**, *29*, 13 – 18.
[36] M. Gargano, P. Giannoccaro, M. Rossi, *J. Organomet. Chem*. **1977**, *129*, 239 – 242.
[37] Review: M. A. Bennett, T. W. Matheson in *Comprehensive Organometallic Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds*, *Vol. 4* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, pp. 931 – 965.
[38] For an excellent review over catalysis with ruthenium complexes see: T. Naota, H. Takaya, S. Murahashi, *Chem. Rev*. **1998**, *98*, 2599 – 2660.
[39] R. A. Grey, G. P. Pez, A. Wallo, *J. Am. Chem. Soc*. **1981**, *103*, 7536 – 7542.
[40] a) D. E. Linn, Jr., J. Halpern, *J. Am. Chem. Soc*. **1987**, *109*, 2969 – 2974; b) J. Halpern, *Pure Appl. Chem*. **1987**, *59*, 173 – 180.
[41] B. R. James, A. Pacheco, S. J. Rettig, I. S. Thorburn, R. G. Ball, J. A. Ibers, *J. Mol. Catal*. **1987**, *41*, 147 – 161.
[42] J. Bakos, I. Tóth, B. Heil, L. Markó, *J. Organomet. Chem*. **1985**, *279*, 23 – 29.
[43] Q. Jiang, Y. Jiang, D. Xiao, P. Cao, X. Zhang, *Angew. Chem*. **1998**, *110*, 1203 – 1207; *Angew. Chem. Int. Ed.* **1998**, *37*, 1100 – 1103.
[44] U. Nagel, C. Roller, *Z. Naturforsch. B* **1998**, *53*, 267 – 270.
[45] X. Zhang, T. Taketomi, T. Yoshizumi, H. Kumobayashi, S. Akutagawa, K. Mashima, H. Takaya, *J. Am. Chem. Soc*. **1993**, *115*, 3318 – 3319.
[46] F. Robin, F. Mercier, L. Ricard, F. Mathey, M. Spagnol, *Chem. Eur. J.* **1997**, *3*, 1365 – 1369.
[47] P. Cao, X. Zhang, *J. Org. Chem*. **1999**, *64*, 2127 – 2129.
[48] For a comprehensive review see: E. J. Corey, C. J. Helal, *Angew. Chem*. **1998**, *110*, 2092 – 2118; *Angew. Chem. Int. Ed*. **1998**, *37*, 1986 – 2012.
[49] T. Nagata, K. Yorozu, T. Yamada, T. Mukaiyama, *Angew. Chem*. **1995**, *107*, 2309 – 2311; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2145 – 2147.
[50] a) S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1992**, *3*, 1475 – 1504; b) L. Deloux, M. Srebnik, *Chem. Rev*. **1993**, *93*, 763 – 784; c) D. J. Mathre, I. Shinkai in *Encyclopedia of Reagents for Organic Synthesis*, *Vol. 4* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 2247 – 2250; d) G. J. Quallich, J. F. Blake, T. M. Woodall in *Reductions in Organic Synthesis: Recent Advances and Practical Applications* (Ed.: A. F. Abdel-Magid), American Chemical Society, Washington, **1996**, chap 7 (*ACS Symp. Ser.* **1996**, *641*, 112 – 126); e) S. Itsuno in ref [3f], *Vol. 1*, pp. 289 – 315.
[51] For reviews on stoichiometric asymmetric hydroboration see: a) H. C. Brown, P. V. Ramachandran, *Acc. Chem. Res.* **1992**, *25*, 16 – 24; b) M. M. Midland, L. A. Morell in ref [14b], *Vol. E21d*, pp. 4082 – 4098; c) P. V. Ramachandran, H. C. Brown in *Reductions in Organic Synthesis: Recent Advances and Practical Applications* (Ed.: A. F. Abdel-Magid), American Chemical Society, Washington, **1996**, chap 5 (*ACS Symp. Ser.* **1996**, *641*, 84 – 97).
[52] S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2039 – 2044.
[53] T. Imai, T. Tamura, A. Yamamuro, T. Sato, T. A. Wollmann, R. M. Kennedy, S. Masamune, *J. Am. Chem. Soc*. **1986**, *108*, 7402 – 7404.
[54] a) I. Ojima, K. Hirai in ref [14a], *Vol. 5*, chap 4; b) H. Brunner, H. Nishiyama, K. Itoh in ref [3c], chap 6; c) H. Brunner in ref [14b], *Vol. E21d*, pp. 4074 – 4081; d) H. Brunner in ref [1m], *Vol.* 2, pp. 131 – 140; e) H. Nishiyama in ref [3f], *Vol. 1*, pp. 267 – 287.
[55] a) H. Brunner, R. Becker, G. Riepl, *Organometallics* **1984**, *3*, 1354 – 1359; b) H. Nishiyama, M. Kondo, T. Nakamura, K. Itoh, *Organometallics* **1991**, *10*, 500 – 508; c) J. Sakaki, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1993**, *76*, 2654 – 2665; d) M. Sawamura, R. Kuwano, Y. Ito, *Angew. Chem*. **1994**, *106*, 92 – 93; *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 111 – 113; e) M. B. Carter, B. Schiøtt, A. Gutiérrez, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 11667 – 11670; f) Y. Nishibayashi, K. Segawa, H. Takada, K. Ohe, S. Uemura, *Chem. Commun*. **1996**, 847 – 848; g) D. K. Heldmann, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 1096 – 1110; h) J. Yun, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 5640 – 5644.
[56] a) J. D. Morrison, H. S. Mosher in *Asymmetric Organic Reactions*, Prentice-Hall, New Jersey, **1971**, chap 5; b) U. Matteoli, P. Frediani, M. Bianchi, C. Botteghi, S. Gladiali, *J. Mol. Catal*. **1981**, *12*, 265 – 319; c) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, *92*, 1051 – 1069; d) C. F. de Graauw, J. A. Peters, P. H. van Bekkum, J. Huskens, *Synthesis* **1994**, 1007 – 1017; e) K. Krohn in ref [14b], *Vol. E21d*, pp. 4099 – 4142; f) S. Gladiali, G. Mestroni in ref [1m], *Vol. 2*, pp. 97 – 119; g) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry* **1999**, *10*, 2045 – 2061.
[57] a) D. Müller, G. Umbricht, B. Weber, A. Pfaltz, *Helv. Chim. Acta* **1991**, *74*, 232 – 239; b) D. A. Evans, S. G. Nelson, M. R. Gagné, A. R. Muci, *J. Am. Chem. Soc*. **1993**, *115*, 9800 – 9801; c) T. Langer, G. Helmchen, *Tetrahedron Lett*. **1996**, *37*, 1381 – 1384.
[58] a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97 – 102; b) M. J. Palmer, M. Willis, *Tetrahedron: Asymmetry* **1999**, *10*, 2045 – 2061.
[59] a) *Reduction: Techniques and Applications in Organic Synthesis* (Ed.: R. L. Augustine), Marcel Dekker, New York, **1968**; b) *Stereoselective Reductions (Benchmark Papers in Organic Chemistry*, *Vol. 6)* (Eds.: M. P. Doyle, C. T. West), Dowden, Hutchinson & Ross, Stroudsburg, Pennsylvania, **1976**; c) M. Hudlický, *Reductions in Organic Chemistry*, 2nd ed., American Chemical Society, Washington, DC, **1996**; d) *Reductions in Organic Synthesis: Recent Advances and Practical Applications* (Ed.: A. F. Abdel-Magid), American Chemical Society, Washington, **1996** (*ACS Symp. Ser.* **1996**, *641*); e) J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed., Wiley-VCH, New York, **1997**
[60] Reviews: a) E. R. Grandbois, S. I. Howard, J. D. Morrison in ref [14a], *Vol. 2*, chap 3; b) Y. Inouye, J. Oda, N. Baba in ref [14a], *Vol. 2*, chap 4; c) H. Haubenstock, *Top. Stereochem*. **1983**, *14*, 231 – 300; d) M. Nishizawa, R. Noyori in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 159 – 182; e) M. M. Midland, L. A. Morell in ref [14b], *Vol. E21d*, pp. 4049 – 4066; f) see ref [15h], chap 3; g) see ref [15i], chap 6; h) see ref [15k], chap 7; i) A. K. Beck, R. Dahinden, F. N. M. Kühnle in ref [59d], chap 3; j) see ref [59e], pp. 55 – 65.
[61] a) M. L. H. Green, G. Parkin, K. J. Moynihan, K. Prout, *J. Chem. Soc. Chem. Commun*. **1984**, 1540; b) S. Shambayati, W. E. Crowe, S. L. Schreiber, *Angew. Chem*. **1990**, *102*, 273 – 290; *Angew. Chem. Int. Ed. Engl*. **1990**, *29*, 256 – 272; c) S. Shambayati, S. L. Schreiber in *Comprehensive Organic Synthesis*, *Vol. 1* (Eds.: B. M. Trost, I. Fleming, S. L. Schreiber), Pergamon, Oxford, **1991**, pp. 283 – 324.
[62] a) *Selectivities in Lewis Acid Promoted Reactions* (Ed.: D. Schinzer), Kluwer, Dordrecht, **1988**; b) M. Santelli, J.-M. Pons, *Lewis Acids and Selectivity in Organic Synthesis*, CRC Press, Boca Raton, FL, USA, **1996**; c) *Lewis Acid Reagents: A Practical Approach* (Ed.: H. Yamamoto), Oxford University Press, Oxford, **1999**.
[63] a) Y.-H. Huang, J. A. Gladysz, *J. Chem. Educ*. **1988**, *65*, 298 – 303; b) J. A. Gladysz, B. J. Boone, *Angew. Chem*. **1997**, *109*, 566 – 602; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 550 – 583.
[64] For example: a) see ref [1d], chap 5; b) see ref [1i], chap 6.

