26
The other Bisphosphine Ligands for Enantioselective Alkene Hydrogenation

Yongxiang Chi, Wenjun Tang, and Xumu Zhang

26.1
Introduction

This chapter describes atropisomeric biaryl bisphosphine ligands; modified DIOP-type ligands; P-chiral bisphosphane ligands; other bisphosphane ligands; and their applications in the enantioselective hydrogenation of olefins.

26.2
Chiral Bisphosphine Ligands

26.2.1
Atropisomeric Biaryl Bisphosphine Ligands

In 1980, Noyori and Takaya reported an atropisomeric C_2-symmetric bisphosphine ligand, BINAP [1]. This ligand was first used in Rh-catalyzed enantioselective hydrogenation of α-(acylamino)acrylic acids, and high selectivities were reported for some substrates [2]. However, the significant impact of BINAP in asymmetric hydrogenation did not gain very much attention until it was applied in ruthenium chemistry. In 1986, Noyori and Takaya prepared a BINAP–Ru dicarboxylate complex for the asymmetric hydrogenation of various functionalized alkenes [3]. Subsequently, these authors discovered that the halogen-containing BINAP–Ru complexes were also efficient catalysts for enantioselective hydrogenation of a range of functionalized ketones [4]. During the mid-1990s, another major breakthrough was made on BINAP–Ru chemistry when Noyori discovered that the Ru–BINAP/diamine complexes were efficient catalysts for the enantioselective hydrogenation of some unfunctionalized ketones [5]. This advance addressed a long-standing challenging problem in enantioselective hydrogenation. Importantly, the catalytic system can selectively reduce ketones in the presence of carbon–carbon double or triple bonds [6]. Inspired by Noyori's studies on the BINAP chemistry, other research groups developed many excellent atropisomeric biaryl bisphosphine ligands. For example, Miyashima reported a BI-

The Handbook of Homogeneous Hydrogenation.
Edited by J.G. de Vries and C.J. Elsevier

ISBN: 978-3-527-31161-3

CHEP ligand, which was successfully applied in both Rh- and Ru-catalyzed enantioselective hydrogenation [7]. Schmid et al. reported BIPHEMP [8] and MeO-BIPHEP [9] ligands, both of which were successfully applied in many Ru-catalyzed hydrogenations. Achiwa also developed several atropisomeric ligands such as BIMOP [10], FUPMOP [11], and MOC-BIMOP (Fig. 26.1) [12].

Modification of the electronic and steric properties of BINAP, BIPHEMP, and MeO-BIPHEP can lead to the development of new efficient atropisomeric ligands (Fig. 26.1). In fact, Takaya has found that a modified BINAP ligand, H_8-BINAP, provides better enantioselectivity than BINAP in the Ru-catalyzed hydrogenation of unsaturated carboxylic acids [13]. Mohr has developed a bis-steroidal bisphosphine **1**, which has shown similar catalytic results to BINAP in the Ru-catalyzed enantioselective hydrogenation [14]. Hiemstra has developed a dibenzofuran-based bisphosphine BIFAP, which has shown excellent enantioselectivity in the Ru-catalyzed hydrogenation of methyl acetoacetate [15]. The dihedral angle of the biaryl backbone is expected to have a strong influence on the enantioselectivity. Another chiral biaryl bisphosphine ligand, SEGPHOS, was developed in Takasago. The ligand, which possesses a narrower dihedral angle than BINAP, has provided greater enantioselectivity than BINAP in the Ru-catalyzed hydrogenation of a wide variety of carbonyl compounds [16]. Chan [17a] and Genêt [17b,c] have reported a closely related ligand bisbenzodioxanPhos (SYNPHOS) independently. In order systematically to investigate the influence of the dihedral angle of biaryl ligands on enantioselectivity, Zhang has developed a series of TunePhos ligands with tunable dihedral angles. When the TunePhos ligands are applied in the Ru-catalyzed enantiomeric hydrogenation of β-keto esters, the ee-values obtained fluctuate with the different dihedral angles of the TunePhos ligands [18]. C4-TunePhos shows comparable or superior enantioselectivity to BINAP in Ru-catalyzed hydrogenation of β-keto esters. More applications of the TunePhos ligands have shown that different asymmetric catalytic reactions may require a different TunePhos ligand with a different dihedral angle. When TunePhos ligands are applied in the Ru-catalyzed hydrogenation of enol acetates, C2-TunePhos is the best ligand in terms of enantioselectivity [19]. However, C3-TunePhos provided the best enantioselectivities for the synthesis of cyclic β-amino acids [20], and the hydrogenation of α-phathalimide ketones [21]. Genêt and Marinetti have developed a non-C_2 symmetric biaryl bisphosphine, MeO-NAPhePHOS, which has shown comparable results to C_2-symmetric biaryl bisphosphine in Ru-catalyzed hydrogenation [22].

Structural variation of BINAP or MeO-BIPHEP can also be made on the aromatic rings of the biaryl backbone (Fig. 26.1). For example, the aromatic rings can be replaced by five- or six-membered heteroaromatic rings. Sannicolò et al. have discovered a series of biheteroaryl bisphosphines such as BITIANP, TetraMe-BITIANP [23], and TetraMe-BITIOP [24]. These ligands have shown comparably good results to BINAP in Ru-catalyzed enantioselective hydrogenation. Chan has reported a dipyridylphosphine ligand P-Phos for Ru-catalyzed enantioselective hydrogenation, and high enantioselectivities and reactivities have been obtained in the hydrogenation of β-keto esters, α-arylacrylic acids, and simple ketones [25].

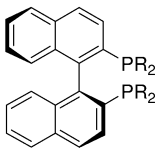
An *ortho*-substituted BIPHEP ligand, *o*-Ph-HexaMeO-BIPHEP, has been recently developed by Zhang [26]. With two phenyl groups at the *ortho* positions of two diphenylphosphino groups, *o*-Ph-HexaMeO-BIPHEP is specially designed to restrict the rotation of the P-phenyl groups, which is considered to be detrimental for some enantioselective reactions. The design is effective when *o*-Ph-HexaMeO-BIPHEP is employed in the Rh-catalyzed enantioselective hydrogenation of cyclic enamides. While chiral ligands without *ortho*-substituents such as BINAP, BIPHEP, and HexaMeO-BIPHEP provide very poor selectivities, *o*-Ph-HexaMeO-BIPHEP shows excellent enantioselectivity in the hydrogenation of a series of cyclic enamides [26]. Zhang also reported another *ortho*-substituted BIPHEP type ligand – *o*-Ph-MeO-BIPHEP – which afforded excellent enantioselectivities in the hydrogenation of α-dehydroamino acids [27].

Henschke and Casy prepared a biaryl bisphosphine ligand, HexaPhemp, which performed as well as, or better than, the corresponding BINAP ligands [28]. Dellis and Genêt have developed a new electron-deficient atropisomeric ligand based on a SEGPHOS backbone, difluorphos, which has a narrow dihedral angle and electronic-withdrawing substituents. The electron-deficiency was shown to be crucial to reach high levels of enantioselectivity in hydrogenation of some challenging β-keto ester substrates [29].

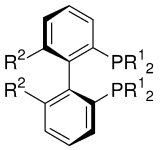
Chan has discovered a completely atropdiasteroselective synthesis of a biaryl diphosphine based on an enantioselective intramolecular Ullmann coupling or a Fe(III)-promoted oxidative coupling. A chiral atropisomeric biaryl bisphosphine ligand **2** was synthesized through this central-to-axial chirality transfer [30]. Recently, a xylyl-biaryl bisphosphine ligand, Xyl-TetraPHEMP was introduced by Moran, and found to be effective for the Ru-catalyzed hydrogenation of aryl ketones [31].

A family of tunable 4,4′-substituted BINAP was reported by Lin: 4,4-$[SiMe_3]_2$-BINAP **3** and polar 4,4-$[P(O)OH_2]_2$-BINAP **4** have shown high enantioselectivities (up to 99.6% ee) in the hydrogenation of a variety of β-aryl ketoesters [32]. 4,4-$[SiMe_3]_2$-BINAP **3** is also effective for the asymmetric hydrogenation of α-phthalimide ketones and 1,3-diaryl diketones [33]. The 4,4′-bulky groups were shown to be responsible for the enhancement of enantioselectivity and diastereoselectivity in these reactions. Lemaire prepared 4,4′- or 5,5′-diamBINAP, with a 4,4′- or 5,5′-diaminomethyl substituent; the hydrosoluble HBr salt of the Ru complex based on these ligands afforded high enantioselectivity (>97% ee) in the water/organic solvent biphasic hydrogenation of β-keto esters [34]. Lemaire also reported 4,4′- or 5,5′-perfluoroalkylated BINAP, **5** and **6**, which showed the same activities and enantioselectivities as 4,4′- or 5,5′-diamBINAP in the hydrogenation of β-keto esters (Fig. 26.1) [35].

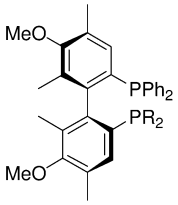
As with most chiral atropisomeric ligands, resolution or enantioselective synthesis is requisite. Mikami developed a novel ligand-accelerated hydrogenation catalyst in which the chirality of an atropos but achiral triphos–Ru complex could be controlled by chiral diamines. Using (*S*)-dm-dabn as controller, a single diastereomeric triphos–Ru complex was obtained through isomerization of the (*R*)-triphos–Ru complex in dichloroethane at 80 °C (Scheme 26.1) [36].



