1
Rhodium-Catalyzed Asymmetric Hydrogenation

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1.1
Introduction

Molecular chirality plays a very important role in science and technology. For example, the biological activity of many pharmaceuticals and agrochemicals is often associated with a single enantiomer. The increasing demand for enantiomerically pure pharmaceuticals, agrochemicals, and fine chemicals has therefore driven the development of asymmetric catalytic technologies [1, 2]. Asymmetric hydrogenation, using molecular hydrogen to reduce prochiral olefins, ketones, and imines, has become one of the most efficient, practical, and atom-economical methods for the construction of chiral compounds [3]. During the last few decades of the 20th century, significant attention was devoted to the discovery of new asymmetric catalysts, in which transition metals bound to chiral phosphorous ligands have emerged as preferential catalysts for asymmetric hydrogenation. Thousands of efficient chiral phosphorous ligands with diverse structures have been developed, and their application to asymmetric hydrogenation has been established. Indeed, many represent the key step in industrial processes for the preparation of enantiomerically pure compounds. The immense significance of asymmetric hydrogenation was recognized when the Nobel Prize in Chemistry was awarded to Knowles and Noyori.

In this chapter, we focus on the rhodium-catalyzed hydrogenation and the development of chiral phosphorous ligands for this process. Although there are other chiral phosphorous ligands, which are effective for ruthenium-, iridium-, platinum-, titanium-, zirconium-, and palladium-catalyzed hydrogenation, they are not discussed in this account. However, this does not preclude complexes of other transition metals as effective catalysts for asymmetric hydrogenation. Fortunately, there are numerous reviews and books that discuss this particular aspect of asymmetric hydrogenation [3].

1.2
Chiral Phosphorous Ligands

The invention of efficient chiral phosphorous ligands has played a critical role in the development of asymmetric hydrogenation. To a certain extent, the development of asymmetric hydrogenation parallels that of chiral phosphorous ligands.

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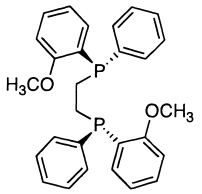
The introduction of Wilkinson's homogeneous hydrogenation catalyst, $[RhCl(PPh_3)_3]$ [4], prompted the development of the analogous asymmetric hydrogenation by Knowles [5] and Horner [6] using chiral monodentate phosphine ligands, albeit with poor enantioselectivity. Kagan and Knowles each demonstrated that improved enantioselectivities could be obtained using bidentate chiral phosphine ligands. For example, Kagan and Knowles independently reported the C_2-symmetric bisphosphine ligands, DIOP [7] and DIPAMP [8], for rhodium-catalyzed asymmetric hydrogenation. Due to its high catalytic efficiency in rhodium-catalyzed asymmetric hydrogenation of dehydroamino acids, DIPAMP was employed in the industrial production of L-DOPA [9]. Subsequently to this work, several other successful chiral phosphorous ligands were developed, as exemplified by Kumada's ferrocene ligand BPPFOH [10] and Achiwa's BPPM ligand [11].

The mechanism of the asymmetric hydrogenation is fairly well established, due to the seminal work of Halpern [12] and Brown [13]. Indeed, much of the early work in this area focused on the development of chiral rhodium catalysts, rather than expanding the reaction's substrate scope, which was limited to α-dehydroamino acids. In 1980, Noyori and Takaya reported an atropisomeric C_2-symmetric bisphosphine ligand, BINAP [14, 15]. This ligand was first used in rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids, in which high selectivities were reported for certain substrates [16]. The discovery that the Ru–BINAP system could efficiently and selectively affect the asymmetric hydrogenation of various functionalized olefins [17], functionalized ketones [18], and unfunctionalized ketones [19] led to the development of other atropisomeric biaryl bisphosphine ligands, as exemplified by Miyashita's BICHEP ligand [20] and Schmid's BIPHEMP/MeO-BIPHEP [21, 22] ligands.

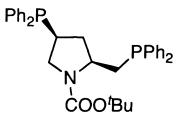
Achiwa has successfully developed the modified DIOP ligands, MOD-DIOP and Cy-DIOP, by varying their electronic and steric properties; MOD-DIOP was applied to the asymmetric hydrogenation of itaconic acid derivatives with up to 96% enantioselectivity [23]. A series of modified BPPM ligands such as BCPM and MCCPM were also developed by Achiwa [24], and some excellent chiral 1,2-bisphosphane ligands such as NORPHOS [25] and PYRPHOS (DEGUPHOS) [26] have been developed for the rhodium-catalyzed asymmetric hydrogenation. Several 1,3-bisphosphane ligands, such as BDPP (SKEWPHOS) [27], have been prepared and examined.

Hayashi and Ito developed the (aminoalkyl)ferrocenylphosphine ligand **L1**, which was successfully applied to the rhodium-catalyzed hydrogenation of trisubstituted acrylic acids [28]. In the early 1990s, significant progress was achieved with the application of the chiral bisphosphorous ligands, DuPhos and BPE developed by Burk *et al.* [29, 30], to the enantioselective hydrogenation of α-(acylamino)acrylic acids, enamides, enol acetates, β-keto esters, unsaturated carboxylic acids, and itaconic acids. Scheme 1.1 shows the several important chiral phosphine ligands studied before the early 1990s.

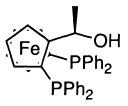
Inspired by the excellent results of chiral ligands such as BINAP and DuPhos, many research groups have devoted their efforts to designing and discovering new efficient and selective chiral phosphorous ligands. A major feature in the design of the new chiral phosphorus ligands is the ability to tune the steric and electronic properties of ligands within a given scaffold. These new ligands, which have proven efficient and selective for the asymmetric rhodium-catalyzed hydrogenation, can be divided into several different categories.



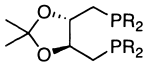
(*S*,*S*)-DIPAMP



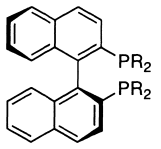
(*S*,*S*)-BPPM



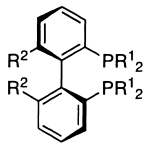
(*R*,*S*)-BPPFOH



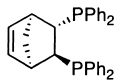
(*S*,*S*)-DIOP: R = Ph
(*S*,*S*)-Cy-DIOP: R = Cy
(*S*,*S*)-MOD-DIOP:
R = 3, 5-$(Me)_2$-4-(MeO)C_6H_2



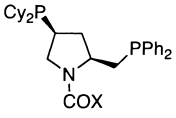
(*S*)-BINAP: R = Ph
(*S*)-TolBINAP: R = 4-MeC_6H_4
(*S*)-XylBINAP: R = 3,5-$(Me)_2C_6H_3$



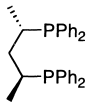
(*S*)-BICHEP: R^1 = Cy; R^2 = CH_3
(*S*)-BIPHEMP: R^1 = Ph; R^2 = CH_3
(*S*)-BIPHEP: R^1 = Ph; R^2 = OCH_3



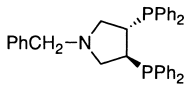
(*S*,*S*)-NORPHOS



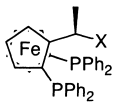
(*S*,*S*)-BCPM: X = O^{t}Bu
(*S*,*S*)-MCCPM: X = NHMe

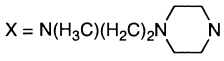


(*S*,*S*)-BDPP

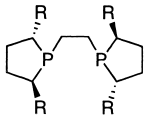


(*S*,*S*)-PYRPHOS

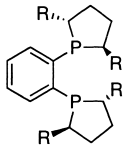




(*R*)-(*S*)-**L1**



(*S*,*S*)-Me-BPE: R = Me
(*S*,*S*)-Et-BPE: R = Et
(*S*,*S*)-^{i}Pr-BPE: R = ^{i}Pr

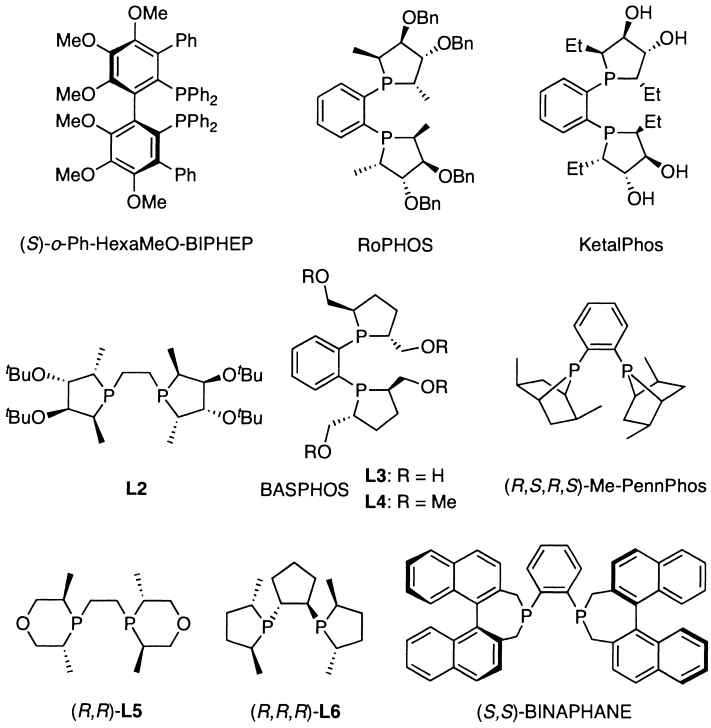


(S,*S*)-Me-DuPhos: R = Me
(*S*,*S*)-Et-DuPhos: R = Et
(*S*,*S*)-^{i}Pr-DuPhos: R = ^{i}Pr

Scheme 1.1

1.2.1
Atropisomeric Biaryl Bisphosphine Ligands

Modification of the electronic and steric properties of BINAP, BIPHEMP, and MeO-BIPHEP led to the development of new efficient atropisomeric ligands. Although most of them are efficient for ruthenium-catalyzed asymmetric hydrogenation [3], Zhang *et al.* have recently reported an *ortho*-substituted BIPHEP ligand, *o*-Ph-HexaMeO-BIPHEP, for the rhodium-catalyzed asymmetric hydrogenation of cyclic enamides (Scheme 1.2) [31].