[65] a) M. Yamakawa, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 6327 – 6335; b) M. Yamakawa, R. Noyori, *Organometallics* **1999**, *18*, 128 – 133.

[66] a) D. S. Matteson, *Organomet. Chem. Rev. A* **1969**, *4*, 263 – 305; b) D. A. Evans, *Science* **1988**, *240*, 420 – 426; c) E. J. Corey, P.-W. Yuen, F. J. Hannon, D. A. Wierda, *J. Org. Chem.* **1990**, *55*, 784 – 786; d) H. Steinhagen, G. Helmchen, *Angew. Chem.* **1996**, *108*, 2489 – 2492; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2339 – 2342.

[67] M. Nakamura, E. Nakamura, N. Koga, K. Morokuma, *J. Am. Chem. Soc.* **1993**, *115*, 11016 – 11017.

[68] M. Tokunaga, Dissertation, Nagoya University, **1995**.

[69] a) M. Bartók, *Stereochemistry of Heterogeneous Metal Catalysis*, Wiley, Chichester, **1985**; b) *Handbook of Heterogeneous Catalysis*, *Vol. 1 – 5* (Eds.: G. Ertl, H. Knözinger, J. Weitkamp), VCH, Weinheim, **1997**; c) J. M. Thomas, W. J. Thomas, *Principles and Practice of Heterogeneous Catalysis*, VCH, Weinheim, **1997**; d) "Heterogeneous Catalysis and Fine Chemicals IV": *Stud. Surf. Sci. Catal.* **1997**, *108*; e) "Science and Technology in Catalysis 1998": *Stud. Surf. Sci. Catal.* **1999**, *121*.

[70] a) H. B. Kagan in ref [14a], *Vol. 5*, chap 1; b) H. Brunner, *Top. Stereochem.* **1988**, *18*, 129 – 247; c) H.-U. Blaser, *Chem. Rev.* **1992**, *92*, 935 – 952; d) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835 – 875; e) L. Schwink, P. Knochel, *Chem. Eur. J.* **1998**, *4*, 950 – 968; f) C. J. Richards, A. J. Locke, *Tetrahedron: Asymmetry* **1998**, *9*, 2377 – 2407; g) D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724 – 2772; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580 – 2627.

[71] Acceleration of Ru-catalyzed CO_2 hydrogenation with a small amount of H_2O or CH_3OH was explained by this mechanism. See: P. G. Jessop, Y. Hsiao, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 344 – 355.

[72] Certain chiral Lewis acid/Brønsted acid combined systems can be used for asymmetric protonation: K. Ishihara, S. Nakamura, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 12854 – 12855.

[73] Examples: a) B. Rosenberg, L. Van Camp, E. B. Grimley, A. J. Thomson, *J. Biol. Chem.* **1967**, *242*, 1347 – 1352; b) J. Reedijk, *Inorg. Chim. Acta* **1992**, *198 – 200*, 873 – 881; c) *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy 2* (Eds.: H. M. Pinto, J. H. Schornagel), Plenum, New York, **1996**; d) *Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug* (Ed.: B. Lippert), Wiley-VCH, Weinheim, **1999**; e) E. Wong, C. M. Giandomenico, *Chem. Rev.* **1999**, *99*, 2451 – 2466; f) E. R. Jamieson, S. J. Lippard, *Chem. Rev.* **1999**, *99*, 2467 – 2498; g) J. Reedijk, *Chem. Rev.* **1999**, *99*, 2499 – 2510; h) Z. Guo, P. J. Sadler, *Angew. Chem.* **1999**, *111*, 1610 – 1630; *Angew. Chem. Int. Ed.* **1999**, *38*, 1512 – 1531.

[74] T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2675 – 2676.

[75] J. Takehara, S. Hashiguchi, A. Fujii, S. Inoue, T. Ikariya, R. Noyori, *Chem. Commun.* **1996**, 233 – 234.

[76] For the concept of ligand-accelerated catalysis see: D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159 – 1171; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059 – 1070.

[77] see for example: a) H. D. Kaesz, R. B. Saillant, *Chem. Rev.* **1972**, *72*, 231 – 281; b) D. S. Moore, S. D. Robinson, *Chem. Soc. Rev.* **1983**, *12*, 415 – 452.

[78] J.-E. Bäckvall, R. L. Chowdhury, U. Karlson, G.-Z. Wang in *Perspectives in Coordination Chemistry* (Eds.: A. F. Williams, C. Floriani, A. E. Merbach), VHCA, Basel, **1992**, pp. 463 – 486, and refs therein.

[79] 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.

[80] S. Cenini, F. Porta, M. Pizzotti, *J. Mol. Catal.* **1982**, *15*, 297 – 308.