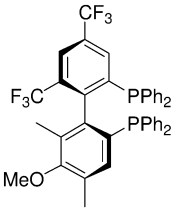
(*S*)-BINAP: R = Ph
(*S*)-TolBINAP: R = 4-MePh
(*S*)-XylBINAP: R = 3,5-$(Me)_2$Ph



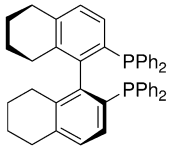
(*S*)-BICHEP: R^1 = Cy; R^2 = CH_3
(*S*)-BIPHEMP: R^1 = Ph; R^2 = CH_3
(*S*)-MeO-BIPHEP: R^1 = Ph; R^2 = OCH_3



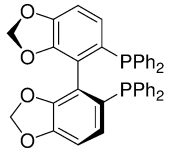
(*S*)-BIMOP: R = Ph
(*S*)-MOC-BIMOP: R = Cy



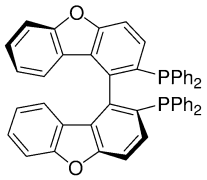
(*S*)-FUPMOP



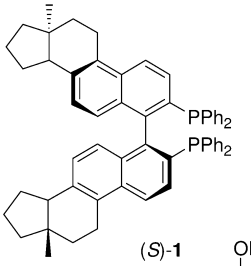
(*S*)-H_8-BINAP



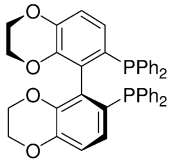
(*S*)-SEGPHOS



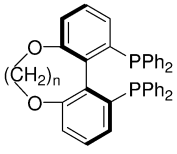
(*S*)-BIFAP



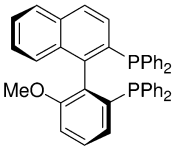
(*S*)-**1**



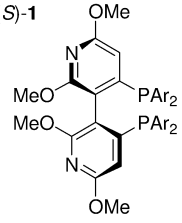
(*S*)-BisbenzodioxanPhos
(SYNPHOS)



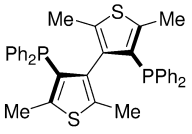
(*S*)-Cn-TunePhos
n = 1-6



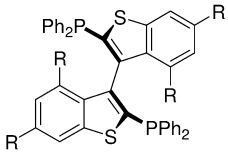
(*S*)-MeO-NAPhePHOS



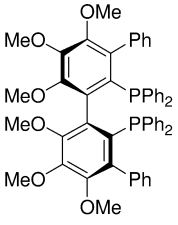
(*S*)-P-Phos: Ar = Ph
(*S*)-Tol-P-Phos: Ar = 4-MePh
(*S*)-Xyl-P-Phos: Ar = 3,5-$(Me)_2$Ph



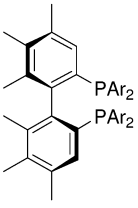
(*R*)-TetraMe-BITIOP



(*R*)-TetraMe-BITIANP: R = Me
(*R*)-BITIANP: R = H

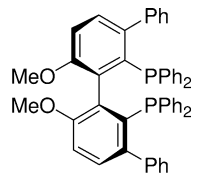


(*S*)-*o*-Ph-HexaMeO-BIPHEP

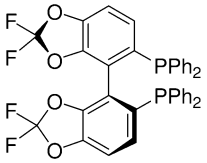


(*S*)-HexaPhemp, Ar=Ph
(*S*)-Xyl-HexaPhemp, Ar=Xyl

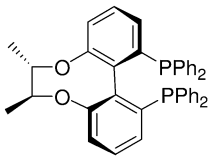
Fig. 26.1 Atropisomeric biaryl bisphosphine ligands.



(*S*)-***o*-Ph-MeO-BIPHEP**



(*S*)-Difluorphos



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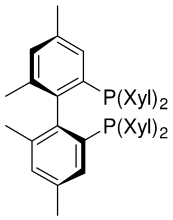
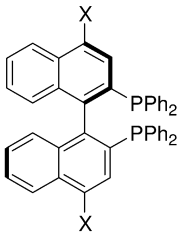
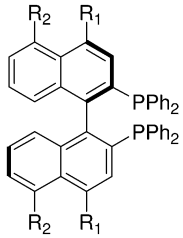


(*S*)-**Xyl-TetraPHEMP**



(*R*)-**3**,X=TMS

(*R*)-**4**, X=P(O)(OH)$_2$



(*R*)-4,4'-diamBINAP, R_1=CH_2NH_2, R_2=H

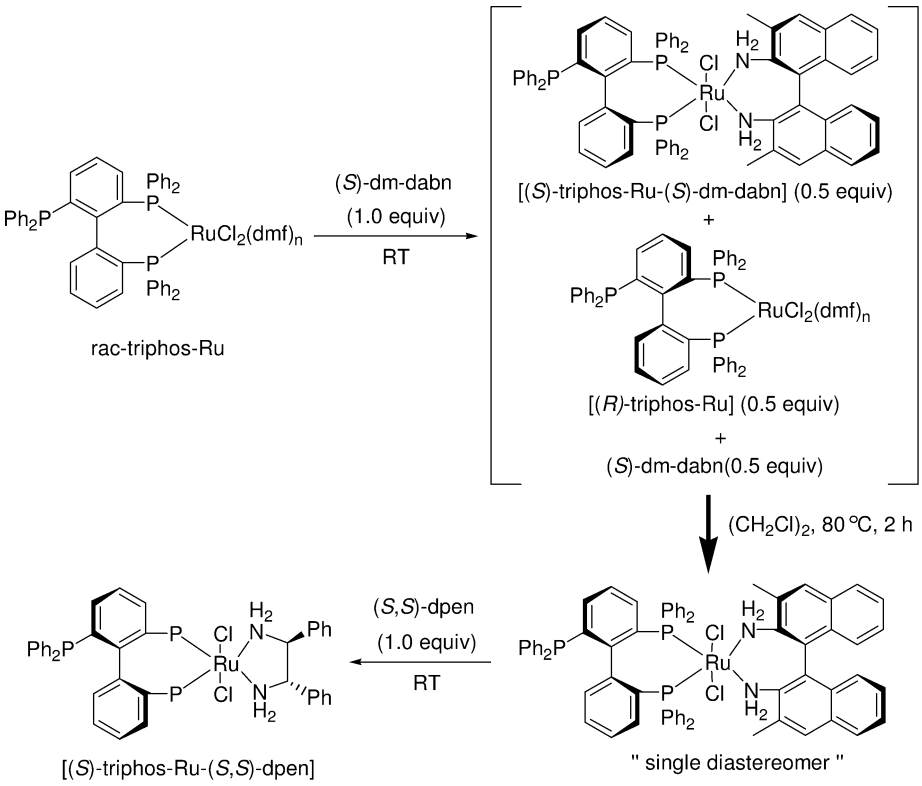
(*R*)-5,5'-diamBINAP, R_1=H, R_2=CH_2NH_2

(*R*)-**5**, R_1=C_6F_{13}, R_2=H

(*R*)-**6**, R_1=H, R_2=C_6F_{13}

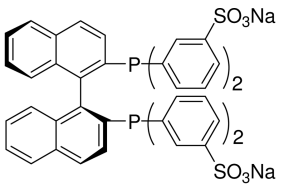
Fig. 26.1 (continued)

Some BINAP or BIPHEP derivatives have also been made in order to make the catalysts water-soluble or recyclable (Fig. 26.2). The literature on supported homogeneous catalysts in the field of asymmetric hydrogenation using BINAP derivatives has recently been reviewed [37]. Davis et al. reported a sulfonated BINAP ligand, BINAP-4-SO_3Na, and found that its water-soluble Ru complex has comparable catalytic properties to the unmodified BINAP-Ru catalyst for hydrogenation of 2-acetamidoacrylic acid [38]. Schmid et al. have developed a water-soluble MeO-BIPHEP type ligand, MeOBIPHEP-S. The ligand has the sulfonato group attached at the *para* position of each P-phenyl group to minimize the possible steric interactions of the sulfonato groups with the inner ligand sphere of a coordinated metal, and thus to retain the high enantioselectivity of the non-sulfonated catalyst. Indeed, MeOBIPHEP-S has shown similarly high enantioselectivity and reactivity to MeO-BIPHEP in the Ru-catalyzed hydrogenation of unsaturated carboxylic acids [39]. Genêt has recently reported some recyclable BINAP ligands such as *Digm*-BINAP and PEG-*Am*-BINAP, which were obtained by tethering BINAP with guanidine and PEG groups, respectively. The Ru catalysts of these ligands maintained high enantioselectivity after three or four recycles [40]. Many polymer-supported BINAP ligands have been developed. For instance, Bayston incorporated the BINAP framework onto an insoluble polymer (polystyrene). The resulting polymer-bound BINAP, after treatment with [Ru(cod)(2-methylallyl)$_2$]$_2$ and HBr, induces high ee-values in the hydrogenation of *β*-keto esters and acrylic acids [41]. The polymer can be recycled as the cata-

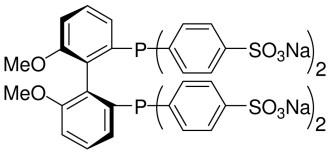


Scheme 26.1

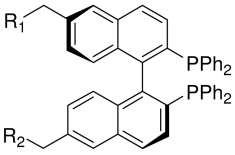
lyst several times, while high ee-values are maintained. Noyori used the same polymer-bound BINAP to create a polymer-bound BINAP/diamine Ru catalyst, which has furnished high ee-values and turnover numbers (TONs) in the hydrogenation of simple ketones [42]. Chan has developed a highly effective polyester-supported BINAP ligand through copolymerization of chiral 5,5′-diaminoBINAP, chiral pentanediol, and terephthaloyl chloride [43]. The ligand has been successfully applied repeatedly in the Ru-catalyzed enantioselective hydrogenation of 2-(6′-methoxy-2-naphthyl)acrylic acid. A dendrimer-supported BINAP ligand has also been reported [44]. Pu has developed several polymer-based chiral ligands such as poly(BINAP) and BINOL-BINAP. These ligands have been applied successfully in the Rh-catalyzed hydrogenation of (*Z*)-methyl *α*-(benzamido)cinnamate and in the Ru-catalyzed hydrogenation of simple ketones [45]. Lemaire et al. have reported a poly-NAP Ru complex, which provides 99% ee in the hydrogenation of methyl acetoacetate, even after four recycles of the catalyst [46].



