Tetrahedron Vol 45, No 22, pp 6901–6939, 1989
Printed in Great Britain

0040-4020/89 $5 00+ 00
Pergamon Press plc

TETRAHEDRON REPORT NUMBER 264

RECENT ADVANCES IN CATALYTIC ASYMMETRIC REACTIONS PROMOTED BY TRANSITION METAL COMPLEXES

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(*Received* 20 *December* 1988)

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1. INTRODUCTION

This review describes recent advances (1983 to present) in catalytic asymmetric reactions promoted by chiral transition metal complexes. A previous review on this topic, *Asymmetric Synthesis*, Vol. 5—*Chiral Catalysis* edited by Morrison (1985)[1a] compiles important contributions through 1982. Another book, *Asymmetric Catalysis*, edited by Bosnich also covers contributions up to early 1984.[1b]

In 1971, an excellent book, *Asymmetric Organic Reactions*, by Morrison and Mosher,[2] reviewed all earlier important work on the subject and compiled ca. 850 relevant publications through 1968 including some papers published in 1969. In the early 1980s, a survey of publications dealing with 'asymmetric synthesis' (in a broad sense) indicated that the total number of papers in this area of research published in the ten years after the Morrison/Mosher book, i.e., 1971–1980, was almost the same as that of all the papers published before 1971.[3] This doubling of output clearly indicates

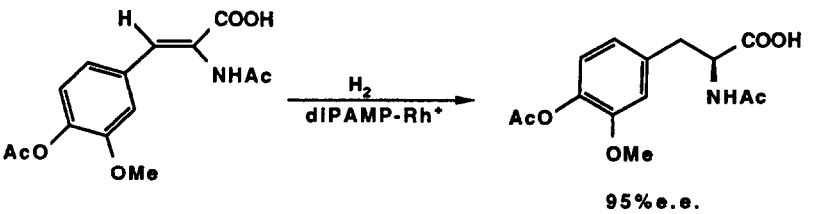
the attention paid to this important topic in the 1970s. In the 1980s, research on 'asymmetric synthesis' has become even more important and popular since availability of enantiomerically pure compounds became necessary for the total synthesis of natural products, pharmaceuticals, and agricultural agents.

Among the types of asymmetric reactions, the most desirable and the most challenging is *catalytic* asymmetric synthesis, since one chiral catalyst molecule can create millions of chiral product molecules, just as enzymes do in biological systems. Catalytic asymmetric synthesis often has significant economic advantages over stoichiometric asymmetric synthesis in industrial scale production of enantiomerically pure compounds. In fact, a number of catalytic asymmetric reactions, including the 'Takasago Process' (asymmetric isomerization; see Section 3) and the 'Sumitomo Process' (asymmetric cyclopropanation; see Section 4) and the 'Arco Process' (asymmetric epoxidation; see Section 5.1) have been commercialized in the 1980s. These supplement the 'Monsanto Process' (asymmetric hydrogenation; see Section 2) established in the early 1970s. As this review will disclose, there are several other excellent catalytic asymmetric reactions that have high potential as commercial processes. Extensive research on new and effective catalytic asymmetric reactions also continues. For recent advances in asymmetric synthesis on an industrial scale, reviews by Parshall and Nugent[4a,b] and by Scott[4c] discuss representative processes, including non-catalytic reactions, from a view of process development.

This review deals with the following catalytic asymmetric reactions: asymmetric hydrogenation, isomerization, cyclopropanation, oxidation, hydrocarbonylation, hydrosilylation and carbon–carbon bond forming reactions.

2. ASYMMETRIC HYDROGENATION

Among the asymmetric organic reactions catalyzed by chiral transition metal complexes, asymmetric hydrogenation has been one of the best studied, due in large part to the fact that it is the basis for the first commercialized catalytic asymmetric process, Monsanto's L-DOPA synthesis (eqn. 1),[4] which was introduced in 1972. This achievement by Knowles and his collaborators spurred



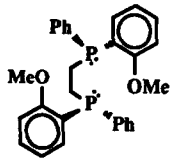
(1)

many chemists in the fields of catalysis, organometallic and synthetic organic chemistry to initiate research on catalytic asymmetric organic reactions. The magnitude of this effect is indicated by a CAS ONLINE search showing that ca. 260 papers, including parent patents on *Catalytic Asymmetric Hydrogenation* had been published by the end of 1987, with work in the area still ongoing. In this review, we will not attempt exhaustive coverage of those papers and patents, but rather will focus on new aspects of the reaction.

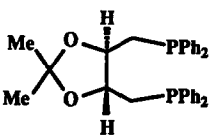
As chiral catalysts for the reactions, rhodium(I) complexes with chiral phosphine ligands have been the most extensively used. However, the recent development of highly effective chiral ruthenium–diphosphine complex catalysts[53–60] has brought about a new era of catalytic asymmetric hydrogenation. While the rhodium-based systems seem to be limited to preparation of amino acids, the ruthenium catalysts give good to excellent results with a much broader group of hydrogenation substrates that are useful intermediates for a variety of organic syntheses.

2.1. *Chiral rhodium catalysts*

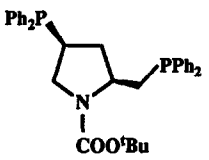
There are continuing efforts to develop newer, easier to synthesize, and more efficient chiral ligands for the rhodium catalysts. Virtually, all of the new ligands are chiral phosphines or diphosphines with chirality residing in a supporting carbon skeleton. A standard for the evaluation of the efficiency of these new chiral ligands is the asymmetric hydrogenation of N-acyldehydro-α-amino acids. Accordingly, papers that deal with the asymmetric hydrogenation of N-acyldehydro-α-amino acids still comprise the largest portion of total publications on this reaction. Chart 1 shows the structures of typical chiral phosphine ligands developed in the last five years (ten ligands shown in the lower rows, i.e., Prolophos-BDPAB), which give high enantioselectivities (>95% *ee*) in the asymmetric hydrogenation of N-acyldehydro-α-amino acids, as well as commonly used chiral ligands that had already proved to be effective prior to that period.



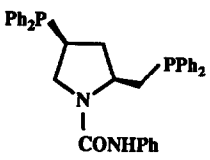
DIPAMP[5,19]



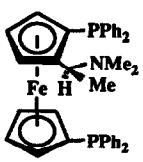
(-)DIOP[6]



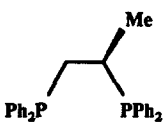
(-)BPPM[7]



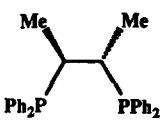
Ph-CAPP[8]



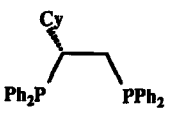
BPPFA[9]



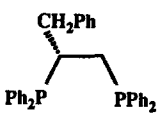
Prophos[10]



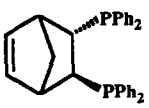
Chiraphos[11]



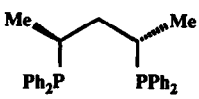
Cyphos[12]



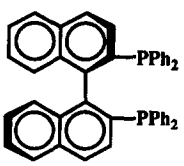
Phephos[13]



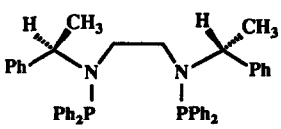
Norphos[14]



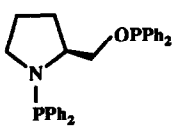
BDPP[15]



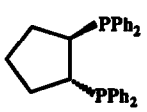
(+)BINAP[16]



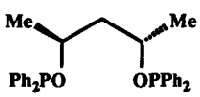
PNNP[17]



Prolophos[18]



DPCP[19]



BDPODP[20]

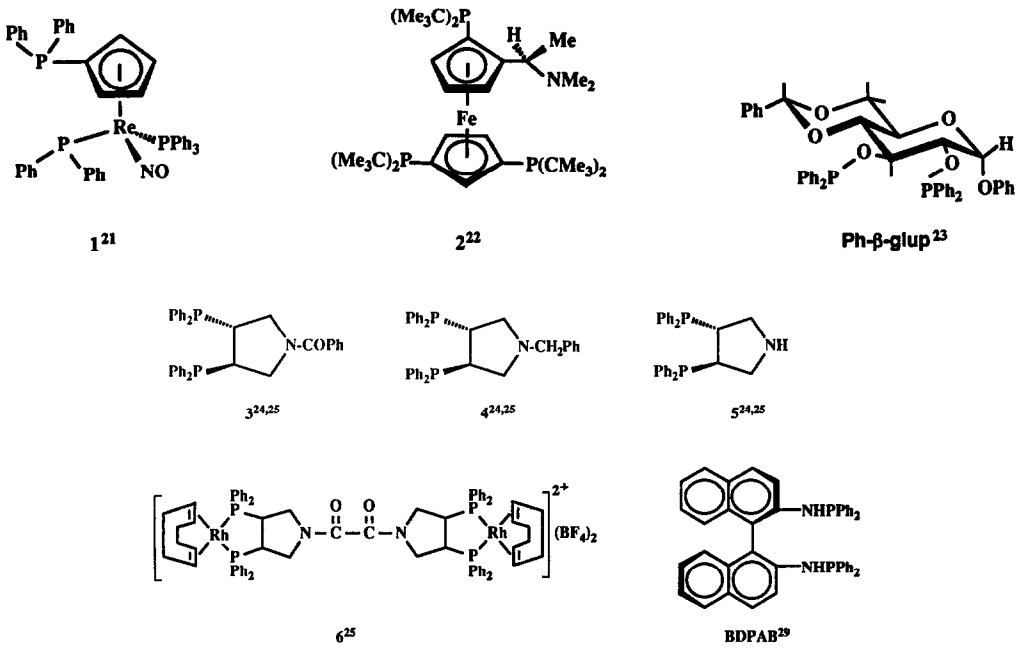


Chart 1. Typical chiral phosphine ligands for rhodium complex-catalyzed asymmetric hydrogenations of N-acyldehydro-α-amino acids

Among many newer chiral ligands, particularly worthy of mention due to their extremely high efficiency as well as the simplicity of their structures are the new diphosphine ligands **3**–**5** developed by Nagel and collaborators at Degussa.[24,25] As was previously demonstrated in the cases of PPM[7] and the ferrocenylphosphines,[9] modification of the basic structure **5** readily provides many ligands, including **3** and **4**. The cationic rhodium complex of ligand **4**, 'Degphos', can hydrogenate (*Z*)-2-acetamidocinnamic acid (Ac–Δ–Phe–OH) to (*S*)-N-acetylphenylalanine of >99% *ee* at a substrate : catalyst ratio of more than 10,000 : 1. The unique cationic rhodium complex with a bridged bis-pyrrolidinodiphosphine ligand (**6**) is also extremely effective, giving (*S*)-N-acetylphenylalanine of 96.5% *ee* at a substrate : catalyst ratio of 50,000 : 1.[25]* Heterogeneous rhodium catalysts on silica gel and the Merrifield resin obtained from a derivative of **5** give 95% *ee* in the same reaction. These catalysts are recyclable without loss of catalytic activity.[24] Although there have been many previous efforts to immobilize homogeneous chiral rhodium catalysts for the asymmetric hydrogenation of dehydroamino acids, the polymer-anchored catalysts developed by Nagel *et al.* seem to be the best so far.

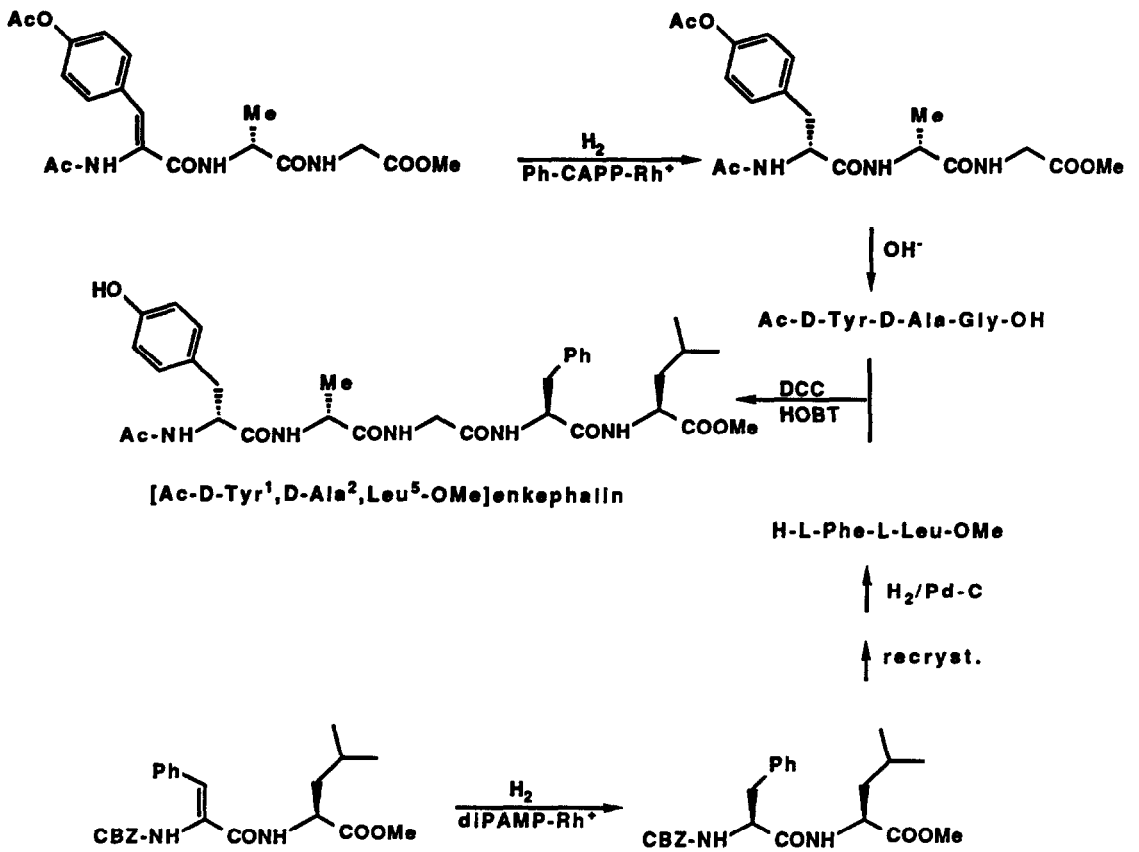
The preparation of ligands **3**–**5** from tartaric acid without optical resolution is straightforward and practical. It also should be mentioned that the Degphos–Rh^+ catalyzed reaction is not sensitive to the hydrogen pressure, viz., the enantioselectivity does not decrease at higher hydrogen pressures that are often employed to accelerate the reaction.

* It should be noted that the catalytic turnover number is very sensitive to experimental details and the experimental technique of the investigator. Thus, many apparently poorer ligands might, in fact, be very good if reaction optimization was carried out. Accordingly, it may not be fair to compare those numbers reported from academic institutions with those from industrial research laboratories where the optimization is performed. On the other hand, however, many investigations using only enantiomeric excess (*ee*) as the criterion for success, lack consideration of catalytic efficiency which is equally important for such reactions to be practical.

Many chiral aminophosphine–phosphinite (P–N–O–P) ligands were prepared, at least in part because of their ease of synthesis. However, none of them showed >95% *ee* in the asymmetric hydrogenation of dehydro-α-amino acids.

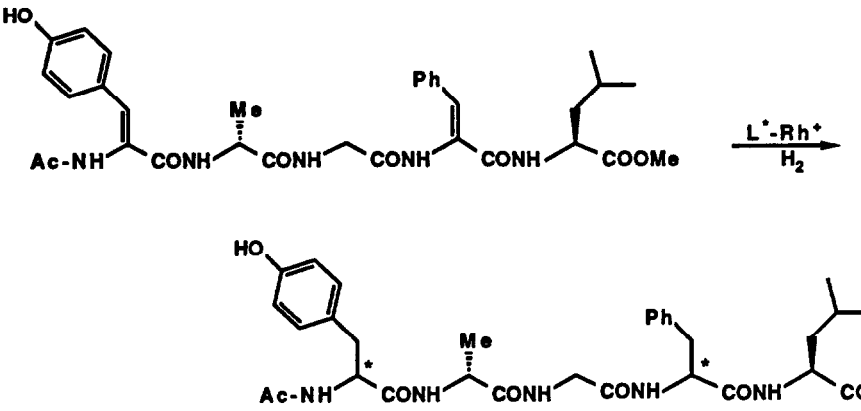
A bis-aminophosphine, PNNP, developed by Firioni and Giongo,[17] at Enichem, is being used in Italy[28] for the commercial synthesis of (*S*)-phenylalanine in connection with the production of a non-nutritious sweetener, aspartame®. This second example of a commercialized catalytic asymmetric synthesis promoted by a chiral transition metal complex clearly builds on the precedent set by the Monsanto Process. Miyano *et al.* have developed another efficient P–N–N–P ligand, BDPAB, for this reaction.[29]

The asymmetric hydrogenation of dehydropeptides has been studied in Ojima's,[30] Kagan's[31] and Yamagishi's[32] laboratories. The reactions generally give extremely high stereoselectivities though substantial 'double asymmetric induction'[33] is observed. As an example, Ojima *et al.* have synthesized several analogues of leucine–enkephalin, a brain peptide hormone (Scheme 1).[30] A 'double asym-



Scheme 1.