[81] Preparation of *trans*-$[RuCl_2\{P(C_6H_5)_3\}_2\{NH_2(CH_2)_2NH_2\}]$: $[RuCl_2\{P(C_6H_5)_3\}_3]$ (1.11 g, 1.16 mmol) was placed in a 50-mL Schlenk flask in which the air had been replaced with argon. CH_2Cl_2 (10 mL) and $NH_2(CH_2)_2NH_2$ (0.15 mL, 2.2 mmol) were then added. The mixture was degassed with three cycles of vacuum and argon replacement and was stirred at 25 °C for 3 h. After removal of turbidity by filtration, the filtrate was concentrated to ca. 5 mL, hexane (20 mL) was then added and a light brown powder was obtained. The supernatant solution was removed and the resulting solid was dried under reduced pressure (1 Torr) to give analytically pure *trans*-$[RuCl_2\{P(C_6H_5)_3\}_2\{NH_2(CH_2)_2NH_2\}]$ (0.55 g, 63 % yield). Decomposition point (DP): 176 °C; IR (KBr): $\tilde{\nu}$ [cm^{-1}]: 3220, 3320 (H-N); ^1H NMR (400 MHz, C_6D_6, 25 °C, TMS): $\delta = 2.1$ (m, 4H; $2CH_2$), 2.8 (m, 4H; $2NH_2$), 6.8 – 8.0 (m, 30H; aromatics); ^{31}P NMR (81 MHz, C_6D_6, 10 % H_3PO_4 as external standard) $\delta = 45.5$ (s).

[82] In order to obtain high catalytic activity, particularly in the reaction of a high S/C value, the substrate should be washed with a base solution prior to use.

[83] T. Ohkuma, M. Koizumi, H. Ikehira, T. Yokozawa, R. Noyori, *Org. Lett.* **2000**, *2*, 659 – 662.

[84] a) V. K. Pendse, B. R. Madan, *Indian J. Physiol. Pharmacol.* **1969**, *13*, 29 – 36; b) P. A. J. Janssen, FR-B 2014487, **1970** [*Chem. Abstr.* **1971**, *74*, 53848s]; c) E. Regel, W. Draber, K. H. Büchel, M. Plempel, DE-B 2461406, **1976** [*Chem. Abstr.* **1976**, *85*, 160095t]; d) F. Awouters, C. J. E. Niemegeers, J. Van den Berk, J. M. Van Nueten, F. M. Lenaerts, M. Borgers, K. H. L. Schellekens, A. Broeckaert, J. De Cree, P. A. J. Janssen, *Experientia* **1977**, *33*, 1657 – 1659; e) K. Meguro, M. Aizawa, T. Sohda, Y. Kawamatsu, A. Nagaoka, *Chem. Pharm. Bull.* **1985**, *33*, 3787 – 3797.

[85] a) K. Bowden, M. Hardy, *Tetrahedron* **1966**, *22*, 1169 – 1174; b) G. T. Bruce, A. R. Cooksey, K. J. Morgan, *J. Chem. Soc. Perkin Trans. 2* **1975**, 551 – 553; see also: H. C. Brown, O. H. Wheeler, K. Ichikawa, *Tetrahedron* **1957**, *1*, 214 – 220.

[86] Reviews: a) H. C. Brown, S. Krishnamurthy, *Tetrahedron* **1979**, *35*, 567 – 607; b) N. Greeves in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 1 – 24; c) see ref [59c], chap 13; d) H. C. Brown, P. V. Ramachandran in ref [59d], chap 1; e) see ref [59e], chap 3.

[87] Reviews: a) R. L. Augustine, *Adv. Catal.* **1976**, *25*, 56 – 80; b) E. Keinan, N. Greenspoon in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 523 – 578.

[88] a) J. M. Grosselin, C. Mercier, G. Allmang, F. Grass, *Organometallics* **1991**, *10*, 2126 – 2133; b) B. Cornils, W. A. Herrmann, R. W. Eckl, *J. Mol. Catal. A Chemical* **1997**, *116*, 27 – 33.

[89] Other examples with homogeneous catalysts: a) K. Hotta, *J. Mol. Catal.* **1985**, *29*, 105 – 107; b) K. Hotta, *Kagaku to Kogyo (Tokyo)* **1986**, *60*, 196 – 205 (*Chemistry and Chemical Industry*); c) E. Farnetti, M. Pesce, J. Kaspar, R. Spogliarich, M. Graziani, *J. Mol. Catal.* **1987**, *43*, 35 – 40.

[90] With heterogeneous catalysts: a) W. F. Tuley, R. Adams, *J. Am. Chem. Soc.* **1925**, *47*, 3061 – 3068; b) S. Galvagno, Z. Poltarzewski, A. Donato, G. Neri, R. Pietropaolo, *J. Chem. Soc. Chem. Commun.* **1986**, 1729 – 1731; c) Y. Nitta, Y. Hiramatsu, T. Imanaka, *Chem. Express* **1989**, *4*, 281 – 284; d) Y. Nitta, Y. Hiramatsu, T. Imanaka, *J. Catal.* **1990**, *126*, 235 – 245; e) A. Giroir-Fendler, D. Richard, P. Gallezot, *Catal. Lett.* **1990**, *5*, 175 – 181; f) J. M. Planeix, N. Coustel, B. Coq, V. Brotons, P. S. Kumbhar, R. Dutartre, P. Geneste, P. Bernier, P. M. Ajayan, *J. Am. Chem. Soc.* **1994**, *116*, 7935 – 7936.

[91] With polymer-bound rhodium catalysts: a) K. Kaneda, T. Mizugaki, *Organometallics* **1996**, *15*, 3247 – 3249; b) T. Mizugaki, Y. Kanayama, K. Ebitani, K. Kaneda, *J. Org. Chem.* **1998**, *63*, 2378 – 2381.

[92] E. Farnetti, J. Kašpar, R. Spogliarich, M. Graziani, *J. Chem. Soc. Dalton Trans.* **1988**, 947 – 952.

[93] K. Mashima, T. Akutagawa, X. Zhang, H. Takaya, T. Taketomi, H. Kumobayashi, S. Akutagawa, *J. Organomet. Chem.* **1992**, *428*, 213 – 222.

[94] J. F. Daeuble, J. M. Stryker in *Catalysis of Organic Reactions* (Eds.: M. G. Scaros, M. L. Prunier), Marcel Dekker, New York, **1995**, pp. 235 – 247.

[95] C. S. Chin, B. Lee, S. C. Park, *J. Organomet. Chem.* **1990**, *393*, 131 – 135.

[96] Heterogeneous hydrogenation: a) P. S. Gradeff, G. Formica, *Tetrahedron Lett.* **1976**, 4681 – 4684; b) J. Ishiyama, S. Maeda, K. Takahashi, Y. Senda, S. Imaizumi, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1721 – 1726.

[97] T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 10417 – 10418.

[98] D. Evans, J. A. Osborn, F. H. Jardine, G. Wilkinson, *Nature* **1965**, *208*, 1203 – 1204.

[99] 1-Phenyl-3-butyn-1-one, an α,β-acetylenic ketone, could not be hydrogenated under such conditions.

[100] Recent reviews: A. P. Davis in ref. [14b], *Vol. E21d*, pp. 3988 – 4048. Reduction with dissolving metals: A. M. El-Khawaga, H. M. R. Hoffmann in ref. [14b], *Vol. E21d*, pp. 3967 – 3987; reduction with metal alkoxides: K. Krohn in ref. [14b], *Vol. E21d*, pp. 4099 – 4142.