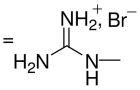
BINAP-4SO_3Na

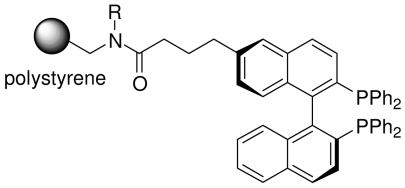


MeOBIPHEP-S



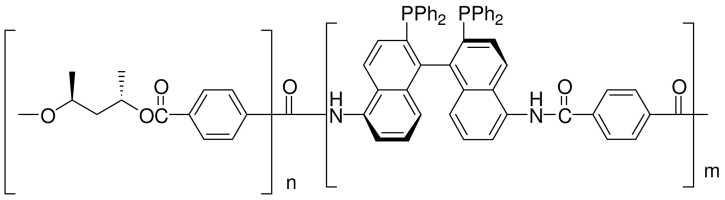
Digm-BINAP: $R_1 = R_2 =$



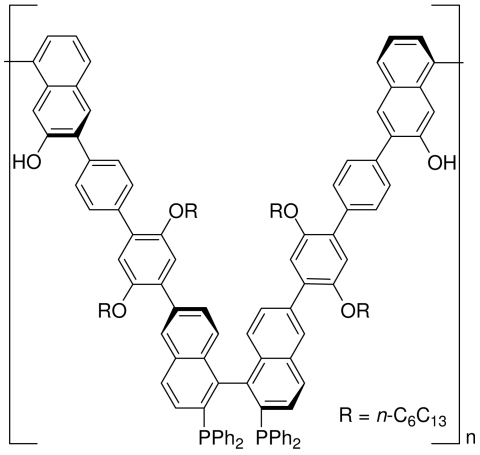


polystyrene-supported BINAP

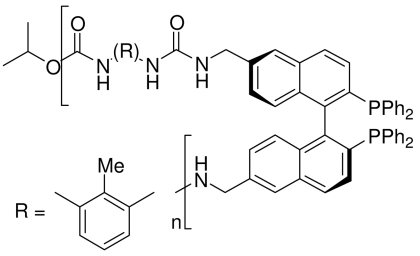
PEG-*Am*-BINAP: R_1 = $MeO(CH_2CH_2O)n\text{-}CO(CH_2)_3CONH$, $R_2 = NH_2$



polyester-supported BINAP



BINOL-BINAP



poly-BINAP

Fig. 26.2 Water-soluble or recyclable BINAP or BIPHEP derivative catalysts.

26.2.2
Chiral Bisphosphine Ligands Based on DIOP Modifications

Kagan's pioneering studies on the development of DIOP has had significant impact on the design of new efficient chiral ligands for enantioselective hydrogenation [47]. However, DIOP itself provides only moderate to good enantioselectivity in the enantioselective hydrogenation of dehydroamino acid derivatives, and its application in highly enantioselective hydrogenation has rarely been disclosed. A possible reason for this is that the seven-membered chelate ring of the DIOP metal complex is conformationally flexible. These conformational ambiguities, as depicted in Figure 26.3, may be responsible for its low efficiency.

Achiwa successfully developed several modified DIOP ligands by varying the electronic and steric properties of DIOP. MOD-DIOP was applied in the rhodium-catalyzed enantioselective hydrogenation of itaconic acid derivatives, and up to 96% ee was obtained [48]. In order to rigidify the conformational flexibility of DIOP, Zhang has introduced a rigid 1,4-diphosphane ligand BICP with two five-membered carbon rings on its backbone (Fig. 26.4). BICP was found to be an efficient ligand for the hydrogenation of α-dehydroamino acids, β-dehydroamino acids, arylenamides, and MOM-protected β-hydroxy enamides [49]. Genov introduced several BICP family ligands, and developed a new catalytic system comprising Ru–**7** or Ru–**8** complexes in combination with a nonchiral 2-(alkylthio)amine or 1,2-diamine and an alkoxide as a base for the highly enantioselective hydrogenation of aryl ketones [50]. Several rigidified DIOP-type ligands have been developed. Zhang [51] and RajanBabu [52] have independently reported the development of DIOP* by introducing two alkyl substituents at the α-positions of the diphenylphosphine groups. The (*S*,*R*,*R*,*S*)-DIOP* was found to provide excellent enantioselectivity in the Rh-catalyzed hydrogenation of arylenamides and MOM-protected β-hydroxy enamides [51]. However, its isomeric ligand (*S*,*S*,*S*,*S*)-DIOP*, which was first synthesized by Kagan [53], provided much lower enantioselectivity. It is believed that the two methyl groups of (*S*,*R*,*R*,*S*)-DIOP* orientate at pseudoequatorial positions in the "effective" conformer of the DIOP* metal complex, thereby stabilizing the "effective" conformer to promote high enantioselectivity. On the other hand, its isomeric ligand (*S*,*S*,*S*,*S*)-DIOP* has two methyl groups at pseudoaxial positions, which destabilize the "effective" conformer and lead to diminished ee-values. Lee has developed 1,4-diphosphane ligands BDPMI, **9** and **10**, with an imidazolidin-2-one backbone [54]. The *gauche* steric interaction between the *N*-substituents and

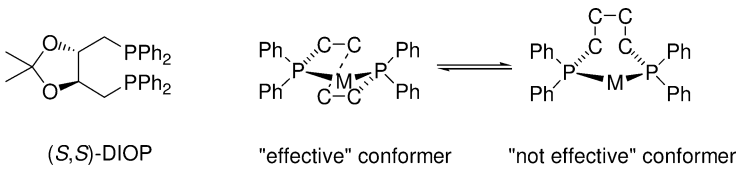


Fig. 26.3 Conformation analysis of DIOP metal complex.

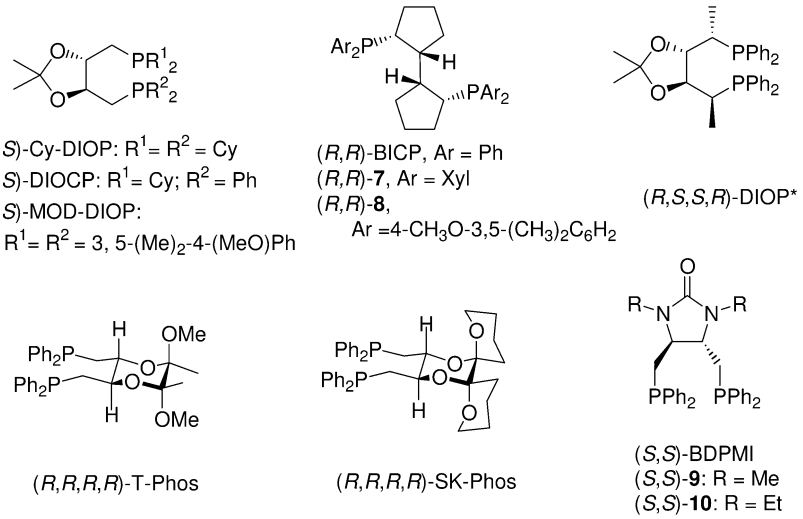


Fig. 26.4 Chiral bisphosphane ligands based on DIOP modifications.

phosphanylmethyl group of the ligands may restrict the conformational flexibility of the seven-membered metal chelate ring. The BDPMI ligands have been successfully applied in the Rh-catalyzed hydrogenation of arylenamides, and up to 99% ee-values have been obtained. A series of 1,4-diphosphane ligands with a conformationally rigid 1,4-dioxane backbone such as T-Phos, and SK-Phos have been developed by Zhang and found to be efficient (up to 99% ee) in the rhodium-catalyzed asymmetric hydrogenation of arylenamides and MOM-protected β-hydroxyl enamides [55].

26.2.3
P-Chiral Bisphosphine Ligands

Knowles made the important discovery of the first C_2-symmetric chelating bisphosphine ligand, DIPAMP, which performed much better than the monomeric PAMP [56]. Due to its high catalytic efficiency in the Rh-catalyzed enantioselective hydrogenation of dehydroamino acids, the first P-chiral bisphosphane DIPAMP was quickly employed in the industrial production of L-Dopa [57]. However the development of new efficient P-chiral bisphosphanes was slow, partly because of the difficulties in the ligand synthesis. It was not until Imamoto [58] discovered a series of efficient P-chiral ligands such as BisP* that the development of P-chiral phosphorus ligands regained attention (Fig. 26.5). The BisP* ligands have induced high activity and enantioselectivity in the rhodium-catalyzed hydrogenation of α-dehydroamino acids, enamides [59], (*E*)-β-(acylamino)-acrylates [60], and α,β-unsaturated-α-acyloxyphosphonates [61]. Mechanistic studies on enantioselective hydrogenation with ^{t}Bu-BisP* as the ligand by Gridnev and Imamoto provided evidence that the Rh-catalyzed hydrogenation can proceed by a different mechanism

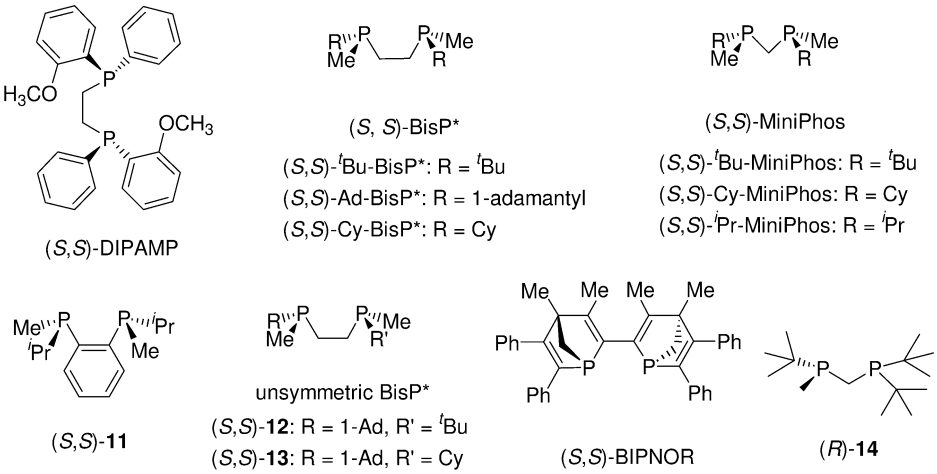


Fig. 26.5 P-chiral ligands.

with an electron-rich phosphorus ligand. A dihydride pathway [62] was suggested, which is different from the classic unsaturated pathway [63, 64] proposed by Halpern and Brown. In addition to Bisp*, several other P-chiral bisphosphanes such as MiniPhos [65], 1,2-bis(isopropylmethylphosphino)benzene (**11**) [66], and unsymmetrical P-chiral BisP* (such as **12** and **13**) [67] have been developed by Imamoto. Imamoto has also developed the P-chirogenic trialkylphosphonium salts derived from Bisp* and MiniPhos. These air-stable salts were conveniently applied in the Rh-catalyzed enantioselective hydrogenation of enamides [68].

