Part One
Alkene Reductions

1
Reduction of Functionalized Alkenes

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1.1
Introduction

While a variety of methods is now available for the stereoselective reduction of olefins, catalytic hydrogenation continues to be the most useful technique for addition of hydrogen to various functional groups. Catalytic hydrogenations can be carried out under homogeneous or heterogeneous conditions, both employing a similar range of metals. Heterogeneous catalysts have had a strong impact on the concept of catalysis. They have provided powerful tools to the chemical industry and organic chemistry, allowing the chemo-, regio- and stereo-selective reduction of a wide range of functional groups and generally easy catalyst separation [1]. Homogeneous catalysts have found applications in a number of special selectivity problems or where enantioselectivity is the most important. Today, highly selective catalysts have revolutionized asymmetric synthesis. For two decades, homogeneous asymmetric hydrogenation has been dominated by rhodium(I)-based catalysts of prochiral enamides. Knowles and Horner initiated the development of homogeneous asymmetric hydrogenation in the late 1960s using modified Wilkinson's catalysts [2]. An important improvement was introduced when Kagan and Dang demonstrated that the biphosphine DIOP, having the chirality located within the carbon skeleton, was superior to a monophosphine in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids [3]. Knowles made a significant discovery of a C_2-symmetric chelating P*-stereogenic biphosphine DIPAMP that was employed with rhodium(I) for the industrial production of L-DOPA [4].

In the 1990s, the next breakthrough was Noyori's demonstration that the well-designed chiral complex containing Ru(II)-BINAP catalyzes asymmetric hydrogenation of prochiral olefins and keto groups to produce enantiomerically enriched compounds with excellent enantioselectivity [5]. Not surprisingly, such versatile Rh- and Ru-based systems have had significant industrial impact and have been widely investigated in modern organometallic laboratories. For these beautiful achievements W. S. Knowles [6] and R. Noyori [7] were awarded the 2001 Nobel Prize in chemistry. Today, asymmetric hydrogenation is a core technology [8];

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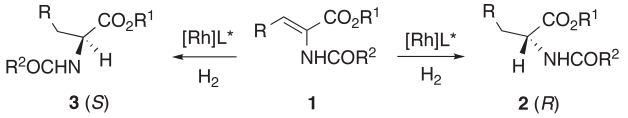
thousands of very efficient chiral ligands with diverse structures have been developed [9]. Combinatorial approaches combined with high-throughput screening techniques have facilitated the discovery of new catalysts and increased the cost-effectiveness of a given process [10]. The catalysts used in asymmetric hydrogenation are not limited to those with Rh or Ru metals. Catalysts derived from other transition metals such as Ir, Pd, Ti, Pt are also effective. Asymmetric hydrogenation of functionalized olefins with Rh, Ru and Ir will be the predominant topics of this chapter.

1.2
Asymmetric Hydrogenation of Dehydroamino Acids

1.2.1
Rh-Catalyzed Reactions

Since the invention of the well-designed Rh-complexes containing chiral biphosphines for the asymmetric hydrogenation of dehydroamino acids and the synthesis of L-DOPA [4], this reaction has become the model reaction to evaluate the efficiency of new chiral ligands. Indeed, a wide range of chiral phosphorus ligands with great structural diversity have been found to be effective for the synthesis of (*R*)- or (*S*)-enantiomers (Scheme 1.1).

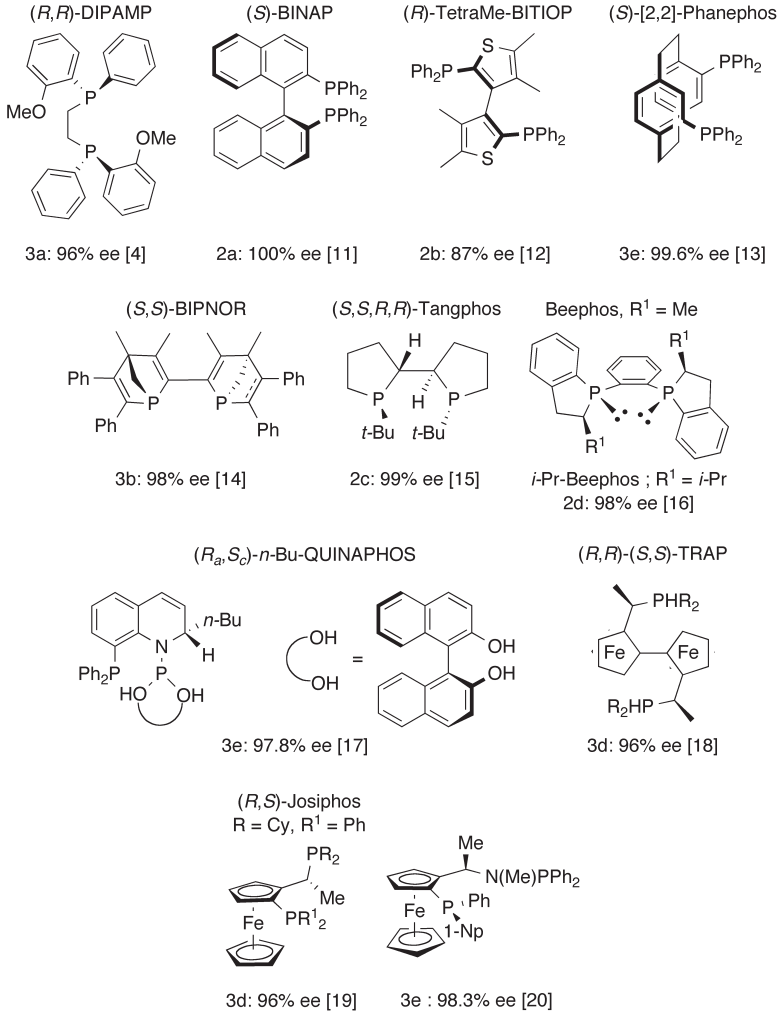


a: R = Ph, R^1 = H, R^2 = Ph
b: R = Ph, R^1 = H, R^2 = Me
c: R = *p*-FPh, R^1 = H, R^2 =Me
d: R = Ph, R^1 = Me, R^2 = Me
e: R = H, R^1 = Me, R^2 = Me
f: R = C_3H_7, R^1 = Me, R^2 = H
g: R = R^1 = H, R^2 = Me

Scheme 1.1 Rh-catalyzed reduction of dehydroamino acids.

1.2.1.1 Hydrogenation with Chiral Bisphosphine Ligands

For the Rh-catalyzed hydrogenation of 2-(acetamido)acrylic acid derivatives and (*Z*)-2-(acetamido) cinnamic acids and esters, cationic Rh catalysts and low hydrogen pressure are generally used. Examples are shown in Scheme 1.2. The reaction of (*Z*)-α-(acetamido)cinnamic acid in the presence of preformed [Rh-(*S*)-BINAP(MeOH)$_2$]ClO_4 produces (*S*)-*N*-acetylphenylalanine with nearly 100% ee [11]. The Rh-tetra-Me-BITIOP and Rh-CyP-PHOS catalysts developed by Sannicolo and Chan respectively were also found efficient in this reaction [12]. Pye and Rossen have developed a ligand based on a paracyclophane backbone, [2,2]-



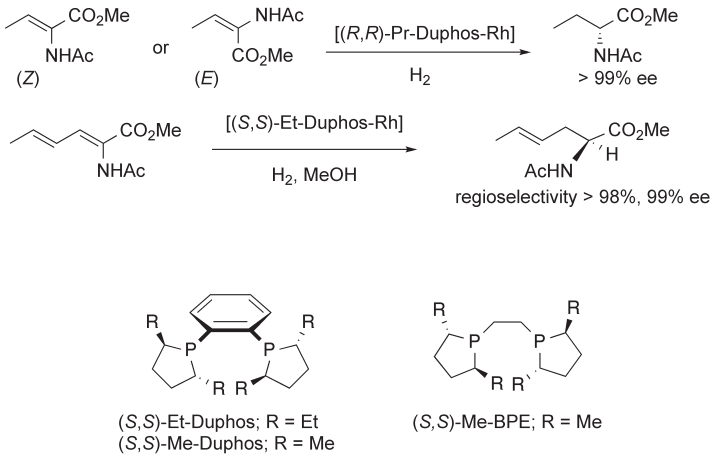
Scheme 1.2 Selected examples of Rh-asymmetric hydrogenation of dehydroamino acids **(1)**.

Phanephos, which has shown high enantioselectivity, up to 99% ee, in rhodium-catalyzed hydrogenation [13].

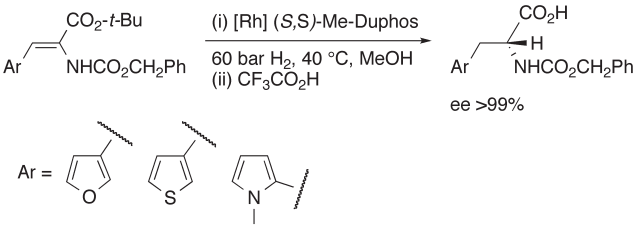
Twenty years after the discovery of DIPAMP by Knowles [4], several new generations of P*-chiral bisphosphines have been developed. Mathey and coworkers have designed BIPNOR, a bisphosphane with two chiral non-racemizable bridgehead phosphorus centers. BIPNOR has shown good enantioselectivities up to 98% ee in the hydrogenation of α-(acetamido) cinnamic acids [14]. A rigid P*-chiral bisphospholane ligand Tangphos has been reported by Zhang. This readily accessible ligand is very efficient for asymmetric hydrogenation of (acylamino)acrylic acid [15]. A new class of bisphosphine bearing one or two benzophospholanes has

been designed by Saito (1,2-bis-(2-isopropyl-2,3-dihydro-1*H*-phosphindo-1-1-yl) benzene (*i*-Pr-BeePHOS)). *i*-Pr-Beephos has been found to provide high enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acids [16]. Leitner has developed a series of mixed phosphoramidite-phosphine (Quinaphos) [17a], phosphinite-phosphine [17b, c] and Ito the TRAP ligands [18] that have obtained excellent efficiency in Rh-asymmetric hydrogenation of dehydroalanine derivatives. Since the discovery in 1994 of Josiphos, a ferrocene-based ligand devised by Togni and Spindler [19a], this class of bisphosphines including Taniaphos, Mandyphos families [19b], phosphinoferrocenyl phosphines [20] and (iminophosphoranyl) ferrocenes [21] have also shown excellent enantioselectivities in Rh-catalyzed reactions. As shown in Scheme 1.2, the biphosphines are highly efficient in the asymmetric hydrogenation of (*Z*)-dehydroamino acid derivatives with very high enantioselectivity. However, there are many reactions of interest where catalysts bearing these phosphines perform poorly in terms of enantioselectivity and efficiency. In particular, the hydrogenation of the (*E*)-isomeric substrates gives poor enantioselectivities and proceeds at a much lower rate. Interestingly, a new class of C_2-symmetric bisphospholane ligands has been prepared by Burk *et al.* and used in rhodium-catalyzed asymmetric hydrogenation. The Rh-Duphos catalyst provides high enantioselectivities for both (*E*)- and (*Z*)-dehydroamino acid derivatives [22] as shown in Scheme 1.3. In these hydrogenations, no separation of (*E*)- and (*Z*)-isomeric substrates is necessary. The hydrogenation of α,β-dienamides with Rh-Duphos proceeds chemoselectively, only one alkene function being reduced to give chiral γ,γ-unsaturated amino acids with both high regioselectivity (>98%) and ee (99%).