[101] Highly diastereoselective Selectride reduction: a) H. C. Brown, S. Krishnamurthy, *J. Am. Chem. Soc.* **1972**, *94*, 7159 – 7161; b) S. Krishnamurthy, H. C. Brown, *J. Am. Chem. Soc.* **1976**, *98*, 3383 – 3384.

[102] G. Boireau, A. Deberly, R. Toneva, *Synlett* **1993**, 585 – 587.

[103] a) E. L. Eliel, R. J. L. Martin, D. Nasipuri, *Org. Synth. Coll. Vol.* **1973**, *5*, 175 – 178; b) G. B. Fisher, J. C. Fuller, J. Harrison, S. G. Alvarez, E. R. Burkhardt, C. T. Goralski, B. Singaram, *J. Org. Chem.* **1994**, *59*, 6378 – 6385; c) M. C. Barden, J. Schwartz, *J. Org. Chem.* **1995**, *60*, 5963 – 5965; d) G. Godjoian, G. B. Fisher, C. T. Goralsky, B. Singaram in ref [59d], chap 10.

[104] T. Ohkuma, H. Ooka, M. Yamakawa, T. Ikariya, R. Noyori, *J. Org. Chem*. **1996**, *61*, 4872 – 4873.

[105] Hydrogenation of 4-*tert*-butylcyclohexanone with a $[RuCl_2\{P(C_6H_5)_3\}_3]/NH_2(CH_2)_2NH_2/KOH$ catalyst system: Half molar 2-propanol solutions of $NH_2(CH_2)_2NH_2$ (39 mL, 0.0195 mmol) and KOH (78 mL, 0.038 mmol) were added to 2-propanol (5 mL) in a 20-mL Schlenk flask. The solution was degassed by three freeze-thaw cycles. Solid $[RuCl_2\{P(C_6H_5)_3\}_3]$ (18.7 mg, 0.0195 mmol) was added to the diamine/KOH solution under a stream of argon, and the resultant mixture was further degassed by two freeze-thaw cycles, sonicated for 30 min, and used as a catalyst stock solution. 2-Propanol (100 mL) charged into a second 250-mL Schlenk flask by hypodermic syringe and was also degassed. Solid 4-*tert*-butylcyclohexanone (30.0 g, 194.5 mmol) was placed into a 500-mL glass autoclave equipped with a Teflon-coated magnetic stirring bar, a pressure gauge, and a gas inlet tube attached to a hydrogen source. 2-Propanol and the catalyst solution were subsequently transferred by cannula to the autoclave. Hydrogen was introduced initially into the autoclave at a pressure of 4 atm and was then reduced to 1 atm by carefully releasing the stop valve. After repeating this procedure five times, the vessel was pressurized to 4 atm. The reaction mixture was vigorously stirred at 28 °C for 80 h, during which time the open hydrogen cylinder remained connected. After this time, the yield and *cis*:*trans* ratio as determined by GC analysis (TC-WAX (polyethylene glycol) column) were 99.8 % and 98.4:1.6, respectively. After the hydrogen gas was carefully vented, the solvent was removed under reduced pressure. The residue was purified by distillation giving *cis*-4-*tert*-butylcyclohexanol (98.3 % pure, 29.2 g, 96 % yield), BP: 112 – 115 °C (19 Torr). Recrystallization of this product from a water – ethanol mixture gave 99.6 % pure compound (23.4 g, 82 % yield).

[106] a) S. Tomoda, T. Senju, *Tetrahedron* **1997**, *53*, 9057 – 9066; b) S. Tomoda, *Chem. Rev.* **1999**, *99*, 1243 – 1263.

[107] a) S. Mitsui, H. Saito, Y. Yamashita, M. Kaminaga, Y. Senda, *Tetrahedron* **1973**, *29*, 1531 – 1539; b) S. Nishimura, M. Ishige, M. Shiota, *Chem. Lett*. **1977**, 963 – 966.

[108] M. Balasubramanian, A. D'Souza, *Tetrahedron* **1968**, *24*, 5399 – 5408.

[109] Examples of other catalytic stereoselective methods. Transfer hydrogenation: a) H. B. Henbest, T. R. B. Mitchell, *J. Chem. Soc. C* **1970**, 785 – 791; b) K. Konishi, T. Aida, S. Inoue, *J. Org. Chem.* **1990**, *55*, 816 – 820. Hydrosilylation: c) I. Ojima, M. Nihonyanagi, Y. Nagai, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3722; d) M. F. Semmelhack, R. N. Misra, *J. Org. Chem.* **1982**, *47*, 2469 – 2471; e) M. Fujita, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 5405 – 5415. Hydrostannation: f) J.-P. Quintard, M. Pereyre, *Bull. Soc. Chim. Fr.* **1972**, 1950 – 1955.

[110] a) E. L. Eliel, N. L. Allinger, S. J. Angyal, G. A. Morrison, *Conformational Analysis*, Wiley, New York, **1965**; b) E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**; c) *Conformational Behavior of Six-Membered Rings: Analysis, Dynamics, and Stereoelectronic Effects* (Ed.: E. Juaristi), VCH, New York, **1995**.

[111] a) see ref [110a], pp. 112 – 121; b) K. Krohn in *Methoden Org. Chem. (Houben-Weyl)*, *4th ed.*, *Vol. 6/1b*, **1984**, pp. 339 – 341; c) see ref [110b], pp. 731 – 737.

[112] B. Rickborn, *J. Am. Chem. Soc.* **1962**, *84*, 2414 – 2417.

[113] M. Emura, T. Toyota, N. Seido, M. Harada, R. Noyori, T. Ikariya, T. Ohkuma, JP-A 241195, **1997** [*Chem. Abstr*. **1997**, *127*, 292919k].

[114] a) D. J. Cram, F. A. A. Dlhafez, *J. Am. Chem. Soc.* **1952**, *74*, 5828 – 5835; b) D. J. Cram, F. D. Greene, *J. Am. Chem. Soc.* **1953**, *75*, 6005 – 6010.

[115] M. Chérest, H. Felkin, N. Prudent, *Tetrahedron Lett.* **1968**, 2199 – 2204.

[116] a) N. T. Anh, O. Eisenstein, *Tetrahedron Lett.* **1972**, 155 – 158; b) N. T. Anh, O. Eisenstein, *Nouv. J. Chim*. **1977**, *1*, 61 – 70; c) N. T. Anh, *Top. Curr. Chem*. **1980**, *88*, 145 – 162.

[117] a) E. L. Eliel in ref [14a], *Vol. 2*, chap 5; b) E. Juaristi in *Introduction to Stereochemistry and Conformational Analysis*, Wiley, New York, **1991**, chap 11; c) A. Mengel, O. Reiser, *Chem. Rev*. **1999**, *99*, 1191 – 1223.

[118] Multiple stereodifferentiation: S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem*. **1985**, *97*, 1 – 31; *Angew. Chem. Int. Ed. Engl*. **1985**, *24*, 1 – 30.

[119] 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.

[120] S.-J. Wey, K. J. O'Connor, C. J. Burrows, *Tetrahedron Lett*. **1993**, *34*, 1905 – 1908.

[121] R. Noyori, T. Ohkuma, *Pure Appl. Chem*. **1999**, *71*, 1493 – 1501.