Scheme 1.2

1.2.2

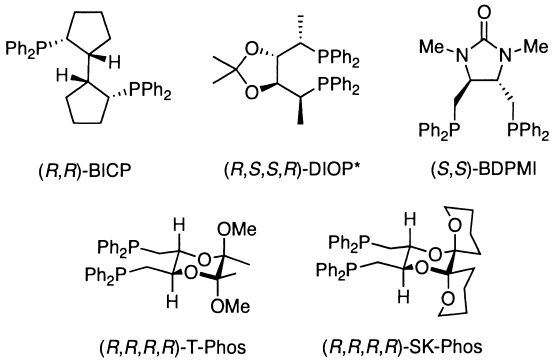
Chiral Bisphosphane Ligands Based on the Modification of DuPhos and BPE

An array of bisphosphanes has emerged based on modification of the DuPhos and BPE ligands, which have proven so successful for the asymmetric hydrogenation of functionalized olefins and ketones (Scheme 1.2). Börner [32], Zhang [33], and Rajan-Babu [34] have independently reported a series of modified DuPhos and BPE ligands – RoPhos, KetalPhos, and **L2** – derived from readily available D-mannitol. The ligand with four hydroxy groups, KetalPhos, enabled the hydrogenation to be carried out in aqueous solution with high enantioselectivity. Another water-soluble ligand, BASPHOS (**L3**), developed by Holz and Börner, also exhibits high efficiency for asymmetric hydrogenation in aqueous solution [35].

Zhang *et al.* reported a sterically bulky and conformationally rigid bisphosphane, PennPhos, which shows excellent enantioselectivity for rhodium-catalyzed hydrogenation of aryl/alkyl methyl ketones [36], cyclic enamides, and cyclic enol acetates [37]. Helmchen's bisoxaphosphinane ligand **L5** [38] and Zhang's bisdinaphthophosphepine ligand BINAPHANE [39] provide excellent enantioselectivity (up to 99% *ee*) for hydrogenation of *E*/*Z*-isomeric mixtures of *β*-substituted arylenamides. The BPE analog (*R*,*R*,*R*)-1,2-bis(phospholano)cyclopentane, **L6**, provides improved enantioselectivity for the hydrogenation of dehydroamino acids [40].

1.2.3
Chiral Bisphosphane Ligands Based on the Modification of DIOP

Although the development of DIOP prompted significant advances in asymmetric hydrogenation, the enantioselectivity is often inferior to that of other chiral bisphosphines. A possible reason for the diminished selectivity may be the formation of a conformationally flexible seven-membered chelate of the DIOP ligand with the metal. In order to rigidify the conformational flexibility of the DIOP ligand, several rigidified DIOP-type ligands have been developed (Scheme 1.3). Zhang [41, 42] and RajanBabu [43] have independently reported the development of BICP and DIOP* ligands. Lee has developed a type of 1,4-diphosphane ligand BDPMI with an imidazolidin-2-one backbone [44], which has successfully been applied to the asymmetric rhodium-catalyzed hydrogenation of arylenamides, with up to 99% enantioselectivity. A series of 1,4-diphosphane ligands with a conformationally rigid 1,4-dioxane backbone, as exemplified by T-Phos and SK-Phos, developed by Zhang, have proven highly efficient and selective (up to 99% *ee*) for the asymmetric hydrogenation of arylenamides and MOM-protected *β*-hydroxyl enamides [45].



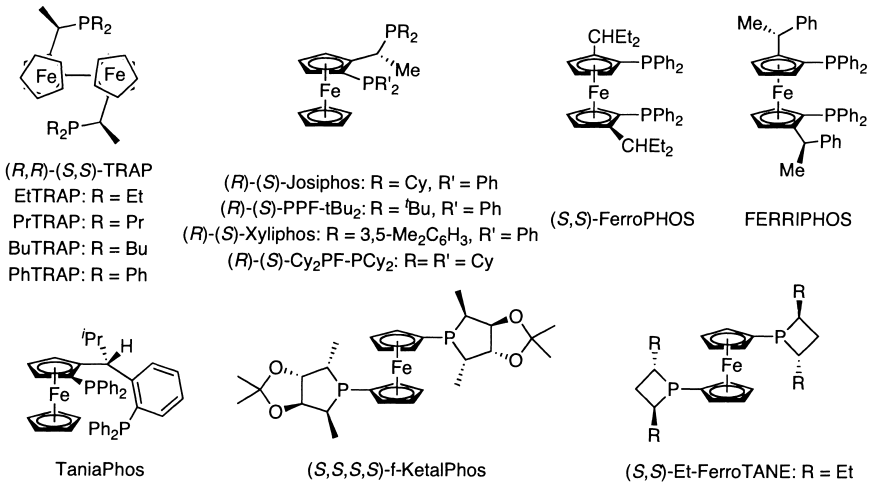
Scheme 1.3

1.2.4
Chiral Ferrocene-Based Bisphosphane Ligands

Recently, many effective chiral bisphosphane ligands with a ferrocene backbone have been developed (Scheme 1.4). Ito has successfully developed a series of *trans*-chelating bisphosphane ligands, TRAPs, which are highly selective for rhodium-catalyzed asymmetric hydrogenation [46].

Togni and Spindler introduced non-C_2-symmetric ferrocene-based Josiphos-type ligands [47], which are effective for rhodium-catalyzed hydrogenation of *α*-(acetamido)cinnamate, dimethyl itaconate, and *β*-keto esters. The Josiphos-type ligands have been applied as the stereodefining step in a number of industrial processes, as exemplified the use of PPF-^{t}Bu$_2$ for the commercial synthesis of (+)-biotin [48], and Xyli-Phos for the preparation of the herbicide (*S*)-metolachlor [49].

Two C_2-symmetric bisphosphane ligands, namely Kang's FerroPhos [50] and Knochel's FERRIPHOS (MandyPhos) [51], have provided excellent enantioselectivities in



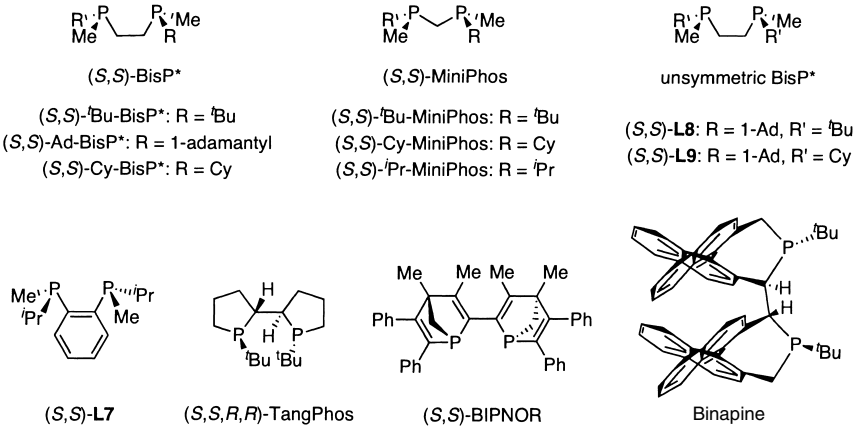
Scheme 1.4

asymmetric hydrogenation of α-dehydroamino acids. A non-C_2-symmetrical ferrocene-based 1,5-diphosphane ligand (TaniaPhos), has also been developed by Knochel [52] for asymmetric hydrogenation.

Marinetti [53] and Burk [54] reported the preparation of chiral 1,1′-bis(phosphetano)ferrocenes (FerroTANE) independently, in which Et-FerroTANE demonstrated excellent enantioselectivity in the rhodium-catalyzed hydrogenation of itaconates. Zhang has reported a 1,1′-bis(phospholanyl)ferrocene ligand (f-KetalPhos) with ketal substituents at 3,4-positions [55], which proved an excellent ligand for the enantioselective hydrogenation of α-dehydroamino acid derivatives [56].