A short and efficient synthesis of optically pure (*R*)- and (*S*)-3-(hetero) alanines has been developed from isomerically pure (*Z*)-α-amino-α,β-dehydro-*t*-butyl esters using Rh-MeDuphos (Equation 1.1) [23b].

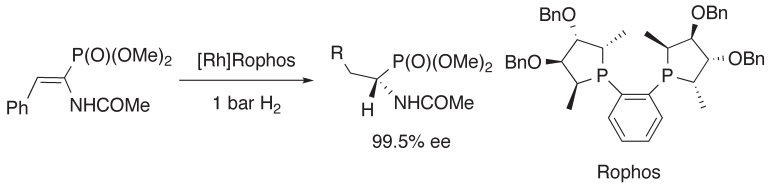


Scheme 1.3 Asymmetric hydrogenation of **(1)** with Rh-Duphos catalysts.



(1.1)

Hydrogenation of β,β-disubstituted-α-dehydroamino acids remains a relatively difficult problem. Duphos ligands and analogues provide excellent enantioselectivity up to 99% ee for a wide range of substrates [23a]. The modular nature of these ligands, which allows simple adjustment of their steric and electronic properties, can be achieved through the ability to modify both the phospholane core and the R-substituents. Since their useful application in Rh-asymmetric hydrogenation of olefins [22c], many structural modifications of the phospholane core have been reported. The conformationally rigid and bulky bisphosphane Penphos has been designed by Zang [24]. A series of modified Duphos and DPE ligands containing hydroxyl ether and ketal groups at C3 and C4 of the phospholane have been reported [25]. The ligands **(4)** with four hydroxyl groups enabled hydrogenation to be carried out in aqueous solution while maintaining the high efficacy of Duphos and DPE ligands [25a]. The fully functionalized enantiopure bisphospholane Rophos is highly effective for the hydrogenation of unsaturated phosphonate (Equation 1.2).



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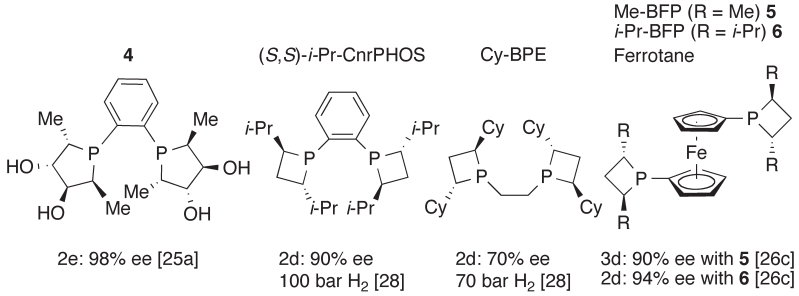
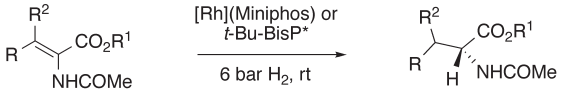
The synthesis of a new class of chiral bisphosphetane ligands related structurally to the Duphos and DPE ligands (Scheme 1.4) such as 1,2-bis(phosphetano)



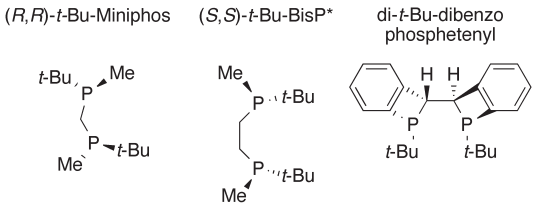
Scheme 1.4 Rh-asymmetric hydrogenation of **(1)** with **(4)** and bisphosphetane ligands.

benzenes CnrPHOS, 1,2-bis(phosphetano) ethanes BPE and 1,1-bis(phosphetano) ferrocene has been reported by Marinetti and Genet [26]. Later in 2000, Burk *et al*. reported a similar synthesis of these interesting 1,1-bis(phosphetano)ferrocene ligands named FerroTANE [27]. Interestingly, (*S,S*)-*i*-Pr-CnrPHOS provides moderate ee of (*R*)-methyl-*N*-acetylphenylalanine at 5 bar (500 kPa) of hydrogen (74%). However, at 100 bar of H_2 higher optical yields are observed (up to 90% ee) [28]. This nonconventional stereochemical issue can be related to the electron-rich nature of the phosphetane ligands.

Imamoto and coworkers have developed a series of electron-rich P*-chiral bisphosphanes [29] such as BisP*, Miniphos and 1,1′-di-*t*-butyl-2,2′-dibenzophosphenetyl. The Miniphos ligand leads to highly strained C_2-symmetric chelates when bound to a metal center. These ligands having both a conformational rigidity and an ideal chiral environment have shown significant enantioselectivities up to 99% ee in the hydrogenation of α-dehydroamino acids as shown in Scheme 1.5.



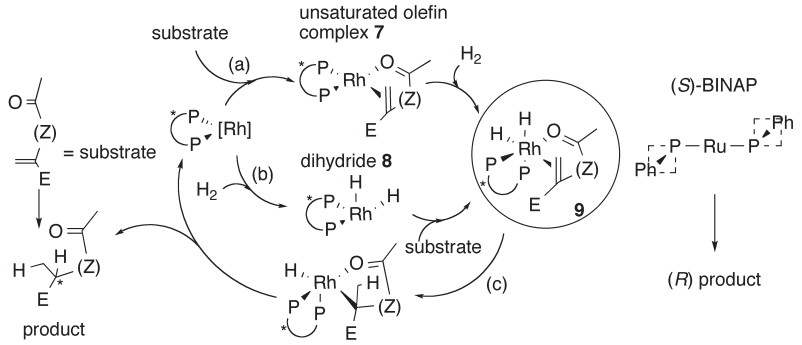
R, R^2 = -$(CH_2)_5$-	97% ee	Miniphos
R = R^2 = R^1 = H	99% ee	Miniphos
R = Ph, R^2 = H, R^1 = Me	99.9% ee	BisP*



Scheme 1.5 Reduction of α-dehydroamino acids with electron-rich P*-chiral bisphosphanes.

1.2.1.2 **Mechanism of the Asymmetric Hydrogenation with Rhodium Catalysts**

The practical importance of asymmetric hydrogenation has stimulated a great interest in the mechanistic aspects of this reaction. Over the last 30 years, the mechanism of the rhodium-catalyzed asymmetric hydrogenation has been actively investigated. Success in this field is evident from theoretical and experimental studies [8d, 30]. The acylamino substituent plays a crucial role in the enantioselection. The amide carbonyl group provides an additional binding site for the catalyst, placing the substrate precisely within the coordination sphere of rhodium (Scheme 1.6) giving rise to two diastereomeric catalyst–substrate complexes competing for H_2 addition. Previously, it has been well accepted that the "unsaturated-alkene" mechanism (Halpern-Brown), pathway (a), Scheme 1.6, via **(7)** was



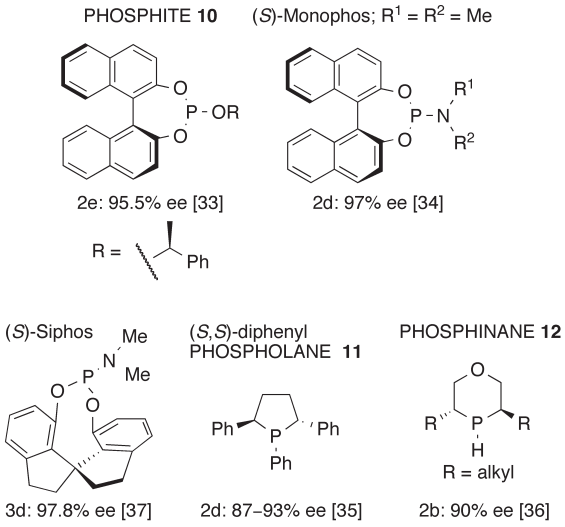
Scheme 1.6 General of the aspects mechanism of the Rh-catalyzed hydrogenation of **(1)**.

operating with a wide range of phosphines, the Rh-(*S*)-BINAP giving (*R*) configured α-amino acids.

Gridnev and Imamoto, through experimental and computational studies, have established that the Rh-catalyzed asymmetric hydrogenation with electron-rich P*-stereogenic ligands such as Miniphos proceeds with a different mechanism. A "dihydride" mechanism (pathway (b), Scheme 1.6) via **(8)** is proposed [31]. However, it is suggested that the differences in these mechanisms are not significant in the stereoselection since they join at a single pathway (c), forming the common intermediate **(9)** before stereoselection occurs. They also suggested a new approach for the prediction of the sense of enantioselectivity [31].

1.2.1.3 Rh-Catalyzed Hydrogenation with Monophosphorus Ligands

The high degree of enantioselectivity resulting from chiral biphosphanes in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acids can be explained as a result of decreased rotational freedom in the postulated metallacycle of the catalytic pathway [3]. However, isolated cases have been reported in which this long-standing theory is not as general as usually assumed [32]. More recently, it has been recognized that chiral phosphite **(10)** [33], phosphoramidites such as Monophos [34], monodentate phospholane **(11)** [35] and phosphinane **(12)** [36], are excellent ligands in this hydrogenation reaction as shown in Scheme 1.7. Zhou introduced a novel monodentate phosphorus ligand containing 1,1′-spirobiindane backbone which was found to be particularly effective in the hydrogenation of methyl-2-acetamidocinnamate at 1 bar (10^5 Pa) pressure of H_2, with up to 97.8% ee at 0 °C [37]. Interestingly, enantioselectivities up to 99% were achieved in the rhodium-catalyzed asymmetric hydrogenation of the *N*-formyl dehydroamino ester using Monophos ligand where a mixture of *E* and *Z* isomers was reduced with excellent ee values using 2 mol% of catalyst [34c]. Ding has recently reported an efficient system of heterogenization of Ferringa's catalyst by a self-supported strategy that can be recycled several times for the enantioselective hydrogenation of dehydroalanine derivatives [38].



Scheme 1.7 Hydrogenation of dehydroamino acids with chiral Rh-monophosphorus ligand catalysts.

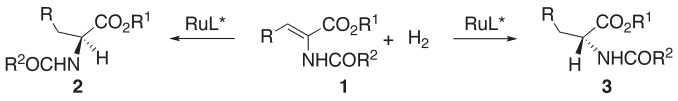
1.2.2 Ruthenium- and Iridium-Catalyzed Reactions

1.2.2.1 Ruthenium

The development of chiral ruthenium-BINAP complexes has considerably enhanced the scope of enantioselective hydrogenation of olefins and keto groups [5, 7]. The axially 1,1′-binaphthyl moiety generally displays very high chiral recognition properties. The optically active bis-(triarylphosphines), BIPHEMP and MeO-BIPHEMP, containing the axially chiral biphenyl core have been developed by Roche [39]. In this context, several structural variations of the BINAP and MeO-BIPHEMP have been designed by many research groups and applied extensively to the reduction of olefins and keto groups.