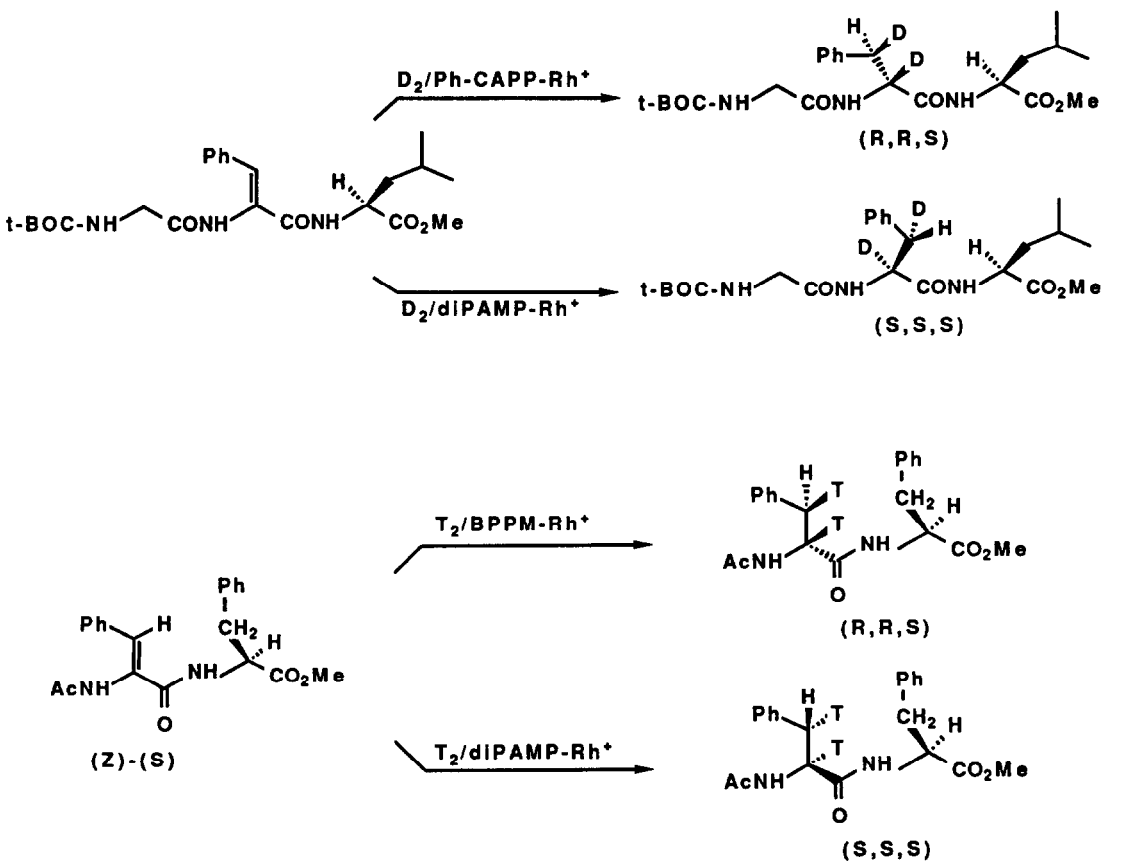
metric hydrogenation' of an enkephalin analogue precursor which has two dehydroamino acid residues in a molecule was also performed with excellent stereoselectivity (eqn. 2).[34] Chiral diphosphinite ligands developed by Yamagishi *et al.* showed excellent stereoselectivities (>98% *de*) in the asymmetric hydrogenation of a dehydrodipeptide although those ligands were not so effective for the reaction of dehydroamino acids.[32]



(2)

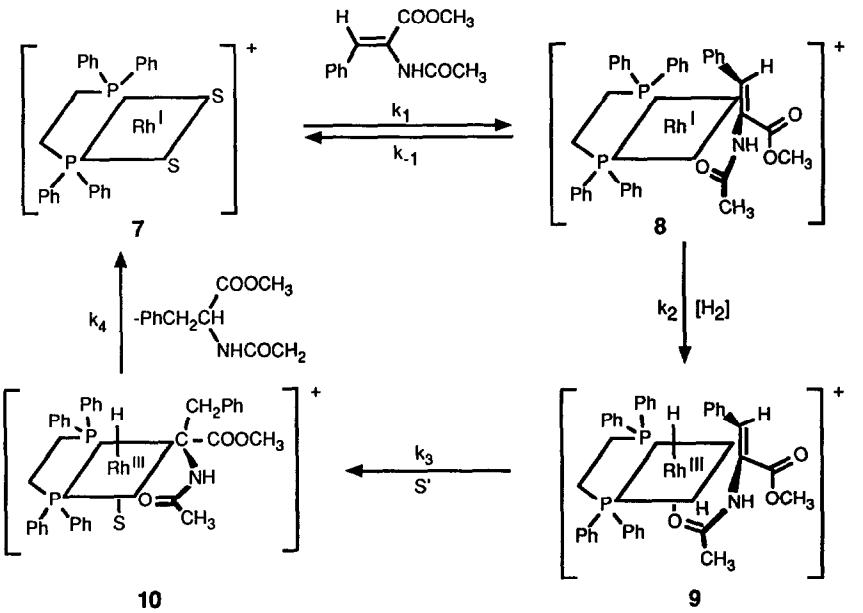
L*=PhCAPP or diPAMP

The method provides an effective and convenient route to labeled peptides for metabolic studies (Scheme 2).[30,31] Typically, Kagan[31] and Ojima[30] and their collaborators use chiral rhodium catalysts ligated with BPPM, PhCAPP, or diPAMP.



Scheme 2.

The mechanism of asymmetric hydrogenation of dehydroamino acids catalyzed by cationic chiral rhodium complexes with *cis*-chelating diphosphine ligands has been revealed in exquisite detail through the work of Halpern and his coworkers.[35] Namely, Halpern *et al.* have disclosed virtually whole key steps of this fascinating and sophisticated reaction on the basis of extensive NMR spectroscopic study, kinetics, and X-ray crystallography of a key intermediate, and explained how such excellent stereoselection is achieved by the chiral catalyst. Scheme 3 shows a basic catalytic



Scheme 3. Mechanism of the $[Rh(diphos)]^+$-catalyzed hydrogenation of MAC.

cycle of a diphosphine–Rh^+ complex (**7**) in the hydrogenation of methyl (*Z*)-2-acetamidocinnamate (MAC), in which the oxidative addition of molecular hydrogen to $[Rh(diphos)(MAC)]^+$ (**8**) is the rate-determining step. In asymmetric hydrogenation, two catalytic cycles giving *S* and *R* products, respectively, are competing, and thus each intermediate complex (**8**–**10**) has a pair of diastereomers, in which the oxidative addition of molecular hydrogen to **8** is the enantioselectivity-determining step as well as the rate-determining step. The most striking discovery by Halpern *et al.* is the fact that the minor intermediate $\mathbf{8}_{[minor]}$ reacts with molecular hydrogen much faster than the major intermediate $\mathbf{8}_{[major]}$ does, to give the predominant enantiomer of product as schematically depicted in Fig. 1 for $[Rh(diPAMP)–(MAC)]^+$ complexes. The 'Halpern's mechanism' can successfully explain unique dependence of enantioselectivity on hydrogen pressure (higher hydrogen pressure decreases stereoselectivity and sometimes reverse enantioselection is observed) and temperature (higher temperature increases stereoselectivity). Namely, higher hydrogen pressure or lower temperature changes the rate-determining step from the oxidative addition of molecular hydrogen to **8** to the olefin complexation to **7**, which favors the predominant formation of less reactive $\mathbf{8}_{[major]}$ and thus lowers stereoselectivity and even causes the reversal of enantioselection, i.e., the major intermediate ($\mathbf{8}_{[major]}$) gives the major enantiomer of product.

James *et al.* have disclosed the mechanism of an interesting catalyst system, $[Rh(DIOP)_2]^+ BF_4^-$, which forms a dihydride intermediate, $[RhH_2(DIOP)_2]^+BF_4^-$. This property makes a sharp contrast to those of usual cationic rhodium complexes bearing only one *cis*-chelating diphosphine to the rhodium in which the 'Halpern's mechanism' is operative. The asymmetric hydrogenation of

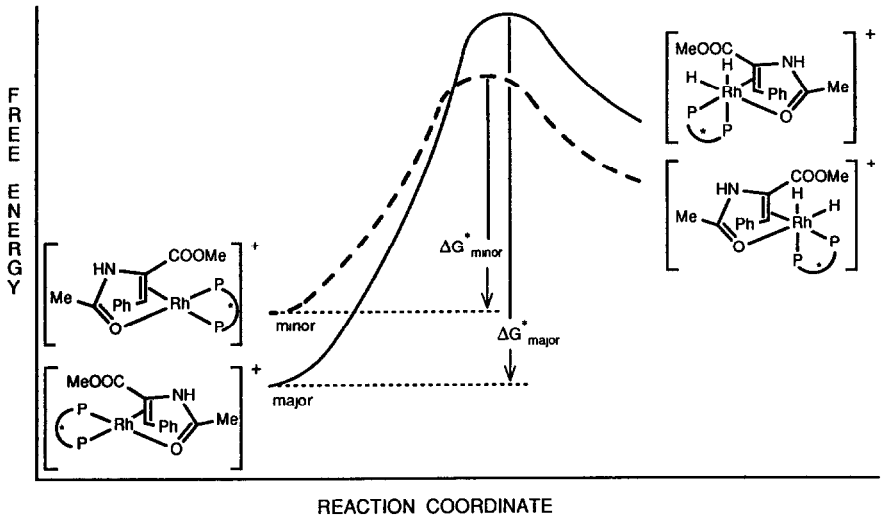
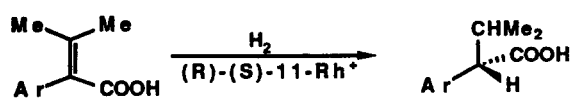


Fig. 1. Schematic reaction coordinate profiles for the enantioselectivity-determining steps of the diastereomeric [Rh(diPAMP)(MAC)]$^+$ catalyst–substrate adducts with molecular hydrogen.

dehydroamino acids catalyzed by this chiral catalyst is considerably slower than the corresponding $[Rh(DIOP)(COD)]^+ClO_4^-$, but the stereoselectivity is substantially higher in some cases. It should be noted that this type of rhodium catalyst, with BINAP ligands, serves as an industrial catalyst for the asymmetric isomerization of terpene allylic amines (see Section 3).

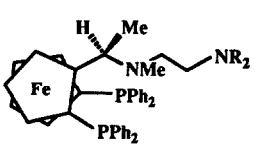
Although extremely high stereoselectivities have been achieved for the asymmetric hydrogenation of dehydro-N-acyl-α-amino acids and their peptides, the scope of this reaction in terms of applicability to a variety of unsaturated substrates is rather limited. Accordingly, more challenging substrates for the reaction are less-functionalized olefins, imines and carbonyl compounds including α,β-unsaturated aldehydes, ketones and esters.

The asymmetric hydrogenation of tetrasubstituted olefins is one of the most difficult tasks for the usual chiral phosphine–rhodium catalysts. However, Hayashi *et al.* have recently succeeded in achieving extremely high enantioselectivity (92–98% *ee*) and reasonably good catalytic activity in the asymmetric hydrogenation of 2-aryl-3-methyl-2-butenoic acids by using rhodium catalysts with chiral (aminoalkyl)ferrocenylphosphines (**11**)[37] (eqn. 3). In a typical run, a substrate : Rh ratio of 200 : 1 at room temperature and 50 atm of hydrogen was used.



(3)

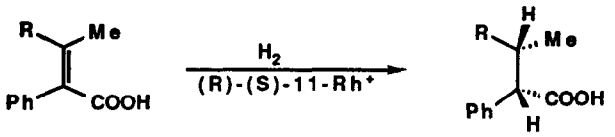
Ar=Ph,4-Cl-C_6H_4,4-MeO-C_6H_4,2-Naphthyl



11

NR_2 = piperidino, dibutylamino, diethylamino, pyrrolidino.

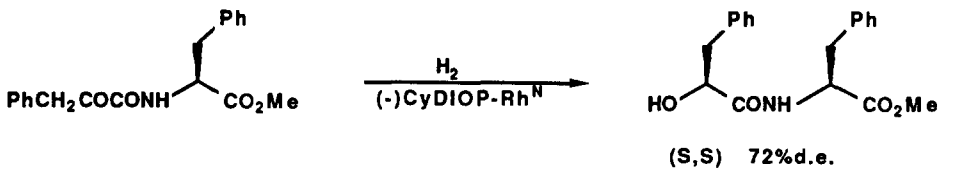
When (*E*)-2-phenyl-3-ethyl-2-butenoic acid and (*E*)-2,3-diphenyl-2-butenoic acid were employed as substrates, the reactions created two chiral centers through the expected *cis* addition of hydrogen giving the corresponding 2-phenyl-3-substituted-butanoic acids with 97.3% *ee* and 92.1% *ee*, respectively (eqn. 4).[37]



R=Et,Ph (4)

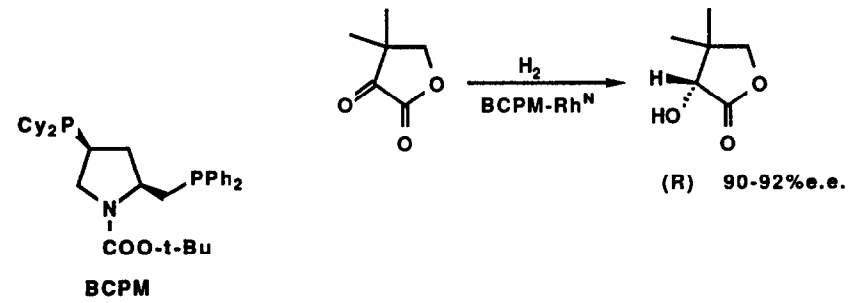
Dang *et al.* carried out the asymmetric hydrogenation of geranial and neral to citronellal, a key intermediate for (−)-menthol (see 'Takasago Process' in Section 3), using a rhodium complex catalyst with 1,2-bis(diphenylphosphinomethyl)cyclobutane (TBPC) as the chiral ligand.[38] The reactions gave 58% *ee* for geranial and 71% *ee* for neral. It should be noted that the synthetic route, neral → citronellal → (−)-menthol, has industrial potential, and thus this approach would be a commercial process in the future provided that an extremely high enantioselectivity is achieved.

An epinephrine synthesis by Hayashi *et al.* (95% *ee*; BPPFOH–Rh^N)[39] and a pantoyl lactone synthesis by Ojima *et al.* (87% *ee*; BPPM–Rh^N)[40] both in the late 1970s, exemplify carbonyl reductions as applied to the asymmetric synthesis of biologically relevant compounds (Rh^N stands for neutral rhodium complex). However, the catalytic activities of the chiral complexes were not high enough to be the basis for commercial processes. Thus, a hydrogen pressure of 20–50 atm and rather long reaction time were necessary to complete the reaction although the stereoselectivity reached a level high enough to consider a commercial synthesis. One approach to improvement of catalyst activity has been demonstrated by Tani *et al.*, who have synthesized CyDIOP, in which all four phenyl groups of DIOP were substituted by cyclohexyl groups, and examined its efficiency as a chiral ligand for a neutral rhodium catalyst in the asymmetric reduction of ketones, keto amides, and keto esters.[41] The reactions catalyzed by CyDIOP–Rh^N proceeded smoothly at ambient temperature and pressure of hydrogen to give the corresponding alcohols, hydroxy amides, and hydroxy esters, e.g., N-benzylmandelamide, 77% *ee*;[41b] pantoyl lactone, 54% *ee*;[42] mandelylphenylalanine methyl ester, 72% *de* (eqn. 5).[43] Tani *et al.* and Yamamoto *et al.*[45] independently developed a convenient method for the conversion of chiral diphosphine ligands such as DIOP and PPM[7] to the corresponding cyclohexyl analogues through the hydrogenation of the phenyl groups over Rh/Al_2O_3 or Ru/C catalyst; a CyCAPP–Rh^N complex prepared by this method gave pantoyl lactone with 66% *ee*.[44]



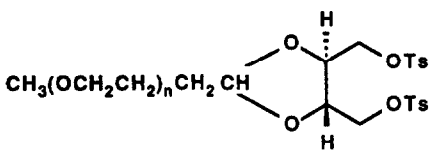
(5)

In a modification of Tani's approach, Achiwa *et al.* developed a new series of pyrrolidinodiphosphines by substituting one of the diphenylphosphine moieties of PPM ligands by a dicyclohexylphosphino group.[46] One of those ligands, BCPM, showed a remarkable increase in reaction rate and a slight increase in enantioselectivity (90–92% *ee*) when it was used as a chiral ligand for a neutral rhodium complex catalyst in the asymmetric hydrogenation of ketopantoyl lactone (eqn. 6); the BCPM–Rh^N catalyst works well even at a substrate : catalyst ratio of 10,000 : 1, giving (*R*)-pantoyl lactone with 90% *ee*.[46b]