[122] Preparation of *trans*-$[RuCl_2\{(R)\text{-binap}\}\{(R,R)\text{-dpen}\}]$: $[\{RuCl_2(\text{benzene})\}_2]$ (129 mg, 0.258 mmol) and (*R*)-BINAP (341 mg, 0.55 mmol) were placed in a 50-mL Schlenk flask. After the air in the flask was replaced with argon, DMF (9 mL) was added to the flask, the mixture was degassed by three cycles of vacuum and argon replacement and then heated at 100 °C for 10 min while stirred giving a reddish brown solution. After the solution was cooled to 25 °C, (*R*,*R*)-DPEN (117 mg, 0.55 mmol) was added and the mixture was stirred for 3 h. DMF was removed under reduced pressure (1 Torr) at 25 °C and then at 50 °C. The residue was resolved in CH_2Cl_2 (10 mL) and turbidity was removed by filtration. The filtrate was concentrated to ca. 1 mL, then ether (10 mL) was added and a light brown powder was obtained. The supernatant was removed and the resulting solid was dried under reduced pressure to give analytically pure *trans*-$[RuCl_2\{(R)\text{-binap}\}\{(R,R)\text{-dpen}\}]$ (0.34 g, 66 % yield). DP: 235 °C; IR: $\tilde{\nu}$ [cm^{-1}]: 3225, 3320 (H-N); ^{1}H NMR (400 MHz): $\delta = 3.3$ (m, 2H, 2NH*H*), 3.45 (m, 2H, 2NH*H*), 4.55 (m, 2H, $2NH_2CH$), 6.3 – 8.8 (m, 42H, aromatics); ^{31}P NMR (81 MHz, C_6D_6, 10 % H_3PO_4 as external standard) $\delta = 47.4$ (s).

[123] D. A. Buckingham, A. M. Sargeson, *Top. Stereochem.* **1971**, *6*, 219 – 277.

[124] S. Törös, B. Heil, L. Kollár, L. Markó, *J. Organomet. Chem*. **1980**, *197*, 85 – 86.

[125] a) P. D. Theisen, C. H. Heathcock, *J. Org. Chem*. **1988**, *53*, 2374 – 2378; b) O. Dirat, C. Kouklovsky, Y. Langlois, *J. Org. Chem*. **1998**, *63*, 6634 – 6642.

[126] For the sake of formal consistency, the Scheme lists results obtained with an (*S*)-diphosphane/(*S*)- or (*S*,*S*)-diamine combined system. Some experiments were actually performed by using the enantiomeric catalyst.

[127] Asymmetric hydrogenation of acetophenone using *trans*-$[RuCl_2\{(S)\text{-tolbinap}\}\{(S,S)\text{-dpen}\}]$: 2-Propanol (20 mL) charged into a 100-mL Schlenk flask was degassed by three vacuum – nitrogen replacement cycles. Solid *trans*-$[RuCl_2\{(S)\text{-tolbinap}\}\{(S,S)\text{-dpen}\}]$ (22 mg, 0.020 mmol) was dissolved in the 2-propanol and used as a catalyst stock solution. Acetophenone (601 g, 5.0 mol) and solid $(CH_3)_3COK$ (5.6 g, 0.050 mol) were placed in a 10-L stainless steel autoclave. Air present in the autoclave was replaced by nitrogen. 2-Propanol (1.5 L) and an aliquot of the catalyst solution (2.0 mL, 0.002 mmol; molar ratio ketone:Ru:base = 2400000:1:24000) were added to the autoclave under a stream of nitrogen. The mixture was degassed by three cycles of vacuum – nitrogen replacement. Hydrogen was introduced initially into the autoclave at a pressure of 10 atm and then reduced to 1 atm by carefully releasing the stop valve. After this procedure was repeated three times, the vessel was pressurized to 45 atm. The reaction mixture was vigorously stirred for 48 h at 30 °C to give *R*-enriched 1-phenylethanol. The yield and *ee* value determined by GC (Cyclodextrin-β-236M column) were 100 and 80 %, respectively. After the hydrogen gas was carefully vented, the solvent was removed under reduced pressure. The residue was passed through silica gel (300 g) eluting with ethyl acetate, and then distilled to give

(*R*)-1-phenylethanol (577 g, 94% yield). Bp: 99 °C (15 Torr); $[\alpha]_D^{24} = +38.1°$ ($c = 1.02$, CH_2Cl_2).

[128] T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529 – 13530.

[129] P. V. Ramachandran, A. V. Teodorovic, H. C. Brown, *Tetrahedron* **1993**, *49*, 1725 – 1738.

[130] a) E. J. Corey, R. K. Bakshi, *Tetrahedron Lett.* **1990**, *31*, 611 – 614; b) E. J. Corey, X.-M. Cheng, K. A. Cimprich, S. Sarshar, *Tetrahedron Lett.* **1991**, *32*, 6835 – 6838; c) J. M. Chong, E. K. Mar, *J. Org. Chem.* **1991**, *56*, 893 – 896.

[131] J. P. Vigneron, M. Dhaenens, A. Horeau, *Tetrahedron* **1973**, *29*, 1055 – 1059.

[132] a) see ref [2], chap 5; b) H. Wynberg, B. Feringa, *Tetrahedron* **1976**, *32*, 2831 – 2834.

[133] S. Kan, unpublished results from our laboratories .

[134] X. Zhang, H. Kumobayashi, H. Takaya, *Tetrahedron: Asymmetry* **1994**, *5*, 1179 – 1182.

[135] a) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562 – 7563; b) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521 – 2522.

[136] a) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925 – 7926; b) E. J. Corey, C.-P. Chen, G. A. Reichard, *Tetrahedron Lett.* **1989**, *30*, 5547 – 5550; c) E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1989**, *30*, 6275 – 6278.

[137] a) T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. Jones, R. A. Reamer, F. E. Roberts, E. J. J. Grabowski, *J. Org. Chem.* **1991**, *56*, 763 – 769; b) D. J. Mathre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, E. J. J. Grabowski, *J. Org. Chem.* **1993**, *58*, 2880 – 2888; c) A. M. Salunkhe, E. R. Burkhardt, *Tetrahedron Lett.* **1997**, *38*, 1523 – 1526.

[138] M. Kawasaki, Y. Suzuki, S. Terashima, *Chem. Lett.* **1984**, 239 – 242.

[139] H. C. Brown, J. Chandrasekharan, P. V. Ramachandran, *J. Am. Chem. Soc.* **1988**, *110*, 1539 – 1546.

[140] Asymmetric hydrogenation of *o*-chlorobenzophenone with *trans*-[$RuCl_2${(*S*)-xylbinap}{(*S*)-daipen}]: Solid *trans*-[$RuCl_2${(*S*)-xylbinap}-{(*S*)-daipen}] (28.7 mg, 0.0235 mmol) and *o*-chlorobenzophenone (101.8 g, 0.47 mol) were placed in a 1.5-L stainless steel autoclave equipped with a mechanical stirring blade, a pressure gauge, and a gas inlet tube attached to a hydrogen source. Air in the autoclave was replaced by argon. 2-Propanol (150 mL) and a 1.0 M $(CH_3)_3COK$ solution in *tert*-butyl alcohol (4.7 mL, 4.7 mmol) were added to the autoclave under a stream of argon. The mixture was degassed by three cycles of vacuum– argon replacement. The vessel was pressurized with H_2 to 8 atm, and then the reaction mixture was vigorously stirred for 55 h at 30 °C. The yield and *ee* value of (*S*)-*o*-chlorobenzhydrol determined by GC (HP-INNOWax (polyethylene glycol) column) and chiral HPLC (CHIRALCEL OD column) analysis were 99 and 97%, respectively. After the hydrogen gas was carefully vented, the solvent was removed under reduced pressure. Distillation of the residue gave the *S* alcohol (97.5 g, 95% yield). Bp: 138 – 139 °C (0.3 Torr); $[\alpha]_D^{20} = -21.51°$ ($c = 1.14$, $CHCl_3$).