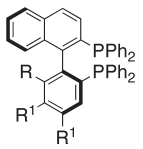
Unlike the Rh-based hydrogenation of α-(arylamino) acrylates, the corresponding Ru-chemistry has not been studied extensively. The first two examples were described 20 years ago by Ikariya-Saburi using Ru-(*S*)-BINAP and by James and coworkers with Ru-(*S,S*)-Chiraphos. These complexes catalyze the hydrogenation of (*Z*)-α-(acylamino) cinnamates giving (*S*)-phenylalanine derivatives with 92% [40] and 97% ee respectively [41]. More recently several chiral Ru-(bisphosphine) catalysts have been used in this reaction as shown in Table 1.1. The [Ru-(*R,R*)-DIPAMP(Br_2)] and [Ru-(*R,R*)-DIPAMP(2-methylallyl)$_2$] [42] complexes also catalyze the asymmetric hydrogenation of *N*-acetyldehydroalanine giving (*R*)-*N*-acetylalanine with 35–38% ee The non-C_2 symmetric biaryl (bisphosphino)-MeO-NAPhePHOS and TriMe-NAPhePHOS (R = R^1 = H) ligands designed by Genet and Marinetti have been used in Ru-catalyzed asymmetric hydrogenation of dehydroamino acids giving 70% ee [43]. These results are comparable to those obtained with MeO-BIPHEP (68%).

Table 1.1 Ruthenium-catalyzed hydrogenation of (*Z*)-α-(acylamino) cinnamates.

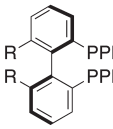


Substrate	*Catalyst*	*H_2 (bar)*	*ee%*	*Product*	*Reference*
1b	Ru(*S*)-BINAP	2	86	2b(*S*)	[40]
1e	Ru(*S*)-BINAP	2	87	2e(*S*)	[40]
1b	Ru(*S,S*)-Chiraphos	1	97	2b(*S*)	[41]
1g	Ru(*R,R*)-DIPAMP	12	35	2g(*R*)	[42b]
1e	Ru(*S*)-BIPHEMP	2	80	2e(*S*)	[36]
1d	Ru(*R*)-MeO-NaPhePHOS	10	70	3d(*R*)	[43b]
1d	Ru(*R*)-MeO-BIPHEP	10	69	2d(*R*)	[46b]
1b	$RuCl_2$(*R*)-13-$(DMF)_2$	4	87	3b(*R*)	[44]
1a	Ru(*S*)-Synphos	5	86	2a(*S*)	[45c]
1d	Ru(*R*)-P-Phos	1	88	3(*R*)	[46]

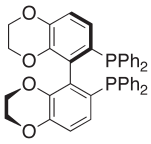
TriMe-NAPhePHOS
R = R^1 = H
MeO-NAPhePHOS
R = MeO, R^1 = H



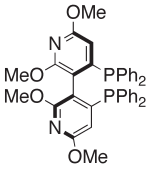
(*R*)-BIPHEMP; R = Me
(*R*)-MeO-BIPHEP; R = OMe



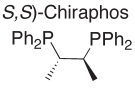
(*R*)-Synphos



(*S*)-P-PHOS



(*S,S*)-Chiraphos



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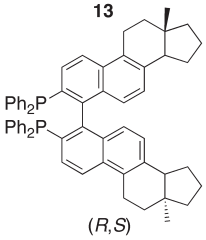


The bis-steroidal atropisomeric phosphine **(13)** has been developed from equilenine and gives up to 87% ee in the hydrogenation of (*Z*)-α-acetamidocinnamic acid [44]. A new atropisomeric ligand containing a bis-benzodioxane core Synphos was reported independently by Genet and Vidal [45] and by Chan [46]. A Ru-(*S*)-Synphos complex catalyzes asymmetric hydrogenation of (*Z*)-(acylamino)cinnamate giving (*S*)-protected phenylalanine in 86% ee [45c]. Chan and coworkers have developed a P-PHOS ligand containing a dipyridyl unit that is highly efficient for the asymmetric hydrogenation of (*Z*)-2-acetamidocinnamate obtaining 88% ee at 1 bar (10^5 Pa) of H_2 [47]. Lemaire and coworkers have reported a Ru-(5,5′)-

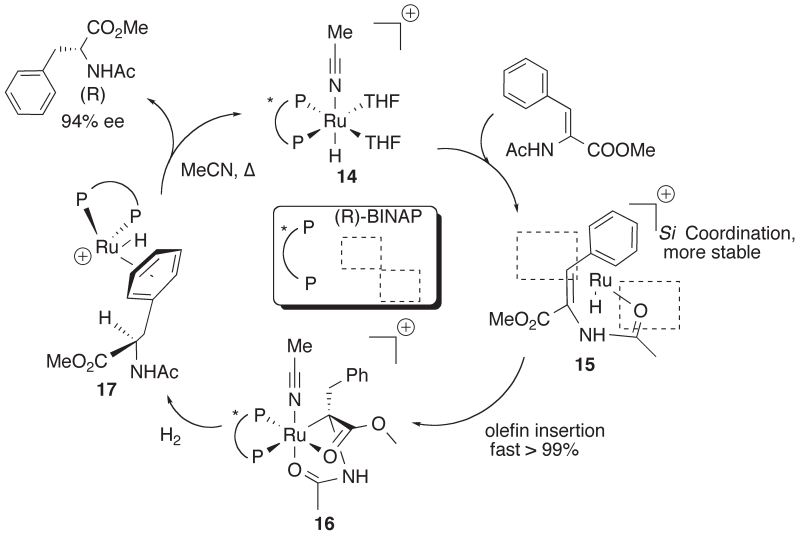
perfluoroalkylated BINAP which is a useful catalyst in the asymmetric hydrogenation of methyl-2-acetamidoacrylate in supercritical carbon dioxide with full conversion and high enantioselectivity (74% ee) [48].

The Ru-complexes of the atropisomeric family exhibit slight differences in enantioselectivity toward the same substrate. This may be attributed to the electronic and stereoelectronic properties of these ligands. The optical purities are significantly reduced in comparison with those of the Rh-catalyzed reaction. More interestingly, the Rh and Ru hydrogenation catalysts consisting of the same chiral biphosphines exhibit an opposite sense of asymmetric hydrogenation of dehydroamino acids.

1.2.2.2 Mechanism of the Ruthenium-Catalyzed Asymmetric Hydrogenation

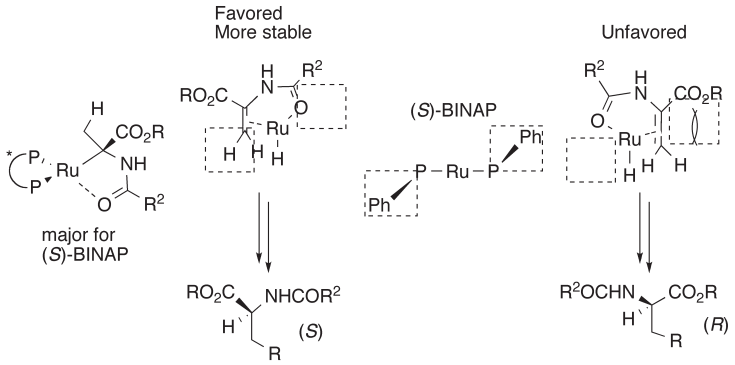
In contrast to the Rh-catalyzed reaction involving a Rh-dihydride intermediate, the Ru-hydrogenation proceeds via a Ru monohydride species. Bergens and coworkers using (*Z*)-methyl-α-acetamidocinnamate (MAC) and [Ru-(*R*)-(BINAP)(H)(MeCN)(solv)$_2$]BF_4 **(14)** (solv = MeOH or THF) [49] have found that the stoichiometric reaction between MAC and the Ru-catalyst resulted in rapid formation of a predominant species in solution. As shown in Scheme 1.8, the reaction of MAC with H_2 gas resulted in formation of $MACH_2$ and [Ru(*R*)-(BINAP)(H)(η^6-$MACH_2$)]$^+$ **(17)**. $MACH_2$ was then liberated in refluxing acetonitrile with an ee of up to 94%. They also have established that at −40 °C the *Si*-olefin catalyst adduct **(15)** is formed which is the immediate precursor of **(16)** [49c].

Bergen's investigations paved the way for a deeper understanding of the mechanism of Ru-catalyzed asymmetric hydrogenation of enamides. Noyori and cowork-



Scheme 1.8 Mechanism of [Ru-(*R*)-(BINAP)(H)(MeCN)]BF_4-catalyzed hydrogenation of MAC. Anion is $^-BF_4$.

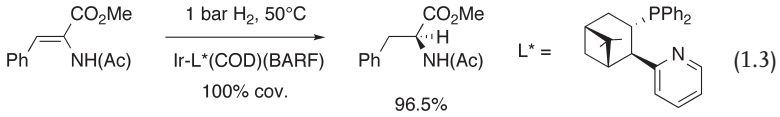
ers have investigated the hydrogenation of α-(acylamino) acrylic esters using [Ru-(*S*)-BINAP(CH_3CO_2)$_2$] by means of kinetic studies, deuterium labeling experiments, isotope effect NMR measurements and X-ray analysis of Ru complexes. They have established that the Ru-BINAP diacetate-catalyzed reaction occurs via a monohydride-unsaturated pathway for both the major and minor enantiomers, and they form a short-lived enamide complex that delivers the hydride at C3 giving a five-membered metallacycle. Actually, the enantioselection is controlled by the stability of diastereoisomeric RuH/olefin complexes [50] as shown in Scheme 1.9 and is opposite to that of the hydrogenation using Rh(I) complexes with the same BINAP ligand.



Scheme 1.9 Enantioselection control via diastereoisomeric RuH/olefin complexes.

1.2.2.3 **Iridium**

The Ir-catalyzed hydrogenation of unsaturated enamides to amino acid derivatives has been much less studied. One successful example has been reported by Knochel [51] using a new type of P,N ligand derived from camphor. The hydrogenation of methyl (*Z*)-α-(acetamido)cinnamate in the presence of [Ir(L*)(COD)Cl] produces (*S*)-*N*-acetyl phenylalanine with 96.5% ee (Equation 1.3).

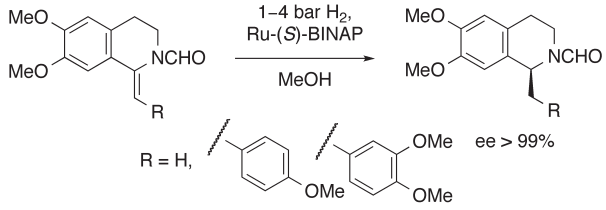


(1.3)

1.3
Simple Enamides

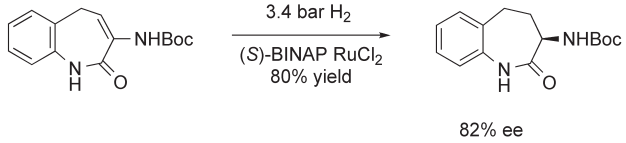
Rh-catalyzed hydrogenation of enamides has attracted much attention recently opening up an enantioselective route to chiral protected amines. Noyori has reported a general and straightforward method for synthesizing enantiomerically pure tetrahydroisoquinoline alkaloids [5a]. Ru-(*S*)-BINAP and Ru-(*S*)-BIPHEMP

complexes give almost perfect enantioselectivities in enamide hydrogenation for a wide array of tetrahydroquinolines (Equation 1.4) [52]. The present reaction provides access to morphinic and synthetic morphinans and benzomorphans analogues.