(6)

As a new approach to the facile separation of a chiral catalyst after an asymmetric hydrogenation, the development of water-soluble chiral catalysts has been studied, particularly by Shinou *et al.*[47] The water-soluble catalysts were synthesized, for example, by attaching polyether chains to DIOP and Prophos to give ligands **12** and **13**.[47] Sulfonated diphosphine ligands such as **14** and **15**,[48,49] or carboxylic acid and sulfonic acid homologues of PPM such as **16** and **17** were also prepared.[50] Hydrogenations were carried out in water, water–alcohol mixtures or water–organic two-phase solvent systems. In general, the enantioselectivities (10–35% *ee*) achieved by those catalysts in the asymmetric hydrogenation of dehydroamino acids and itaconic acid *in water* were substantially lower than those obtained in alcohols, but the sulfonated diphosphine–rhodium catalyst **15** worked well (72–88% *ee*) in water–organic two-phase solvent systems.[49]



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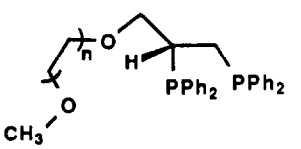

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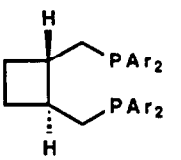

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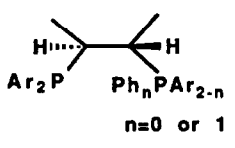

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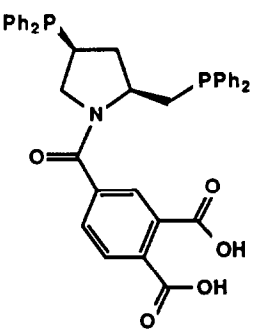

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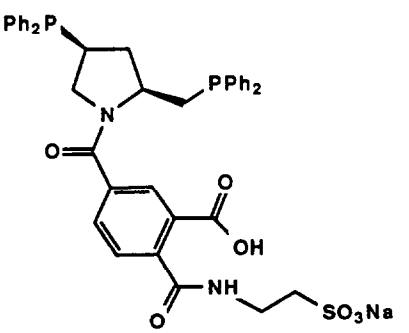

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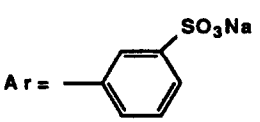
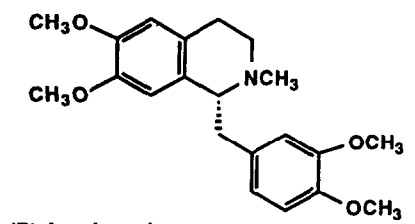


2.2. *Chiral ruthenium catalysts*

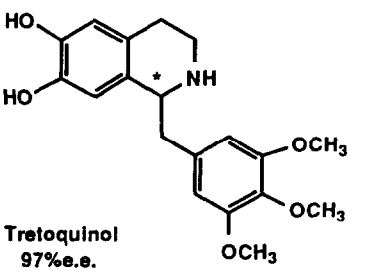
One of the most remarkable advances in asymmetric hydrogenation in the last three years is the development of extremely effective chiral ruthenium(II) catalysts. Chiral Ru(II) catalysts with BINAP as ligand have brought a new era to catalytic asymmetric hydrogenation. It can be said that these BINAP–Ru(II) complexes are the 'second generation chiral catalysts' for asymmetric hydrogenation.

In 1985, Ikariya, Saburi and their coworkers prepared $Ru_2Cl_4[(S)\text{-BINAP}]_2\text{–}(NEt_3)$ (**18**) and used as the catalyst for the asymmetric hydrogenation of dehydro-N-acyl-α-amino acids at 35°C and 2 atm of hydrogen, giving the corresponding N-acyl-α-amino acids with 65–92% *ee*.[51] Similar hydrogenations with itaconic acid and phenylitaconic acid gave the corresponding succinic acids with 88 and 90% *ee*, respectively.[52] The catalyst system was also applied to the asymmetric reduction of 3-substituted glutaric anhydrides to give the corresponding chiral lactones with 33–39% *ee*.[51] However, those results are not surprising since chiral rhodium catalysts had already achieved higher stereoselectivities, especially in the asymmetric hydrogenation of dehydroamino acids (*vide supra*).

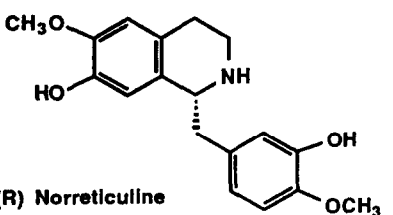
In 1986, Noyori, Takaya, and coworkers synthesized new (*R*)- and (*S*)-BINAP–Ru(II) complexes with carboxylate ligands, $(BINAP)Ru(OCOR)_2$ (**19**). These new chiral Ru complexes brought a breakthrough to the asymmetric hydrogenation of prochiral olefins other than dehydroamino acids and related compounds. First, the $(BINAP)Ru(OAc)_2$ catalyst was used in the asymmetric hydrogenation of isoquinoline alkaloid precursors (eqn. 7).[53] Although the reactions are rather sluggish (>45 h is necessary to complete the reactions), extremely high enantioselectivities (>99.5% *ee*) are achieved for several key-intermediates to isoquinoline alkaloids (Chart 2). The reaction is



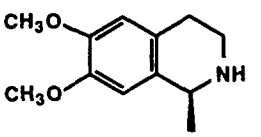
(R) Laudanosine
>99.5%e.e.



Tretoquinol
97%e.e.



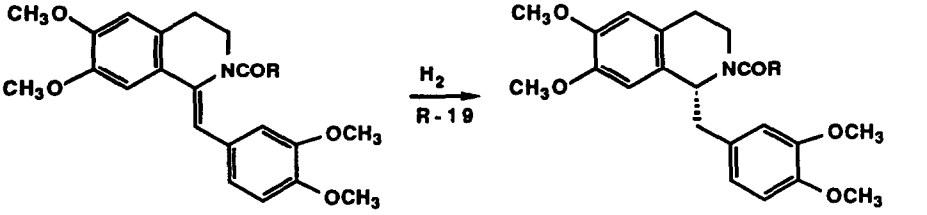
(R) Norreticuline
95%e.e.



(S) Salsolidine
96%e.e.

Chart 2.

very sensitive to the stereochemistry of enamides, viz., only (*Z*)-enamides are hydrogenated while their (*E*)-isomers are recovered intact. It is worthy of note that the asymmetric hydrogenation of these enamides by $BINAP\text{–}Rh^+$ catalysts give only ca. 70% *ee*. The $(BINAP\text{–}Ru)_2(NEt_3)$ (**18**) catalyst which was developed by Ikariya *et al.*[51] is also effective (99% *ee* for **20**).[53]

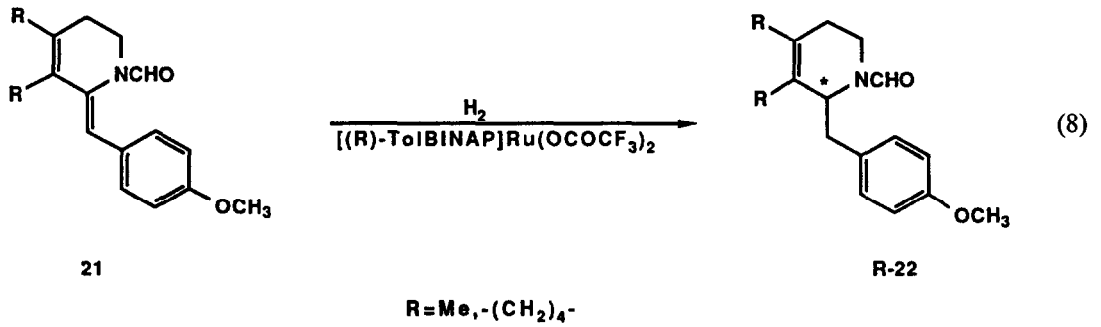


(7)

>99.5%e.e.
R=CH_3,CF_3,CMe_3,C_6H_5,p-BrC_6H_4,H.

Noyori *et al.* further applied this catalytic process to the asymmetric synthesis of benzomorphans and morphinans.[54] Thus, an N-formyl-(*Z*)-enamide **21** (*R* = Me) was submitted to the asymmetric hydrogenation catalyzed by [(*R*)-tolBINAP)]Ru–$(OCOCF_3)_2$ (tolBINAP = $(p\text{-tolyl})_2$P– version of BINAP) at 25°C and 100 atm of hydrogen for 120 h to give the corresponding (*R*)-N-formyltetrahydropyridine derivative *R*-**22** (*R* = Me, 98% *ee*) in 98% yield (eqn. 8). The (*S*)-isomer, *S*-**22** (*R* = Me, 97% *ee*) was also obtained by using (*S*)-tolBINAP–Ru catalyst. The formyl base, (*S*)-**22** (*R*–*R* = $-(CH_2)_4-$), can be converted to dextromethorphan through acid-catalyzed Grewe type cyclization followed by reduction.[54]

The ready availability of both (*R*)- and (*S*)-BINAP opens effective routes to a variety of alkaloid drugs, e.g., (−)-metazocine and (−)-pentazocine, potent nonaddictive narcotic analgesics; dextromethorphan, antitussive agent; levallorphan and oxilorphan, narcotic antagonists; butorphanol, analgesic. It is apparent that this method has high potential to be a commercial process for these pharmaceuticals.

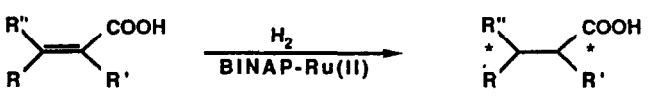


(8)

21 **R-22**

R=Me,-$(CH_2)_4$-

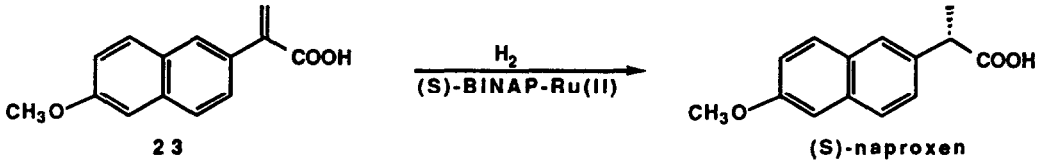
The (BINAP)$Ru(OAc)_2$ catalysts were successfully applied to the asymmetric hydrogenation of substituted acrylic acids **23** which lack an acylamino moiety.[55a] Those compounds are known to be very 'difficult' substrates for chiral rhodium catalysts to attain high enantioselectivities and reaction rates. A variety of substituted acrylic acids **23** are converted to the corresponding saturated carboxylic acids with 83–97% *ee* through asymmetric hydrogenation catalyzed by the BINAP–Ru catalysts (eqn. 9).[55a] Remarkable effects of hydrogen pressure on the enantioselectivity are observed, viz., some substrates require 100–135 atm of hydrogen to achieve excellent selectivity while some others prefer much lower hydrogen pressure (4 atm). This fact implies that these BINAP–*ruthenium* catalyzed reactions do not follow the 'Halpern's mechanism' for the chiral *rhodium* complex-catalyzed reactions of dehydroamino acids (*vide supra*). It is suggested that the *ruthenium* system includes ruthenium hydride species as a key intermediate which reacts with olefin,[55b] in sharp contrast to the *rhodium* system in which the oxidative addition of molecular hydrogen takes place after the formation of the rhodium–olefin complex (see Fig. 1 and Scheme 3). Detailed understanding of the mechanism of the reactions catalyzed by BINAP–Ru complexes must wait further investigation.



(9)

83-97%e.e.

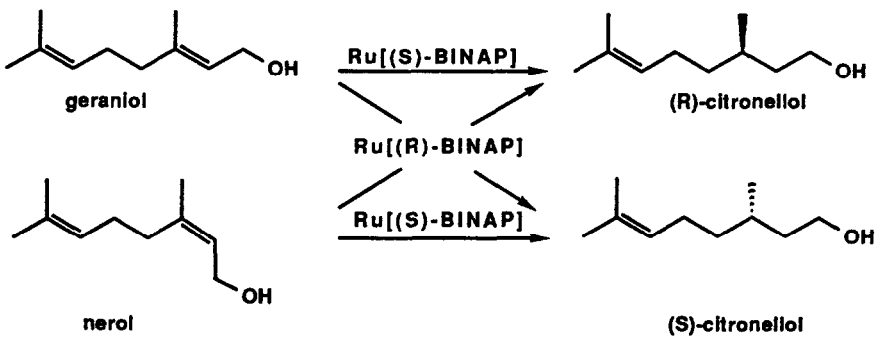
It is noteworthy that (*S*)-naproxen, an effective antiinflammatory drug, with 97% *ee* was obtained in 92% yield through the (*S*)-BINAP–Ru(II)-catalyzed hydrogenation of the α-(methoxynaphthyl)acrylic acid (**24**) at 130 atm of hydrogen for 12 h (eqn. 10).[55a]



23 (S)-naproxen (10)

Takaya, Noyori, and coworkers have also applied the BINAP–Ru(II)-dicarboxylate catalysts to the asymmetric hydrogenation of prochiral allylic and homoallylic alcohols. Thus, geraniol and nerol gave (*R*)- or (*S*)-citronellol, depending on the chiral ligand used; the enantioface differentiation is consistent in that geraniol is converted to (*R*)-citronellol with (*S*)-BINAP–Ru catalyst while nerol is converted to (*S*)-citronellol with the same catalyst (96–99% *ee*) (Scheme 4).[56] The reaction is extremely regioselective in that only the allylic double bonds are reduced while the isolated double bonds remain intact without any isomerization. The chiral catalysts, (BINAP)Ru $(OCOCF_3)_2$ and (tolBINAP)Ru$(OCOCF_3)_2$, are so efficient that the substrate:catalyst ratio of 50,000 : 1 is enough to complete the reaction within 12–14 h at 18–20°C and 30 atm of hydrogen. Moreover, the catalysts can be recovered and reused without appreciable loss of activity. Accordingly, it is apparent that this process fulfills all necessary requirements to be commercialized. It should be added that the BINAP–Rh catalyst systems are much more sluggish and give only 18–58% *ee* for the same reactions.[57]

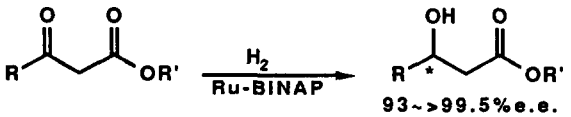
Homogeraniol is converted to homocitronellol with 92% *ee* with (BINAP)Ru$(OAc)_2$, but the two carbon homologue of geraniol is inert under the standard conditions.



Scheme 4.

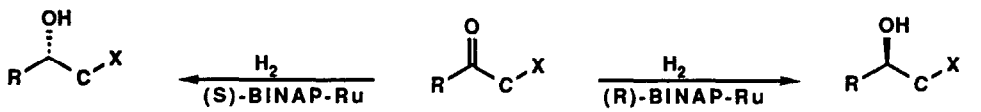
The BINAP–Ru catalyzed process was further applied to the asymmetric synthesis of the side chain of α-tocopherol (vitamin E) in combination with the BINAP–Rh^+-catalyzed asymmetric isomerization of a geranylamine (see Section 3).[56]

Noyori *et al.* have expanded the BINAP–Ru(II)-catalyzed asymmetric hydrogenation process to the reductions of β-keto esters and functionalized ketones.[58,59] Interestingly, it is found that (BINAP)Ru$(OCOR)_2$ complexes (**19**) are inactive for the asymmetric hydrogenation of β-keto esters while '$[(BINAP)RuX_2]_n$' complexes (X = Cl, Br), which are prepared by reacting (BINAP) Ru$(OAc)_2$ with HX (2 equiv.), are very active at 70–100 atm of hydrogen; Ru_2Cl_4 $(BINAP)_2(NEt_3)$ (**18**) is also effective.[58] The reactions give the corresponding (*R*)- and (*S*)-β-hydroxy esters with 93 → 99.5% *ee* (eqn. 11), providing a very practical and powerful method for the synthesis of those useful compounds. This process, because of its cleanness, high enantiomeric purity and the availability of both *R* and *S* enantiomers, may replace the fermentation processes using baker's yeast for the production of chiral β-hydroxy esters.

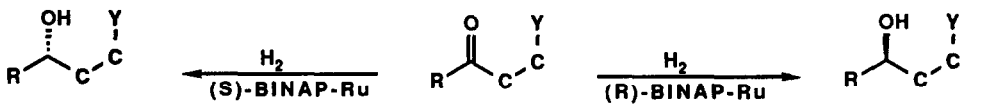


(11)

Both BINAP–Ru–dicarboxylate complexes and $[(BINAP)RuX_2]_n(NEt_3)_m$ ($m = 0, 1$) complexes are excellent catalysts for the asymmetric hydrogenation of functionalized ketones.[59] As shown in eqns 12 and 13, the reaction requires the simultaneous coordination of the carbonyl oxygen and heteroatom, X or Y, to the Ru atom to form a five or six-membered ring chelate to achieve a high degree of stereodifferentiation. It should be noted that halogens are suitable heteroatoms. For example, *o*-bromoacetophenone gives 1-(*o*-bromophenyl)ethanol with 92% *ee* in 97% yield while *m*- and *p*-bromoacetophenones and acetophenone itself are almost inactive (< 1% yields) under the comparable reaction conditions.[59] For a variety of functionalized ketones, the BINAP–Ru catalysts achieve excellent enantioselectivities (92–100% *ee*) at 20–32°C and 50–100 atm of hydrogen. In the asymmetric reduction of 1,3-diketones, Noyori, Takaya *et al.*[59] and Saburi *et al.*[60] independently reported that the catalyst systems showed excellent enantio- as well as diastereoselectivity. These effective asymmetric catalytic reactions will complement asymmetric cross aldol condensation approaches to natural products containing 1,3-diol functionalities.