1.2.5
P-Chiral Bisphosphane Ligands

Although development of the first *P*-chiral bisphosphane, DIPAMP, was achieved over 30 years ago, that of new *P*-chiral bisphosphanes has been comparatively slow due to difficulties associated with their synthesis. Imamoto [57] initiated their revival through the synthesis of a series of *P*-chiral ligands, BisP* (Scheme 1.5), which demonstrate excellent catalytic activity and enantioselectivity in the hydrogenation of α-dehydroamino acids, enamides [58], (*E*)–β(acylamino)acrylates [59], and α,β-unsaturated-α-acyloxyphosphonates [60]. In addition to BisP*, several other *P*-chiral bisphosphanes have been introduced by Imamoto, as exemplified by MiniPhos [61], 1,2-bis(isopropylmethylphosphino)-benzene (**L7**) [62], and the unsymmetrical *P*-chiral BisP* (**L8** and **L9**) [63]. Zhang has recently reported two rigid *P*-chiral bisphospholane ligands, TangPhos [64] and BINAPINE [65]. TangPhos provides an efficient ligand for the rhodium-catalyzed hydrogenation of a variety of functionalized olefins such as α-dehydroamino acids, α-arylenamides, β-(acylamino)acrylates [66], itaconic acids, and enol acetates [67]. The BINAPINE ligand, on the other hand, demonstrates excellent enantioselectivity and reactivity, with turnover numbers up to 10 000, for the asymmetric hydrogenation of *Z*-aryl(β-acylamino)acrylates. Mathey's bisphosphane ligand BIPNOR is also effective

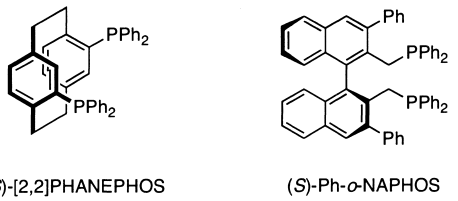


Scheme 1.5

in the enantioselective hydrogenation of α-(acetamido)cinnamic acids and itaconic acids [68].

1.2.6
Other Bisphosphane Ligands

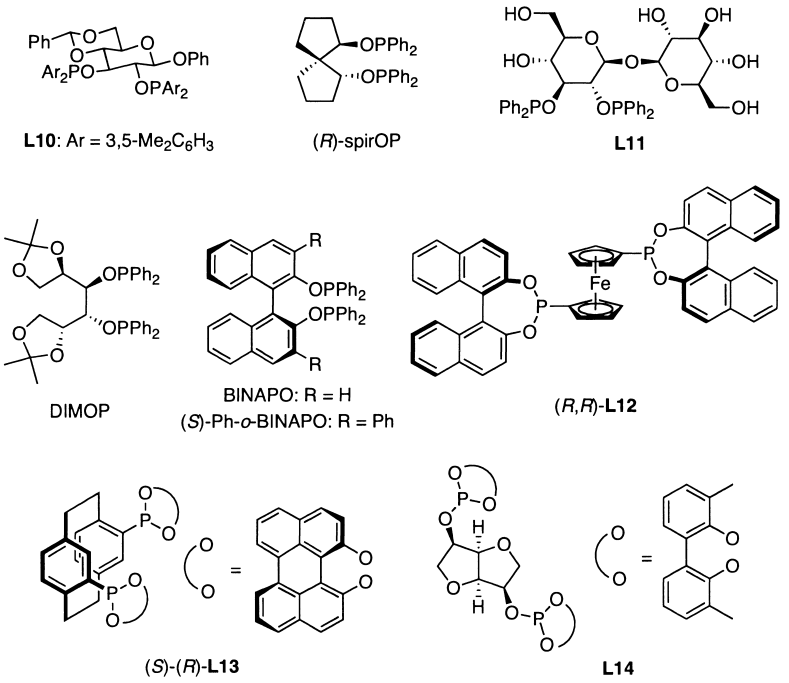
Pye and Rossen have developed a planar chiral bisphosphine ligand, [2.2]PHANEPHOS, based on a paracyclophane backbone (Scheme 1.6) [69]. Moreover, the *ortho*-phenyl substituted NAPHOS ligand, Ph-*o*-NAPHOS, has been successfully applied for the rhodium-catalyzed hydrogenation of α-dehydroamino acid derivatives [70].



Scheme 1.6

1.2.7
Bisphosphinite, Bisphosphonite, and Bisphosphite Ligands

The development of bisphosphinites, bisphosphonites, and bisphosphites for asymmetric hydrogenation has lagged behind that of chiral bisphosphane ligands, due to the former groups' greater conformational flexibility and instability. Nevertheless, some efficient P–O ligands with rigid backbones have been discovered (Scheme 1.7). Rajan-Babu has developed a series of bisphosphinites (**L10**), based on a sugar backbone, that demonstrate excellent enantioselectivity in hydrogenation of α-dehydroamino acid derivatives [71]. Chan and Jiang's rigid spirocyclic bisphosphinite ligand (spirOP) has been



Scheme 1.7

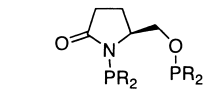
applied in the hydrogenation of α-dehydroamino acid derivatives [72]. The D-manitol derived bisphosphinite ligand DIMOP, which was prepared by Chan, affords enantioselectivities of up to 97% *ee* for the hydrogenation of α-dehydroamino acids [73]. A water-soluble rhodium complex of the bisphosphinite ligand **L11**, which is derived from the β,β-trehalose backbone, provided an effective catalyst for the enantioselective hydrogenation of α-dehydroamino acid derivatives in water or an aqueous/organic biphasic medium (up to 99.9% *ee*) [74]. In order to rigidify the flexible structure of BINAPO, Zhang has recently reported a series of *o*-BINAPO ligands with substituents at the 3,3′-positions of the binaphthyl group [75]. The ligand Ph-*o*-BINAPO with phenyl groups at the 3,3′-positions provides an effective ligand for hydrogenation of α-dehydroamino acid derivatives [70].

Some excellent bisphosphonite ligands have also been developed. For example, Reetz's binaphthol-derived ferrocene-based bisphosphonite ligand **L12** has demonstrated to have excellent reactivity and enantioselectivity in the rhodium-catalyzed hydrogenation of itaconates and α-dehydroamino acid derivatives [76]. Zanotti-Gerosa's bisphosphonite ligand **L13** has also been successfully applied to the asymmetric hydrogenation of α-dehydroamino acid derivatives with up to 99% *ee* [77].

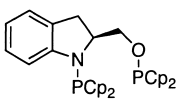
A few efficient bisphosphite ligands have been used for asymmetric hydrogenation of itaconates or α-dehydroamino acid derivatives. Reetz has developed a series of C_2-symmetric bisphosphite ligands such as **L14**, which are based on the structure of 1,4:3,6-dianhydro-D-mannite [78]. The ligands exhibit excellent reactivity and enantioselectivity for the asymmetric hydrogenation of itaconates.

1.2.8
Chelating Aminophosphine- and Amidophosphine-phosphoramidites

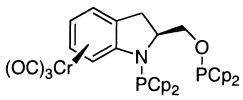
Several efficient amidophosphine- and aminophosphine-phosphinite ligands have been reported by Agbossou and Carpentier [79]. The amidophosphine-phosphinite ligands (*S*)-Cy,Cy-oxoProNOP, (*S*)-Cp,Cp-oxoProNOP, (*S*)-Cp,Cp-IndoNOP and (*S*,2*S*)-Cr(CO)-3-Cp,Cp-IndoNOP (Scheme 1.8) have been demonstrated to be effective for rhodium-catalyzed hydrogenation of dihydro-4,4-dimethyl-2,3-furandione. Another aminophosphine-phosphinite, DPAMPP, reported by Jiang and Mi [80] recently, has shown excellent enantioselectivity for hydrogenation of a series of α-dehydroamino acid derivatives. Some bisaminophosphine ligands such as H_8-BDPAB and BDPAB have been reported by Chan, and have been successfully applied for hydrogenation of arylenamides [81]. Xyl-BDPAB is also found to be an efficient ligand for asymmetric hydrogenation of α-dehydroamino acid derivatives [82]. Boaz has developed a family of ferrocene-based phosphine-aminophosphine ligands, BoPhoz [83], which are air-stable and exhibit excellent reactivity and selectivity for hydrogenation of α-dehydroamino acid derivatives and itaconic acids.