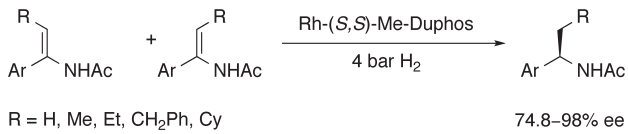
(1.4)

An efficient asymmetric synthesis of *N*-Boc-(*R*)-3-amino-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one, an important intermediate for the preparation of an angiotensin-converting enzyme inhibitor, based on asymmetric hydrogenation of an acyclic enamide, has been reported by Merck (Equation 1.5) [53].



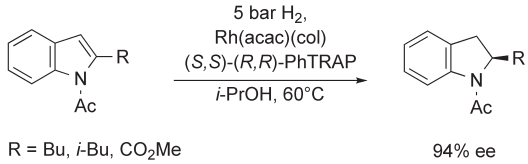
(1.5)

The most general method for the hydrogenation of simple enamides has been reported by Burk and coworkers using Rh-Duphos or DPE ligand. *E*/*Z* mixtures of β-substituted enamides can be hydrogenated without purification since both are reduced to acyl amines with high enantioselectivities ranging from 74.8% to 98.5% ee (Equation 1.6) [54].



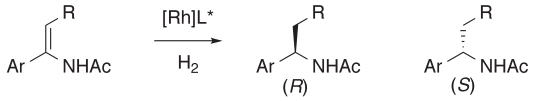
(1.6)

A series of 2-substituted *N*-acetylindoles can be reduced to optically active indolines by using the Rh-Ph-TRAP catalyst with enantioselectivities up to 94% (Equation 1.7) [55].

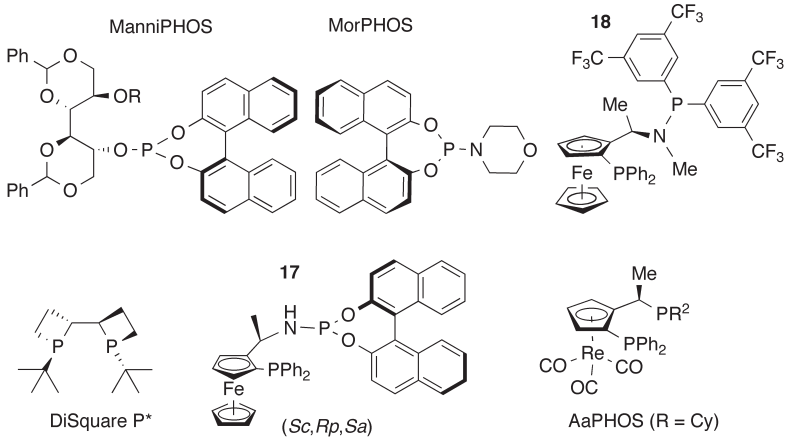


(1.7)

Table 1.2 Rhodium-catalyzed reduction of enamides.

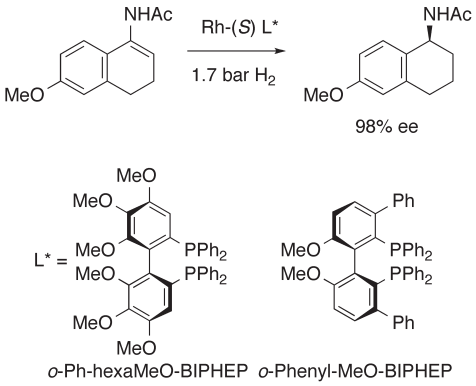


Substrate	*Ligand*	*H_2 (bar)*	*ee*	*Configuration*	*Reference*
R = H, Ar = Ph	Manniphos R = Me	10	99.5	(*R*)	[56]
R = H, Ar = *p*-CF_3Ph	Tangphos	1.4	99	(*R*)	[15]
R = H, Ar = *p*-NO2Ph	DiSquare P*	2	99	(*R*)	[57]
R = H, Ar = *p*-ClPh	Morphos	55	99	(*R*)	[58]
R = H, Ar = Ph	Aaphos	10	87	(*R*)	[59]
R = H, Ar = Ph	**(17)**	10	93	(*R*)	[60]
R = H, Ar = *m*-CO_2MePh	*t*-Bu-BisP*	3	97	(*S*)	[29d]
R = H, Ar = Ph	**(18)**	20.6	96.5	(*S*)	[61]



Monophosphites derived from D-mannitol (Manniphos) have been reported very recently and are highly efficient for Rh-catalyzed asymmetric hydrogenation of simple acyclic and endocyclic enamides [56]. Very high ee values have been obtained with Rh-catalysts using the P*-chiral ligand Tangphos [15], *t*-Bu-BisP* [29d], DiSquare P* [57], phosphoramidite (Morphos) mixture of phosphates, phosphonites and phosphines [58], chiral planar cyrhetrenes [59] and ferrocenylethylamine-monophosphoramidites **(17)** [60]. The air stable fluorinated ferrocenylphosphine aminophosphine ligand **(18)** has also been applied and allows efficient hydrogenation of enamides. These reactions afford *N*-acylated aryl amines with high enantioselectivities up to 96.5% ee (Table 1.2) [61].

The *o*-Ph-hexane-BIPHEP and *o*-phenyl-MeO-BIPHEP, Rh-catalysts have been applied successfully to hydrogenation of cyclic enamides (Equation 1.8) [62].



(1.8)

The hydrogenation of enamides bearing an endocyclic tetra substituted carbon–carbon double has also been reported at 100 bar (10 MPa) of H_2 using a Rh-Duphos catalyst generated in situ from [Ru(COD)(methylallyl)$_2$] and HBF_4 with high diastereoselectivity and acceptable ee up to 72% [63].

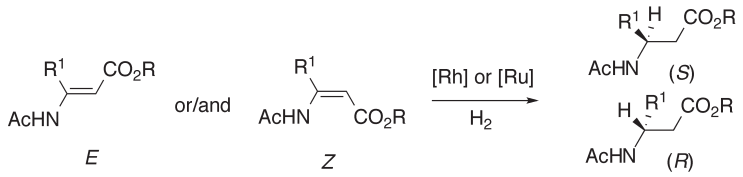
1.4 Hydrogenation of β-(Acylamino) Acrylates

The synthesis of optically active β-amino acids and their derivatives has gained much attention in view of their pharmacological activities and usefulness as chemical building blocks. In recent years, good to excellent enantioselectivities have been obtained by employing chiral monodentate and bidentate phosphorus-containing ligands for Rh- or Ru-catalyzed asymmetric hydrogenation of β-(acylamino) acrylates. Some selected examples are shown in Table 1.3.

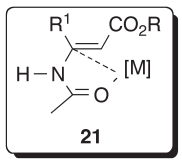
For example, BINAP [64], *t*-BuBisP* [65], phenyl P-Phos [66] and mixtures of two different chiral monodentate ligands, phosphites **(19)** and phosphonites **(20)** [67], were all found to be efficient in the hydrogenation of (*E*)-β-alkyl-β-(acylamino) acrylates. However, the hydrogenation of (*Z*)-isomers, especially (*Z*)-β-aryl-β-(acylamino) acrylates, were less selective, though significant improvements have been made using Rh-catalyzed hydrogenation with Duphos [68], BICP [69] or Ferrotane [70]. Recently, a Rh(I) catalyst containing the hybrid ferrocenyl phosphine phosphoramidite ligand **(17)** has been used in the hydrogenation of both (*E*)- and (*Z*)-isomers under identical conditions (10 bar (1 MPa) of H_2) affording β-amino acid derivatives with excellent enantioselectivities of 92–99% ee [71]. Hoge and coworkers have reported efficient Rh-trichickenPHOS and Rh-P* chirogenic bisphosphine catalysts for reductions both (*E*)- and (*Z*)-β-acetamido dehydroamino acids [72].

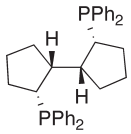
A significant drawback to this reaction is the requirement of an acyl group on nitrogen. This group is considered essential to satisfy the chelation requirements between the substrate and the metal **(21)**. The first general and highly enantioselective method for hydrogenation of unprotected β-enamine esters

Table 1.3 Ruthenium- and rhodium-catalyzed reduction of β-(acylamino) acrylates.

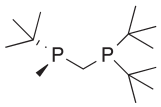


	Substrate	*Catalyst*	*H_2 (bar)*	*ee %*	*Configuration*	*Reference*
(*E*)	R = R^1 = Me	Ru (*R*)-BINAP	1	96	(*S*)	[64]
(*Z*)	R = R^1 = Me	Ru (*R*)-BINAP	4	5		[64]
(*E*)	R = R^1 = Me	Rh (*S,S*)-*t*-BuBISP*	3	98.7	(*R*)	[65]
(*E*)	R = Me, R^1 = *i*-Pr	Rh (*R*)-P-PHOS	4	97.4	(*R*)	[66]
(*Z*)	R = Et, R^1 = *i*-Pr	Rh (*R,R*)-BICP	10	90.7	(*R*)	[69]
(*Z*)	R = R^1 = Me	Rh (*S,S*)-Et-Duphos	1	86.7	(*S*)	[68]
(*E*)	R = Me, R^1 = Ph	Rh (*R,R*)-Et-Ferrotane	1	>99	(*S*)	[70]
(*Z*)	R = Ph, R^1 = Et	Rh-**(17)**		98	(*R*)	[71]
(*E*) or (*Z*)	R = Et, R^1 = *i*-Pr	Rh (*R*)-Trichickenphos	1.5	99	(*R*)	[72]

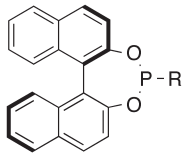




(*R,R*)-BICP

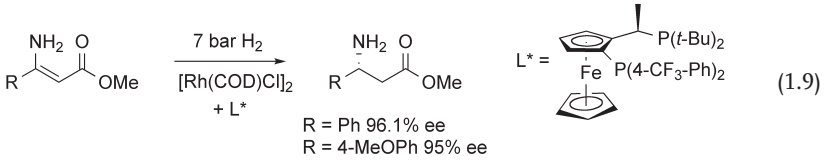


TrichickenPHOS



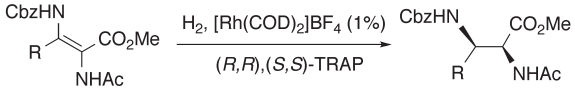
R = OMe **19**
R = Me **20**

has been reported using a Rh-ferrocenophosphine complex under relatively mild conditions, proceeding with high enantioselectivity up to 96.1% ee (Equation 1.9) [73].