Mathey has reported a bisphosphane ligand BIPNOR which contains two chiral bridgehead phosphorus centers [69]. BIPNOR has shown high enantioselectivity in the rhodium-catalyzed hydrogenation of α-(acetomido)cinnamic acid and itaconic acid. Recently, a three-hindered quadrant P-chirogenic ligand (*R*)-**14** was also reported by Hoge (Fig. 26.5) [70]. Using (*R*)-**14**–Rh as catalyst, both *E*- and *Z*-(β-acylamino) acrylates have been hydrogenated with high enantioselectivities (up to 99% ee) [71].

26.2.4
Other Bisphosphine Ligands

Some other efficient chiral bisphosphane ligands are illustrated in Figure 26.6. These include Bosnich's CHIRAPHOS [72] and PROPHOS [73], Achiwa's BPPM [74], and Rhône-Poulenc's TBPC [75]. A series of modified BPPM ligands such as BCPM and MOD-BPPM were also developed by Achiwa [76]. Some excellent chiral 1,2-bisphosphane ligands such as NORPHOS [77], PYRPHOS (DEGUPHOS) [78], and DPCP [79] for Rh-catalyzed enantioselective hydrogenation were also developed during this period. A few 1,3-bisphosphine ligands such as BDPP (SKEWPHOS) [80] and PPCP [81] were also prepared.

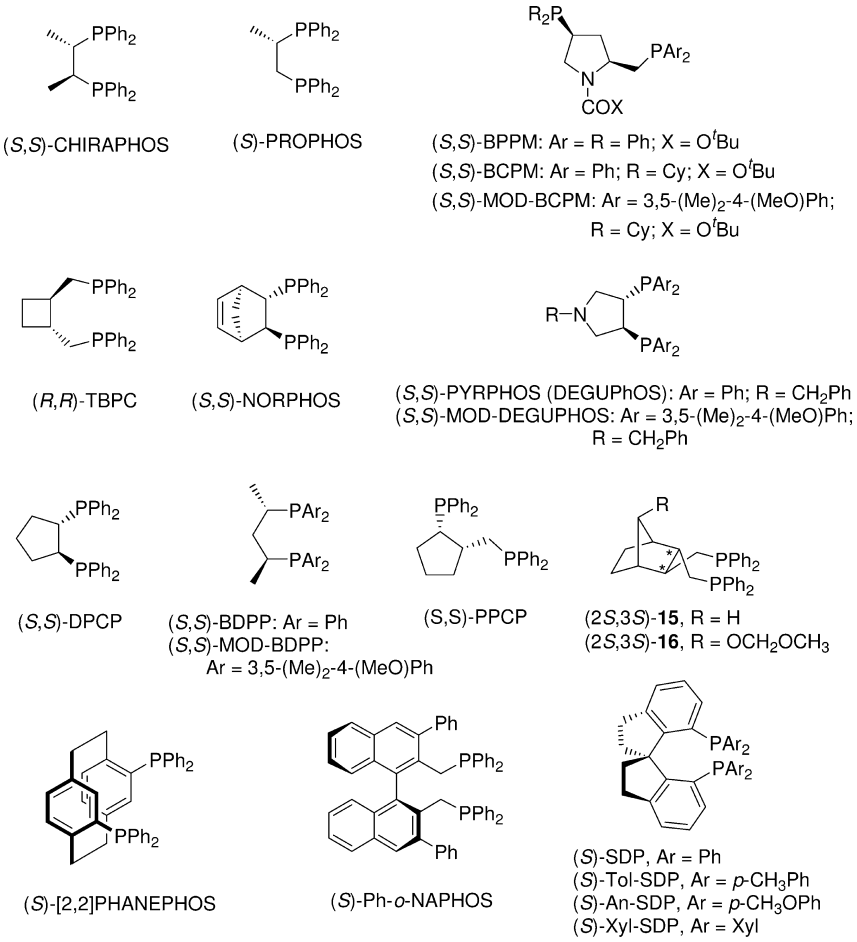


Fig. 26.6 Other efficient chiral bisphosphane ligands.

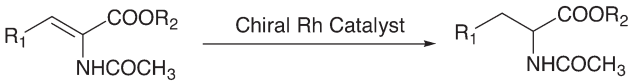
Pye and Rossen have developed a planar chiral bisphosphine ligand, [2.2] PHANEPHOS, based on a paracyclophane backbone [82]. The ligand has shown excellent enantioselectivity in Rh- or Ru-catalyzed hydrogenations. An *ortho*-phenyl substituted NAPHOS ligand, Ph-*o*-NAPHOS, has been applied successfully in the Rh-catalyzed hydrogenation of *α*-dehydroamino acid derivatives [83]. Compared to NAPHOS, Ph-*o*-NAPHOS has a more rigid structure and provides higher enantioselectivities. The chiral norbornane diphosphine ligands, **15** and **16**, were reported by Morimoto, and applied in Rh-catalyzed enantioselective hydrogenation [84]. Zhou reported a family of chiral spirodiphosphine ligands such as SDP, containing 1,1′-spirobi-indane as a new scaffold, which are effective for the hydrogenation of simple ketones (Fig. 26.6) [85].

26.3
Applications in Enantioselective Hydrogenation of Alkenes

26.3.1
Enantioselective Hydrogenation of α-Dehydroamino Acid Derivatives

Hydrogenation of α-dehydroamino acid derivatives has been a typical reaction to test the efficiency of new chiral phosphorus ligands. Indeed, a large number of chiral phosphorus ligands with great structural diversity are found to be effective for the Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives. Since (*Z*)-2-(acetamido) cinnamic acid, 2-(acetamido) acrylic acid and their methyl esters are the most frequently applied substrates, and some efficient examples (>95% ee) of hydrogenation of these substrates with different chiral ligands are listed in Table 26.1. Generally, cationic Rh complexes and low hydrogenation pressure are applied in these hydrogenation reactions.

Table 26.1 Enantioselective hydrogenation of α-dehydroamino acid derivatives.



A: R_1 = H, R_2 = H B: R_1 = H, R_2 = CH_3
C: R_1 = Ph, R_2 = H D: R_1 = Ph, R_2 = CH_3

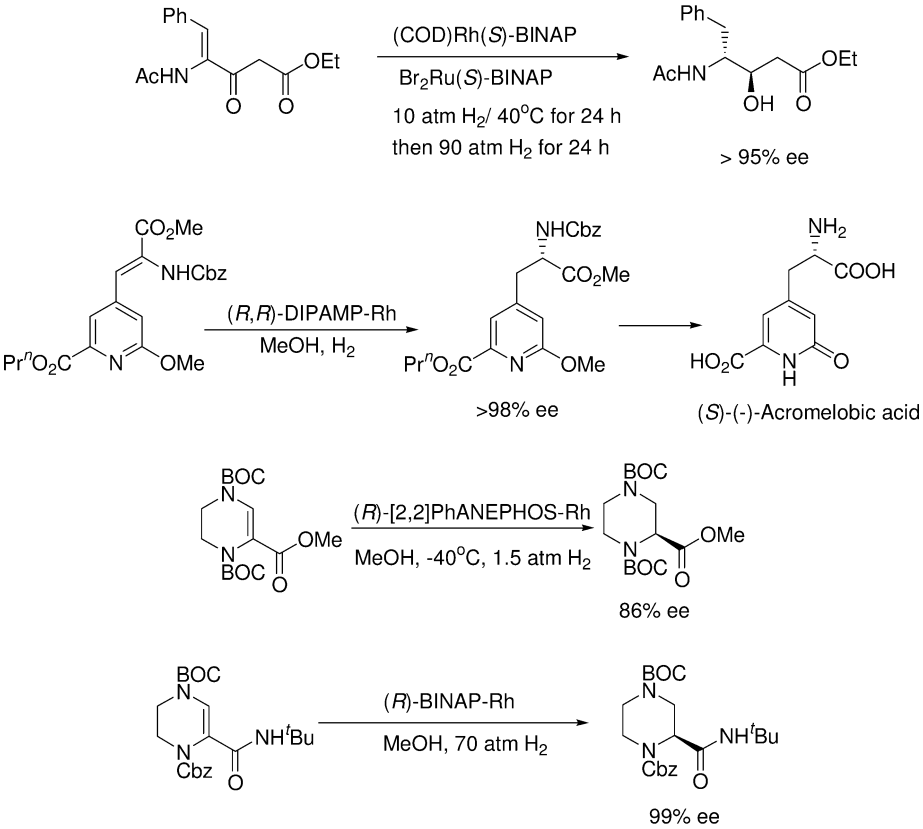
Ligand	Substrate	SCR	Reaction conditions	% ee of product (config.)	Reference
(*S*)-BINAP	D [a]	100	EtOH, rt, 3 atm H_2	100 (*S*)	1
(*R*)-BICHEP	D [b]	1000	EtOH, rt, 1 atm H_2	95 (*S*)	7c
(*S*)-*o*-Ph-MeO-BIPHEP	A	100	CH_2Cl_2, rt, 1.7 atm H_2	>99 (*S*)	27
(*R*,*R*)-BICP	A	100	THF, Et_3N, rt, 1 atm H_2	97.5 (*S*)	49a
(*R*,*R*)-DIPAMP	D	900	MeOH, 50 °C, 3 atm H_2	96 (*S*)	56a
(*S*,*S*)-^{t}Bu-BisP*	D	500	MeOH, rt, 2 atm H_2	99.9 (*R*)	58a
(*S*,*S*)-^{t}Bu-MiniPhos	B	500	MeOH, rt, 2 atm H_2	99.9 (*R*)	65
(*S*,*S*)-**11**	B	500	0 °C, 2 atm H_2	97 (*S*)	66
(*S*,*S*)-**12**	D	500	MeOH, rt, 2 atm H_2	99.2 (*R*)	67a
(-)-BIPNOR	C	100	EtOH, rt, 3 atm H_2	>98 (*S*)	69a
(*R*)-**14**	A	100	MeOH, rt, 3.4 atm H_2	>99 (*R*)	70
(*R*)-**14**	C	100	MeOH, rt, 3.4 atm H_2	>99 (*R*)	70
(*R*,*R*)-NORPHOS	C	95	MeOH, rt, 1.1 atm H_2	96 (*R*)	77
(*R*,*R*)-PYRPHOS	D	50000	MeOH, rt, 61 atm H_2	96.5 (*S*)	78b
(*R*)-PHANEPHOS	B	100	MeOH, rt, 1 atm H_2	99.6 (*R*)	82a
(*S*)-Ph-o-NAPHOS	B	100	MeOH, rt, 3 atm H_2	98.7 (*S*)	83