[141] Asymmetric reduction using silicon- and boron-based hydrides: a) J.-F. Peynonel, J.-C. Fiaud, H. B. Kagan, *J. Chem. Res. Miniprint* **1980**, 4057 – 4080; b) H. Brunner, A. Kürzinger, *J. Organomet. Chem.* **1988**, *346*, 413 – 424; c) E. Brown, A. Penfornis, J. Bayma, J. Touet, *Tetrahedron: Asymmetry* **1991**, *2*, 339 – 342; d) E. Brown, A. Lézé, J. Touet, *Tetrahedron: Asymmetry* **1992**, *3*, 841 – 844; e) W.-C. Shieh, W. R. Cantrell, Jr., J. A. Carlson, *Tetrahedron Lett.* **1995**, *36*, 3797 – 3800; f) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1995**, *36*, 9153 – 9156; g) P. V. Ramachandran, G.-M. Chen, H. C. Brown, *Tetrahedron Lett.* **1996**, *37*, 2205 – 2208; h) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, *37*, 4837 – 4840; i) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, *37*, 5675 – 5678.

[142] a) C. van der Stelt, W. J. Heus, W. T. Nauta, *Arzneim. Forsch.* **1969**, *19*, 2010 – 2012; b) R. F. Rekker, H. Timmermann, A. F. Harms, W. T. Nauta, *Arzneim. Forsch.* **1971**, *21*, 688 – 691.

[143] T. Ireland, J. J. A. Perea, P. Knochel, *Angew. Chem.* **1999**, *111*, 1560 – 1562; *Angew. Chem. Int. Ed.* **1999**, *38*, 1457 – 1460.

[144] T. Ohkuma, M. Koizumi, M. Yoshida, R. Noyori, *Org. Lett.* **2000**, *2*, 1749 – 1751.

[145] Asymmetric hydrogenation of 2-acetylfuran with *trans*-[$RuCl_2${(*R*)-xylbinap}{(*R*)-daipen}]: Solid *trans*-[$RuCl_2${(*R*)-xylbinap}{(*R*)-daipen}] (30.5 mg, 0.025 mmol) and 2-acetylfuran (110.1 g, 1.00 mol) were placed in a 1.5-L stainless steel autoclave equipped with a mechanical stirring blade, a pressure gauge, and a gas inlet tube attached to a hydrogen source. Air present in the autoclave was replaced by argon. 2-Propanol (100 mL) and a 1.0 M $(CH_3)_3COK$ solution in *tert*-butyl alcohol (7.5 mL, 7.5 mmol) were added to the autoclave under a stream of argon. The mixture was degassed by three cycles of vacuum-filling with argon. The vessel was pressurized to 50 atm, and then the reaction mixture was vigorously stirred for 22 h at 24 °C. The yield and *ee* values of (*S*)-1-(2-furyl)ethanol determined by GC analysis (HP-INNOWax and Chirasil-DEX CB columns) were 96 and 99%, respectively. After the hydrogen gas was carefully vented, the solvent was removed under reduced pressure. Distillation of the residue gave (*S*)-1-(2-furyl)ethanol (92.8 g, 83% yield). Bp: 76 °C (18 Torr); $[\alpha]_D^{24} = -20.1°$ ($c = 1.00$, $CHCl_3$).

[146] P. V. Ramachandran, G.-M. Chen, Z.-H. Lu, H. C. Brown, *Tetrahedron Lett.* **1996**, *37*, 3795 – 3798.

[147] a) M. M. Midland, J. I. McLoughlin, J. Gabriel, *J. Org. Chem.* **1989**, *54*, 159 – 165; b) G. J. Quallich, T. M. Woodall, *Tetrahedron Lett.* **1993**, *34*, 785 – 788; c) K. R. K. Prasad, N. N. Joshi, *Tetrahedron: Asymmetry* **1997**, *8*, 173 – 176; d) M. Masui, T. Shioiri, *Synlett* **1997**, 273 – 274; e) E. J. Corey, B. E. Roberts, *J. Am. Chem. Soc.* **1997**, *119*, 12425 – 12431.

[148] a) C. Rüchardt, H. Gärtner, U. Salz, *Angew. Chem.* **1984**, *96*, 166 – 167; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 162 – 164; b) A. Franck, C. Rüchardt, *Chem. Lett.* **1984**, 1431 – 1434; see also: R. Chinchilla, C. Nájera, M. Yus, A. Heumann, *Tetrahedron: Asymmetry* **1991**, *2*, 101 – 104.

[149] M. R. Uskoković, R. L. Lewis, J. J. Partridge, C. W. Despreaux, D. L. Pruess, *J. Am. Chem. Soc.* **1979**, *101*, 6742 – 6744.

[150] a) R. Sablong, C. Newton, P. Dierkes, J. A. Osborn, *Tetrahedron Lett.* **1996**, *37*, 4933 – 4936; b) R. Sablong, J. A. Osborn, *Tetrahedron Lett.* **1996**, *37*, 4937 – 4940.

[151] P. Allevi, P. Ciuffreda, G. Tarocco, M. Anastasia, *J. Org. Chem.* **1996**, *61*, 4144 – 4147; see also: A. Dondoni, D. Perrone, *Aldrichimica Acta* **1997**, *30*, 35 – 46.

[152] a) T. Osawa, *Chem. Lett.* **1985**, 1609 – 1612; b) T. Osawa, T. Harada, A. Tai, *J. Mol. Catal.* **1994**, *87*, 333 – 342; c) T. Osawa, A. Tai, Y.Imachi, S. Takasaki in ref [3e], pp. 75 – 81; d) T. Harada, T. Osawa in ref [3e], pp. 83 – 88; e) T. Osawa, T. Harada, A. Tai, O. Takayasu, I. Matsuura in ref [69d], pp. 199 – 206; f) T. Osawa, T. Harada, A. Tai, *Catal. Today* **1997**, *37*, 465 – 480.

[153] a) T. Hayashi, A. Katsumura, M. Konishi, M. Kumada, *Tetrahedron Lett.* **1979**, 425 – 428; b) T. Hayashi, M. Kumada, *Acc. Chem. Res.* **1982**, *15*, 395 – 401.

[154] H. Takeda, T. Tachinami, M. Aburatani, H. Takahashi, T. Morimoto, K. Achiwa, *Tetrahedron Lett.* **1989**, *30*, 363 – 366.

[155] a) S. Törös, L. Kollár, B. Heil, L. Markó, *J. Organomet. Chem.* **1982**, *232*, C17 – C18; b) K. Yoshikawa, N. Yamamoto, M. Murata, K. Awano, T. Morimoto, K. Achiwa, *Tetrahedron: Asymmetry* **1992**, *3*, 13 – 16; c) M. Devocelle, F. Agbossou, A. Mortreux, *Synlett* **1997**, 1306 – 1308; d) C. Pasquier, S. Naili, L. Pelinski, J. Brocard, A. Mortreux, F. Agbossou, *Tetrahedron: Asymmetry* **1998**, *9*, 193 – 196.