(1.9)

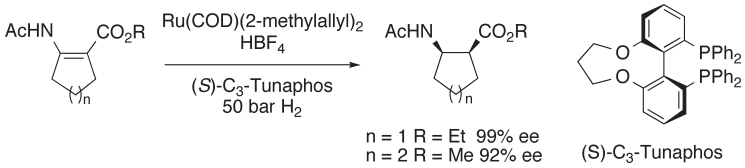
Enantioselective hydrogenation of tetrasubstituted olefins of cyclic or acyclic β-(acylamino) acrylates is much more difficult to accomplish. The asymmetric hydrogenation of (*E*)-α,β-bis(*N*-acylamino) acrylates using Rh-(*R,R*)-(*S,S*)-PrTRAP provides optically active (2*S*,3*R*)-2,3-bis(*N*-acylamino)carboxylates with 79–82% ee (Equation 1.10) [74].



(1.10)

R = Me, Et, *t*-Bu

Recently Zhang and coworkers have been successful in the hydrogenation of tetrasubstituted olefins [75] using monomeric [Ru(COD)(2-methylallyl)$_2$] and HBF_4 in the presence of a chiral phosphorus ligand such as (*S*)-C_3-Tunaphos or biaryl ligands providing high *cis* selectivity and enantioselectivities up to 99% ee with cyclopentenyl and cyclohexenyl derivatives (Equation 1.11). However, lower ee values were obtained in the hydrogenation of cycloheptenyl and cyclooctenyl substrates (44–80% ee). This procedure for the generation of Ru-catalysts was previously reported for the industrial production of dehydrojasmonate [76]; see Section 1.6.



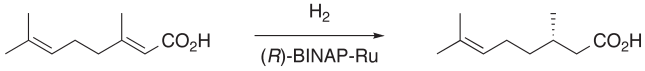
n = 1 R = Et 99% ee
n = 2 R = Me 92% ee

(S)-C_3-Tunaphos

(1.11)

1.5 Hydrogenation of Unsaturated Carboxylic Acids and Esters

Noyori provided a breakthrough in this area with the discovery of Ru-BINAP dicarboxylate complexes [5a]. The ruthenium-BINAP dicarboxylate complexes afford high enantioselectivities in the hydrogenation of α,β-unsaturated acids. However, the catalytic efficiencies are highly sensitive to the substitution pattern and reaction conditions, particularly the hydrogen pressure [8a]. Interestingly, in the asymmetric hydrogenation of geranic acid, only the double bond closest to the carboxyl group is reduced (Equation 1.12) [5b].

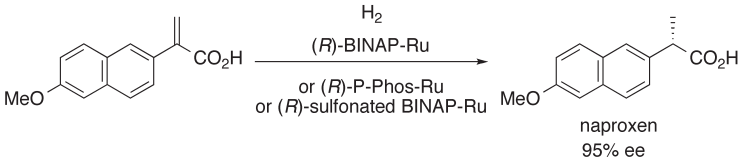


81% ee

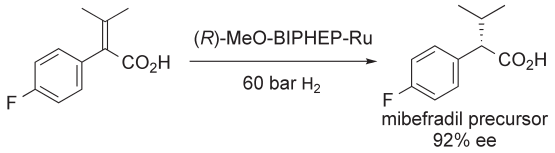
(1.12)

Other Ru-atropisomeric complexes such as [Ru-BIPHEMP-(2-methylallyl)$_2$] or [Ru-(*R*)-MeO-BIPHEP(Br_2)] [42a, 77] [Ru-BINAP-(allyl)(acac-F_6)] [78] can also be used in this transformation. Asymmetric hydrogenation of α-aryl-substituted acrylic acids has been extensively studied due to the pharmaceutical importance of the resulting products. The anti-inflammatory drugs (*S*)-naproxen and (*S*)-ibuprofen can be efficiently obtained by high-pressure hydrogenation of 2-(6′-methoxynapthyl-2′-yl) acid using [Ru-(*S*)-BINAP($OCOCH_3$)$_2$] [79a, b]. [Ru-(*R*)-(P-Phos)(acac)$_2$] was also found to be an economically attractive system for the synthesis of (*R*)-

naproxen with up to 96% ee obtained (Equation 1.13) [79c]. A Ru-sulfonated BINAP catalyst absorbed in a polar solvent phase onto a porous glass bead has been designed by Davis [79d, e], this system can be efficiency recycled and the efficiency rivals that of solution chemistry (95% ee). Roche has reported the efficient synthesis of a pharmaceutical intermediate toward Mibefradil, (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid (Equation 1.14) [80].

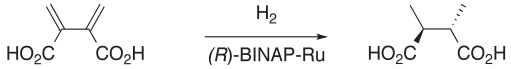


(1.13)



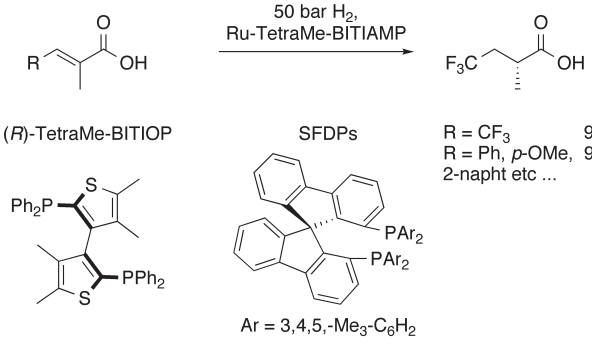
(1.4)

The hydrogenation of tiglic acid in supercritical CO_2 and ionic liquids catalyzed by the H_8-BINAP-Ru(II) complex proceeds cleanly with *cis* stereochemistry affording 2-methylbutanoic acid with 89–93% ee and over 99% yield [81]. 2-2-Dimethylidenesuccinic acid [82] is hydrogenated by Ru-(*R*)-BINAP complex at 100 bar (10 MPa) giving (2*S*,3*S*)-dimethyl succinic acid as the major product (96%) and a minor amount of the meso isomer (1.2%) (Equation 1.15).



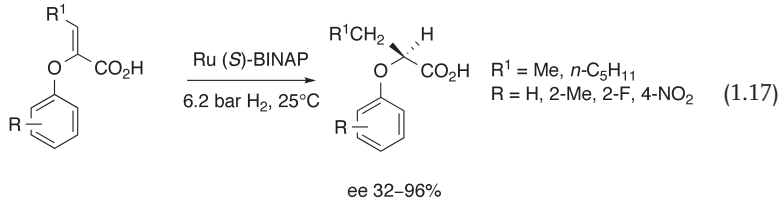
(1.15)

A trifluoromethyl-substituted unsaturated acid was hydrogenated by Chemi on a large scale (340 kg) with {Ru(*p*-cymene)[(–)tetraMe-Bitiop]I_2} to the corresponding fluorinated saturated acid with 92% ee (Equation 1.16) [12, 83a]. Recently Zhou designed a new spirofluorene-biphosphane ligand SFDPs with a high rigidity and a large dihedral angle, with a 3,4,5-trimethylphenyl group. This ruthenium complex is highly efficient for asymmetric hydrogenation of a wide range of methylhydrocinnamic acids (Equation 1.16) [83b].



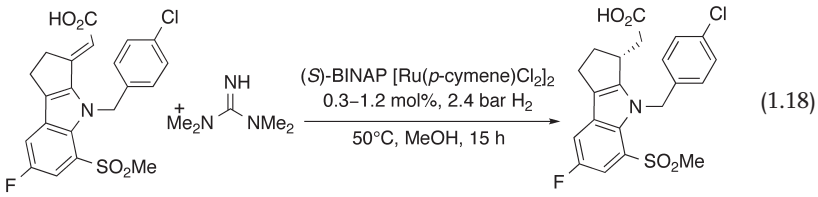
(1.16)

Very recently Gladiali has developed an interesting system for the reduction of α,β-unsaturated acids and esters using the Ph-BINEPINE ligand [84] by hydrogen transfer using formic acid as the reducing agent in the presence of a Rh(I) complex. A facile preparation of a series of chiral α-aryloxy carboxylic acids via asymmetric hydrogenation of the corresponding unsaturated acids using [Ru-(*S*)-BINAP(Cl)] and NEt_3 in methanol has been reported (Equation 1.17) [85].



(1.17)

Very recently [4-(4-chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,4-dihydrocyclopenta[*b*]indol-3-(2*H*)ylidene] acetic acid was reduced enantioselectively (up to 92% ee) with the [Ru-(*S*)-BINAP-(*p*-cymene)Cl_2] catalyst giving the prostaglandin D_2 (PGD2) receptor antagonist (Equation 1.18) [86].

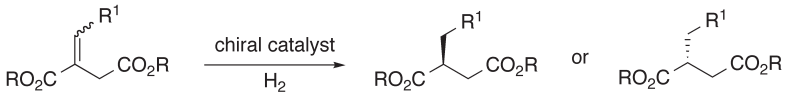


(1.18)

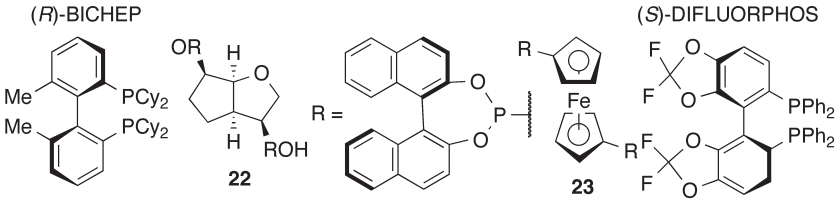
Hydrogenations of itaconic acids and derivatives have been studied extensively (Table 1.4) [8a]. Reactions using a cationic-Rh-BICHEP complex proceed at 5 bar (500 kPa) of H_2 giving 2-methylsuccinic acid in 93% ee [87]. High reactivity is generally observed with bisphosphinamidite electron-rich phosphane ligands such as Et-Duphos [88] and Tangphos [89]. A biphosphite [90a], derived from dianhydro-D-mannite [90b] and biphosphonite, spirophosphoramidite [91] and *t*-BuBisP* [92] ligands are also suitable for this reaction. The Ru-catalyzed hydrogenation of itaconate derivatives has recently been reported using the two atropisomeric ligands (*S*)-Difluorophos [93] and (*S*)-Synphos having a narrow dihedral angle [45]. Under 4 bar (400 kPa) at 50 °C the hydrogenation of dimethyl itaconate afforded the (*S*) product in 92% ee (Synphos) and 85% ee (Difluorophos). These differences in selectivity are probably due to the steric and electronic properties of the biaryl backbone of these ligands [93b].

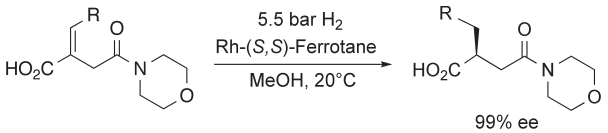
The hydrogenation of β-substituted itaconic acids and derivatives is more difficult. However, Burk and coworkers using a chiral 1,1′-biphosphetanylferrocene ligand (Et-Ferrotane) [27] have developed a very efficient Rh-catalyst for the hydrogenation of β-substituted monoamido itaconates derived from morpholine (Equation 1.19).