a) Benzoyl derivative.
b) Ethyl ester.
SCR: substrate:catalyst ratio.

Several chiral ligands, such as PYRPHOS [78b], have been shown to be very efficient ligands for the hydrogenation of α-dehydroamino acid derivatives in terms of both high enantioselectivity and reactivity.

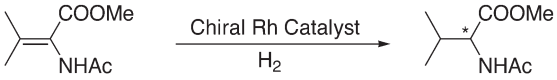
In contrast to the high enantioselectivity achieved for the *Z*-isomeric substrates, hydrogenation of the *E*-isomeric substrates usually proceeds at a much lower rate and gives poor enantioselectivities [86]. With the Rh–BINAP system as the catalyst and tetrahydrofuran (THF) as solvent, hydrogenation of the *Z*- and *E*-isomeric substrates generates products with different configurations [2].

Many synthetic applications of Rh-catalyzed hydrogenation of α-dehydroamino acid derivatives have recently been explored (Scheme 26.2). Takahashi has reported a one-pot sequential enantioselective hydrogenation utilizing a BINAP–Rh and a BINAP–Ru catalyst to synthesize 4-amino-3-hydroxy-5-phenylpentanoic acids in over 95% ee. The process involves a first step in which the dehydroamino acid unit is hydrogenated with the BINAP–Rh catalyst, followed by hydrogenation of the β-keto ester unit with the BINAP–Ru catalyst [87]. A hindered pyridine substituted α-dehydroamino acid derivative has been hydrogenated by a



Scheme 26.2

Table 26.2 Enantioselective hydrogenation of β,β-dimethyl α-dehydroamino acid esters.



Ligand	SCR	Reaction conditions	% ee of product (config.)	Reference
(*S*,*S*)-Cy-BisP*	500	MeOH, rt, 6 atm H_2	90.9 (*R*)	58a
(*S*,*S*)-^{t}Bu-MiniPhos	500	MeOH, rt, 6 atm H_2	87 (*R*)	65
(*S*,*S*)-**11**	500	rt, 6 atm H_2	87 (*S*)	66
(*S*,*S*)-**13**	100	MeOH, rt, 20 atm H_2	96.1 (*R*)	67b

SCR: substrate:catalyst ratio.

DIPAMP–Rh complex to give the corresponding chiral α-amino acid derivative in over 98% ee. The chiral product has been used for the synthesis of (*S*)-(–)-acromelobic acid [88]. Hydrogenation of a tetrahydropyrazine derivative catalyzed by a PHANEPHOS–Rh complex at –40 °C gives an intermediate for the synthesis of Crixivan in 86% ee [82a]. Hydrogenation of another tetrahydropyrazine carboxamide derivative catalyzed by an (*R*)-BINAP–Rh catalyst leads to the chiral product in 99% ee [89].

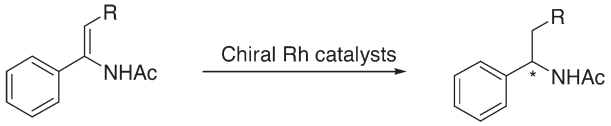
The hydrogenation of β,β-disubstituted α-dehydroamino acids remains a relatively challenging problem. The Rh complexes of chiral ligands such as Cy-BisP* [58a], MiniPhos [65], and unsymmetrical BisP* **13** [67b] have shown high efficiencies for some β,β-disubstituted α-dehydroamino acid substrates. Some efficient examples of hydrogenation of β,β-dimethyl α-dehydroamino acid esters with different chiral phosphorus ligands are listed in Table 26.2.

26.3.2 Enantioselective Hydrogenation of Enamides

Rh-catalyzed hydrogenation of simple enamides has attracted much attention recently. With the development of increasingly efficient chiral phosphorus ligands, extremely high ee-values can be obtained in the Rh-catalyzed hydrogenation of α-aryl enamides. *E*/*Z*-isomeric mixtures of β-substituted enamides can also be hydrogenated, with excellent ee-values. Some efficient examples (>95% ee) of hydrogenation of α-phenylenamide and *E*/*Z*-isomeric mixtures of β-methyl-α-phenylenamide are listed in Table 26.3.

Some alkyl enamides such as *tert*-butylenamide or 1-adamantylenamide can also be hydrogenated with a ^{t}Bu-BisP*–Rh catalyst in 99% ee. Notably, the configurations of the hydrogenation products of these bulky alkyl enamides are opposite to those of aryl enamides. A mechanistic study [90] by Gridnev and Imamoto [59] using nuclear magnetic resonance (NMR) techniques indicates that the hydrogenations of bulky alkyl enamides and aryl enamides involve different

Table 26.3 Enantioselective hydrogenation of enamides.



A: R = H B: R = CH_3 (*E*/*Z*)

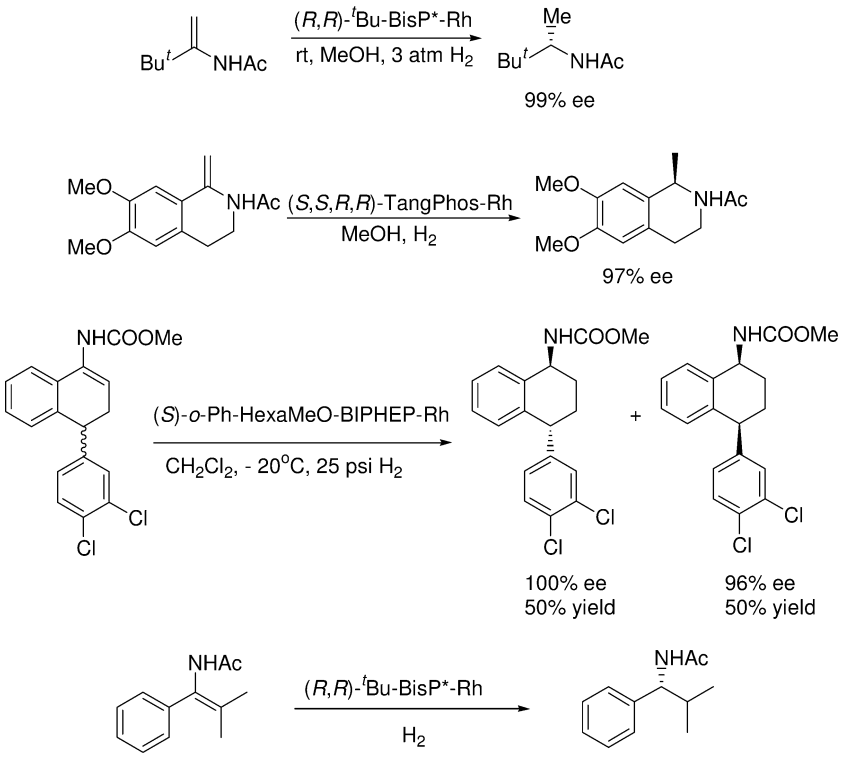
Ligand	Substrate	SCR	Reaction conditions	% ee of product (config.)	Reference
(*R*,*R*)-BICP	B	100	Toluene, rt, 2.7 atm H_2	95.0 (*R*)	49b
(*R*,*S*,*S*,*R*)-DIOP*	A	50	MeOH, rt, 10 atm H_2	98.8 (*R*)	51
	B	50	MeOH, rt, 10 atm H_2	97.3 (*R*)	51
(*S*,*S*)-**9**	A	100	CH_2Cl_2, rt, 1 atm H_2	98.5 (*R*)	54a
	B	100	CH_2Cl_2, rt, 1 atm H_2	>99 (*R*)	54a
(*R*,*R*,*R*,*R*)-T-Phos	B	100	MeOH, rt, 3.1 atm H_2	98 (*S*)	55
(*R*,*R*,*R*,*R*)-SK-Phos	B	100	MeOH, rt, 3.1 atm H_2	97 (*S*)	55
(*S*,*S*)-^{t}Bu-BisP*	A	100	MeOH, rt, 3 atm H_2	98 (*R*)	59

SCR: substrate:catalyst ratio.