[156] M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 629 – 631.

[157] T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, *J. Am. Chem. Soc.*; in press.

[158] T. Kawaguchi, K. Saito, K. Matsuki, T. Iwakuma, M. Takeda, *Chem. Pharm. Bull.* **1993**, *41*, 639 – 642.

[159] a) K. Naito, T. Nagao, M. Otsuka, S. Harigaya, H. Nakajima, *Jpn. J. Pharmacol.* **1985**, *38*, 235 – 241; b) H. Yokoyama, T. Yanagisawa, N. Taira, *J. Cardiovasc. Pharmacol.* **1988**, *12*, 323 – 331; c) M. R. Bristow, R. E. Hershberger, J. D. Port, W. Minobe, R. Rasmussen, *Mol. Pharmacol.* **1989**, *35*, 295 – 303, refs therein

[160] D. W. Robertson, J. H. Krushinski, R. W. Fuller, J. D. Leander, *J. Med. Chem.* **1988**, *31*, 1412 – 1417, refs therein

[161] R. S. Rogers, *Chem. Eng. News* **1998**, *76*(48), 11 – 13.

[162] J. P. Yevich, J. S. New, W. G. Lobeck, P. Dextraze, E. Bernstein, D. P. Taylor, F. D. Yocca, M. S. Eison, D. L. Temple, Jr., *J. Med. Chem.* **1992**, *35*, 4516 – 4525.