Table 1.4 Reduction of itaconic acids.



Substrate	*Catalyst*	*H_2 (bar)*	*ee %*	*Configuration*	*Ref.*
R^1 = R = H	Rh(*R*)-(bichep)(nbd)X	1	96	(*R*)	[87]
R^1 = *i*-Pr	[Rh(*S,S*)-Et-Duphos(cod)]BF_4	5.5	99	(*R*)	[88]
R^1 = R = H	Rh(Tangphos)	1.5	99	(*S*)	[89]
R^1 = H, R = Me	$Rh(cod)_2BF_4$-**(22)**		96	(*R*)	[90]
R^1 = H, R = Me	Rh *t*-BuBisP*	2	98.6		[92]
R^1 = H, R = Me	Ru(*S*)-Difluorphos/(*S*)-Synphos	4	85–92	(*S*)	[93]

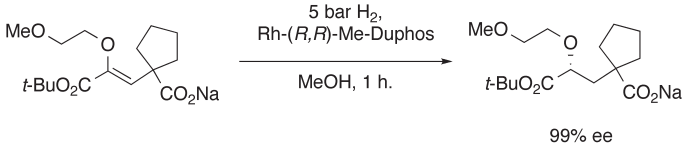




(1.19)

R = Ph, *p*-F-C_6H_4, thienyl, *n*-Bu, *t*-Bu

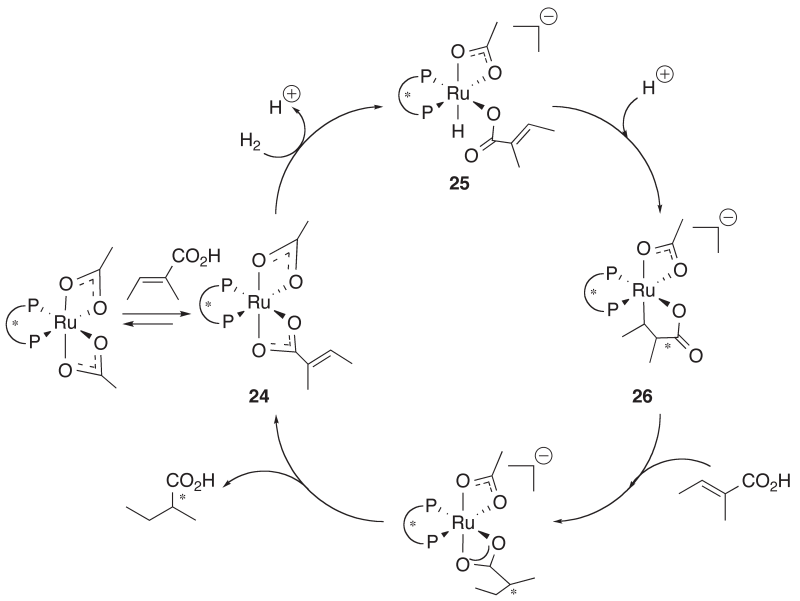
An interesting example is shown in Equation 1.20 with Rh-Me-Duphos in which a trisubstituted olefin is reduced to afford a chiral succinate [94]. The Ru-MeO-BIPHEP catalyst is also very efficient in this process, providing access to the large-scale production of this intermediate for the synthesis of candoxatril (see Section 1.8.)



(1.20)

1.5.1
Mechanistic Aspects of the Ru-(BINAP)-Catalyzed Hydrogenation of Carboxylic Acids

Several groups, most notably those of Noyori [95], Halpern *et al.* [96], Brown *et al.* [97] and Chan [98], have reported on the mechanism of enantioselective



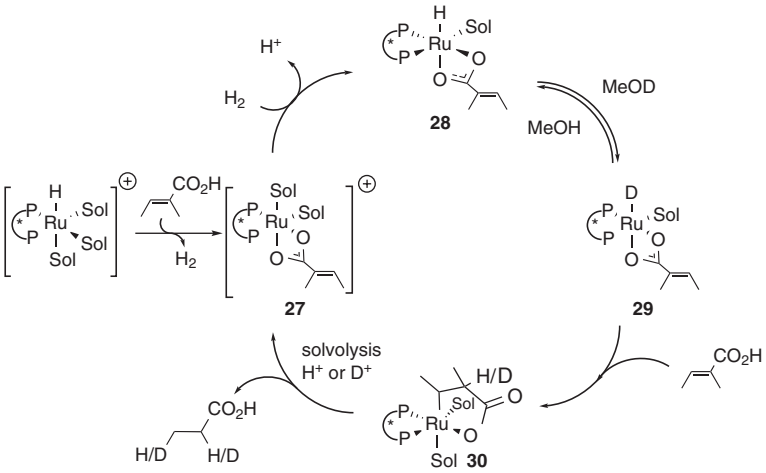
Scheme 1.10 Halpern's mechanism.

hydrogenation of α,β-unsaturated acids/esters in alcohols using ruthenium-bis(phosphine)-dicarboxylate species as catalyst. These studies have revealed (Scheme 1.10) that the mechanism follows four main steps: first, a rapid equilibration between the catalyst and tiglic acid by carboxylate ligand exchange **(24)**; second, heterolytic cleavage of dihydrogen generating a monohydride ruthenium intermediate **(25)**; third, olefin-hydride insertion giving the 5-membered heterometallacycle **(26)**; and fourth, solvolysis of the Ru—C bond to complete the cycle.

Very recently Bergens and coworkers [99] using [Ru-(*R*)-BINAP(H)(solv)$_{3-n}$(MeCN)$_n$]BF_4 (n = 0–3) have examined the hydrogenation of tiglic and angelic acids. The catalyst enters the catalytic cycle by reaction with the substrate to generate the carboxylate compound **(27)** and dihydrogen. Isotope labeling studies support Halpern's mechanism, heterolytic cleavage of H_2 resulting in formation of monohydride **(28)** and rapid H—D exchange between **(28)** and methanol-d_4 gives **(29)**. Olefin hydride or deuteride insertion leads to the five-membered metallacycle intermediate **(30)**; solvolysis of the ruthenium–carbon bond completes the catalytic cycle (Scheme 1.11).

1.6
Hydrogenation of Unsaturated Esters, Lactones, Amides and Ketones

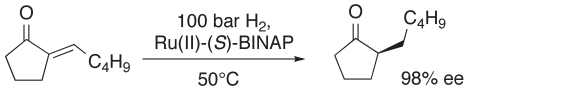
There are several highly selective catalysts for the hydrogenation of α-(acylamino) acrylic acids, enamides, α,β-unsaturated carboxylic acids, and allylic and homoal-



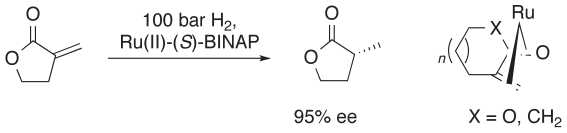
Scheme 1.11 Proposed catalytic cycle for ruthenium bis(phosphine) catalysts.

lylic alcohols. In contrast, reports of efficient enantioselective hydrogenation of olefins with aprotic oxygen or nitrogen functionalities such as esters, ketones and lactones are limited.

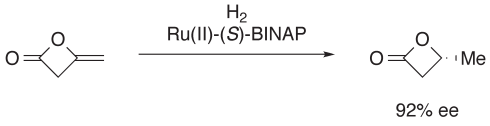
However, Takaya and coworkers have established that several Ru-BINAP systems are efficient for the hydrogenation of alkylidene ketones or lactones [100]. Using [RuCl-(*S*)-BINAP-benzene]Cl, [Ru-(*S*)-BINAP(OAc)$_2$] or [Ru$_2$-(*S*)-BINAP(Cl)$_4$]$_2$(NEt$_3$), alkylidene ketones or lactones were reduced to their corresponding chiral products with high selectivity (Equations 1.21 and 1.22). Interestingly, (*R*)-4-methyl-2-oxetanon was prepared in 85% yield and with good enantioselectivity (92%) (Equation 1.23). In this reaction, chelation of the substrate to a Ru(II) species also seems to be important for high selectivity. Exocyclic C=C olefins are particularly good substrates; in contrast, endo compounds gave poor enantioselectivity.



(1.21)

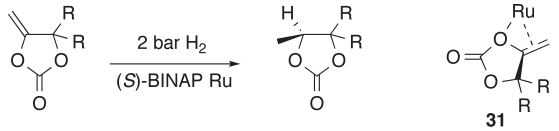


(1.22)



(1.23)

Bruneau and Dixneuf have described the enantioselective hydrogenation of α-methylene-1,3-dioxolane-2-ones catalyzed by chiral biphosphine ruthenium [101]. The use of [Ru-(*S*)-BINAP$(O_2CF_3)_2$] leads to optically active cyclic carbonates with enantioselectivies up to 95% ee (Equation 1.24). The excellent enantioselectivities observed may be due to the formation of the chelate intermediate **(31)**.

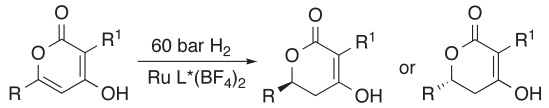


31

(1.24)

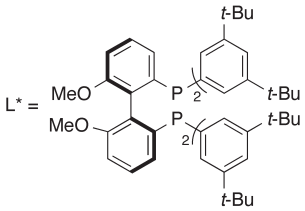
R = Me, R-R spirocylopentyl, spirohexenyl

Consiglio *et al*. at Roche used a cationic ruthenium containing the bulky electron-rich ligand (6,6′-dimethoxybiphenyl-2,2′diyl)bis[3,5-di(*t*-butyl-phenylphosphine)], have described the chemoselective and enantioselective hydrogenation of various substituted 2-pyrones to the corresponding 5,6-dihydropyrones (ee values up to 97%) (Equation 1.25) [102].