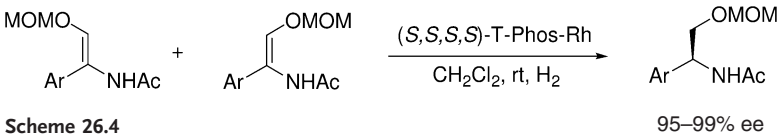
coordination pathways. *o*-Ph-HexaMeO-BIPHEP [26] has shown high efficiency in the Rh-catalyzed hydrogenation of cyclic enamides. A racemic cyclic enecarbamate has been hydrogenated with an *o*-Ph-HexaMeO-BIPHEP–Rh catalyst to yield the *cis* chiral carbamate in 96% ee [26]. The chiral product can be used directly for the synthesis of sertraline, an anti-depressant. Hydrogenation of some tetra-substituted enamides has also been reported. ^{t}Bu-BisP* and ^{t}Bu-MiniPhos have provided excellent ee-values in the Rh-catalyzed hydrogenation of a *β*,*β*-dimethyl-*α*-phenyl enamide derivatives (Scheme 26.3). Using an *o*-Ph-BIPHEP–Rh catalyst [26], tetra-substituted enamides derived from 1-indanone and 1-tetralone have been hydrogenated with excellent enantioselectivities.

The hydrogenation of a series of *E*/*Z*-isomeric mixtures of *α*-arylenamides with a MOM-protected *β*-hydroxyl group catalyzed by a Rh-complex of 1,4-diphosphane T-Phos with a rigid 1,4-dioxane backbone led to chiral *β*-amino alcohol derivatives in excellent enantioselectivities (Scheme 26.4) [55]. DIOP*–Rh is also effective for this transformation [51b].

In addition to the Rh chemistry, the Ru–BINAP system has shown excellent enantioselectivity in the hydrogenation of (*Z*)-*N*-acyl-1-alkylidenetetrahydroisoquinolines. Thus, a series of chiral isoquinoline products can be efficiently synthesized [3a,b, 91]. Using Ru–BINAP, the cyclic enamides, 6-bromotetralone-eneacetamide [92] and 7-methyltetralone-eneacetamide [93] are hydrogenated to give the corresponding chiral amide in 97% and 94% ee, respectively (Scheme 26.5). Ru–Biphemp also provided good selectivity (92% ee) in the enantiomeric hydrogenation of a cyclic enamide derived from 3-chromanone (Scheme 26.5) [93].



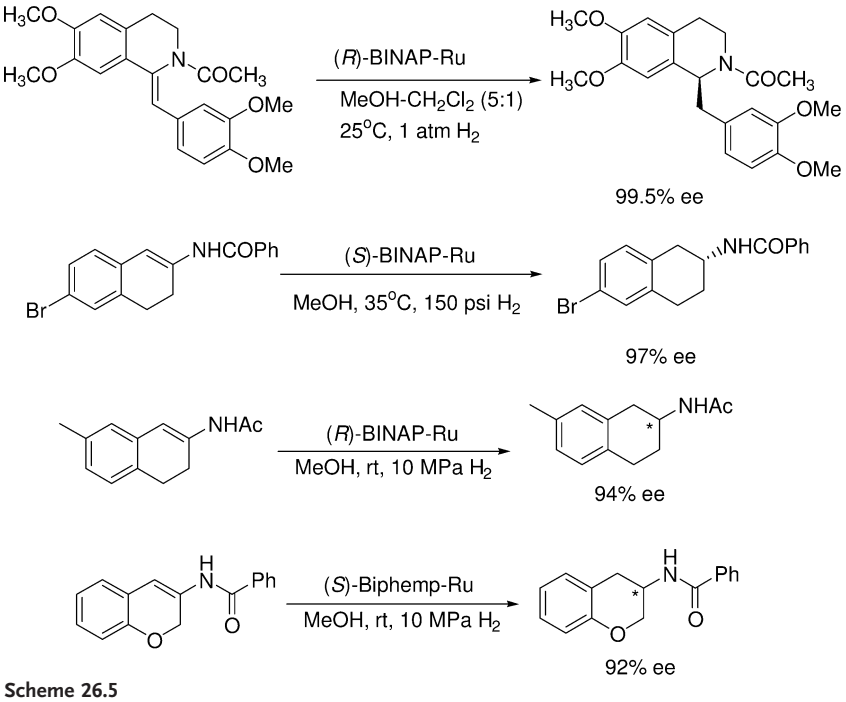
Scheme 26.3



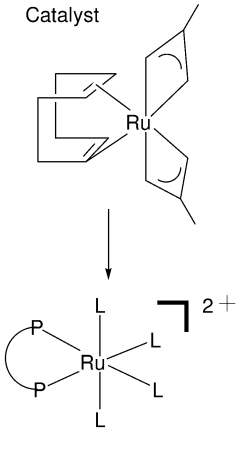
Scheme 26.4

26.3.3
Enantioselective Hydrogenation of (β-Acylamino) Acrylates

Enantioselective hydrogenation of (β-acylamino) acrylates has gained much attention recently because the β-amino acid products are important building blocks for chiral drugs [94]. Since most synthetic methods produce mixtures of *Z*- and *E*-isomeric substrates, it is important that both isomers can be hydrogenated with high enantioselectivity for the practical synthesis of β-amino acid derivatives via enantioselective hydrogenation. Some Rh and Ru complexes with chiral phosphorus ligands such as BINAP [95], BICP [49e], BDPMI [54b], ligand **4** [30], ^{t}Bu-BisP* [60], (*R*)-**14** [71], and Xyl-P-Phos [25c] are found to be effective for hydrogenation of (*E*)-alkyl (β-acylamino) acrylates. However, only a



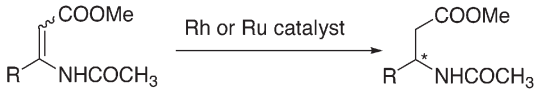
Scheme 26.5



Substrate	Product	ee%
AcHN COOEt	AcHN COOEt	99
AcHN COOMe	AcHN COOMe	99
BocHN COOEt	BocHN COOEt	98
AcHN COOEt, N COOEt	AcHN COOEt, N COOEt	95
AcHN COOEt	AcHN COOEt	92

Scheme 26.6

Table 26.4 Enantioselective hydrogenation of (*β*-acylamino) acrylates.



Ligand	R	Geometry	Reaction conditions	% ee of product (config.)	Reference
(*R*)-BINAP–Ru	CH_3	*E*	MeOH, 25 °C, 1 atm H_2	96 (*S*)	95
(*R*)-Xyl-P-Phos–Ru	CH_3	*E*	MeOH, 0 °C, 8 atm H_2	98.1 (*S*)	25c
(*S*)-HexaPHEMP–Rh	CH_3	*E*	MeOH, rt, 9.5 atm H_2	95 (*R*)	28
2–Rh	CH_3	*E*	MeOH, 0 °C, 17 atm H_2	97.7 (*S*)	30
2–Rh	^{i}Pr	*E*	MeOH, 0 °C, 17 atm H_2	98.8 (*S*)	30
(*R,R*)-BICP–Rh	CH_3	*E*	Toluene, rt, 2.7 atm H_2	96.1 (*R*)	49e
(*S,S*)-**9**–Rh	CH_3 [a]	*E*	CH_2Cl_2, rt, 1 atm H_2	94.6 (*R*)	54b
(*S,S*)-^{t}Bu-BisP*–Rh	CH_3	*E*	THF, rt, 3 atm H_2	98.7 (*R*)	60
(*S,S*)-MiniPhos–Rh	CH_3	*E*	THF, rt, 3 atm H_2	96.4 (*R*)	60
(*R*)-**14**–Rh	CH_3	*E*	MeOH, rt, 1.4 atm H_2	99 (*R*)	71
(*S,S*)-**9**–Rh	CH_3 [a]	*Z*	CH_2Cl_2, rt, 6.8 atm $_{H2}$	95 (*R*)	54b
(*R*)-**14**–Rh	CH_3	*Z*	EtOAc, rt, 1.4 atm H_2	98 (*R*)	71
(*R*)-**14**–Rh	CH_3	*E*/*Z* [b]	THF, rt, 1.4 atm H_2	98 (*R*)	71

a) Ethyl ester.
b) *E*:*Z* ratio = 1 : 1.

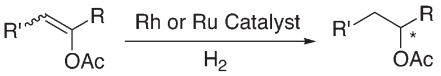
few chiral ligands such as BDPMI [54b] and (*R*)-**14** [71] can provide over 95% ee hydrogenation for hydrogenation of (*Z*)-alkyl (*β*-acylamino) acrylates (Table 26.4). With (*R*)-**14**–Rh catalyst, an *E*/*Z*-isomeric mixtures of methyl 3-acetamido-2-butenoate was hydrogenated in THF to give (*R*)-methyl 3-acetamidobutanoate in 98% ee [71].

By employing a Ru catalyst generated *in situ* from Ru(COD)(methallyl)$_2$, (*S*)-C3-TunePhos, and HBF_4, a series of cyclic *β*-(acylamino) acrylates were hydrogenated with excellent ee-values. As shown in Scheme 26.6, 99% ee was obtained in the hydrogenation of both 2-acetylamino-cyclopent-1-enecarboxylic acid methyl ester and ethyl ester. A heterocyclic *β*-(acylamino) acrylate is also hydrogenated to give the *cis*-product in excellent enantioselectivity (95% ee). Hydrogenation of a cyclohexenyl substrate provided the corresponding *cis* product in 92% ee [20].

26.3.4
Enantioselective Hydrogenation of Enol Esters

Enol esters have a similar structure as enamides. However, in contrast to many highly enantioselective examples on enantioselective hydrogenation of enamides, only a few successful results have been reported for the hydrogenation of

Table 26.5 Enantioselective hydrogenation of enol esters.