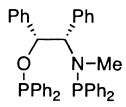
(*S*)-Cy,Cy-oxoProNOP: R = Cy
(*S*)-Cp,Cp-oxoProNOP: R = Cp



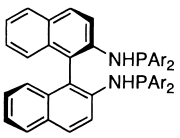
(*S*)-Cp,Cp-IndoNOP



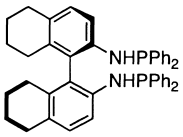
(*S*,2*S*)-Cr(CO)$_3$-Cp,Cp-IndoNOP



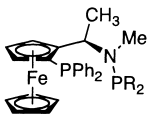
(*1R*,2*S*)-DPAMPP



(*R*)-BDPAB: Ar = Ph
(*R*)-Xyl-BDPAB:
Ar = 3,5-Me$_2$C$_6$H$_3$



(*R*)-H$_8$-BDPAB

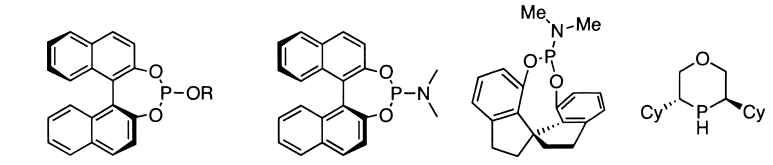


BoPhoz
L15: R = Ph
L16: R = Cy

Scheme 1.8

1.2.9
Chiral Monophosphorous Ligands

Compared to the rapid development of chelating bisphosphorous ligands, the discovery of effective monophosphorous ligands has been relatively slow [84]. Scheme 1.9 illustrates several monophosphorous ligands for rhodium-catalyzed asymmetric hydrogenation. Reetz has developed a series of monophosphite ligands which have shown excellent reactivity and enantioselectivity for asymmetric hydrogenation of dimethyl itaconate [85]. de Vries and Feringa have developed a phosphoramidite ligand, named MonoPhos, which has shown high enantioselectivity in asymmetric hydrogenation of dehydroamino acid derivatives [86] and arylenamides [87]. Zhou reported a monophosphoramidite ligand SIPHOS, based on a chiral 1,1′-spirobiindane-7,7′-diol, which affords enantio-



(*S*)-(*R*)-**L17**: R = (*R*)-CH(Me)Ph (*S*)-MonoPhos (*S*)-SIPHOS (*R*,*R*)-**L18**

Scheme 1.9

selectivities of up to 99% *ee* for the asymmetric hydrogenation of *α*-dehydroamino acids, arylenamides, and itaconates [88]. The secondary monodentate phosphane **L18** reported by Helmchen is also very effective for hydrogenation of itaconates [38].

1.3 Applications of Chiral Phosphorous Ligands in Rhodium-Catalyzed Asymmetric Hydrogenation

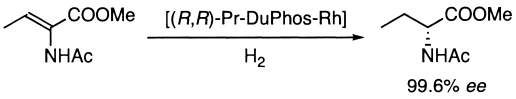
1.3.1 Hydrogenation of Olefins

1.3.1.1 Hydrogenation of Dehydroamino Acid Derivatives

Several chiral phosphorous ligands with great structural diversity are effective for the rhodium-catalyzed hydrogenation of *α*-dehydroamino acid derivatives. Tab. 1.1 summarizes the asymmetric hydrogenation of (*Z*)-2-(acetamido)cinnamic acid, 2-(acetamido)acrylic acid, and their methyl ester derivatives.

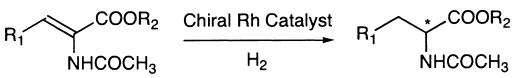
A number of chiral ligands have proven very efficient and selective for the hydrogenation of *α*-dehydroamino acid derivatives. Examples include PYRPHOS [26b], Et-DuPhos [89], f-KetalPhos [55], TangPhos [64], DPAMP [90], and BoPhoz (**L15**) [83], for which substrate-to-catalyst ratios as high as 50000:1 have been observed. Indeed, asymmetric rhodium-catalyzed hydrogenation reactions using the Me-DuPhos and Et-DuPhos ligands are tolerant to *β*-alkyl and aryl substituents (≥95% *ee*), even in supercritical CO_2 [91].

In contrast to the high enantioselectivity achieved for the *Z*-isomeric substrates, hydrogenation of the *E*-isomers usually proceeds with lower rates and afford products with diminished enantioselectivities [92]. The rhodium-catalyzed hydrogenation of the *E*- and *Z*-isomers, with BINAP as a ligand in THF, affords products with opposite absolute configurations [16]. Remarkably, the DuPhos–Rh system provides excellent enantioselectivity for both isomeric substrates with the same absolute configuration, irrespective of the *E*/*Z*-geometry (Eqs. 1 and 2). This result is particularly important for the construction of alkyl dehydroamino acid derivatives, which are difficult to prepare in enantiomerically pure form.



(1)

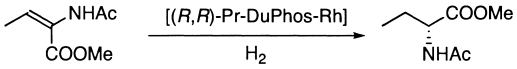
Tab. 1.1



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*	*S/C ratio*	*Reaction conditions*	*% ee (config.)*	*Ref.*
(*R*,*R*)-DIPAMP	D	900	MeOH, 50 °C, 3 atm. H_2	96 (*S*)	8a
(*R*,*R*)-NORPHOS	C	95	MeOH, RT, 1.1 atm. H_2	96 (*R*)	25
(*R*,*R*)-PYRPHOS	D	50000	MeOH, RT, 61 atm. H_2	96.5 (*S*)	26b
(*S*)-BINAP	D [a)]	100	EtOH, RT., 3 atm. H_2	100 (*S*)	15
(*R*)-BICHEP	D [b)]	1000	EtOH, RT, 1 atm. H_2	95 (*S*)	20c
(*S*,*S*)-Et-DuPhos	B	50440	MeOH, RT, 2 atm. H_2	>99 (*S*)	89
(*R*,*R*)-BICP	A	100	THF, Et_3N, RT, 1 atm. H_2	97.5 (*S*)	41a
ROPHOS	D	100	MeOH, RT, 1 atm. H_2	98.4 (*S*)	32a
KetalPhos	C	100	MeOH, RT, 3 atm. H_2	>99 (*S*)	33b
L3	A	100	H_2O, RT, 50 psi H_2	>99 (*S*)	35a
(*R*,*R*)-**L5**	A	1000	MeOH, 20 °C, 1.1 atm. H_2	97.4 (*R*)	38
(*R*,*R*,*R*)-**L6**	D	1000	MeOH, 25 °C, 2 atm. H_2	98 (*R*)	40
(*R*,*R*)-(*S*,*S*)-EtTRAP	B	100	CH_2Cl_2, 60 °C, 0.5 atm. H_2	96 (*R*)	46b
(*R*)-(*S*)-JosiPhos	D	100	MeOH, 35 °C, 1 atm. H_2	96 (*S*)	47
(*S*,*S*)-FerroPhos	C	100	EtOH, RT, 2 atm. H_2	98.9 (*R*)	50a
(*R*)-(*S*)-FERRIPHOS	D	100	MeOH, RT, 1 atm. H_2	98.0 (*S*)	51a
Taniaphos	D	100	MeOH/PhMe, 1 atm. H_2	96.6 (*R*)	52a
(*S*,*S*,*S*,*S*)-f-KetalPhos	B	10000	THF, RT, 3 atm. H_2	100 (*S*)	55
(*S*,*S*)-^{t}Bu-BisP*	D	500	MeOH, RT, 2 atm. H_2	99.9 (*R*)	57a
(*S*,*S*)-^{t}Bu-MiniPhos	B	500	MeOH, RT, 2 bar H_2	99.9 (*R*)	61
(*S*,*S*)-**L7**	B	500	0 °C, 2 bar H_2	97 (*S*)	62
(*S*,*S*)-**L8**	D	500	MeOH, RT, 2 atm. H_2	99.2 (*R*)	63a
(*S*,*S*,*R*,*R*)-TangPhos	D	10000	MeOH, RT, 20 psi H_2	99.8 (*S*)	64
(–)-BIPNOR	C	100	EtOH, RT, 3 atm. H_2	>98 (*S*)	68a
(*R*)-PHANEPHOS	B	100	MeOH, RT, 1 atm. H_2	99.6 (*R*)	69a
(*S*)-Ph-*o*-NAPHOS	B	100	MeOH, RT, 3 atm. H_2	98.7 (*S*)	70
L10	C	1000	THF, RT, 30 psi H_2	99.0 (*S*)	71a
(*R*)-spirOP	C	100	MeOH, RT, 1 atm. H_2	97.9 (*R*)	72a
DIMOP	A	500	Me_2CO, RT, 500 psi H_2	96.7 (*R*)	73
L11	D	100	H_2O, RT, 5 atm. H_2 [c)]	99.9 (*S*)	74
(*S*)-Ph-*o*-BINAPO	B	100	MeOH, RT, 3 atm. H_2	99.9 (*S*)	70
(*R*,*R*)-**L12**	B	1000	CH_2Cl_2, RT, 1.3 atm. H_2	99.5 (*S*)	76
(*S*)-(*R*)-**L13**	B	5000	MeOH, RT, 3.5 atm. H_2	98.5 (*S*)	77
(1*R*,2*S*)-DPAMPP	D	10000	MeOH, RT, 50 atm. H_2	97 (*R*)	80b
(*S*)-Xyl-BDPAB	D	500	MeOH, RT, 50 psi H_2	98 (*S*)	82
L15	D	10000	THF, RT, 10 psi H_2	99.4 (*S*)	83
(*S*)-MonoPhos	B	20	EtOAc, RT, 1 atm. H_2	99.6 (*R*)	86
(*S*)-SIPHOS	D	200	CH_2Cl_2, RT, 1 atm. H_2	96.4 (*S*)	88b

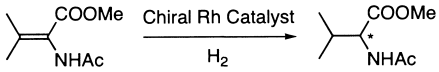
a) Benzoyl derivative.
b) Ethyl ester.
c) Sodium dodecyl sulfate (10 mol%) was added.