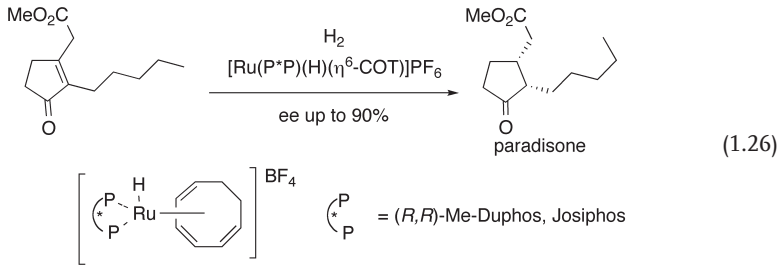


R = $C_{11}H_{23}$, R^1= *n*-C_6H_{13} 94% (99% selectivity) (*R*)

(1.25)

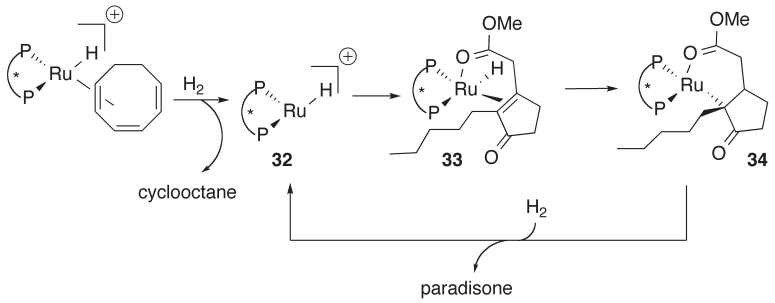


During the course of a collaboration with Firmenich, a considerable breakthrough in the hydrogenation of tetrasubstituted carbon–carbon double bonds was realized by Genet and Rautenstrauch, using [Ru(P*P)(H)(η^6-COT)]PF_6 (COT = cycloocta-1,3,5,7-triene) prepared *in situ* from [Ru(COD)η^3-(methylallyl)$_2$] with HBF_4 and various P*P = (BINAP, DIPAMP, Duphos) ligands in a weakly coordinating solvent [76]. This new type of complex is highly active and has demonstrated its utility in the enantioselective hydrogenation of difficult to reduce β-oxoesters. Thus, the enantioselective hydrogenation of the tetrasubstituted "dehydrodione" with [Ru(P*P)(H)(η^6-COT)]PF_6, (P*P) = (*R,R*)Me-Duphos or Josiphos, leads directly to the (+)-*cis*-methyl dehydrojasmonate with up to 90% ee (Equation 1.26), a commercially important perfume component. Since 1998, Firmenich has developed a process on multi tonnes/year scale for this compound named paradisone.



(1.26)

The success of this system may be attributed (Scheme 1.12), firstly, to the formation under hydrogen pressure of the highly unsaturated ruthenium intermediate **(32)**, which acts as a pre-catalyst. Secondly, the chelation of the oxoester entails metal binding to the double bond to give **(33)**, followed by olefin insertion leading to **(34)**, which by hydrogenolysis delivers paradisone with regeneration of the catalyst [9b].



Scheme 1.12 Ru-catalyzed synthesis of paradisone.

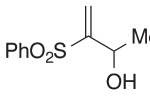
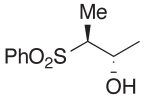
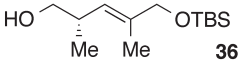
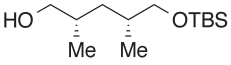
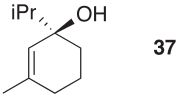
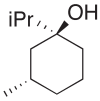
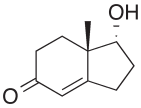
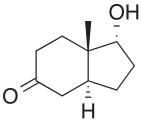
1.7
Hydrogenation of Unsaturated Alcohols

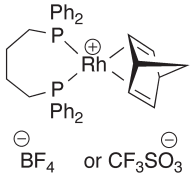
1.7.1
Diastereoselective Hydrogenation with Rh and Ir Catalysts

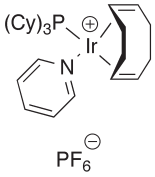
Substrate-directing chemical reactions are a major challenge to organic chemists. Several functional groups and reagents have proved to be highly efficient, giving exceptional levels of stereoselection [103]. The directed hydrogenation of functional olefins employing cationic rhodium or iridium catalysts has considerable potential [104]. The most common directing group, the hydroxyl, acts as a donor to the metal center in the catalytic cycle. Wilkinson's catalyst requires formation of the alkoxide, whereas cationic Rh(I) and Crabtree's catalyst $[Ir(COD)PCy_3(Pyr)]PF_6$ have emerged as the most commonly used catalysts in the hydrogenation of allylic and homoallylic alcohols [105].

For example the cationic rhodium complex is effective for the stereoselective of allylic and homoallylic alcohols **(35)** and **(36)** [106, 107], while the cationic iridium catalyst is less effective in the hydrogenation of **36.** In contrast Crabtree's catalyst is highly efficient in the directed reduction of a number of diverse cyclic olefinic alcohols **37**, **38** [108]. The hydrogenation with iridium gives predominately the *trans*-indanone, Table 1.5 shows some selected examples.

Table 1.5 Diasteroselection of unsaturated alcochols.

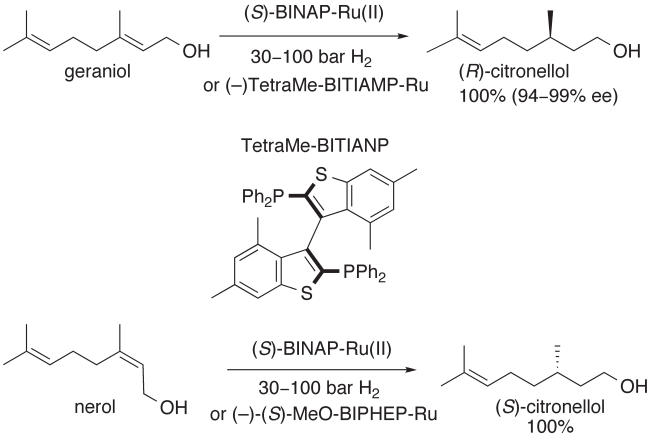
Substrate	*Major product*	*Catalyst*	*Selectivity*	*Reference*
 **35**		$[Rh]^+$	99.5 : 0.5	[106]
 **36**		$[Rh]^+$ $[Ir]^+$	95 : 5 73 : 27	[107]
 **37**		$[Ir]^+$	>99.9	[105]
 **38**		$[Ir]^+$	27 : 1	[108]

$[Rh]^+$ = 

$[Ir]^+$ = 

1.7.2
Enantioselective Hydrogenation with Chiral Ru and Ir Catalysts

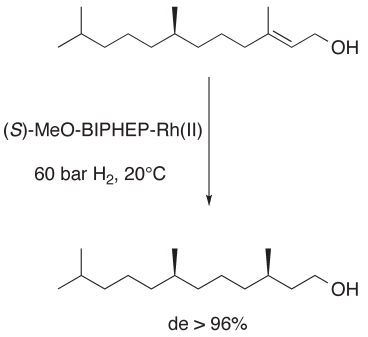
Allylic and homoallylic alcohols can be reduced with high selectively using Ru(BINAP) dicarboxylate, reported by Noyori [109]. For example, geraniol and nerol are quantitatively and chemoselectively converted to citronellol with up to 99.9% ee (Equations 1.27 and 1.28). Only the allylic alcohol is hydrogenated, leaving the isolated C6—C7 double bond. The complex tetra(–)-Me-BITIAMP-$Ru(OAc)_2$ is also effective in reducing geraniol to (*R*)-citronellol (94% ee) [12a].



(1.27)

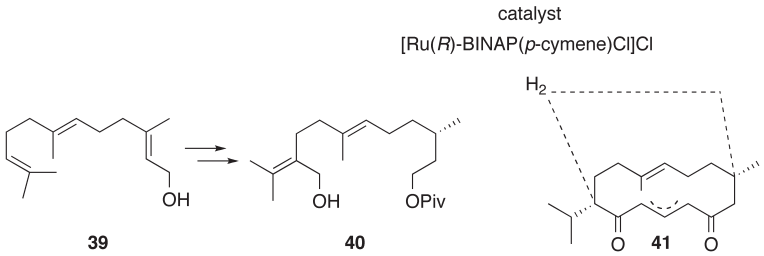
(1.28)

Takasago carries this process out on a 300 t/scale, while Roche has developed a similar process using Ru-(*S*)-MeO-BIPHEMP or Ru-(*S*)-BIPHEMP for (*S*)-citronellol and for the elaboration of a vitamin E intermediate (Equation 1.29) [110].



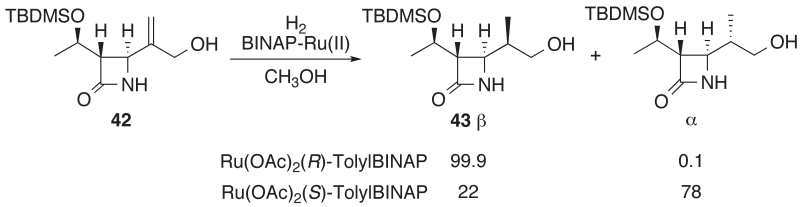
(1.29)

Deslongchamps and coworkers have described a synthetic approach toward the macrocyclic dienone **(41)**, a key intermediate in the synthesis of (+)-chatancin. Major synthetic steps include two sequential enantioselective hydrogenations of the two allylic alcohols **(39)** and **(40)** using a Ru(BINAP) catalyst (Scheme 1.13) [111].



Scheme 1.13 Synthetic approach toward (+)-chatancin.

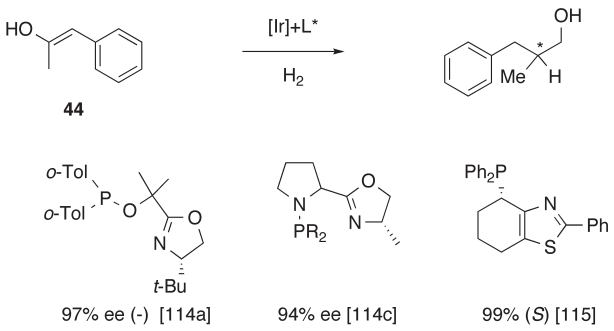
A chiral moiety close to the olefinic bond in an allylic alcohol profoundly affects the stereochemistry of the Ru(II)-catalyzed hydrogenation; Scheme 1.14 shows an interesting application to the synthesis of carbapenem. The extremely high diastereoselectivity in the hydrogenation of **(42)** to the β-product **(43)** with (*R*)-RuTol-BINAP can be explained by the cooperation of the efficient Ru-catalyst, olefin and center of chirality.



Scheme 1.14 Synthesis of carbapenem.

The major stereoisomer has been used the synthesis of the antibiotic precursor 1-β-methylcarbapenem [112]. Homogeneous hydrogenation with (*R*)- or (*S*)-BINAP diacetate complex allows kinetic resolution of allylic secondary alcohols [113].

Recently iridium catalysts containing chiral phosphine-oxazoline [114] and phosphine thiazole [115] ligands have been reported to catalyze the asymmetric hydrogenation of trisubstituted acrylic allylic alcohols **(44)** with high enantioselectivity up to 99% ee (Scheme 1.15).



Scheme 1.15 Ir-catalyzed reduction of allylic alcohols.

1.8
Synthesis of Pharmaceutical Intermediates

The production of enantiomerically pure drugs has brought asymmetric synthesis to the forefront of drug discovery [116]. Asymmetric hydrogenation of functionalized alkenes has been very successful, given the vast array of efficient catalysts now available, and this technique has been employed in the synthesis of many

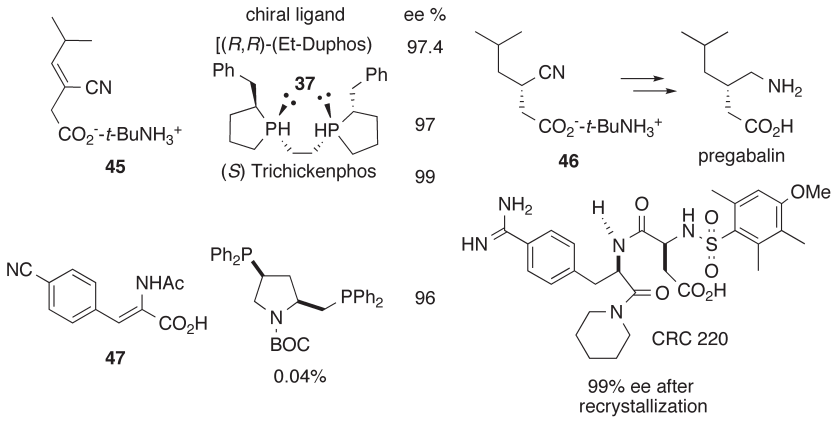
pharmaceutical intermediates. Some selected examples using asymmetric hydrogenation are shown in Schemes 1.16–1.19.