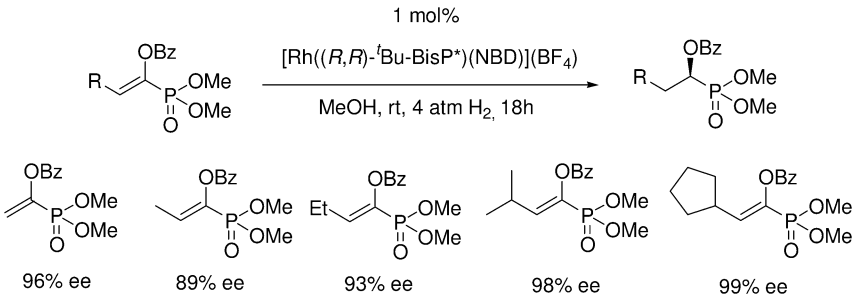


Catalyst	R	R′	Geometry	Reaction conditions	% ee of product (config.)	Reference
(*R*,*R*)-DIPAMP–Rh	CO_2Et	^{i}Pr	*E*/*Z*[a)]	MeOH, rt, 3 atm H_2	92 (*S*)	97
(*R*)-BINAP–Ru	CO_2Et	^{i}Pr	*E*/*Z*[a)]	MeOH, 50 °C, 50 atm H_2	98 (*S*)	97
(*R*,*R*)-DIPAMP–Rh	CO_2Et	Ph	*Z*	MeOH, rt, 3 atm H_2	88 (*S*)	97
(*S*)-C2-TunePhos–Ru	1-Np	H	N/A	EtOH/CH_2Cl_2, rt, 3 atm H_2	97.7 (*S*)	19
2–Rh	1-Np	H	N/A	EtOH/CH_2Cl_2, rt, 3.4 atm H_2	96.7 (*R*)	30
2–Rh	*p*-F-C_6H_4	H	N/A	EtOH/CH_2Cl_2, rt, 3.4 atm H_2	97.1 (*R*)	30

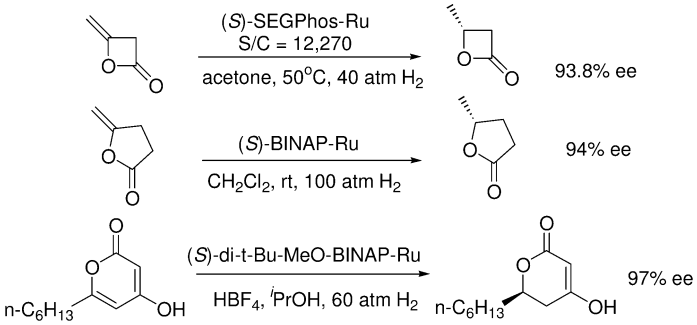
a) *E*:*Z* ratio = 70 : 30.
N/A: not applicable.

enol esters. One possible reason is that the acyl group of an enol ester has a weaker coordinating ability to the metal catalyst than that of the corresponding enamide substrate. Some Rh and Ru complexes associated with chiral phosphorus ligands such as DIPAMP [96,97] and BINAP [97] are effective for the enantioselective hydrogenation of *α*-(acyloxy) acrylates. Some chiral phosphorus ligands such as BINAP [98] and TunePhos [19] have been applied to the Rh- or Ru-catalyzed enantioselective hydrogenation of aryl enol acetates without other functionalities (Table 26.5). C2-TunePhos–Ru [19] and **2**-Ru [30] catalysts are found to be equally effective for this transformation.

Enantioselective hydrogenation of a series of enol phosphates with a ^{t}Bu-MiniPhos–Rh or a ^{t}Bu-BisP*–Rh catalyst provides moderate to excellent ee-values (Scheme 26.7) [99].



Scheme 26.7



Scheme 26.8

Although high hydrogen pressure is required, BINAP and its analogous ligands gave superior results in the Ru-catalyzed hydrogenation of four- and five-membered cyclic lactones or carbonates bearing an exocyclic methylene group (Scheme 26.8) [98]. A (*S*)-SEGPHOS–Ru catalyst provided 93.8% ee in the hydrogenation of a diketene with high turnover numbers (TONs) [100]. With a (*S*)-BINAP–Ru catalyst, 94% ee was obtained in the hydrogenation of 4-methylene-γ-butyrolactone. In the presence of a small amount of HBF_4, a di-*t*-Bu-MeOBIPHEP–Ru catalyst allows the hydrogenation of a 2-pyrone substrate with 97% ee [101].

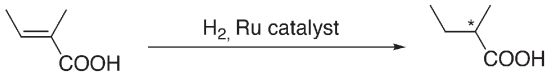
26.3.5
Enantioselective Hydrogenation of Unsaturated Acids and Esters

26.3.5.1 *α,β*-Unsaturated Carboxylic Acids

Significant advance has been achieved in the enantiomeric hydrogenation of *α,β*-unsaturated carboxylic acids with chiral Ru catalysts. The Ru–BINAP-dicarboxylate complex has shown excellent enantioselectivities in the hydrogenation of some *α,β*-unsaturated carboxylic acids, although the catalytic efficiencies are still highly sensitive to the substrates, reaction temperature, and hydrogen pressure [3 d]. Other atropisomeric ligands, such as H_8-BINAP [102], MeO-BIPHEP [103], BIPHEMP [103], P-Phos [25], TetraMe-BITIANP [23 b], and TetraMe-BITIOP [24] are also effective for this transformation. Ru complexes prepared in different forms may exhibit slightly different efficiencies. Some examples of the hydrogenation of tiglic acid with different metal–ligand complexes are listed in Table 26.6. The H_8-BINAP ligand with a larger dihedral angle gives superior results compared to the BINAP ligand.

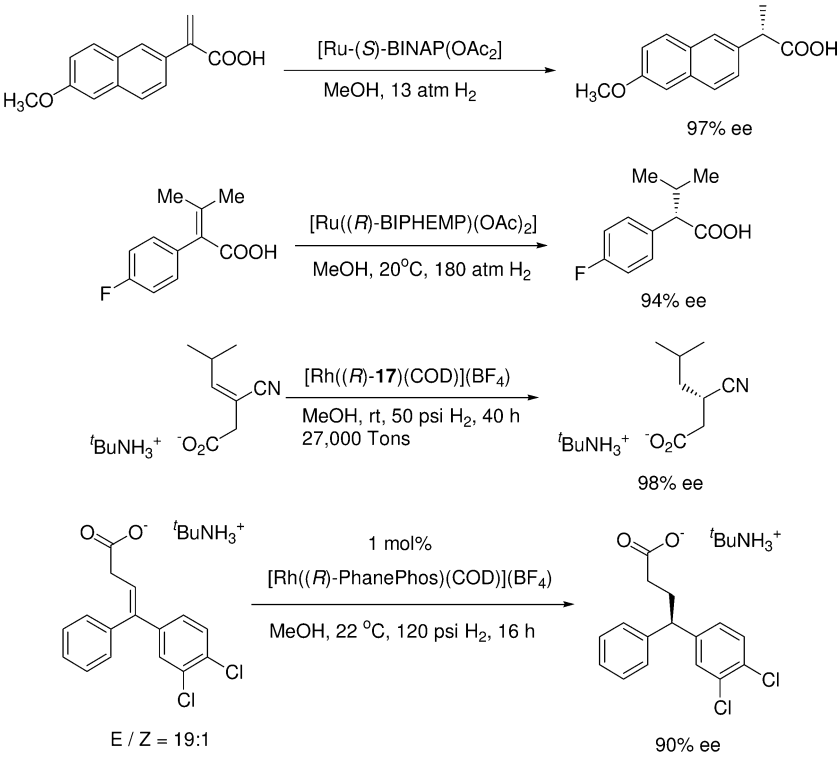
With a BINAP–Ru [3 d,104], H_8-BINAP–Ru [102], or P-Phos–Ru [25] catalyst, the anti-inflammatory drugs (*S*)-ibuprofen and (*S*)-naproxen could be efficiently synthesized via enantioselective hydrogenation (Scheme 26.9). In these cases, high hydrogenation pressure and low temperature are required to achieve good enantioselectivity. With an (*R*)-BIPHEMP–Ru catalyst, (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid, a key intermediate for the synthesis of the calcium antago-

Table 26.6 Enantioselective hydrogenation of tiglic acid.



Catalyst	SCR	Reaction conditions	% ee of product (config.)	Reference
$Ru(OAc)_2$[(*R*)-BINAP]	100	MeOH, 15–30 °C, 4 atm H_2	91 (*R*)	3d
Ru[(*R*)-BINAP](2-methallyl)$_2$	100	MeOH, 20 °C, 4 atm H_2	90 (*R*)	103
$Ru(OAc)_2$[(*S*)-H8-BINAP]	200	MeOH, 10–25 °C, 1.5 atm H_2	97 (*S*)	102
[(*R*)-MeO-BIPHEP]$RuBr_2$	100	MeOH, 20 °C, 1.4 atm H_2	92 (*R*)	103
$[NH_2Et_2]$[{RuCl[(*S*)-BIPHEMP]}$_2$(μ-Cl)$_3$]	100	MeOH, 20 °C, 4 atm H_2	98 (*S*)	103
Ru(*p*-cymene)[(–)-TetraMe-BITIANP]I_2]	500	MeOH, 25 °C, 10 atm H_2	92 (*S*)	23b
[Ru(–)-TetraMe-BITIOP](2-methally)$_2$]	3000	MeOH, 25 °C, 10 atm H_2	94 (*R*)	24

SCR: substrate:catalyst ratio.



Scheme 26.9

nist mibefradil, could be reduced in 94% ee [105]. Using (*R*)-**14**–Rh as catalyst, enantioselective hydrogenation of *tert*-butylammonium (3*Z*)-3-cyano-5-methyl-3-hexenoate produced the precursor to CI-1008 (pregabalin, indicated for psychotic disorder, seizure disorder and pain) with a TON of 27 000 and 98% ee (Scheme 26.9) [70]. Using PhanePhos–Rh as catalyst, an isomeric mixture (*E*/*Z* = 19:1) of 4,4′-diaryl-3-butenoate was hydrogenated to provide a chiral intermediate for the antidepressant sertraline, with 90% ee (Scheme 26.9) [106].