99.4% *ee* (2)

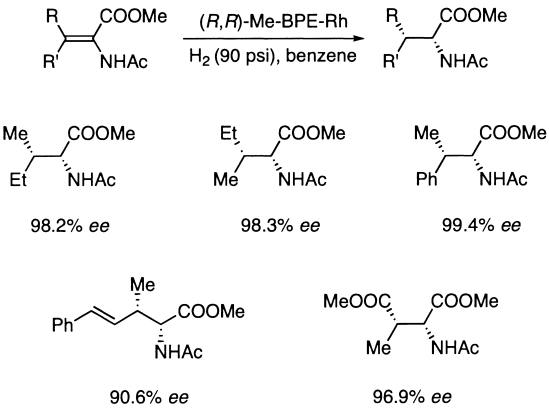
Hydrogenation of *β*,*β*-disubstituted *α*-dehydroamino acids remains a challenging problem. Remarkably, the less bulky DuPhos- or BPE-type ligands, such as Me-DuPhos and Me-BPE, provide excellent enantioselectivity for a variety of this type of substrate [93]. The rhodium complexes of chiral ligands such as BuTRAP [46 b], f-KetalPhos [55], Cy-BisP* [57a], MiniPhos [61], and unsymmetrical BisP* (**L9**) [63 b] have also shown high efficiencies for some *β*,*β*-disubstituted *α*-dehydroamino acid substrates, as outlined in Tab. 1.2.

Tab. 1.2



Ligand	*S/C ratio*	*Reaction conditions*	*% ee (config.)*	*Ref.*
(*R*,*R*)-(*S*,*S*)-BuTRAP	100	^{i}PrOH, 15 °C, 1 atm. H_2	88 (*S*)	46 b
(*S*,*S*)-Me-DuPhos	500	PhH, 25 °C, 90 psi H_2	96.0 (*S*)	93
(*R*,*R*)-Me-BPE	500	PhH, 25 °C, 90 psi H_2	98.2 (*R*)	93
(*S*,*S*,*S*,*S*)-f-KetalPhos	100	THF, RT, 15 psi H_2	87.3 (*S*)	55
(*S*,*S*)-Cy-BisP*	500	MeOH, RT, 6 atm. H_2	90.9 (*R*)	57 a
(*S*,*S*)-^{t}Bu-MiniPhos	500	MeOH, RT, 6 atm. H_2	87 (*R*)	61
(*S*,*S*)-**L7**	500	RT, 6 atm. H_2	87 (*S*)	62
(*S*,*S*)-**L9**	100	MeOH, RT, 20 atm. H_2	96.1 (*R*)	63b

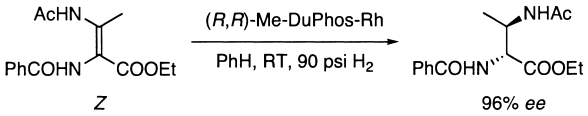
The asymmetric hydrogenation of *β*,*β*-disubstituted *α*-dehydroamino acids, in which the *β*-substituents are nonequivalent, provides the opportunity to selectively construct two stereogenic centers. The Me-DuPhos or Me-BPE ligands facilitate the rhodium-catalyzed hydrogenation of the *E*- and *Z*-isomers of *β*,*β*-disubstituted *α*-dehydroamino acid



Scheme 1.10

derivatives with excellent enantioselectivity (Scheme 1.10). Moreover, excellent chemoselectivity is observed in hydrogenation of substrates that contain additional olefin functionality [94]. Thus hydrogenation of β-substituted α,β,γ,δ-unsaturated amino acids with the Me-DuPhos and Me-BPE ligands provides a series of β-substituted γ,δ-unsaturated amino acids with good enantioselectivity.

The asymmetric hydrogenation of the *E*- or *Z*-isomer of β-(acetylamino)-β-methyl-α-dehydroamino acids with Me-DuPhos–Rh catalyst provides either diastereomer of the *N,N*-protected 2,3-diaminobutanoic acid derivatives with excellent enantioselectivity (Eqs. 3 and 4) [95].



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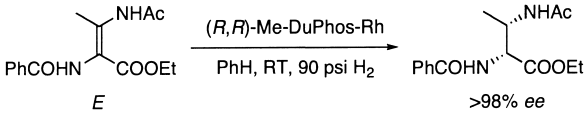


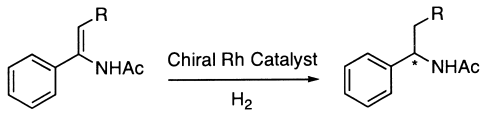
(4)

1.3.1.2 **Hydrogenation of Enamides**

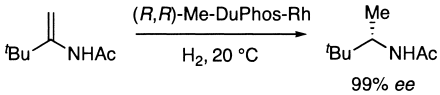
Recently, high enantioselectivity was obtained in the rhodium-catalyzed hydrogenation of α-aryl enamides and *E*/*Z*-isomeric mixtures of β-substituted enamides. Tab. 1.3 lists some examples for the hydrogenation of α-phenylenamide and the *E*/*Z*-isomeric mixture of β-methyl-α-phenylenamide. A *P*-chiral ligand, TangPhos, proved to be particularly efficient for the rhodium-catalyzed hydrogenation of enamides, given the excellent enantioselectivity and reactivity, with up to 10 000 turnovers.

Some alkyl enamides, such as *tert*-butylenamide or 1-admantylenamide, can also be hydrogenated using a ^{t}Bu-BisP*–Rh catalyst [58] or a Me-DuPhos–Rh catalyst [97] with excellent enantioselectivity (≥99% *ee*; Eq. 5). Hydrogenation of *N*-acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroquinoline can be catalyzed by an (*S,S,R,R*)-TangPhos–Rh complex to afford (*R*)-(–)-*N*-acetylsalsolidine in 97% *ee* (Eq. 6) [64]. PennPhos [37a], *o*-Ph-HexaMeO-BIPHEP [31], and Me-BPE [97] have also shown high efficiencies in the rhodium-catalyzed hydrogenation of cyclic enamides (Eq. 7). The racemic cyclic enecarbamate was hydrogenated with an *o*-Ph-HexaMeO-BIPHEP–Rh catalyst to furnish the *cis*-carbamate in 96% *ee* (Eq. 8) [31]. The enantiomerically enriched product was then directly employed for the synthesis of sertraline, an antidepressant agent. Interestingly, 2-substituted *N*-acetylindoles can also be effectively hydrogenated by the Ph-TRAP–Rh catalyst with excellent enantioselecitivities (Eq. 9) [46g]. Hydrogenation of some tetra-substituted enamides has also been reported. ^{t}Bu-BisP* and ^{t}Bu-MiniPhos have provided excellent enantioselectivity for the hydrogenation of β,β-dimethyl-α-phenyl enamide derivatives (Eq. 10). The PennPhos–Rh [37a] and *o*-Ph-BIPHEP–Rh catalysts [31] facilitate the hydrogenation of tetra-substituted enamides derived from 1-indanone and 1-tetralone with excellent enantioselectivity.

Tab. 1.3



Ligand	*Substrate*	*S/C ratio*	*Reaction conditions*	*% ee (config.)*	*Ref.*
(*R*,*R*)-Me-BPE	A	500	MeOH, 22 °C, 6 psi H_2	95.2 (*R*)	96
	B	500	MeOH, 22 °C, 6 psi H_2	95.4 (*R*)	96
KetalPhos	A	100	MeOH, RT, 10 atm. H_2	96 (*S*)	33b
(*S*,*S*)-BINAPHANE	B	100	CH_2Cl_2, RT, 20 psi H_2	99.1 (*S*)	39a
(*R*,*R*)-BICP	B	100	PhMe, RT, 40 psi H_2	95.0 (*R*)	41b
(*R*,*S*,*S*,*R*)-DIOP*	A	50	MeOH, RT, 10 bar H_2	98.8 (*R*)	42
	B	50	MeOH, RT, 10 bar H_2	97.3 (*R*)	42
(*R*,*R*,*R*,*R*)-T-Phos	B	100	MeOH, RT, 45 psi H_2	98 (*S*)	45
(*R*,*R*,*R*,*R*)-SK-Phos	B	100	MeOH, RT, 45 psi H_2	97 (*S*)	45
(*S*,*S*)-BDPMI	A	100	CH_2Cl_2, RT, 1 atm. H_2	98.5 (*R*)	44a
	B	100	CH_2Cl_2, RT, 1 atm. H_2	>99 (*R*)	44a
(*S*,*S*)-^{t}Bu-BisP*	A	100	MeOH, RT, 3 atm. H_2	98 (*R*)	58
(*S*,*S*,*R*,*R*)-TangPhos	A	10^4	MeOH, RT, 20 psi H_2	99.3 (*R*)	64
	B	100	MeOH, RT, 20 psi H_2	98 (*R*)	64
(*R*)-H_8-BDPAB	A	200	THF, 5 °C, 1 atm. H_2	96.8 (*R*)	81a
(*S*)-MonoPhos	A	100	CH_2Cl_2, –20 °C, 300 psi H_2	95 (*S*)	87
(*S*)-SIPHOS	A	200	toluene, 5 °C, 10 atm. H_2	98.7 (*S*)	88a