(12)

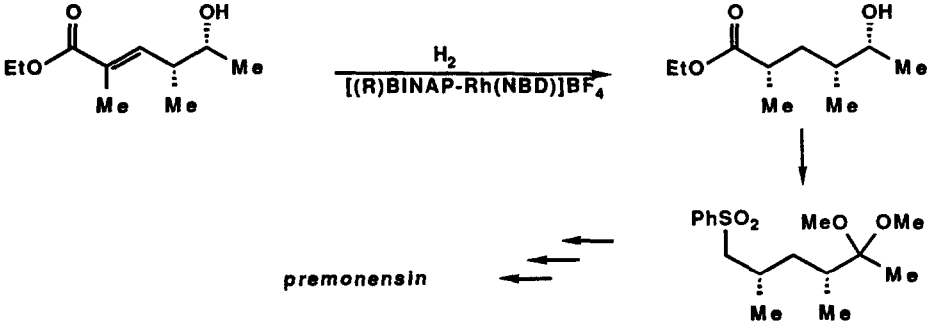


(13)

X=Y=dialkylamino,hydroxyl,alkoxyl,siloxyketo,alkoxycarbonyl, alkylthiocarbonyl,dialkylaminocarbonyl,carboxyl,etc.

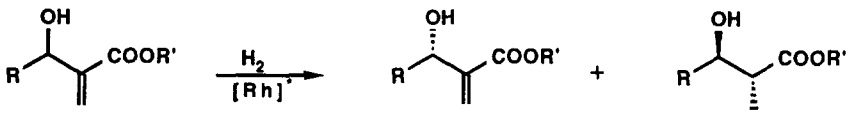
2.3. *Miscellaneous*

'Hydroxy-directed stereochemical control' demonstrated by Brown,[61] Evans,[62] and their co-workers, has expanded the scope of asymmetric hydrogenation. As described above, effective asymmetric hydrogenation had relied on attractive interactions between rhodium metal and carboxyl and/or amide groups of a substrate, typically a dehydro-N-acyl-α-amino acid. Although the 'hydroxy-directed stereochemical control' is applicable only to diastereoselective hydrogenations, it is useful in the asymmetric synthesis of certain natural products containing polyhydroxyl groups (Scheme 5).[63] Brown has discussed the factors affecting the stereochemical control in those double and triple asymmetric inductions.[61c]



Scheme 5.

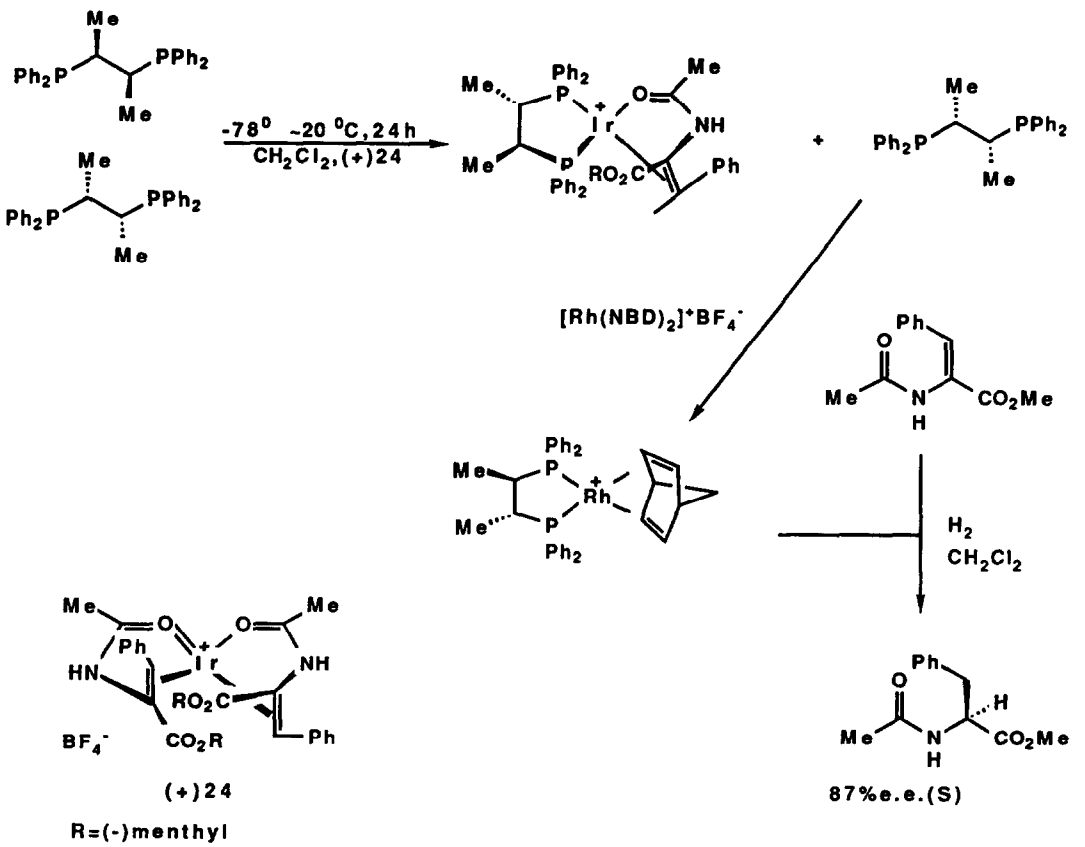
Since it was found[61–63] that diphosphine–rhodium catalysts showed excellent *anti*-selectivity in the asymmetric hydrogenation of α-(hydroxyalkyl)acrylates and other allylic alcohols, an effective kinetic resolution of racemic compounds could, in principle, be performed. That this was in fact the case was demonstrated by Brown and Cutting, who examined the efficiency of chiral rhodium complexes of diPAMP, DIOP, and Chiraphos in this reaction and found that recovered starting acrylates with >90% *ee* were obtained at 70% conversion when diPAMP–Rh^+ catalyst was used (eqn. 14).[64] Quite recently, even better results were obtained by the use of a BINAP–Ru catalyst.



(14)

R=Me,Ph,Furyl
R'=Et,Me,COOMe

Noyori, Takaya and their coworkers carried out a series of asymmetric hydrogenations of racemic allylic alcohols catalyzed by (BINAP)Ru(OAc)$_2$. For cyclic allylic alcohols such as 2-cyclohexenol ($k_{fast}/k_{slow} = 62$), 3-methyl-2-cyclohexenol ($k_f/k_s = 76$), and 4-hydroxy-2-cyclopentenone ($k_f/k_s = 11$), enantiomeric purities of >95% for the unreacted substrates were achieved at 52%, 51%, and 68% conversions, respectively.[65] It is remarkable that a linear allylic alcohol, 1-octene-3-ol, with 95% *ee* was obtained at 64% conversion ($k_f/k_s = 11$). α-(α-Hydroxyethyl)acrylate with

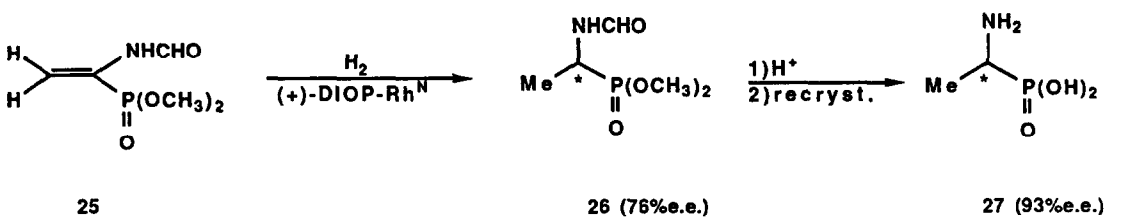


Scheme 6.

>99% *ee* was obtained at 76% conversion ($k_f/k_s = 16$) and 97% *ee* at 63% conversion.[65] It should be noted that (*R*)-4-hydroxy-2-cyclopentenone is an important building block for prostaglandin syntheses.[66]

Alcock *et al.* have described "substrate-induced kinetic resolution of racemic diphosphines *in situ* for homogeneous catalysis".[67] They isolated enantiomerically pure cationic iridium complexes (**24**) with two (−)-menthyl (*Z*)-2-acetamidocinnamate ligands by fractional recrystallization. When the chiral Ir complex, (+)-**24**, is mixed with racemic Chiraphos (2 equiv.) at −78 → 20°C for 24 h in CH_2Cl_2, (*S,S*)-Chiraphos selectively complexes with the Ir complex and leaves (*R,R*)-Chiraphos, which is difficult to obtain by other methods, uncomplexed in solution. Then, $[Rh(NBD)_2]^+BF_4^-$ (0.8 equiv.) is added to the solution, followed by methyl (*Z*)-2-acetamidocinnamate (MAC) (50–100 equiv.). The asymmetric hydrogenation is carried out at ambient temperature and hydrogen pressure to give the corresponding (*S*)-amino acid with 87% *ee* (Scheme 6). An experiment under identical conditions using (−)-**24** gave (*R*)-amino acid with 89.5% *ee*. A control experiment using authentic (*S,S*)-Chiraphos-Rh^+ catalyst gave the (*R*)-amino acid with 90% *ee*. In the reaction system, both the chiral Ir complex with (*S,S*)-Chiraphos and the chiral Rh complex with (*R,R*)-Chiraphos co-exist. However, the chiral Ir complex is virtually inert for the asymmetric hydrogenation, and thus, the reaction is catalyzed solely by the chiral Rh complex. This method will be very useful for the evaluation of chiral ligands whose racemates are easily synthesized and the optical resolution of which through conventional methods is not straightforward.

α-Aminophosphonic acids, as analogues of α-amino acids, have high potential as unique modifiers of biologically active peptides. Schöllkopf *et al.* applied the asymmetric hydrogenation catalyzed by chiral rhodium complexes to the synthesis of (*S*)-(1-aminoethyl)phosphonic acid (**27**). The hydrogenation of N-[1-(dimethoxyphosphoryl)ethenyl]formamide (**25**) with a (+)-DIOP–Rh^N catalyst gave N-[1-(dimethoxyphosphoryl)ethyl]formamide (**26**) with 76% *ee*. This compound was hydrolyzed and crystallized to afford **27** with 93% *ee* (eqn. 15).[68]



25 **26 (76%e.e.)** **27 (93%e.e.)**

(15)

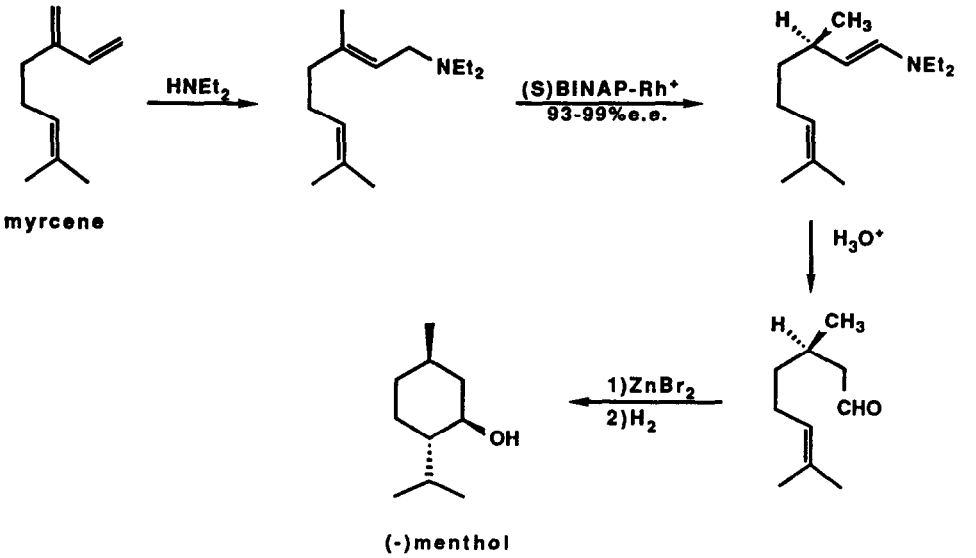
Asymmetric reductions of ketones through transfer hydrogenation have been studied by using chiral Rh, Ir, and Ru catalysts. Although the Ru catalyst, $RuCl_2(DIOP)_3$ gave low stereodifferentiating ability (<10% *ee*),[69] the Rh and Ir catalysts gave relatively good enantioselectivities for this type of reaction, viz., 58% *ee* for 1-phenylethanol with Chiraphos–Rh^+;[70] 66% *ee* for 1-phenyl-propanol with Prophos–Ir^+;[70] 63% *ee* for 1-phenylethanol with AMSO–Rh^N (AMSO = N-acetylmethionine sulfoxide);[71] 75% *ee* for 1-(*p*-tolyl)ethanol with AMSO–Rh^N;[71] 71% *ee* for 1-phenylpropanol with AMSO–Rh^N.[71]

Takeuchi and Ohgo synthesized N,N′-dimethyl-5-benzylhydantoin with 79.1% *ee* through the asymmetric hydrogenation of N,N-dimethyl-5-benzylidenehydantoin catalyzed by a Co(DMG)–PPh_3–chiral amine complex (DMG = dimethylglyoximato).[72]

Attempted asymmetric hydrogenations of tiglic esters with chiral Co, Ni, and Ru catalysts with DIOP, of isophorone with a NMDPP-Co catalyst (NMDPP = neomenthyldiphenylphosphine),[73a] and of α,β-unsaturated ketones with $HRuCl(TBPC)_2$ and $H_2Ru(TBPC)_2$ catalysts[73b,c] (TBPC; *vide supra*) gave only modest stereoselectivities.

3. ASYMMETRIC ISOMERIZATION

One of the most significant advances in the application of chiral catalysis is the 'Takasago Process' (Scheme 7) for the commercial synthesis of (−)-menthol from myrcene. The key step in

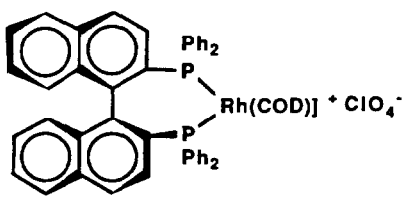


Scheme 7.

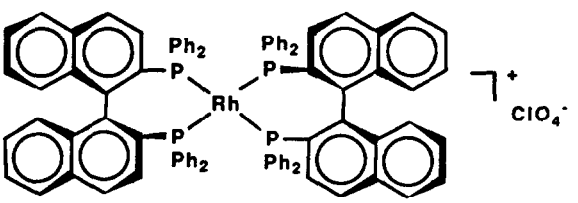
this process is the asymmetric isomerization. The 'Takasago Process' now provides a significant portion of the annual world production of (−)-menthol.

This remarkable process was developed initially by laboratories at two universities and later in collaboration with a process research laboratory at Takasago Perfumery Corp. Initial work by Otsuka, Tani, Akutagawa, and their collaborators using cobalt catalysts with chiral phosphine ligands, gave < 30% *ee* in the asymmetric isomerization of allylamines.[74] However, the combination of a cationic rhodium complex with BINAP, a chiral ligand developed by Noyori, Takaya, and their collaborators,[75] gave rise to the breakthrough to this reaction. Specifically, the BINAP–Rh^+ catalyst achieved 93–99% enantioselectivity in the asymmetric isomerization of geranylamine to the corresponding enamine and the enamine thus obtained was hydrolyzed to citronellol, which was then converted to (−)-menthol through a Lewis acid—catalyzed cyclization followed by hydrogenation (Scheme 7).

It was later found that $[Rh(BINAP)_2]^+ClO_4^-$ is an excellent catalyst for this reaction, which can complete the reaction with a substrate : catalyst ratio of 8,000 : 1 at 80–100°C within several hours, giving the product with 99% *ee*.[76] Moreover, this catalyst is recyclable, and thus is used in the commercial process.