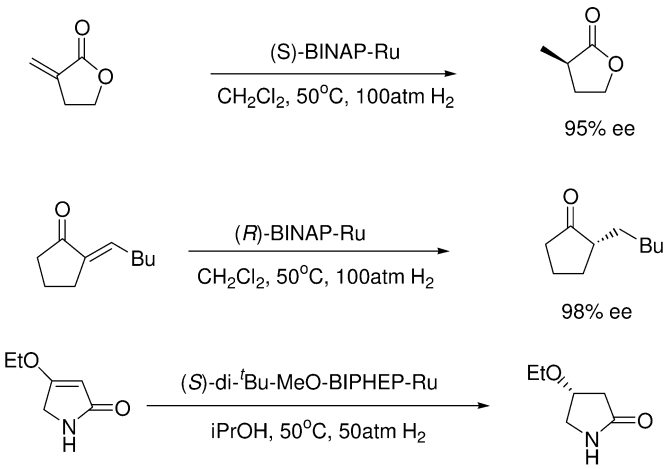
26.3.5.2 *α,β*-Unsaturated Esters, Amides, Lactones, and Ketones

Limited progress has been achieved in the enantioselective hydrogenation of *α,β*-unsaturated carboxylic acid esters, amides, lactones, and ketones (Scheme 26.10). The Ru–BINAP system is efficient for the hydrogenation of 2-methylene-*γ*-butyrolactone, and 2-methylene-cyclopentanone [98]. With a dicationic (*S*)-di-*t*-Bu-MeOBIPHEP–Ru complex under a high hydrogen pressure, 3-ethoxy pyrrolidinone could be hydrogenated in isopropanol to give (*R*)-4-ethoxy-*γ*-lactam in 98% ee [39].

26.3.5.3 Itaconic Acids and Their Derivatives

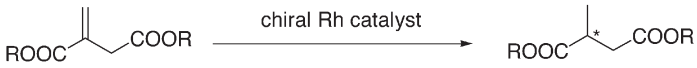
Many chiral phosphorus ligands have shown excellent reactivities and enantioselectivities in the Rh-catalyzed hydrogenation of itaconic acids or esters. Some successful (>95% ee) hydrogenations of itaconic acid or its dimethyl ester with different chiral phosphorus ligands are listed in Table 26.7. High reactivity is observed with electron-rich phosphane ligands such as BICHEP [7c].

In contrast to the many successful examples of hydrogenation of the parent itaconic acid or its dimethyl ester, only a few ligands have been reported to be



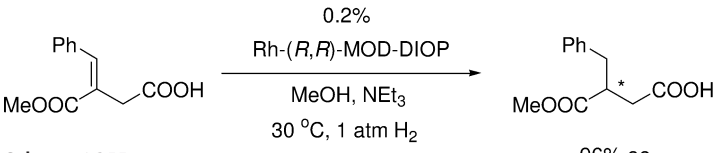
Scheme 26.10

Table 26.7 Enantioselective hydrogenation of itaconic acid derivatives.

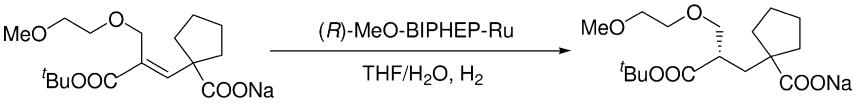


Ligand	R	SCR	Reaction conditions	% ee of product (config.)	Reference
(*R*)-BICHEP	H	1000	EtOH, 25 °C, 1 atm H_2	96 (*R*)	7c
(*S*,*S*)-Ad-BisP*	Me	500	MeOH, rt, 1.6 atm H_2	99.6	58b

SCR: substrate:catalyst ratio.



Scheme 26.11



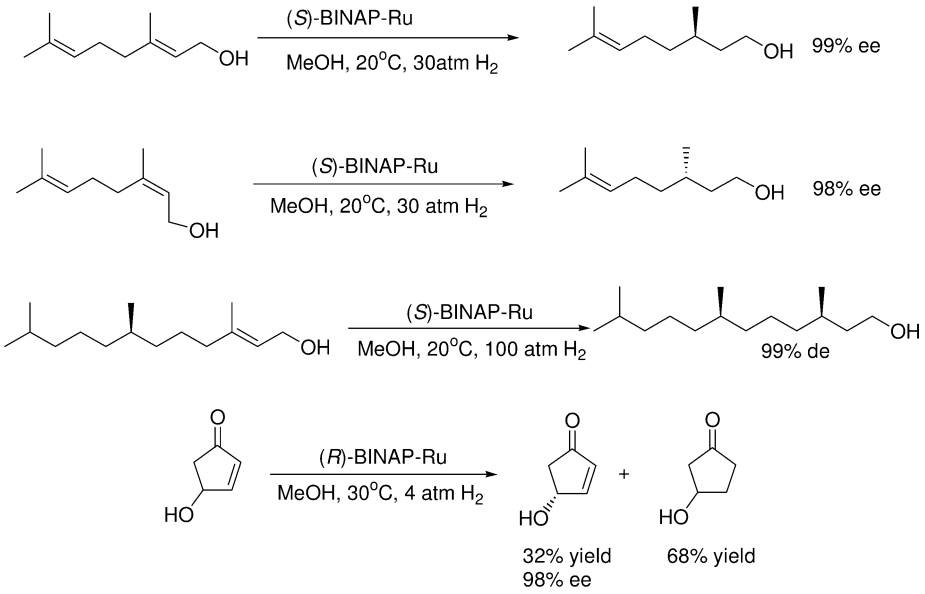
Scheme 26.12

efficient for the hydrogenation of β-substituted itaconic acid derivatives. Rh complexed with MOD-DIOP [48] is efficient for the hydrogenation of several β-substituted itaconic acid derivatives (Scheme 26.11).

A PYRPHOS ligand was found to be effective for the hydrogenation of a β-aryl- or alkyl-substituted monoamido itaconate [107]. A MeO-BIPHEP–Ru catalyst was successfully applied for the enantioselective hydrogenation of an intermediate for the drug candoxatril in a mixed solvent (THF/H_2O) (Scheme 26.12) [108].

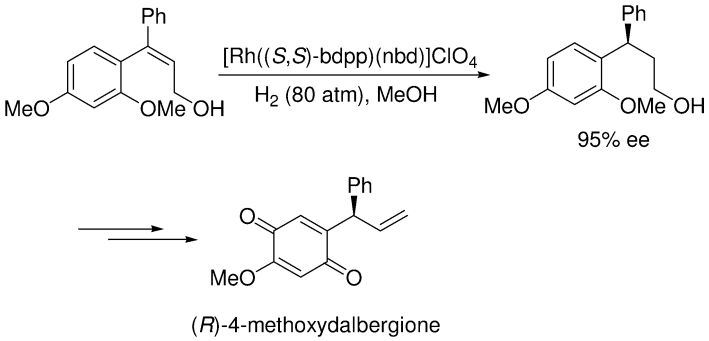
26.3.6
Enantioselective Hydrogenation of Unsaturated Alcohols

Enantioselective hydrogenation of unsaturated alcohols such as allylic and homoallylic alcohols was not very efficient until the discovery of the BINAP–Ru catalyst. With $Ru(BINAP)(OAc)_2$ as the catalyst, geraniol and nerol are successfully hydrogenated to give (*S*)- or (*R*)-citronellol in near-quantitative yield and with 96–99% ee [3c]. A substrate:catalyst ratio (SCR) of up to 48 500 can be applied, and the other double bond at the C6 and C7 positions of the substrate is not reduced. A high hydrogen pressure is required to obtain high enantioselec-



Scheme 26.13

tivity in the hydrogenation of geraniol. Low hydrogen pressure facilitates the isomerization of geraniol to γ-geraniol, which leads to the hydrogenation product with the opposite configuration, resulting in a decreased ee-value [109]. In addition to BINAP, other chiral atropisomeric ligands such as MeO-BIPHEP [9], TetraMe-BITIANP [23b], and TetraMe-BITIOP [24] are also effective for this transformation. The catalytic efficiency of the BINAP–Ru catalyst is strongly sensitive to the substitution patterns of the allylic alcohols. Homoallylic alcohols can also be hydrogenated in high ee-value with the BINAP–Ru catalyst. Its application in the synthesis of (3*R*, 7*R*)-3,7,11-trimethyldodecarol, an intermediate for the synthesis of α-tocopherol, is shown in Scheme 26.13. When racemic



Scheme 26.14

allylic alcohols were subjected to enantioselective hydrogenation with a BINAP–Ru complex, highly efficient kinetic resolutions were achieved [4c]. A racemic 4-hydroxy-2-cyclopentenone was hydrogenated with a (*S*)-BINAP–Ru catalyst to leave unreacted starting material in 98% ee at 68% conversion. The chiral starting material serves as an important building block for three-component coupling prostaglandin synthesis.

A chiral BDPP–Rh complex is an efficient catalyst for the hydrogenation of 3-(2′,4′-dimethoxyphenyl)-3-phenyl-2-propenol. The chiral alcohol product, which was obtained in up to 95% ee, has been used for the synthesis of chiral 4-methoxydalbergione (Scheme 26.14) [110].

26.4 Concluding Remarks

The development of chiral phosphorus ligands has undoubtedly had an enormous impact on the area of enantioselective hydrogenation. Transition-metal catalysts with efficient chiral phosphorus ligands have enabled the synthesis of a variety of chiral products in a very efficient manner, and many practical hydrogenation processes have been exploited in industry for the synthesis of chiral drugs and fine chemicals. However, many challenges remain in the field of enantioselective hydrogenation, and further effort in the quest for new efficient chiral phosphorus ligands, as well as new applications in enantioselective hydrogenation, are needed.

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