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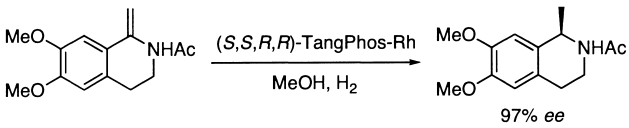

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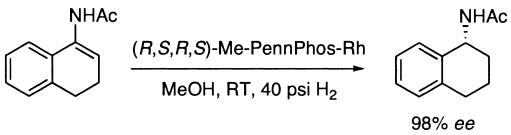

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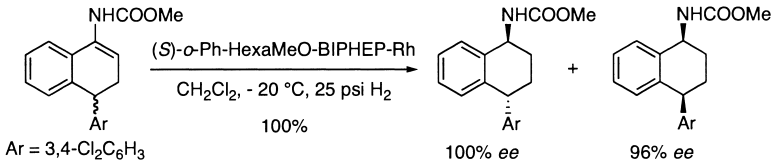

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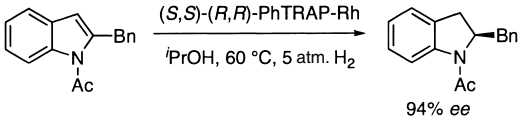

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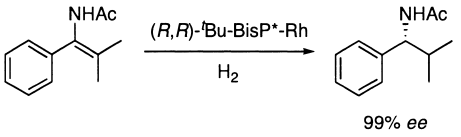
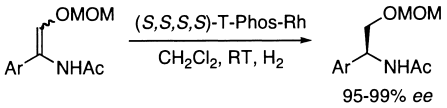


(10)

The hydrogenation of a series of *E*/*Z*-isomeric mixtures of *α*-arylenamides containing a MOM-protected *β*-hydroxyl group, using BICP–Rh and Me-DuPhos–Rh catalysts, affords the *β*-amino alcohol derivatives with excellent enantioselectivity [41c]. A 1,4-diphosphane, T-Phos, with a rigid 1,4-dioxane backbone is also a very effective ligand for this transformation (Eq. 11) [45].

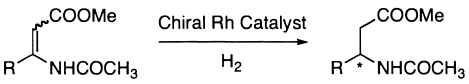


(11)

1.3.1.3 **Asymmetric Hydrogenation of *β*-(Acylamino)acrylates**

Owing to the significance of *β*-amino acid derivatives for pharmaceuticals, asymmetric hydrogenation of *β*-(acylamino)acrylates has gained significant attention in recent years [98]. The ability to utilize mixtures of *E*- and *Z*-isomers that furnish a single enantiomer is very important for the practical synthesis of *β*-amino acid derivatives, since it circumvents the necessity to prepare geometrically defined alkenes. Several rhodium complexes with chiral phosphorous ligands such as DuPhos [99], BICP [41e], BDPMI [44b], *o*-Ph-HexaMeO-BIPHEP [31], ^{t}Bu-BisP* [59], and TangPhos [66] are effective for the hydrogenation of (*E*)-alkyl(*β*-acylamino)acrylates. However, only a few chiral ligands, such as BDPMI and TangPhos, have been reported to effectively hydrogenate the corresponding (*Z*)-alkyl-*β*-(acylamino)acrylates (Tab. 1.4). Although the alkyl-*β*-(acylamino)acrylic acid derivatives have been extensively studied, there has been significantly less work on the aryl-*β*-(acylamino)acrylic acid derivatives. Since (*E*)-*β*-aryl-*β*-(acylamino)acrylic acid derivatives are difficult to obtain compared to the corresponding (*Z*)-*β*-aryl-*β*-(acylamino)acrylic acid derivatives, the *Z*-isomeric substrates represent important substrates for the practical synthesis of enantiomerically enriched *β*-aryl-*β*-amino acids via asymmetric hydrogenation. Few ligands have been reported for the selective hydrogenation of (*Z*)-*β*-aryl-(*β*-acylamino)acrylates. However, the Rh–BINAPINE complex has proven excellent, both

Tab. 1.4



Ligand	*R*	*Geometry*	*S/C ratio*	*% ee (config.)*	*Ref.*
(*S*,*S*)-Me-DuPhos [a)]	CH_3	*E*		98.2 (*S*)	99
(*R*,*R*)-BICP [b)]	CH_3	*E*		96.1 (*R*)	41 e
(*S*,*S*)-BDPMI [c)]	CH_3 [f)]	*E*		94.6 (*R*)	44 b
(*S*,*S*)-^{t}Bu-BisP* [d)]	CH_3	*E*		98.7 (*R*)	59
(*S*,*S*)-MiniPhos [d)]	CH_3	*E*		96.4 (*R*)	59
(*S*,*S*,*S*,*S*)-TangPhos [e)]	CH_3	*E*		99.6 (*R*)	66
(*S*,*S*)-Me-DuPhos [a)]	CH_3	*Z*		87.8 (*S*)	99
(*S*,*S*)-BDPMI [c)]	CH_3 [f)]	*Z*		95 (*R*)	44 b
(*S*,*S*,*R*,*R*)-TangPhos [e)]	CH_3	*Z*	200	98.5 (*R*)	66
(*S*,*S*,*S*,*S*)-TangPhos [e)]	Ph	*E*/*Z*	200	93.8 (*S*)	66
(*S*,*S*,*S*,*S*)-TangPhos [e)]	*p*-F-Ph	*E*/*Z*	200	95.0 (*S*)	66
(*S*,*S*,*S*,*S*)-TangPhos [e)]	*p*-MeO-Ph	*E*/*Z*	200	98.5 (*S*)	66
BINAPINE [e)]	Ph	*Z*	10 000	99 (*S*)	65
BINAPINE [e)]	*p*-F-Ph	*Z*	10 000	99 (*S*)	65
BINAPINE [e)]	*p*-Me-Ph	*Z*	10 000	99 (*S*)	65
BINAPINE [e)]	*p*-MeO-Ph	*Z*	10 000	99 (*S*)	65

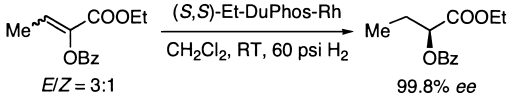
Reaction conditions:
a) MeOH, 25 °C, 1 atm. H_2.
b) PhMe, RT, 40 psi H_2.
c) CH_2Cl_2, RT, 1 atm. H_2.
d) THF, RT, 3 atm. H_2.
e) THF, RT, 20 psi H_2.
f) Ethyl ester.

in terms of enantioselectivity (96 to ≥99% *ee*) and turnover (10 000 turnovers), using a wide range of (*Z*)-*β*-aryl-*β*-(acylamino)acrylic acid derivatives (Tab. 1.4) [65].

1.3.1.4 **Asymmetric Hydrogenation of Enol Esters**

Although enol esters have a similar structure to enamides, they have proven more difficult substrates for asymmetric hydrogenation, which is evident from the significantly fewer number of examples. One possible explanation is the weaker coordinating ability of the enol ester to the metal center, as compared to the corresponding enamide. Some rhodium complexes associated with chiral phosphorous ligands such as DIPAMP [100, 101] and DuPhos [102] are effective for asymmetric hydrogenation of *α*-(acyloxy)acrylates.

For example, a wide range of *α*-(acyloxy)acrylates have been hydrogenated with excellent enantioselectivity using the Et-DuPhos–Rh catalyst. High selectivities are also obtained for the asymmetric hydrogenation of the *E*/*Z*-isomeric mixtures of *β*-substituted derivatives (Eq. 12). Asymmetric hydrogenation of enol phosphates with either DuPhos–Rh or BPE–Rh catalyst provides moderate to excellent enantioselectivity (Eq. 13)



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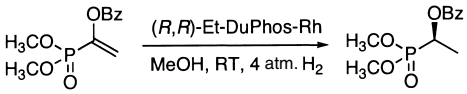
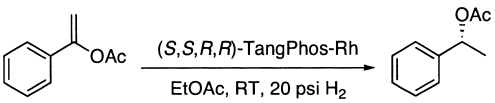


(13)

[103]. Indeed, several rhodium catalysts with chiral phosphorous ligands such as DuPhos [104], KetalPhos [33], and TangPhos [67] have been utilized for the asymmetric hydrogenation of aryl enol acetates lacking additional functionality. For example, aryl enol acetates are hydrogenated with enantioselectivities ranging from 92 to 99% *ee*, using the TangPhos–Rh catalyst (Eq. 14) [67]. The asymmetric hydrogenation of cyclic enol acetates is also a challenging problem. Me-PennPhos is an effective ligand in the rhodium-catalyzed hydrogenation of five- or six-membered cyclic enol acetates (Eq. 15) [37b]. Hydrogenation of acyclic enol acetates is also possible as vinylic, acetylenic [105] and trifluoromethyl [106] enol acetates have also been hydrogenated with both the DuPhos–Rh and BPE–Rh catalysts with excellent enantioselectivity (Eqs. 16 and 17).