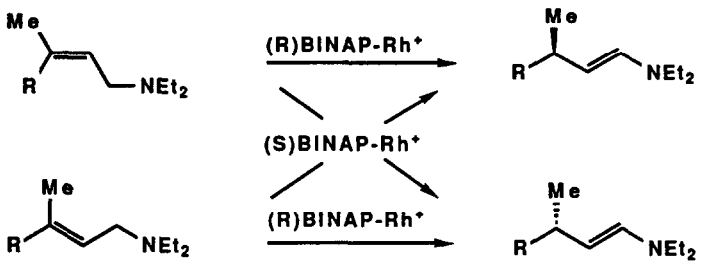


(S)-BINAP-Rh^+



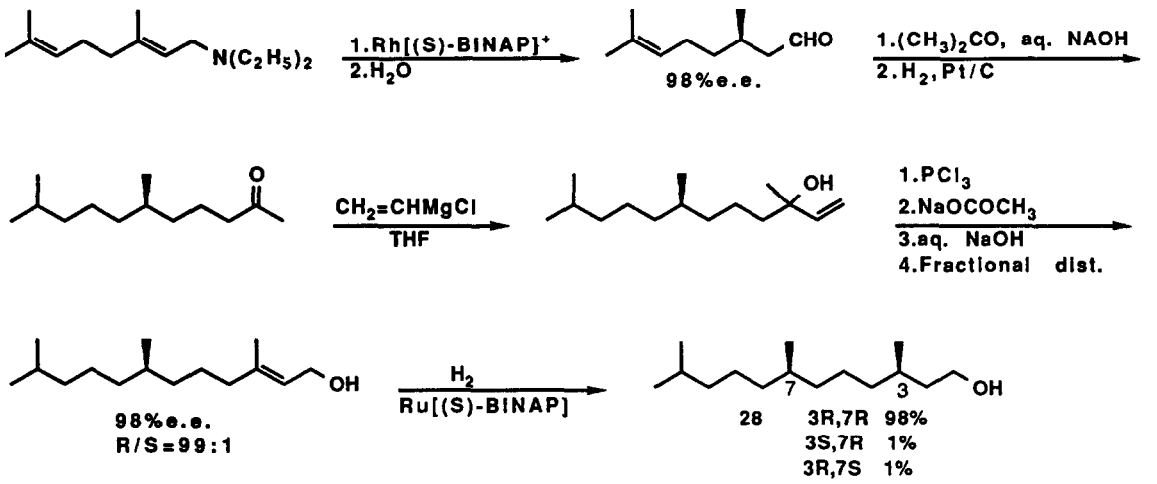
[(S)-BINAP]$_2$$Rh^+$

The mechanism of the reaction was studied in detail and the experiments with deuterium labeled substrates showed that it proceeds with exclusive suprafacial 1,3-hydride shift. As a result, the reaction is extremely stereospecific (Scheme 8).



Scheme 8.

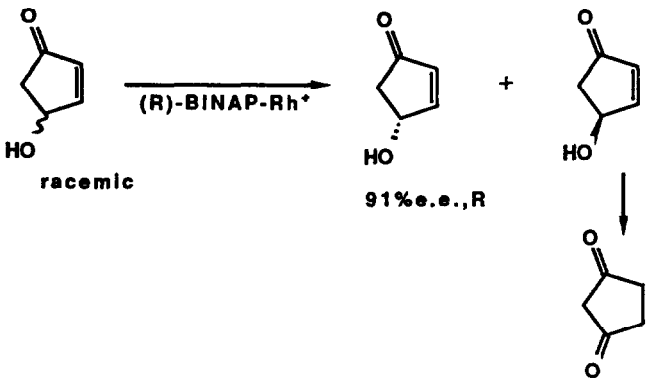
This isomerization method was applied successfully to the asymmetric synthesis of the side chain of α-tocopherol (Vitamin E) by Takabe *et al.*[77] Another efficient synthesis of α-tocopherol was reported in which the BINAP–Ru catalyzed asymmetric hydrogenation (*vide supra*) was combined with the BINAP–Rh^+—catalyzed asymmetric isomerization of a geranylamine: (3*R*,7*R*)-3,7,11-trimethyldodecanol (**28**) (98% *ee* and 96% *de*) was obtained in high overall yield (Scheme 9).[56]



Scheme 9.

In sharp contrast to the extremely successful development in the reaction using allylic amines as substrates, no significant advances are observed for other substrates. The direct conversion of geraniol or nerol to citronellal does not give satisfactorily high enantioselectivity and the chemical yield of the reaction is also low because of side reactions.[78] A chiral nickel complex-catalyzed reaction of 1,2-divinylcyclobutane gives 4-vinylcyclohexene with 22% *ee*.[79] Other reported reactions cannot attain even 5% *ee*. It seems that there is plenty of room for further development of the asymmetric isomerization.

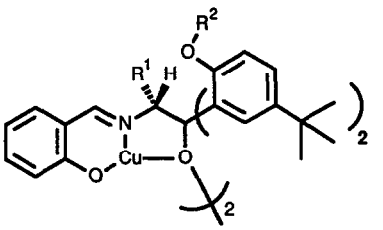
One modest success has been achieved in the use of the BINAP–Rh^+ catalyst for kinetic resolution of (±)-4-hydroxycyclopent-2-en-1-one (eqn. 16). The k_{fast}/k_{slow} ratio is 5 at 0°C in THF. The reaction using (*R*)-BINAP gives (*R*)-hydroxycyclopentenone with 91% *ee* at 72% conversion.



(16)

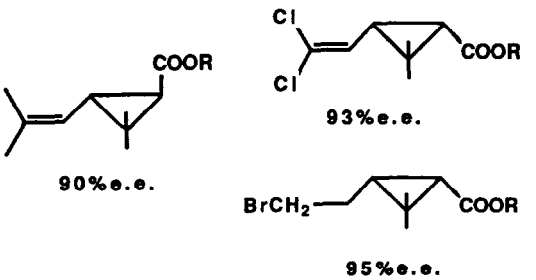
4. ASYMMETRIC CYCLOPROPANATION

Asymmetric cyclopropanation has been extensively studied by Aratani and his collaborators at Sumitomo Chemical Industry in connection with the development of a practical synthesis of chrysanthemic acid and its derivatives. Among numbers of chiral ligands examined, it was found that a copper complex with an iminodiol prepared by the condensation of salicylaldehyde with a chiral amino alcohol (**29a**) is an extremely effective catalyst for the reactions of diazoacetates with

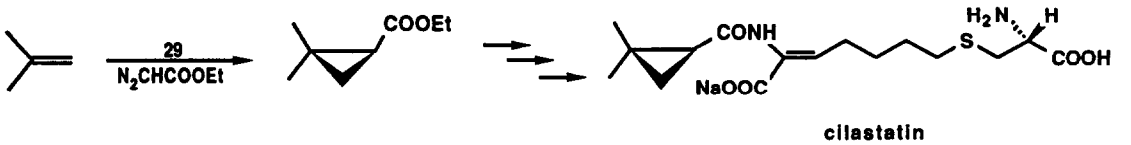


29a (R^1= Me; R^2= n-C_8H_{17})
29b (R^1= $PhCH_2$, R^2= n-C_4H_9)

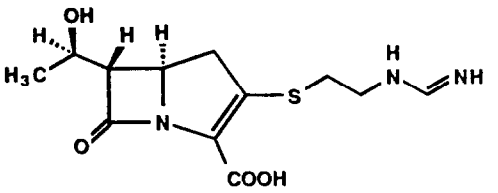
prochiral dienes and olefins. For instance, chrysanthemic acid (*trans*, 90% *ee*), dichlorovinylchrysanthemic acid (*cis*, 93% *ee*), and bromoethylcyclopropanecarboxylic acid (*cis*, 95% *ee*) have been synthesized in this manner.[80a]



The chiral copper complex (**29b**)-catalyzed reaction gives excellent results (92% *ee*) in the asymmetric synthesis of methyl (+)-(1*S*)-2,2-dimethylcyclopropanecarboxylate from 2-methylpropene and ethyl diazoacetate. The dimethylcyclopropanecarboxylic acid is an important intermediate in the commercial synthesis of Merck Sharp & Dohme's cilastatin, an enzyme inhibitor used in combination with the β-lactam antibiotics, imipenem (eqn. 17).[80b,c] In 1986, Aratani's 'Sumitomo Process' was commercialized.



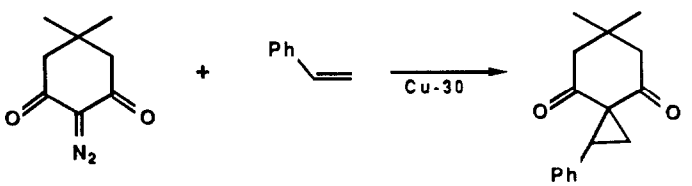
cilastatin



Imipenem

(17)

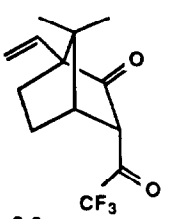
Matlin *et al.* achieved 100% *ee* (NMR) in the asymmetric cyclopropanation of styrene with diazodimedone using, as the catalyst, a chiral copper complex bearing 10-methylene-facamH (**30**)[81] (facamH = 3-trifluoroacetyl-(+)-camphor). The catalyst system, when immobilized on silica gel (**31**), gives the product with 98.3% *ee*, which does not decrease after three cycles.[81] In spite of the fact that Matlin *et al.* used a rather unique diazoalkane, diazodimedone, these examples of catalysis by **30** and **31** clearly indicate the high potential of asymmetric cyclopropanation as a powerful synthetic method in both laboratory and industrial organic syntheses (eqn. 18).



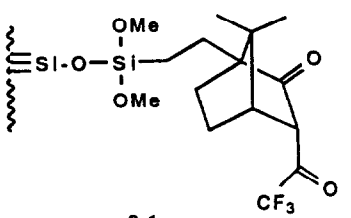
100%e.e.

(18)

In addition to these remarkably successful examples cited above, an application of the method to the synthesis of photostable pyrethroid insecticides (24–38% *ee*)[82] and reactions of ethyl diazoacetate with 1,1-diphenylethene using copper complexes with 37 new Aratani-type chiral salicyladimines as ligands (up to 65% *ee*)[83] have been described.



30



31

To date, asymmetric cyclopropanations other than the chiral copper complex-catalyzed ones have not been reported. However, diastereoselective asymmetric cyclopropanations of styrene with a chiral diazoalkane, (4*R*,5*S*)-1-(diazoacetyl)-4-methyl-5-phenyloxazolidinone, catalyzed by $Rh_2(OAc)_2$ (14% *ee*);[84] of a chiral oxazoline with diazomethane catalyzed by $Pd(OAc)_2$ followed by hydrolysis giving 2-phenylcyclopropanecarboxaldehyde (≥90% *ee*);[85] of styrene with a chiral iron–carbene complex (*trans*, 90% *ee*; *cis* 84–86% *ee*);[86] and of a chiral π-bis(dimethylfumarate)–Co complex with dibromomethane followed by hydrolysis giving *trans*-1,2-cyclopropanedicarboxylic acid (71% *ee*)[87] have been reported.

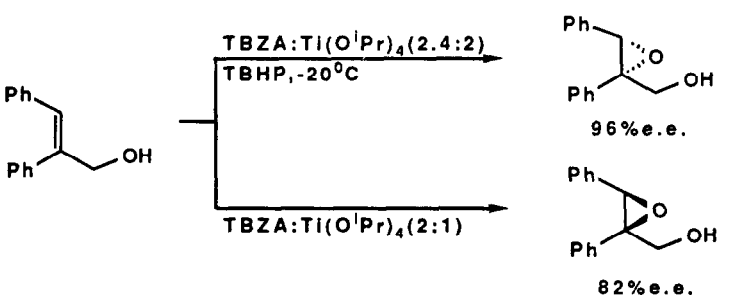
5. ASYMMETRIC OXIDATION

The asymmetric epoxidation of allylic alcohols using chiral tartrate–Ti complexes as promoter, the 'Sharpless Oxidation', has had a significant impact on synthetic organic chemistry.[88] Several excellent reviews have been published on this reaction. The reviews by Sharpless[89] and Katsuki[90] describe the reaction in general; Sharpless *et al.* discuss the mechanistic aspects of the reaction;[91] and Masamune reviewed its application to organic syntheses.[92] Although the tartrate–Ti complexes are used as 'reagent' in most cases, recent work has shown that catalytic amounts of the complexes can promote asymmetric epoxidation under the proper conditions.[67,74] This catalytic version of the 'Sharpless Oxidation' has recently been applied to the commercial production of glycidol by the Arco Chemical Co. Quite recently Sharpless *et al.* have developed a new and efficient asymmetric dihydroxylation of olefins catalyzed by osmium tetroxide–cinchona alkaloid combinations.[94] This may be another breakthrough in non-enzymic catalytic asymmetric oxidations. Accordingly, this section deals with newer aspects of the 'Sharpless Oxidation', the asymmetric oxidation of simple olefins and sulfides, and the asymmetric dihydroxylation of olefins catalyzed by transition metal complexes.

5.1. *Asymmetric epoxidation*

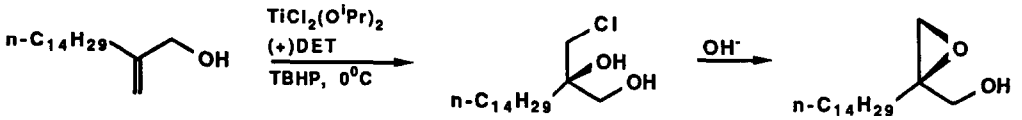
Regarding the efforts to make the 'Sharpless Oxidation' catalytic, Sharpless *et al.* found that the addition of molecular sieves (3 Å or 4 Å) to the reaction system enabled the standard DET/$Ti(O^iPr)_4$ complex system to work as catalyst (5–10 mol%). This finding served as the basis of the Arco's commercial process for glycidol. This catalytic procedure gives a high degree of stereoselectivity (90–95% *ee*) with reaction rates comparable to those of the stoichiometric system;[93] the observed stereoselectivity is, however, 2–3% *ee* lower, in general, than that for the stoichiometric reaction.

It was found that the use of tartaric N,N-dibenzylamide (TBZA) instead of diethyl tartrate (DET) with $Ti(O^iPr)_4$ gave a high degree of asymmetric induction with the same enantioface differentiation as DET *at a TBZA/Ti ratio of 1.2* while *at a TBZA/Ti ratio of 0.5* the reaction showed opposite enantioface differentiation with somewhat lower but still high enantioselectivity (eqn. 19).[95] These results indicate the existence of two dinuclear complexes depending upon the TBZA/Ti ratios. It was found that the dinuclear complex with the TBZA/Ti ratio of 2 can serve as a catalyst (≥2.5 mol%) maintaining a high degree of asymmetric induction (≈80% *ee*).[95]



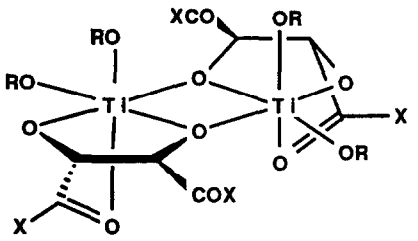
(19)

The use of $TiCl_2(O^iPr)_2$ (DET/Ti = 1) instead of $Ti(O^iPr)_4$ gave a chlorodiol, which was converted to the corresponding chiral oxirane by treatment with a base (eqn. 20). Enantioface differentiation in this system was opposite to that in the standard DET–$Ti(O^iPr)_4$ system; the same result was obtained at a DET/Ti ratio of 0.5.[95] On the other hand, the reversal of enantioface differentiation was not observed when $Ti(O^iPr)_4$ (DET/Ti = 0.5) was used.[95] Those results imply the complexities of the DET–Ti systems.

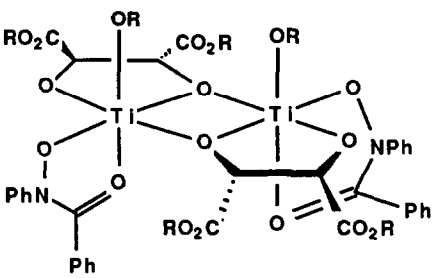


(20)

Sharpless, Lippard, and coworkers succeeded in the X-ray crystallographic analysis of dinuclear complexes, **32** (TBZA/Ti = 1) and **33**, which were prepared from $Ti(OEt)_4$, DET, and PhCON(OH)Ph.[96] The results gave a new insight into the mechanism of the 'Sharpless Oxidation' contradicting the previously-proposed mononuclear catalyst model, and thus, Sharpless proposed dinuclear catalyst models based on the X-ray analysis results.



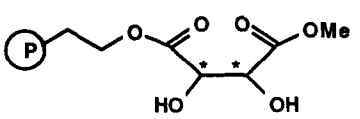
32
R= Pr^i
X= $NHCH_2Ph$



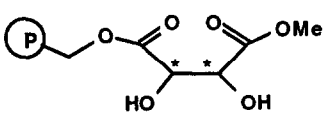
33
R= Et

The attempted asymmetric epoxidation of homoallylic alcohols promoted by the tartrate–Ti complex reagents resulted in marginal enantioselectivities and moderate chemical yields.[97] It is interesting to note that the enantioface differentiation is opposite to that for allylic alcohols. Ikegami *et al.* found that the TBZA/$Zr(O^iPr)_4$ gave better enantioselectivities ($\leqslant$77% *ee*) for the reaction of homoallylic alcohols although the chemical yields remained low.[98]

Farrall *et al.* synthesized two polymer-anchored tartrate–Ti complexes by connecting one of the ester moieties of dimethyl tartrate to polystyrene resin.[99] Polymer A and Polymer B gave 64–66% *ee* and 49% *ee*, respectively, in the asymmetric epoxidation of geraniol (the DET–Ti system gives 95% *ee*). Attempted recycling of the reagent resulted in a substantial decrease of enantioselectivity after three cycles.