The synthesis of pregabalin, (*S*)-3-aminomethyl-5-methylhexanoic acid, a marketed anticonvulsant, has been achieved by the Rh-catalyzed asymmetric hydrogenation of 3-cyano-5-methylhex-3-enoic salt **(45)**. Burk and coworkers (Dowpharma, Chirotech) used [(*R,R*)-Et-Duphos-Rh(COD)]BF_4 to provide the desired (*S*)-3-cyano-5-methylhexanoate in very high ee (97.4%); the reaction takes place at 6.2 bar (620 kPa) of H_2 in 15 min in methanol [117]. Hoge designed two new enantioselective Rh-catalysts using a P-chirogenic, 1,2-bisphospholanoethane **(46)** [118] and (*S*)-trichikenPHOS [119].

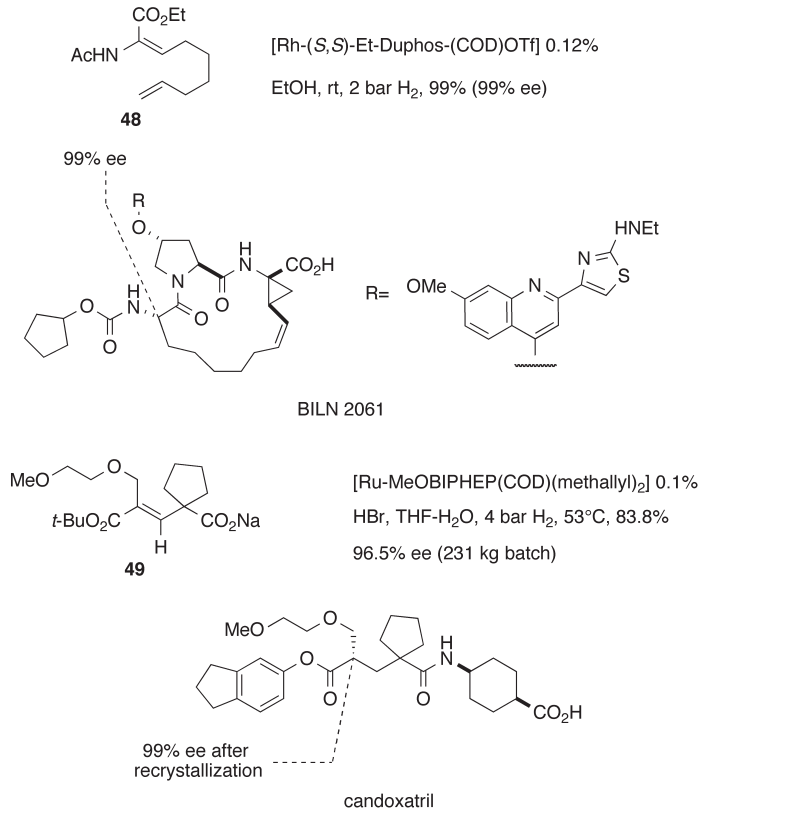
In connection with the synthesis of a thrombin inhibitor (CR220), Jendralla and coworkers (HMR/Aventis) described the enantioselective hydrogenation of dehydroamino acid **(47)** using Rh-(*S,S*)-BPPM with 96% ee. Precipitation from the reaction mixture increased the selectivity to >99.8% ee; this process has been scaled up to 10 kg (Scheme 1.16) [120].

Faucher and coworkers at Boehringer-Ingelheim have prepared ethyl-(*S*)-acetamido-8-nonenoate, one of the building blocks required for the synthesis of BILN 2061, an HCV protease inhibitor. This compound was obtained by enantioselective (99% ee) and chemoselective hydrogenation of the corresponding dehydroamino ester **(48)** using Rh-(*S,S*)-Et-Duphos (Scheme 1.17) [121].

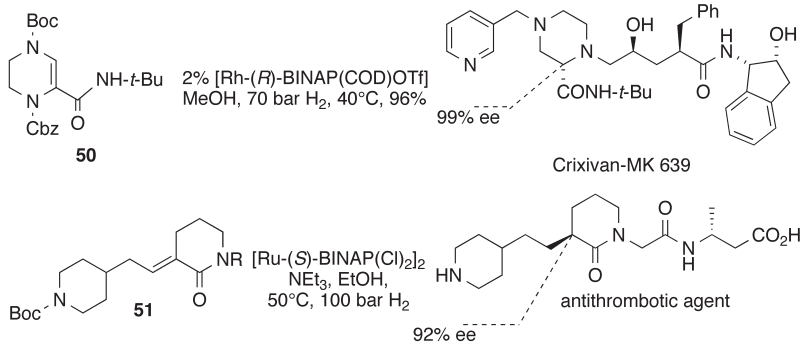
To synthesize the endopeptidase C inhibitor Candoxatril (Pfizer), Challenger devised an enantioselective route [122] using Noyori's catalyst. However, the double bond isomerization limited the chemical yield. As shown previously, Burk *et al.* at Chirotech improved the process using the Rh(I)-Duphos catalyst [94]. Asymmetric hydrogenation of the trisubstituted olefin **(49)** using the procedure of Genet was successfully optimized and scaled up by Bulliard and coworkers at PPG-SIPSY, with the (COD)(methylallyl)$_2$Ru + HBr, MeO-BIPHEP catalyst system (231 kg/batch size). The corresponding chiral succinate was prepared with 96.5% ee as a crude product (>99% ee after recrystallization). This procedure using



Scheme 1.16 Synthesis toward pregabalin and CRC220.



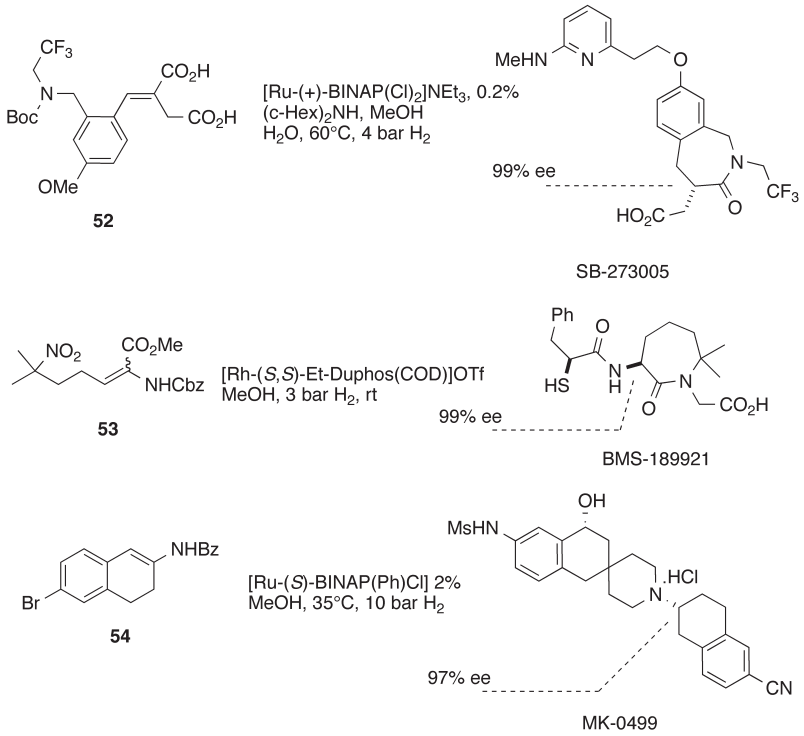
Scheme 1.17 Synthesis toward BILN2061 and candoxatril.



Scheme 1.18 Synthesis toward Crixivan-MK 639 and an anti thrombotic agent.

ruthenium metal is a cost-efficient process and has been used to manufacture more than two tonnes of candoxatril intermediate for phase III clinical trials [123].

Rossen and coworkers (Merck) have developed the preparation of the piperazine subunit of the anti-HIV drug Crixiran MK639. The hydrogenation of **(50)** using a



Scheme 1.19 Synthesis toward SB-273005, BMS-189921 and MK-0499.

Rh-(*R*)-BINAP catalyst at high pressure (70 bar) delivered the target compound in 99% ee (Scheme 1.18) [124]. Another application developed by Merck and reported by Chung and coworkers describes the enantioselective preparation of an antithrombotic agent. The asymmetric hydrogenation of a 3-alkylidene-2-piperidone **(51)** catalyzed by [Ru-(*S*)-BINAP-$Cl_2]_2NEt_3$ at high pressure (100 bar (10 MPa)) leads to the chiral 3-alkyl piperidinone in 92% ee [125].

The large-scale synthesis of SB-273005, a vitronectin receptor antagonist, was developed by Wallace and coworkers (GSK). The enantioselective hydrogenation of an itaconic derivative **(52)** was screened with several rhodium and ruthenium catalysts. The optimization of the catalyst system using $[Ru_2Cl_4$(*R*)-BINAP$)]NEt_3$ in the presence of dicyclohexylamine proved to be the most consistent method to obtain high selectivities (94% ee; 99% after recrystallization) [126]. To prepare the potent vasopeptidase inhibitor (BMS-189921), Singh and coworkers devised a highly enantioselective catalytic hydrogenation of an *E*/*Z* mixture of the dehydroamino acid **(53)**. Based on the literature the reaction was achieved using [Rh-(*S,S*)-EtDuphos(COD)] and as expected excellent ee values (99%) were obtained (Scheme 1.19) [127].

Tschaen and coworkers (Merck) have described the enantioselective hydrogenation of a cyclic enamide **(54)** with a Ru-(*S*)-BINAP catalyst that provided the desired chiral building block in 97% ee for the synthesis of the potent anti-arrhythmic agent (MK-0499) [128].

1.9 Conclusion

Asymmetric hydrogenation of olefins has been the subject of interest of many research groups in academia and industry. The successful hydrogenation reactions described herein proceed generally with both high enantioselectivities and conversions. During the past two decades the field of asymmetric hydrogenation has been growing very rapidly. A wide range of efficient enantioselective methods is now available. As a result, this technology is being more widely practiced and applied to large-scale asymmetric synthesis of fragrances, pharmaceutical and agrochemicals intermediates. It is obvious that many industrial process chemists have integrated these catalytic methods for the development of cost-effective processes. Issues such as development and catalyst activity are now at least as important as selectivity. In this regard, high-throughput and parallel-screening methods offer great assistance in catalyst optimization. Thus, there remain a variety of problems to be solved, as the development of more reactive catalysts is highly desirable. From a synthetic viewpoint, asymmetric hydrogenation has a bright future, particularly in the field of the synthesis of bioactive compounds.

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