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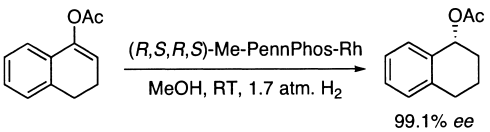

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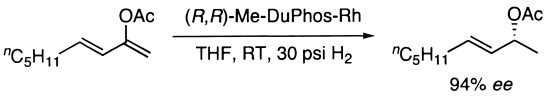

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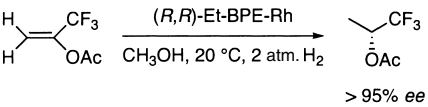

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1.3.1.5 Asymmetric Hydrogenation of Unsaturated Acids and Esters

***α,β*-Unsaturated Carboxylic Acids** Although significant advances have been achieved in the asymmetric hydrogenation of *α,β*-unsaturated carboxylic acids with chiral ruthenium catalysts, there are relatively few systems that have been reported for the rhodium-catalyzed version of this reaction. For example, the (aminoalkyl)ferrocenylphosphine ligand **L1** provides excellent enantioselectivity and turnover for the rhodium-catalyzed hydrogenation of trisubstituted acrylic acids (Eq. 18). The (*R*)-(*S*)-

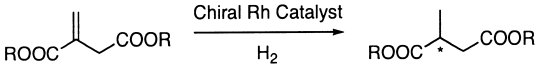
L1–Rh complex was employed for the enantioselective synthesis of (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid (98% *ee*) [107], while the ^{i}Pr-DuPhos–Rh complex was utilized for the enantioselective hydrogenation of *α*,*β*-unsaturated carboxylic acids, as exemplified by tiglic acid [29].

(18)

Itaconic Acids and Their Derivatives Tab. 1.5 outlines some of the chiral phosphorous ligands that provide excellent enantioselectivity and reactivity in the rhodium-catalyzed hydrogenation of itaconic acids or esters. Interestingly, both the electron-rich phosphane ligands (BICHEP [20c], Et-DuPhos [108], and TangPhos [67]) and electron-deficient phosphite or phosphonite ligands (**L12** [76] and **L14**) are effective for this type of transformation [78]. Some monophosphorous ligands, such as MonoPhos [87] and **L17** [85a], are as efficient as bisphosphorous bidentate ligands, as exemplified by the secondary phosphane **L18** [38]. Furthermore, the tetrahydroxy bisphospholane ligand allows the hydrogenation to proceed in aqueous media [33b].

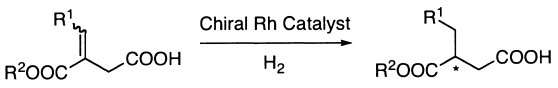
In contrast to the many examples of asymmetric hydrogenation of the parent itaconic acid or its dimethyl ester, very few ligands have been reported for the enantioselec-

Tab. 1.5



Ligand	*R*	*S/C*	*Reaction conditions*	*% ee (config.)*	*Ref.*
(*R*)-BICHEP-Rh	H	1000	EtOH, 25 °C, 1 atm. H_2	96 (*R*)	20c
(*R*,*R*)-Et-DuPhos	Me	10000	MeOH, 25 °C, 5 atm. H_2	98 (*R*)	108
KetalPhos	H	100	MeOH/H_2O (3:97), RT, 10 atm. H_2	>99 (*R*)	33b
L2	Me	100	MeOH, RT, 1 atm. H_2	99.1 (*R*)	32a
L4	Me	100	MeOH, RT, 1 atm. H_2	97.9 (*R*)	34b
(*R*,*R*)-(*S*,*S*)-Et-TRAP	Me	200	CH_2Cl_2, reflux, 1 atm. H_2	96 (*S*)	47c
Taniaphos	Me	100	MeOH, RT, 1 atm. H_2	98 (*S*)	52a
(*S*,*S*)-Et-FerroTANE	Me	200	MeOH, RT, 5.5 atm. H_2	98 (*R*)	54
(*S*,*S*,*S*,*S*)-f-KetalPhos	H	100	MeOH, RT, 80 psi H_2	99.5 (*R*)	55
(*S*,*S*)-Ad-BisP*	Me	500	MeOH, RT, 1.6 atm. H_2	99.6	57b
(*S*,*S*,*R*,*R*)-TangPhos	Me	5000	THF, RT, 20 psi H_2	99 (*S*)	67
(*R*,*R*)-**L12**	Me	5380	CH_2Cl_2, RT, 1.3 bar H_2	>99.5 (*R*)	76
L14	Me	1000	CH_2Cl_2, –10 °C, 0.3 bar H_2	98.7 (*R*)	78
L15	H	100	MeOH, RT, 300 psi H_2	97.4 (*R*)	83
(*S*)-MonoPhos	H	20	CH_2Cl_2, 25 °C, 1 atm. H_2	96.6 (*S*)	87
(*S*)-(*R*)-**L17**	Me	5000	CH_2Cl_2, 20 °C, 1.3 atm. H_2	97.4 (*S*)	85a
(*R*,*R*)-**L18**	H	100	^{i}PrOH, 20 °C, 1.1 atm. H_2	96.0 (*S*)	38

Tab. 1.6

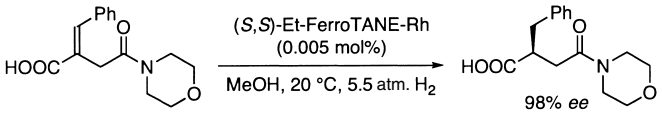


Ligand	R^1	R^2	*Geometry*	*S/C ratio*	*% ee (config.)*	*Ref.*
(*R*,*R*)-MOD-DIOP [a]	Ph	Me	*E*	500	96 (*S*)	23c
(*R*,*R*)-BPPM [a]	Ph	H	*E*	200	94 (*R*)	109
(*S*,*S*)-Et-DuPhos [b]	Ph	Me	*E*/*Z*	3000	97 (*S*)	108
(*S*,*S*,*R*,*R*)-TangPhos [c]	Ph	Me	*E*/*Z*	200	95 (*S*)	67
(*S*,*S*)-Et-DuPhos [b]	^{i}Pr	Me	*E*/*Z*	3000	99 (*R*)	108
(*S*,*S*,*R*,*R*)-TangPhos [c]	^{i}Pr	Me	*E*/*Z*	200	96 (*S*)	67

Reaction conditions:
a) MeOH, NEt_3, 25 °C, 1 atm. H_2.
b) MeOH, RT, 5.5 atm. H_2, 10 mol% NaOMe.
c) THF, RT, 20 psi H_2.

tive hydrogenation of *β*-substituted itaconic acid derivatives. Effective ligands for this class of substrates are MOD-DIOP [23], BPPM, Et-DuPhos, and TangPhos, as illustrated in Tab. 1.6.

Chiral 1,1′-diphosphetanylferrocene Et-FerroTANE serves as an effective ligand for the rhodium-catalyzed hydrogenation of *β*-aryl- and *β*-alkyl-substituted monoamido itaconates (Eqs. 19 and 20) [54]. The Et-DuPhos–Rh catalyst was utilized for the asymmetric hydrogenation of the trisubstituted olefin derivative in the preparation of an important intermediate for the drug candoxatril (≥99% *ee*) [110].



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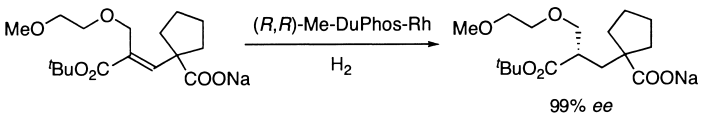

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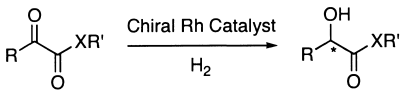
1.3.2 Hydrogenation of Ketones

1.3.2.1 Hydrogenation of Functionalized Ketones

***α*-Keto Esters** Asymmetric hydrogenation of *α*-keto esters has been studied with several rhodium catalysts. Some neutral rhodium catalysts with chiral ligands, such as MCCPM [24b, 111], Cy,Cy-oxoProNOP [79c,d,f], Cp,Cp-IndoNOP [79g], and $Cr(CO)_3$-Cp,Cp-IndoNOP [79g], demonstrate excellent enantioselectivity and reactivity in the hydrogenation of *α*-keto esters or amides (Tab. 1.7). The cyclic *α*-keto ester, such as dihydro-4,4-dimethyl-2,3-furandione, have also been selectively hydrogenated by a number of rhodium

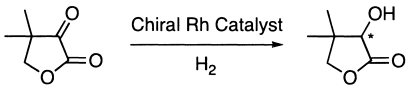
Tab. 1.7



Catalyst	*R*	*XR'*	*S/C ratio*	*% ee (config.)*	*Ref.*
(*S*,*S*)-MCCPM-Rh [a)]	Me	OMe	2000	87 (*R*)	111
(*S*)-Cy,Cy-oxoProNOP- Rh [b)]	Me	OEt	200	95 (*R*)	79 f
L16-Rh [a)]	$Ph(CH_2)_2$	OEt	100	92.4 (*R*)	83
(*S*)-Cp,Cp-IndoNOP-Rh [c)]	Ph	NHBn	200	91 (*S*)	79 g
(*S*,2*S*)-$Cr(CO)_3$-Cp,Cp-IndoNOP-Rh [c)]	Ph	NHBn	200	97 (*S*)	79 g

Reaction conditions:
a) THF, 20 °C, 20 atm. H_2.
b) PhMe, 20 °C, 50 atm. H_2.
c) PhMe, 20 °C, 1 atm. H_2.