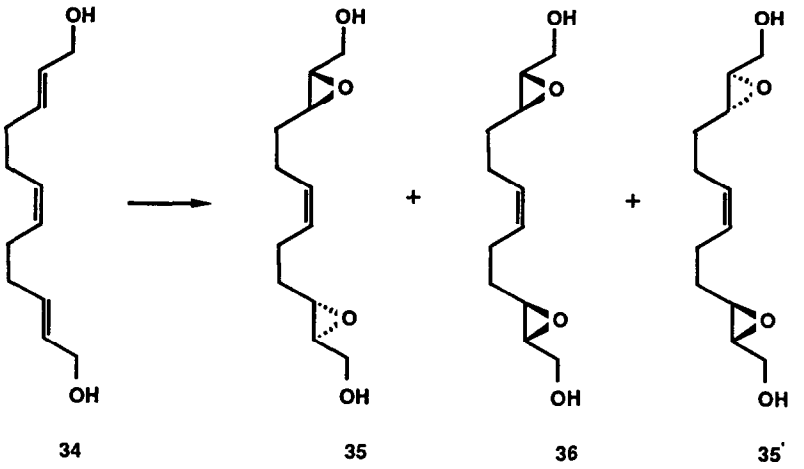
Polymer A



Polymer B

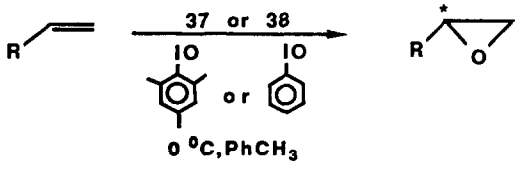
Numerous applications of the 'Sharpless Oxidation' have been reported.[90,92] In general, the coverage of those examples is beyond the scope of this review. However, a 'double Sharpless oxidation' demonstrated by Hoye *et al.* is noteworthy as a new methodology (eqn. 21).[100] In the

asymmetric epoxidation of the trienol **34**, yielding the corresponding diepoxides, it is reasonable to assume that each single epoxidation proceeds with at least 90% *ee*, since much higher enantioselectivities are achieved for simple allylic alcohols. The reaction gives three diepoxides, **35**, **35′**, and **36**; **35** and **35′** are enantiomers and **36** is a *meso* isomer. A simple calculation provides, at 90% *ee*, a ratio of **35**:**36**:**35′** being 361:38:1. Thus, the enantiomeric purity of **35** should be 99.45%. Although precise experimental data are not reported, NMR analyses support this prediction. This is a clever approach to obtaining extremely high stereoselectivity by exploiting C_{2v} and C_s symmetries of the molecule. Hoye *et al.* plan to use the diepoxydiol (**35**) for the synthesis of uvaricin.



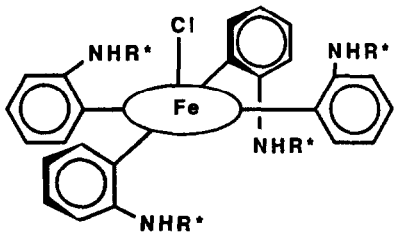
(21)

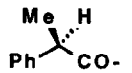
As the 'Sharpless Oxidation' is limited to allylic alcohols, it would be very beneficial if complementary methods were available to achieve a high degree of asymmetric induction in the epoxidation of simple prochiral olefins. As an approach to this challenging problem, asymmetric epoxidation catalyzed by chiral porphyrin–Fe complexes shows promise. Groves *et al.* synthesized catalytic iron–tetraphenylporphyrin (TPP) complexes (**37**, **38**) bearing chiral amides by the reaction of α,β,α,β-tetrakis(*o*-aminophenyl)porphyrin with chiral carboxylic acids, and carried out the asymmetric epoxidation of styrenes using PhIO or 2,4,6-$Me_3C_6H_2IO$ as oxidant (eqn. 22).[101] The reaction catalyzed by Fe(α,β,α,β-Hyd)PPCl (**37**) gave styrene oxide with 31% *ee*. The reactions using FeT(α,β,α,β-BINAP)PPCl (**38**) gave styrene oxide with 48% *ee*, *p*-chlorostyrene oxide with 51% *ee*, and 1-octene oxide with 20% *ee*.

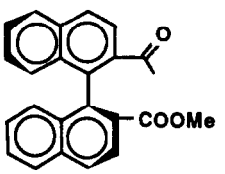


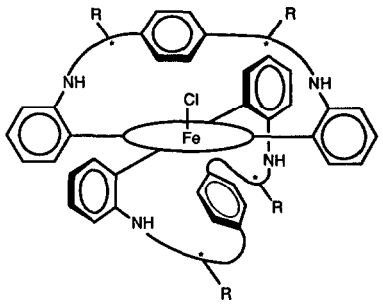
(22)

Mansuy *et al.* prepared a chiral 'Picket Porphyrin'–Fe complex bearing phenylalanyl groups, similar to the Groves' chiral Fe–TPP complex (**37**), and carried out the asymmetric epoxidation of styrene.[102] However, the enantiomeric purity of styrene oxide obtained was only 21% *ee*. Thus, Mansuy *et al.* synthesized the more complex 'Basket Handle Porphyrin'–Fe complex (**39**), which gave *p*-chlorostyrene oxide with 50% *ee*.[102]



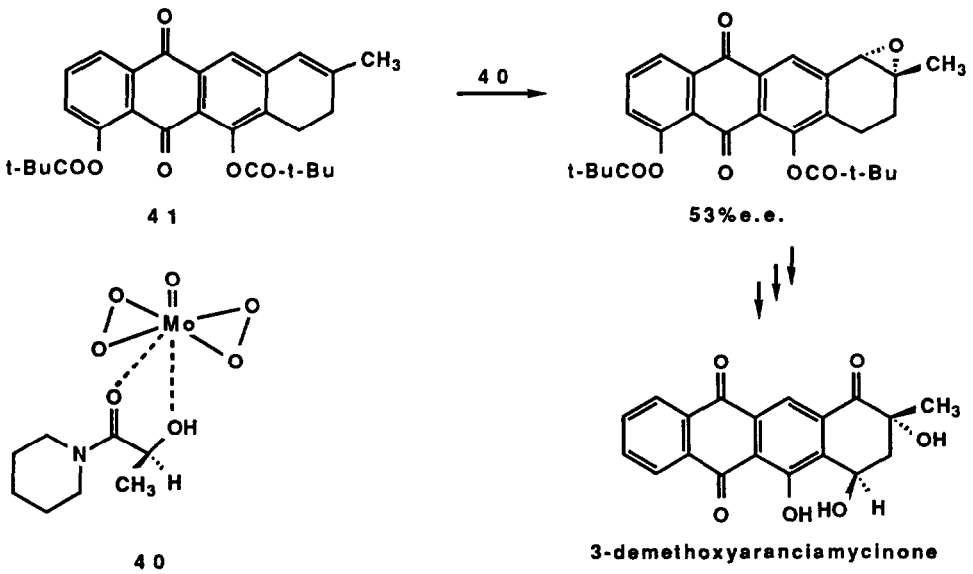
37: R* = 

38: R* = 



39

Another approach, demonstrated by Krohn *et al.*, used the chiral oxodiperoxo–Mo complex (**40**) in the asymmetric epoxidation of the olefin **41**, a key-step for the synthesis of 3-demethoxyaranciamycinone (eqn. 23).[103]



41 53%e.e. (23)

40 3-demethoxyaranciamycinone

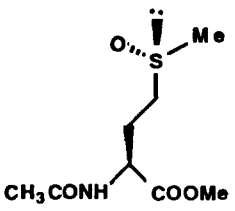
Sinigalia *et al.* synthesized a series of CF_3–platinum(II) complexes with chiral diphosphines such as Chiraphos and Prophos, and used them as catalysts for the asymmetric oxidation of 1-alkenes with hydrogen peroxide.[104] The best result (41% *ee*) was obtained with 1-octene and $[(Chiraphos)Pt(CF_3)(CH_2Cl_2)]^+BF_4^-$ as the chiral catalyst.

5.2. *Asymmetric oxidation of sulfides*

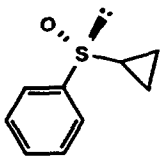
The asymmetric oxidation of unsymmetrical sulfides promoted by DET–Ti complexes has recently been demonstrated.[105–107] Since chiral sulfoxides are important intermediates in asymmetric synthesis, the development of an efficient synthetic method has significant meaning.

According to reports by Kagan *et al.*,[105] the attempted asymmetric oxidation of methyl *p*-

tolyl sulfide under the standard 'Sharpless Oxidation' condition (DET/Ti/TBHP = 1/1/2) gave the corresponding sulfoxide in racemic form. However, use of modified conditions (DET/Ti/TBHP = 2/1/2) dramatically improved the enantioselectivity of the reaction (⩽70% *ee*). Moreover, the addition of one equivalent of water to the DET/Ti/TBHP (2/1/2) system further increased the selectivity to 93% *ee*. Another modified condition (DET/Ti/TBHP = 3/1/2) without water gave 82% *ee* in the same reaction. The reaction is sensitive to the steric bulk of substituents. For example, the enantioselectivity decreases in the order Me (93% *ee*) > Et (75% *ee*) > ^{i}Pr (63% *ee*) > ^{n}Bu (20% *ee*) > $PhCH_2$ (7% *ee*) when *p*-MeC_6H_4–*S*–*R* was employed as the substrate. Dialkyl sulfides gave somewhat lower enantioselectivities, e.g., CH_3–S(O)–C_8H_{17}-*n*, 71% *ee*; CH_3–S(O)–Bu^t, 53% *ee*. The dependence of enantioselectivity on the reaction temperature was studied in detail by using *p*-MeC_6H_4–S–Me as the substrate; it was found that the highest selectivity was obtained at −21°C (95% *ee*), indicating the existence of two competing mechanisms. Kagan suggested that the addition of water may accelerate the formation of an oxo-bridged dimer which is supposed to be the active catalyst.[105] Based on the ρ value (−1.02) obtained from a Hammett plot for the reactions at temperatures between +40 and −20°C, it was concluded that the reaction involves an electrophilic attack of an oxidant to the sulfur atom of sulfide. Kagan also has demonstrated wide applicability of this asymmetric oxidation since a variety of functional groups are tolerant of the reaction conditions.[106] Of note are the reactions of methionine to methionine oxide, proceeding with 92% enantioselectivity, and the reaction of cyclopropyl methyl sulfide, giving the corresponding sulfoxide with 95% *ee*.[105c,106]



92%d.e.

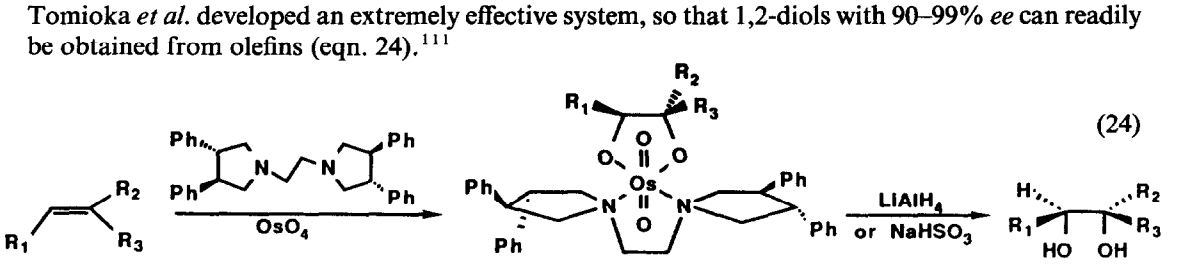


95%e.e.

Independently, Di Furia *et al.* have reported the asymmetric oxidation of sulfides, using DET–Ti, DET–Mo, and DET–V complexes as reagents.[107] This group used another modified condition, i.e., DET/Ti/TBHP = 4/1/2, and obtained *p*-MeC_6H_4–S(O)–Me with 88.3% *ee*; DET–Mo and DET–V complexes gave only 3.5–22.3% *ee* for the same sulfide. Nakajima *et al.* examined several oxovanadium(IV) complexes with chiral salen-type Schiff bases as catalysts for the reaction, using organic hydroperoxides as oxidants.[108] The enantioselectivities so far attained are modest (20–40% *ee*).

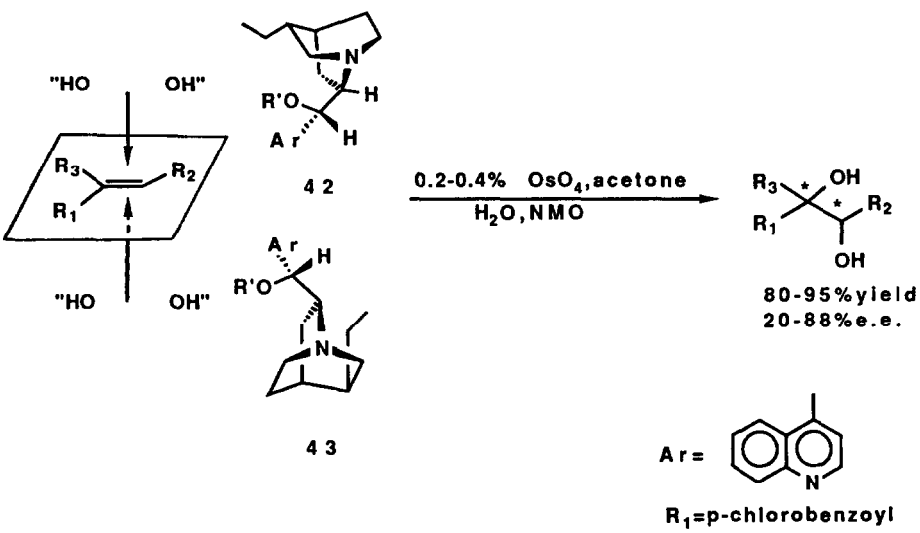
5.3. *Asymmetric dihydroxylation*

The synthesis of 1,2-diols through the cis vicinal dihydroxylation of olefins with osmium tetroxide (osmylation) is a standard method in organic synthesis. The stoichiometric asymmetric osmylation of olefins using chiral amine ligands was first reported by Hentges and Sharpless in 1980,[109] and since then this asymmetric reaction has been studied by several groups.[110] Recently, Tomioka *et al.* developed an extremely effective system, so that 1,2-diols with 90–99% *ee* can readily be obtained from olefins (eqn. 24).[111]



(24)

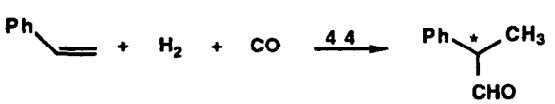
This reaction would be much more useful if it were *catalytic*, since osmium tetroxide is both toxic and expensive. Kokubo *et al.* reported the first catalytic asymmetric osmylation by using bovine serum albumin (BSA)–2-phenylpropane-1,2-diolatodioxo-osmium(IV) complex as the catalyst.[112] The reaction of α-methylstyrene realized a good enantioselectivity (68% *ee*, 40 turnovers), but the selectivities were low (6–18% *ee*) for other olefins such as styrene, β-methylstyrene, and 1-octene. Quite recently, Sharpless *et al.* succeeded in developing an effective catalytic asymmetric osmylation based on their finding of a remarkable 'ligand-accelerated catalysis' in osmium tetroxide–cinchona alkaloid systems using N-methylmorphorine N-oxide as the primary oxidant (Scheme 10).[94] Since dihydroquinidine *p*-chlorobenzoate (**42**) and dihydroquinine *p*-chlorobenzoate (**43**) are 'pseudoenantiomeric', both (*R*,*R*)- (or *R*) and (*S*,*S*)- (or *S*)-1,2-diols can be obtained by changing the cinchona alkaloid ligands. In a typical reaction, a substrate : OsO_4 ratio of 250–500 : 1 is used. However, in a large scale run, a ratio of 50,000 : 1 worked perfectly well. It was also shown that solid osmium trichloride can be used in place of the volatile osmium tetroxide. Although the enantioselectivities attained so far are not uniformly high, further development leading to better chiral amine ligands and optimization of reaction conditions may well bring about excellent stereoselectivities for a wide variety of olefins. This catalytic asymmetric reaction has a high potential as a commercial process.



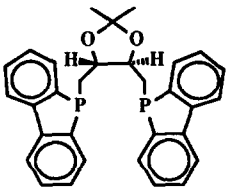
Scheme 10

6. ASYMMETRIC HYDROCARBONYLATION

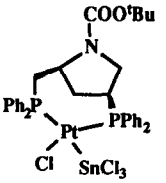
In spite of extensive studies on the asymmetric hydroformylation and hydroesterification of olefins using chiral rhodium and palladium complexes, the best enantioselectivity did not exceed 60% *ee* until Pittman *et al.* reported in 1982 that the asymmetric hydroformylation of styrene catalyzed by $PtCl_2$(DBP–DIOP)–$SnCl_2$ (**44**) achieved 95% *ee* at 50°C and 218 atm (H_2/CO = 2.4) based on the reported maximum specific rotation of 2-phenylpropanal at that time.[113] Although the value was corrected to 73% *ee* in 1983 by Pino *et al.*[114] the result inspired significant further study of the reaction. Pittman's Pt catalyst gave 79.8% *ee* at 314 atm (H_2/CO = 2.9) in the same reaction (eqn. 25).