[163] a) S. Sakuraba, K. Achiwa, *Synlett* **1991**, 689 – 690; b) S. Sakuraba, N. Nakajima, K. Achiwa, *Synlett* **1992**, 829 – 830.
[164] H. Takahashi, T. Morimoto, K. Achiwa, *Chem. Lett*. **1987**, 855 – 858.
[165] a) B. Török, K. Felföldi, K. Balázsik, M. Bartók, *Chem. Commun*. **1999**, 1725 – 1726; b) M. Studer, S. Burkhardt, H.-U. Blaser, *Chem. Commun*. **1999**, 1727 – 1728.
[166] a) P. Wipf in *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, Oxford, **1991**, pp. 827 – 873; b) H. Frauenrath in ref [14b], *Vol. E21d*, pp. 3301 – 3547.
[167] Pd^0-catalyzed allyl substitution: a) R. F. Heck, *Palladium Reagents in Organic Syntheses*, Academic Press, London, **1985**, chap 5; b) see ref [1k], pp. 290 – 422.
[168] Y. Yamamoto in ref [14b], *Vol. E21b*, pp. 2011 – 2040.
[169] a) S. Terashima, N. Tanno, K. Koga, *J. Chem. Soc. Chem. Commun*. **1980**, 1026 – 1027; b) H. C. Brown, G. G. Pai, *J. Org. Chem*. **1982**, *47*, 1606 – 1608; c) R. Noyori, I. Tomino, M. Yamada, M. Nishizawa, *J. Am. Chem. Soc*. **1984**, *106*, 6717 – 6725; d) J. Bach, R. Berenguer, J. Garcia, J. Vilarrasa, *Tetrahedron Lett*. **1995**, *36*, 3425 – 3428.
[170] a) E. J. Corey, A. V. Gavai, *Tetrahedron Lett*. **1988**, *29*, 3201 – 3204; b) E. J. Corey, K. S. Rao, *Tetrahedron Lett*. **1991**, *32*, 4623 – 4626; c) E. J. Corey, H. Kigoshi, *Tetrahedron Lett*. **1991**, *32*, 5025 – 5028; d) A. F. Simpson, P. Szeto, D. C. Lathbury, T. Gallagher, *Tetrahedron: Asymmetry* **1997**, *8*, 673 – 676.
[171] T. Sato, Y. Gotoh, Y. Wakabayashi, T. Fujisawa, *Tetrahedron Lett*. **1983**, *24*, 4123 – 4126.
[172] a) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc*. **1981**, *103*, 6237 – 6240; b) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc*. **1987**, *109*, 5765 – 5780; c) Y. Kitano, T. Matsumoto, F. Sato, *J. Chem. Soc. Chem. Commun*. **1986**, 1323 – 1325.
[173] a) M. Kitamura, K. Manabe, R. Noyori, H. Takaya, *Tetrahedron Lett*. **1987**, *28*, 4719 – 4720; b) M. Kitamura, I. Kasahara, K. Manabe, R. Noyori, H. Takaya, *J. Org. Chem*. **1988**, *53*, 708 – 710.
[174] S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya, R. Noyori, *Angew. Chem*. **1997**, *109*, 300 – 303; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 288 – 290.
[175] H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara, R. Noyori, *J. Am. Chem. Soc.* **1987**, *109*, 1596 – 1597; Berichtigung: H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara, R. Noyori, *J. Am. Chem. Soc.* **1987**, *109*, 4129.
[176] K.-K. Chan, N. Cohen, J. P. De Noble, A. C. Specian, Jr., G. Saucy, *J. Org. Chem*. **1976**, *41*, 3497 – 3505.
[177] S. Terashima, N. Tanno, K. Koga, *Tetrahedron Lett*. **1980**, *21*, 2753 – 2756.
[178] T. Ohkuma, H. Ikehira, T. Ikariya, R. Noyori, *Synlett* **1997**, 467 – 468.
[179] a) K. Mori, P. Puapoomchareon, *Liebigs Ann. Chem*. **1991**, 1053 – 1056; b) K. Mori, *Synlett* **1995**, 1097 – 1109.
[180] T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 1086 – 1087.
[181] R. Croteau, F. Karp in *Perfumes: Art, Science and Technology* (Eds.: P. M. Müller, D. Lamparsky), Blackie Academic & Professional, London, **1991**, chap 4.
[182] Hydrogenation of 2-cyclohexenone catalyzed by an (*S*,*S*)-DIOP/Ir complex gave (*R*)-2-cyclohexenol in 25% *ee*: R. Spogliarich, S. Vidotto, E. Farnetti, M. Graziani, N. V. Gulati, *Tetrahedron: Asymmetry* **1992**, *3*, 1001 – 1002.
[183] R. E. Ireland, P. Bey, *Org. Synth. Collect. Vol.* **1988**, *6*, 459 – 460.
[184] J. M. Fortunato, B. Ganem, *J. Org. Chem*. **1976**, *41*, 2194 – 2200.
[185] A. L. Gemal, J.-L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454 – 5459.
[186] K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc*. **1997**, *119*, 8738 – 8739.
[187] a) C. J. Helal, P. A. Magriotis, E. J. Corey, *J. Am. Chem. Soc*. **1996**, *118*, 10938 – 10939; b) K. A. Parker, M. W. Ledeboer, *J. Org. Chem*. **1996**, *61*, 3214 – 3217.
[188] P. V. Ramachandran, A. V. Teodrović, M. V. Rangaishenvi, H. C. Brown, *J. Org. Chem*. **1992**, *57*, 2379 – 2386.
[189] M. M. Midland, D. C. McDowell, R. L. Hatch, A. Tramontano, *J. Am. Chem. Soc*. **1980**, *102*, 867 – 869.
[190] a) N. Cohen, R. J. Lopresti, C. Neukom, G. Saucy, *J. Org. Chem*. **1980**, *45*, 582 – 588; b) J. P. Vigneron, V. Bloy, *Tetrahedron Lett*. **1980**, *21*, 1735 – 1738.
[191] a) D. Arigoni, E. L. Eliel, *Top. Stereochem*. **1969**, *4*, 127 – 243; b) K. S. Y. Lau, P. K. Wong, J. K. Stille, *J. Am. Chem. Soc*. **1976**, *98*, 5832 – 5840; c) C. D. Poulter, C.-H. R. King, *J. Am. Chem. Soc*. **1982**, *104*, 1420 – 1422.
[192] T. Ohta, T. Tsutsumi, H. Takaya, *J. Organomet. Chem*. **1994**, *484*, 191 – 193.
[193] I. Yamada, R. Noyori, *Org. Let.* **2000** *2*, 3425 – 3427.
[194] a) N. W. Alcock, J. M. Brown, P. J. Maddox, *J. Chem. Soc. Chem. Commun.* **1986**, 1532 – 1534; b) K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 789 – 790; c) J. M. Brown, P. J. Maddox, *Chirality* **1991**, *3*, 345 – 354; d) J. W. Faller, J. Parr, *J. Am. Chem. Soc.* **1993**, *115*, 804 – 805; e) J. W. Faller, M. Tokunaga, *Tetrahedron Lett*. **1993**, *34*, 7359 – 7362; f) J. W. Faller, D. W. I. Sams, X. Liu, *J. Am. Chem. Soc.* **1996**, *118*, 1217 – 1218; g) R. Sablong, J. A. Osborn, J. W. Faller, *J. Organomet. Chem*. **1997**, *527*, 65 – 70.
[195] a) S. Matsukawa, K. Mikami, *Enantiomer* **1996**, *1*, 69 – 73; b) K. Mikami, S. Matsukawa, *Nature* **1997**, *385*, 613 – 615; c) S. Matsukawa, K. Mikami, *Tetrahedron: Asymmetry* **1997**, *8*, 815 – 816; d) T. Volk, T. Korenaga, S. Matsukawa, M. Terada, K. Mikami, *Chirality* **1998**, *10*, 717 – 721; e) K. Mikami, M. Terada in ref [62c], chap 6; f) for a recent review article on asymmetric activation see K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki, R Angelaud, *Angew. Chem.* **2000**, *102*, 3676 – 3701; *Angew. Chem. Int. Ed.* **2000**, *39*, 3532 – 3556.
[196] a) R. Noyori, M. Kitamura, *Angew. Chem*. **1991**, *103*, 34 – 55; *Angew. Chem. Int. Ed. Engl*. **1991**, *30*, 49 – 69; b) N. Oguni, Y. Matsuda, T. Kaneko, *J. Am. Chem. Soc.* **1988**, *110*, 7877 – 7878; c) K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767 – 768; d) C. Bolm in *Advanced Asymmetric Synthesis* (Ed.: G. R. Stephenson), Chapman & Hall, London, **1996**, chap 2; e) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Tetrahedron: Asymmetry* **1997**, *8*, 2997 – 3017; f) C. Girald, H. B. Kagan, *Angew. Chem*. **1998**, *110*, 3088 – 3127; *Angew. Chem. Int. Ed*. **1998**, *37*, 2922 – 2959; g) D. R. Fenwick, H. B. Kagan, *Top. Stereochem*. **1999**, *22*, 257 – 296.
[197] Related diastereomeric Pt-(*R*)-BINOL-DPPE complexes: a) N. M. Brunkan, P. S. White, M. R. Gagné, *Angew. Chem*. **1998**, *110*, 1615 – 1618; *Angew. Chem. Int. Ed*. **1998**, *37*, 1579 – 1582; b) N. M. Brunkan, P. S. White, M. R. Gagné, *J. Am. Chem. Soc.* **1998**, *120*, 11002 – 11003.
[198] M. Oki, *Top. Stereochem*. **1983**, *14*, 1 – 81.
[199] K. Mikami, T. Korenaga, M. Terada, T. Ohkuma, T. Pham, R. Noyori, *Angew. Chem*. **1999**, *111*, 517 – 519; *Angew. Chem. Int. Ed*. **1999**, *38*, 495 – 497.
[200] H. B. Kagan, J. C. Fiaud, *Top. Stereochem*. **1988**, *18*, 249 – 330.
[201] T. Matsumoto, T. Murayama, S. Mitsuhashi, T. Miura, *Tetrahedron Lett*. **1999**, *40*, 5043 – 5046.
[202] T. Rossi, C. Marchioro, A. Paio, R. J. Thomas, P. Zarantonello, *J. Org. Chem*. **1997**, *62*, 1653 – 1661.
[203] see for example: a) R. A. Sanchez-Delgado, J. S. Bradley, G. Wilkinson, *J. Chem. Soc. Dalton Trans.* **1976**, 399 – 404; b) C. W. Jung, P. E. Garrou, *Organometallics* **1982**, *1*, 658 – 666.
[204] H. E. Bryndza, W. Tam, *Chem. Rev*. **1988**, *88*, 1163 – 1188.
[205] 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.
[206] a) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466 – 1478; b) D. A. Alonso, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc*. **1999**, *121*, 9580 – 9588.
[207] a) P. Murray-Rust, J. P. Glusker, *J. Am. Chem. Soc*. **1984**, *106*, 1018 – 1025; b) J. A. Platts, S. T. Howard, B. R. F. Bracke, *J. Am. Chem. Soc*. **1996**, *118*, 2726 – 2733.
[208] K. G. Caulton, *New J. Chem*. **1994**, *18*, 25 – 41.
[209] a) A. A. Danopoulos, G. Wilkinson, B. Hussain-Bates, M. B. Hursthouse, *Polyhedron* **1992**, *11*, 2961 – 2964; b) A. K. Burrell, A. J. Steedman, *J. Chem. Soc. Chem. Commun*. **1995**, 2109 – 2110.
[210] M. D. Fryzuk, P. A. MacNeil, S. J. Rettig, *J. Am. Chem. Soc*. **1987**, *109*, 2803 – 2812.
[211] see for example: a) *Applications of Biochemical Systems in Organic Chemistry*, *Part 1*, *2* (Eds.: J. B. Jones, C. J. Sih, D. Perlman), Wiley, New York, **1976** *(Techniques of Chemistry*, *Vol. 10)*; b) H. Dugas, C.

Penny, *Bioorganic Chemistry: A Chemical Approach to Enzyme Action*, Springer, New York, **1981**; c) *Enzymes in Organic Synthesis: Ciba Foundation Symposium III* (Eds.: R. Porter, S. Clark), Pitman, London, **1985**; d) *Enzymes as Catalysts in Organic Synthesis* (Ed.: M. P. Schneider), Reidel, Dordrecht, **1986**; e) *Enzymes in Synthetic Organic Chemistry* (Eds.: C. H. Wong, G. M. Whitesides), Pergamon, Oxford, **1994** (*Tetrahedron Organic Chemistry Series, Vol. 12*); f) *Enzyme Catalysis in Organic Synthesis*, *Vol. 1*, *2* (Eds.: K. Drauz, H. Waldmann), VCH, Weinheim, **1995**; g) *New Enzymes for Organic Synthesis: Screening*, *Supply and Engineering* (Ed.: T. Scheper), Springer, Berlin, **1997**.