(25)

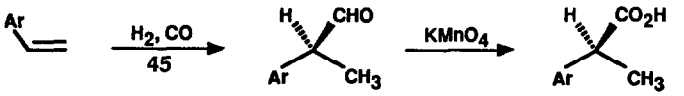


DBP-DIOP



45

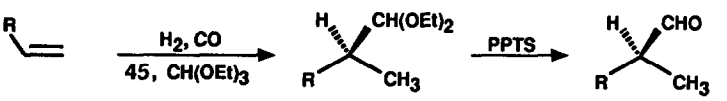
Parrinello and Stille have recently demonstrated that $PtCl_2$(BPPM)–$SnCl_2$ (**45**) is an excellent catalyst for the asymmetric hydroformylation of a variety of olefins.[115] For example, this catalyst system gives 70–80% *ee* for styrene, 80% *ee* for *p*-isobutylstyrene, 77% *ee* for 2-vinylnaphthalene, 81% *ee* for 2-ethenyl-6-methoxynaphthalene, 78% *ee* for 4-(2-thienylcarbonyl)styrene, 82% *ee* for vinyl acetate, 73% *ee* for N-vinylphthalimide, 60% *ee* for methyl methacrylate, and 60% *ee* for norbornene at 60°C and 160–185 atm ($CO/H_2 = 1$) in benzene. Although the branch/normal ratio is low (0.5–0.7) in those cases, the enantioselectivities achieved are considerably higher in some cases than those realized by any other chiral catalyst systems. The chiral aldehydes obtained are oxidized to the corresponding 2-arylpropanoic acids, some of which are anti-inflammatory drugs (eqn. 26).



(26)

Ar= 4-isobutylphenyl, 2-naphthyl, 6-MeO-naphthyl, 4-(2-thienylcarbonyl)phenyl

It is possible to assume that one of the difficulties in achieving high enantioselectivity in the asymmetric hydroformylation is the propensity of the chiral aldehydes to racemize under the reaction conditions. Actually, racemization has been observed in some cases. Accordingly, if the chiral aldehyde can be converted to a much less labile derivative *in situ*, higher enantioselectivity might be anticipated. In fact, Stille *et al.* have succeeded in obtaining the diethylacetals of chiral aldehydes with >96% *ee* by carrying out the reaction in triethyl orthoformate under reaction conditions virtually the same as those for simple hydroformylation in benzene, as described above.[116] The reactions in triethyl orthoformate are considerably slower than those in benzene, but enantioselectivities are excellent (eqn. 27). The acetals thus formed are easily converted to the corresponding aldehydes with pyridinium *p*-toluenesulfonate (PPTS) in acetone without racemization. These results provide a prospect of further development in the asymmetric hydroformylation.

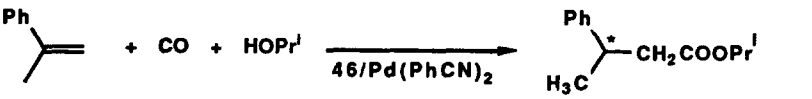


(27)

R= (a) Ph, >96% e.e., b/n= 0.5; (b) 6-MeO-Naph, >96% e.e., b/n= 0.7

(c) Phthalamido, >96% e.e., b/n= 0.5; (d) AcO, >98% e.e., b/n= 1.5

Hayashi *et al.* carried out the asymmetric hydroesterification of 1-methylstyrene using palladium complexes with DBP–DIOP and DBP-1,2-*trans*-diphenylphosphinomethylcyclobutane (**46**) as chiral ligands. The product obtained had a 52.8% *ee*, although the chemical yield was low (eqn. 28).[116]



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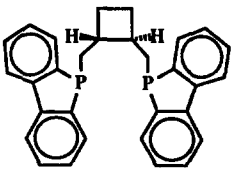
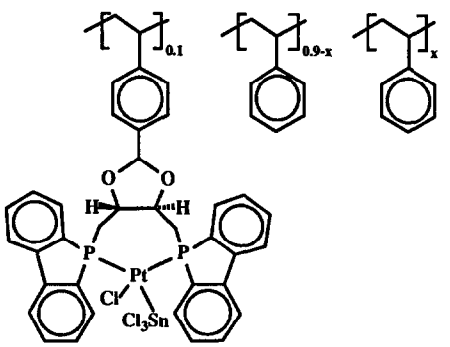


46

These authors also proposed a mechanism for asymmetric induction based on an X-ray crystallographic analysis of the corresponding DBP–DIOP–Ir complex.[117]

Papers by Consiglio and Pino and their coworkers[118] discuss the detailed mechanism of asymmetric induction in hydroformylation using possible stereochemical models and propose that the asymmetric induction arises before or in the process of the formation of diastereomeric alkyl–metal complex intermediates. However, because of the complexity of catalytic cycle, it seems difficult to elucidate the full details of the mechanism.

An important development in asymmetric hydroformylation has been the preparation of polymer-anchored chiral catalysts. In this field, studies performed by Stille and coworkers are representative.[119] For example, a polymer-anchored Pt catalyst prepared by mixing $PtCl_2$, $SnCl_2$ and a copolymer bearing DBP–DIOP as pendant group (**47**), gives 2-phenylpropanal with 65% *ee* in the asymmetric hydroformylation of styrene.[119b] Stille also reported that a chiral Pt catalyst anchored on cross-linked beads bearing PPM as pendant group (**48**) catalyzed the hydroformylation of styrene in the presence of triethyl orthoformate to give virtually the same enantioselectivity (>98% *ee*) as that attained by the homogeneous catalyst, although the reaction rate was considerably lower.[115]



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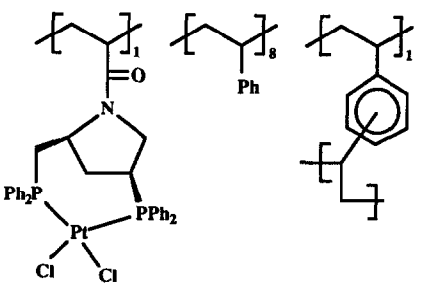
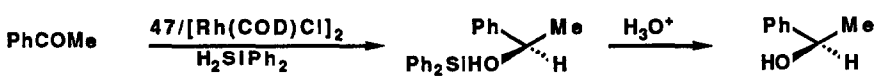


48

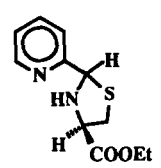
7. ASYMMETRIC HYDROSILYLATION

After a stereoselectivity of 85–86% *ee* was achieved in the asymmetric reduction of α-keto esters through asymmetric hydrosilylation catalyzed by chiral rhodium complexes with (+)- and (−)DIOP as ligands in the 1970s,[120] no eye-catching advance had been observed until Brunner and coworkers reported that a rhodium complex with the new chiral thiazoline ligand (**49**) realized 97.6% *ee* in the asymmetric hydrosilylation of acetophenone with diphenysilane (eqn. 29).[121] The number of new

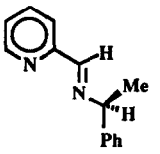


(29)

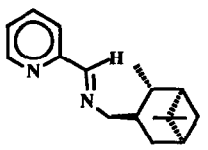
non-phosphine-based chiral ligands reported from Brunner's laboratory has exceeded 100. Typical examples are shown in Chart 3: the values in parentheses are the stereoselectivities observed in the asymmetric reduction of acetophenone.



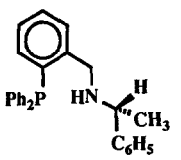
49[120] (97.6% e.e., R)



50[122] (57.3% e.e., R)



51[122] (78.8% e.e., S)

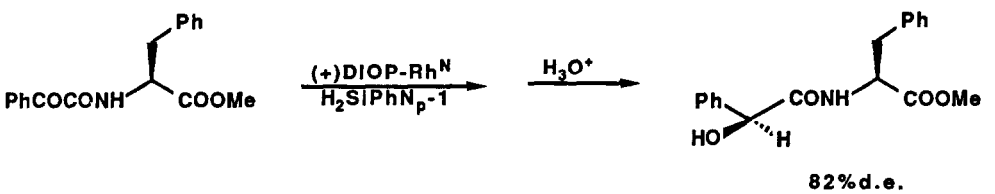


52[123] (52.7% e.e., S)

Chart 3

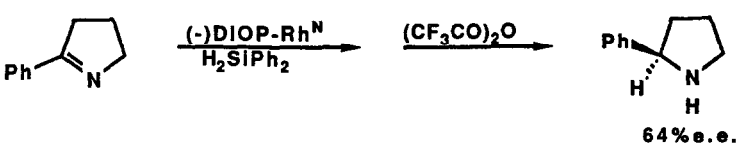
These new ligands show weaker coordination ability to rhodium(I) than phosphine ligands. Thus, the use of a large excess of these new ligands relative to the rhodium(I) complex, $[Rh(COD)Cl]_2$ is necessary to obtain high enantioselectivity.

Asymmetric reductions via hydrosilylation catalyzed by chiral phosphine–Rh complexes, have been key-steps in the syntheses of a chiral building block of depsipeptides (82% *ee*) (eqn. 30)[31a] and a chiral pyrrolidine (64% *ee*) (eqn. 31).[124]



82%d.e.

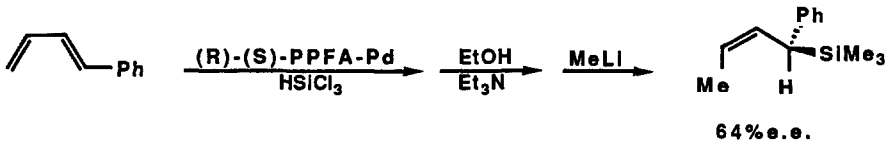
(30)



64%e.e.

(31)

The asymmetric hydrosilylation of carbon–carbon double bonds with a high degree of stereoselectivity is still a much more demanding task than that of carbon–hetero atom double bonds. The highest enantiomeric excess reported to date for the asymmetric hydrosilylation of olefins was 53% *ee*, which was obtained in the reaction of norbornene catalyzed by a PPFA–Pd complex (**53**, *vide infra*).[125] The asymmetric hydrosilylation of cyclopentadiene and 1,3-cyclohexadiene catalyzed by PPFA–Pd complexes gave the corresponding cyclic allylsilanes with only 22–25% *ee*.[126] Better results (31–64% *ee*) were obtained in the reactions of 1-aryl-1,3-butadienes with the same PPFA–Pd catalyst (eqn. 32).[126] Although the stereoselectivity was not particularly good, this asymmetric synthesis had value since the stereochemistry of the reactions of allylsilanes was clarified by using the chiral allylsilanes thus obtained.



(32)

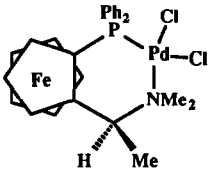
8. ASYMMETRIC CARBON–CARBON BOND FORMING REACTIONS

8.1. *Asymmetric cross Grignard coupling*

Asymmetric cross Grignard coupling reactions were extensively studied by Hayashi, Kumada, and coworkers.[127] Hayashi *et al.* developed two types of chiral catalysts: chiral ferrocenylphosphines[127b] and chiral aminophosphines.[128] Although the highest enantioselectivity attained in the asymmetric coupling of 1-phenylethylmagnesium chloride with vinyl bromide catalyzed by a PPFA–nickel(II) complex was 68% *ee*,[129] much higher selectivities, 85–86% *ee*, were achieved by using a PPFA–palladium(II) complex (**53**) and alkylzinc reagents, Ar(Me)CH–ZnX, instead of the corresponding Grignard reagents (eqn. 33).[130]

(33)

Hayashi *et al.* developed a new series of aminophosphines (**54**) derived from α-amino acids, which are especially effective for the asymmetric Grignard coupling reactions.[128] For example, a nickel(II) complex with Valphos (**54a**, $R = Pr^i$) gave the stereoselectivity of more than 80% *ee* in the reactions of 1-arylethylmagnesium chlorides with vinyl bromide. When *t*-Leuphos (**54b**, $R = Bu^t$)



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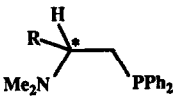
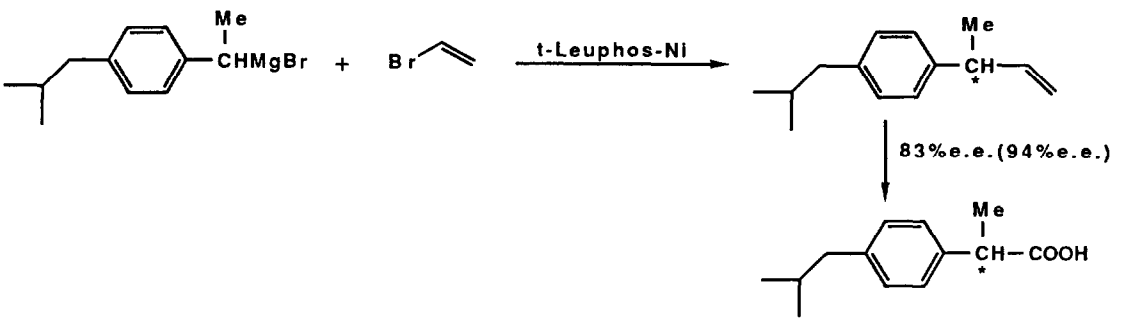


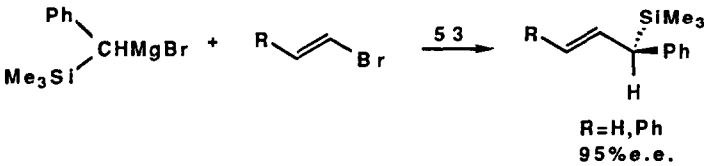
54

was used for the same reaction (Ar = phenyl), 3-(4-isobutylphenyl)-1-butene with 83% *ee* was obtained (eqn. 34): the enantiomeric excess, corrected by the enantiomeric purity of *t*-Leuphos was 94%, which was the highest enantioselectivity ever reported for this type of asymmetric coupling reaction.[128] The chiral 3-aryl-1-butenes thus obtained were converted to antiinflammatory drugs, Ibuprofen (83% *ee*) and its biphenyl analogue (82% *ee*).



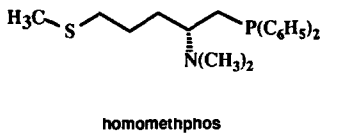
Ibuprofen (34)

The asymmetric cross Grignard coupling reaction catalyzed by PPFA–Pd (**53**) was successfully applied to the synthesis of chiral allylsilanes.[131] Thus, the reactions of phenyl(trimethylsilyl)methylmagnesium bromide with vinyl bromide and 2-bromostyrene gave the corresponding allylsilanes with 95% *ee* (eqn. 35). The enantiomerically enriched allylsilanes thus obtained were used for the asymmetric synthesis of homoallylic alcohols (>85% *ee*) through the reaction with aldehydes as promoted by titanium tetrachloride.[131] This asymmetric coupling reaction was also applied to the reaction of phenyl(trimethylsilyl)methylmagnesium bromide with 1-bromo-2-phenylacetylene and the product, a chiral propargylsilane (18% *ee*), was used for the asymmetric synthesis of chiral allenes.[132]

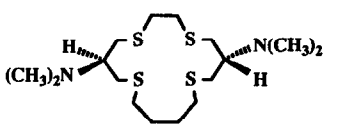


(35)

Kellogg *et al.* designed and synthesized a series of new chiral aminophosphine ligands, having tethers bearing sulfide or amine functionality that were derived from α-amino acids such as cysteine, methionine, penicillamine, lysine, and homomethionine. These chiral ligands were used with nickel catalysts in the asymmetric Grignard cross coupling of 1-phenylethylmagnesium bromide with vinyl bromide.[133] It was found that the chiral ligand derived from homomethionine (homomethphos) gave the best result (88% *ee*).[133a] Kellogg *et al.* also synthesized various chiral macrocyclic tetrasulfide and diaminodisulfide ligands for the reaction, but the best result was only 46% *ee* with the chiral tetrasulfide ligand (**55**).[134]



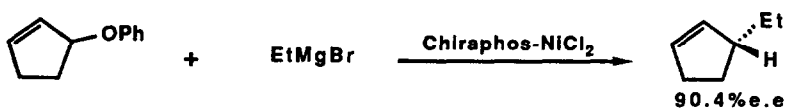
homomethphos



55

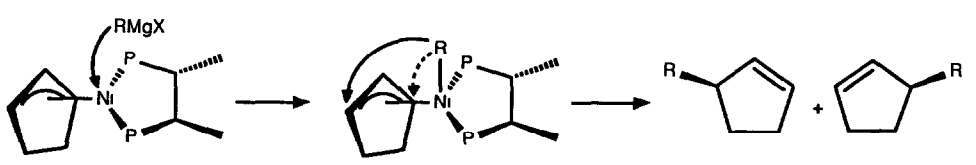
8.2. *Asymmetric allylic alkylation*

Consiglio *et al.* investigated couplings in systems that consisted of a Grignard reagent, an *allylic ether, alcohol, thioether or phosphate*, and a chiral nickel complex.[135] The reaction of ethylmagnesium bromide with 3-phenoxycyclopentene, catalyzed by Chiraphos–$NiCl_2$, gave 3-ethylcyclopentene with 90.4% *ee* (eqn. 36).[135b] A similar reaction with 3-phenoxycyclohexene was originally reported[135a] to give 3-ethylcyclohexene with 97.7% *ee*, but later the value was corrected[135b] to be 51.2% *ee*.



(36)

It is reasonable to assume that the reaction proceeds via π-allyl-Ni complexes, **56** and **57** (eqn. 37). This reaction can be interpreted as the asymmetric alkylation of a chiral π-allyl-Ni complex (**56**), and thus a catalytic 'asymmetric allylic alkylation'.

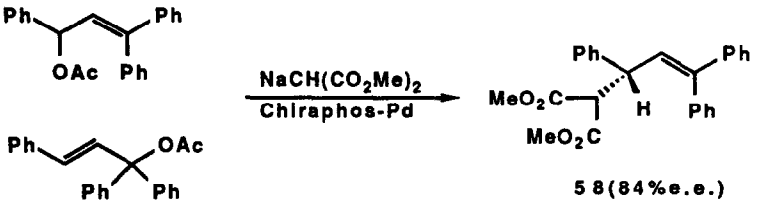


56 57 major minor

(37)

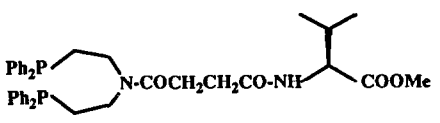
Hiyama and Wakasa independently reported the asymmetric coupling of arylmagnesium bromides with allylic acetates, carbonates or ethers catalyzed by Chiraphos–$NiCl_2$ or Chiraphos–$Ni(PPh_3)_4$, giving the corresponding allylic arylation products with 30–89% *ee*.[136] When 6-methoxy-2-naphthylmagnesium bromide was used, the coupling product was oxidized to naproxen (64% *ee*), an antiinflammatory drug.[136]

Bosnich *et al.* reported an effective asymmetric allylic alkylation of allylic acetates with sodium malonate catalyzed by a Chiraphos–Pd complex, which gave the corresponding allylmalonate (**58**) with 84% *ee* (eqn. 38).[137]



(38)

It has been shown[127] that nucleophilic attack of a Grignard reagent (a hard nucleophile) takes place on the Pd metal of a chiral π-allyl–Pd complex and transfers an alkyl moiety from the Pd metal, whereas a stable carbanion (a soft nucleophile) attacks the π-allyl moiety directly from the outside of the chiral π-allyl–Pd complex. Accordingly, it is apparent that a chiral ligand located on the opposite side of the π-allylic moiety has only a limited effect on the stereodifferentiation for the attack of stable carbanions, which means that some 'remote control' is necessary to realize a high degree of asymmetric induction. Hayashi *et al.* designed a new diphosphine ligand (**59**) bearing a 'chiral arm' and used it as the chiral ligand for the asymmetric allylation of 2-acetylcyclohexanone, giving the coupling product (**60**) with 52% *ee*.[138] It should be noted that the same reaction promoted by DIOP–Pd and Prophos–Pd catalysts, which do not have the 'chiral arm', gave **60** with only 2% *ee* and 11% *ee*, respectively.



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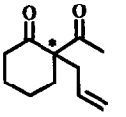
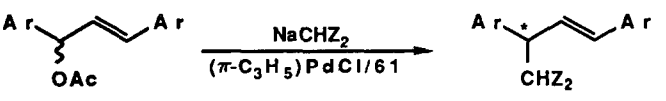


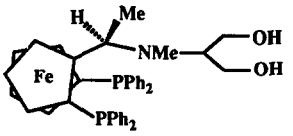
60

Based on this success, Hayashi *et al.* designed a series of new chiral ferrocenyldiphosphines bearing hydroxyl tethers.[139] Of the new chiral ferrocenyldiphosphines, a palladium complex with the ligand **61** worked best, giving 90–92% *ee* for the reactions of 1,3-diaryl-3-acetoxypropenes (racemic) with sodium acetylacetonate (eqn. 39). Nayashi *et al.* proposed a crucial interaction between the hydroxyl group of the chiral ligand and the incoming nucleophile (**62**).

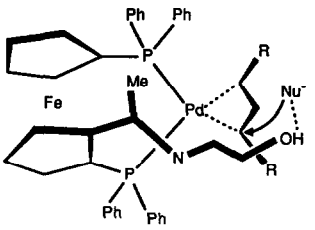


(39)

Ar=Ph,1-Np
CHZ_2=$CH(COMe)_2$,CH(COMe)COPh,CH(COMe)COOMe,$CH(COOMe)_2$

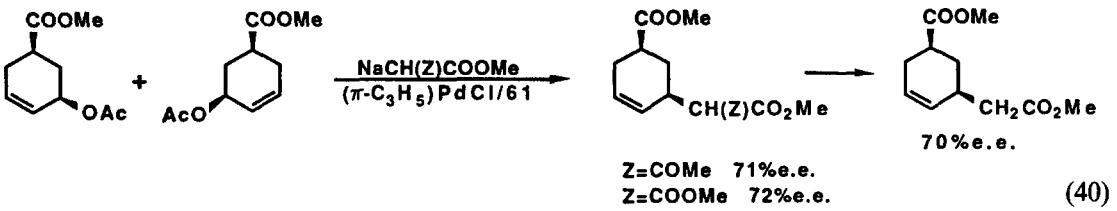


61



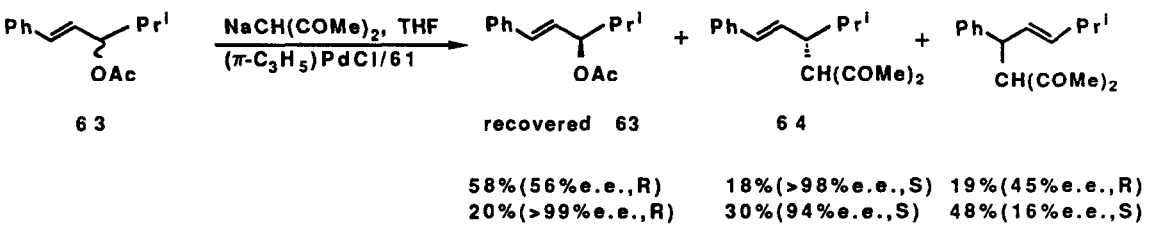
62

The chiral palladium catalyst with **61** is also effective for the reaction of 3-acetoxy-5-methoxycarbonyl-1-cyclohexene (racemic) with sodium acetoacetate or malonate (71–72% *ee*) (eqn. 40).[139]



(40)

In the reactions mentioned above, *meso*-π-allyl–Pd complexes are presumably formed as intermediates, since the same substituents are attached to the 1 and 3 positions of starting allylic acetates. When different substituents are introduced to the allylic system, the reactions will involve chiral π-allyl–Pd intermediates. Although these systems become rather complicated, the substituent effects on the stereoselectivity of the reaction can be estimated. Hayashi *et al.* carried out reactions using 1,3-diaryl-3-acetoxypropenes (racemic) and sodium acetylacetonate, observing 80–95% *ee* for the minor regio-isomers (31–46%) and 24–80% *ee* for the major regio-isomers (69–54%).[140] In principle, this reaction system can be applied to the kinetic resolution of racemic allyl acetates. Indeed, (*R*)-3-acetoxy-4-methyl-1-phenylpentene (**63**) was obtained with >99% *ee* at 80% conversion ($k_{fast}/k_{slow} = 14$) (eqn. 41). It should also be noted that the allylic alkylation product (**64**, *S*) was obtained with >98% *ee* at ca. 40% conversion.[141]

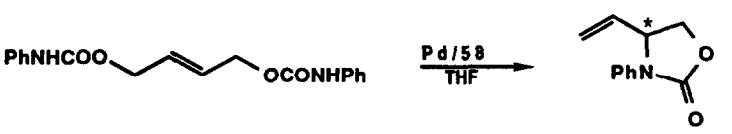


63 recovered 63 64

58%(56%e.e.,R) 18%(>98%e.e.,S) 19%(45%e.e.,R)
20%(>99%e.e.,R) 30%(94%e.e.,S) 48%(16%e.e.,S)

(41)

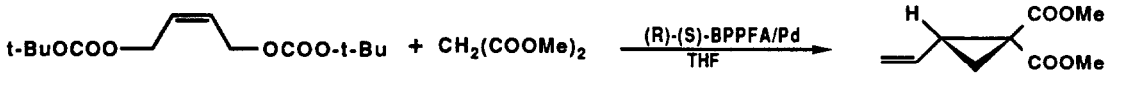
The chiral catalyst **61**-Pd was also applied to the intramolecular asymmetric cyclization of 2-butenylene-1,4-bis(phenylcarbamate) (**65**) to give the 4-vinyloxazolidinone **66** (≤77% *ee*) (eqn. 42).[142]



65 66(77%e.e.)

(42)

The BPPFA–Pd-catalyzed reactions of (*Z*)-2-butenylene-1,4-dicarbonate with active methylene compounds such as malonate, acetoacetate, and acetylacetone, were studied as well.[143] The reaction with dimethyl malonate gave the corresponding vinylcyclopropanedicarboxylate (**67**) with up to 70% *ee* (eqn. 43), while the reaction with methyl acetoacetate or acetylacetone gave the corresponding 5-vinyl-4,5-dihydrofuran (**68**) (40–59% *ee*) (eqn. 44).[143]



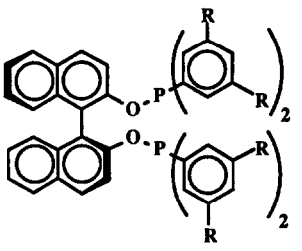
67 (70% e.e.).

(43)

68 (40-59% e.e.)

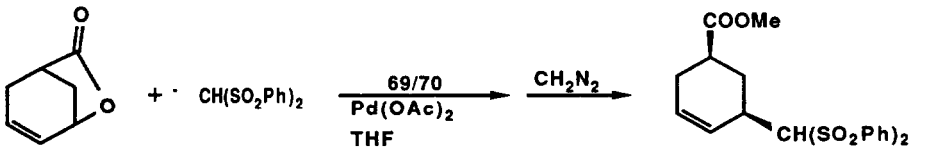
(44)

Trost *et al.* introduced a 'chiral pocket' in a π-allyl–Pd catalyst to control the stereochemical course of the incoming nucleophile. Thus, BINAPO (**69**) and its trimethylsilyl derivative (**70**) were



69 (R= H)
70 (R= $SiMe_3$)

designed and synthesized readily from BINAP and used as ligands for a palladium catalyst in the asymmetric allylic alkylation of lactone **71**.[144] The reactions using the **69**-Pd and the **70**-Pd catalysts gave the corresponding enantiomerically enriched cyclohexenecarboxylate (**72**) with 38% *ee* and 69% *ee*, respectively (eqn. 45).

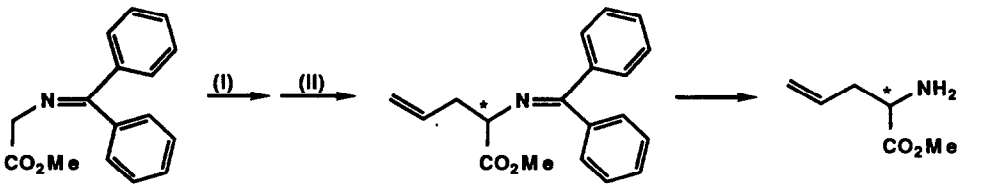


71

72
38% e.e. (69% e.e.)

(45)

Genet *et al.* carried out the asymmetric allylation of the glycine ester enolate generated from N-(diphenylmethylidene)glycine methyl ester (**73**) catalyzed by palladium complexes with chiral diphosphine ligands such as DIOP, Norphos, BINAP, Prophos, BPPM, etc. This led, after the hydrolysis of the N-protecting group, to allylglycine methyl ester (eqn. 46).[145] It is noteworthy that (+)- and (−)-DIOP–Pd catalysts gave significantly better results than other complexes: The best enantioselectivity so far obtained was 57% *ee*.



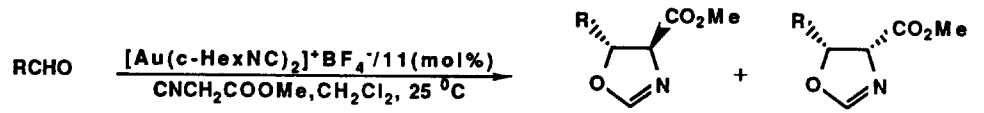
(46)

73

(I)LDA,THF-78°C; (II)CH_2=$CHCH_2OAc$;$Pd(dba)_2$ + L*

8.3. *Asymmetric aldol reaction*

Ito, Hayashi, and coworkers have developed the first practical catalytic asymmetric aldol reaction by using gold(I) complexes with chiral ferrocenyldiphosphines, **11a** (R = diethylamino) and **11b** (R = dimethylamino).[146] Thus, the asymmetric aldol reactions of various aldehydes with methyl cyanoacetate in the presence of the chiral gold catalysts gave the corresponding oxazolines (**74**: *trans*/*cis* ratio = 80/20 ~ 100/0; 72–97% *ee* for *trans* isomers and 31–49% *ee* for *cis* isomers) in excellent yields (eqn. 47). The best result was with pivalaldehyde, $(CH_3)_3C$–CHO, which gave

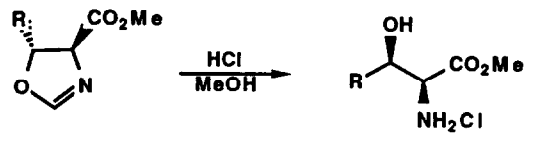


(47)

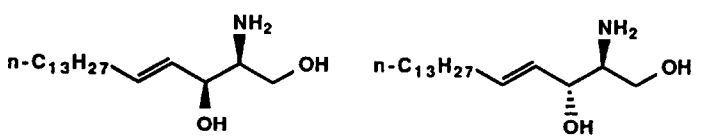
trans-74 cis-74

R=Ph,(E)-n-PrCH=CH,(E)-MeCH=CH,Me,i-Pr,c-Hex,t-Bu.

exclusively the *trans*-oxazoline (**74**) with 97% *ee* in 100% yield. The *trans*-oxazolines (**74**) thus obtained were readily hydrolyzed to the corresponding β-substituted serine methyl ester hydrochlorides (*threo*), which are the apparent asymmetric aldol products (eqn. 48). The reaction was also successfully applied to the asymmetric synthesis of *threo*- and *erythro*-sphinogosines (**75**, 93% *ee*) by use of (*E*)-2-hexadecenal as the aldehyde and a chiral ferrocenyldiphosphine (**11c**: R = N-morphorino) as the chiral ligand.[147]



74



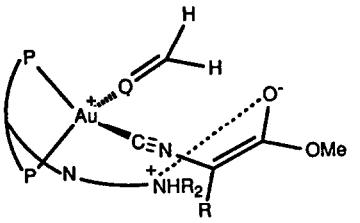
(48)

75-threo 75-erythro

This novel catalytic asymmetric aldol reaction was applied to the asymmetric synthesis of α-alkylserines by using α-cyanoalkanoates and paraformaldehyde in the presence of gold(I) complexes with chiral ferrocenyldiphosphines, **11b** and **11d** (R = N-piperidino) (eqn. 49).[148] The enantiomeric purities of the α-alkylserines thus obtained are in the range of 44 to 81% *ee*.

(49)

The mechanism of the catalytic asymmetric aldol reactions has been proposed, which involves a crucial interaction between the ester enolate oxygen and an amino moiety in the tether of the chiral ferrocenyldiphosphine ligand (**76**).



76

9. CONCLUSION

Catalytic asymmetric reactions promoted by chiral transition metal complexes, started in the late 1960s, have significantly advanced in the last two decades as demonstrated by number of reactions in this review. Those catalytic reactions have apparent technological and economical advantage over stoichiometric asymmetric reactions since one chiral catalyst molecule can produce a large number of chiral product and separation of chiral auxiliary, which is almost inevitable in stoichiometric processes, is unnecessary. On the basis of extensive fundamental research in the 1970s, several catalytic asymmetric reactions have been commercialized in the 1980s, especially; advances in the last five years are impressive. Understanding of the mechanisms of those catalytic reactions has significantly advanced as well. Thus, rational design of effective chiral catalysts becomes feasible in certain cases. Enantioselectivities achieved by those chiral transition metal catalysts become comparable to those by enzymes, and even turnover numbers compete with those in enzymic reactions under the appropriate conditions. As indicated in this review, currently there are, at least, several other efficient reactions which have high potential as industrial processes, and surely more to come. Discovery and development of newer and more efficient catalytic asymmetric reactions will continue and a number of commercial processes based on those reactions will emerge in the next decade.

Acknowledgment—Authors are grateful to Dr. John W. Scott, Hoffmann-La Roche Inc., Professor John K. Stille, Colorado State University, and Professor James D. Morrison for kindly reading this review and giving them valuable comments and advice.

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