Tab. 1.8

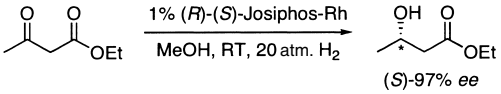


Ligand	*S/C ratio*	*% ee (config.)*	*Ref.*
(*S*,*S*)-BCPM-Rh [a)]	1000	90.5 (*R*)	112
(*S*,*S*)-*m*-MePOPPM [b)]	150 000	95 (*R*)	113
(*S*)-Cp,Cp-oxoProNOP [c)]	70 000	96 (*R*)	79 d
(*S*)-Cp,Cp-IndoNOP [d)]	200	>99 (*R*)	79 g
(*S*,2*S*)-$Cr(CO)_3$-Cp,Cp-In doNOP [d)]	200	>99 (*R*)	79 g
L16 [e)]	100	97.2 (*R*)	83

Reaction conditions:
a) THF, 50 °C, 50 atm. H_2.
b) Toluene, 40 °C, 12 atm. H_2.
c) Toluene, 40 °C, 40 atm. H_2.
d) Toluene, 20 °C, 1 atm. H_2.
e) THF, RT, 20 atm. H_2.

catalysts, with high turnover numbers (Tab. 1.8). For example, (*R*)-pantolactone, a key intermediate for the synthesis of vitamin B and co-enzyme A, has been readily prepared through the asymmetric hydrogenation of the corresponding *α*-keto ester.

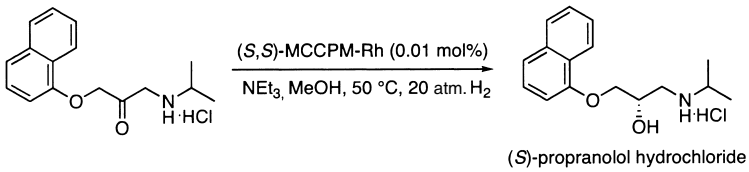
***β*-Keto Esters** Asymmetric hydrogenation of *β*-keto esters has been extensively studied using chiral ruthenium catalysts. However, there are relatively few examples of the analogous rhodium-catalyzed reaction. Nonetheless, the Josiphos–Rh complex provides an effective catalyst for the asymmetric hydrogenation of ethyl 3-oxobutanoate (Eq. 21) [47].



(21)

Amino Ketones Amino ketones and their hydrochloride salts can be effectively hydrogenated with chiral rhodium catalysts (Tab. 1.9). The rhodium precatalysts, combined with chiral phosphorous ligands such as BPPFOH [10b], MCCPM [24f–k], Cy,Cy-oxoProNOP [79c, e], Cp,Cp-oxoProNOP [79c, e], and IndoNOP [79g], have provided excellent enantioselectivity and reactivity for the asymmetric hydrogenation of α, β, and γ-alkyl amino ketone hydrochloride salts.

The enantioselective hydrogenation of amino ketones has been applied extensively to the synthesis of chiral drugs (Eq. 22). For example, the enantioselective hydrogenation of 3-aryloxy-2-oxo-1-propylamine derivatives directly leads to 1-amino-3-aryloxy-2-propanol derivatives, which serve as β-adrenergic blocking agents. (*S*)-Propranolol is obtained in 90.8% *ee* from the corresponding α-amino ketone, using 0.01 mol% of the neutral (*S*,*S*)-MCCPM–Rh complex [24f].



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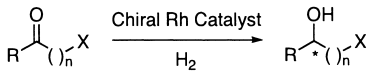
Tab. 1.9



Catalyst	*R*	*n*	*X*	*S/C ratio*	*% ee (config.)*	*Ref.*
(*R*)-(*S*)-BPPFOH-Rh [a)]	(3,4)-$(OH)_2C_6H_3$	1	NHMe·HCl	100	95 (*R*)	10b
(2*S*,4*S*)-MCCPM-Rh [b)]	Ph	1	NEt_2·HCl	100 000	96 (*S*)	114
(*S*)-Cp,Cp-oxoProNOP-Rh [c)]	Ph	1	NMe_2·HCl	200	96 (*S*)	79e
(*S*)-Cp,Cp-oxoProNOP-Rh [c)]	Me	1	NMe_2·HCl	200	97 (*S*)	79e
(*S*)-Cp,Cp-IndoNOP-Rh [d)]	Ph	1	NMe_2·HCl	200	99 (*S*)	79g
(*S*)-Cy,Cy-oxoProNOP-Rh [d)]	Ph	2	NMe_2·HCl	200	93 (*R*)	79g
(2*S*,4*S*)-MCCPM-Rh [e)]	Ph	2	N(Me)Bn·HCl	1000	91 (*R*)	24g
(*S*)-Cy,Cy-oxoProNOP-Rh [f)]	Ph	3	NMe_2·HCl	200	92 (*R*)	79g

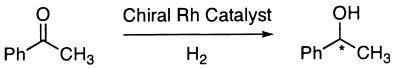
Reaction conditions:
a) NEt_3, MeOH, RT, 50 atm. H_2.
b) NEt_3, MeOH, 50 °C, 20 atm. H_2.
c) MeOH, 20 °C, 50 atm. H_2.
d) PhMe, 20 °C, 20 atm. H_2.
e) MeOH, 50 °C, 30 atm. H_2.
f) PhMe, 80 °C, 50 atm. H_2.

1.3.2.2 Hydrogenation of Unfunctionalized Ketones

The asymmetric hydrogenation of unfunctionalized ketones is a much more challenging task than that of functionalized ketones [3j, 115]. Many chiral catalysts which are effective for functionalized ketones do not provide useful levels of enantioselectivity for unfunctionalized ketones, due to a lack of secondary coordination to the metal center. Zhang demonstrated the enantioselective hydrogenation of simple aromatic and aliphatic ketones using the electron-donating diphosphane PennPhos, which has a bulky, rigid and well-defined chiral backbone, in the presence of 2,6-lutidine and potassium bromide [36].

Aromatic Ketones The DIOP–Rh [116] and DBPP–Rh [117] complexes, in conjunction with a tertiary amine, have been employed in the asymmetric hydrogenation of acetophenone, albeit with moderate enantioselectivity (80 and 82% respectively; Tab. 1.10). The asymmetric hydrogenation of aromatic ketones was significantly improved by using the Me-PennPhos–Rh complex, with which enantioselectivities of up to 96% *ee* were achieved [36]. Interestingly, the additives 2,6-lutidine and potassium bromide were again found to be crucial for optimum selectivity, although their specific role has not been determined.

Tab. 1.10

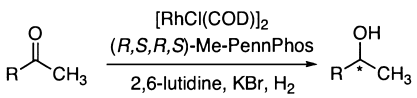


Catalyst	*S/C ratio*	*Yield [%]*	*% ee (config.)*	*Ref.*
$[RhCl(nbd)]_2$-(*S,S*)-DIOP+NEt_3 [a)]	200	64	80	116
$[RhCl(nbd)]_2$-(*S,S*)-BDPP+NEt_3 [a)]	100	72	82 (*S*)	117
$[RhCl(cod)]_2$-(*R,S,R,S*)-Me-PennPhos+2,6-lutidine [b)]	100	97	95 (*S*)	36

Reaction conditions:
a) MeOH, 50 °C, 69 atm. H_2, 6 h.
b) MeOH, RT, 30 atm. H_2, 24 h.

Aliphatic Ketones The asymmetric hydrogenation of simple aliphatic ketones remains a challenging problem. This may be attributed to the difficulty with which the chiral catalyst differentiates between the two-alkyl substituents of the ketone. Promising results have been obtained in asymmetric hydrogenation of aliphatic ketones using the PennPhos–Rh complex in combination with 2,6-lutidine and potassium bromide (Tab. 1.11) [36]. For example, the asymmetric hydrogenation of *tert*-butyl methyl ketone affords the requisite secondary alcohol in 94% *ee*. Similarly, isopropyl, ^{n}Butyl, and cyclohexyl methyl ketones have been reduced to the corresponding secondary alcohols with 85% *ee*, 75% *ee*, and 92% *ee* respectively.

Tab. 1.11



R	*S/C ratio*	*Time*[a)] *[h]*	*Yield [h]*	*% ee (config.)*
^{n}Bu	100	48	96	75 (*S*)
^{i}Bu	100	75	66	85 (*S*)
^{i}Pr	100	94	99	84 (*S*)
Cyclohexyl	100	106	90	92 (*S*)
^{t}Bu	100	96	51	94 (*S*)

a) Other reaction conditions: MeOH, RT, 30 atm. H_2.

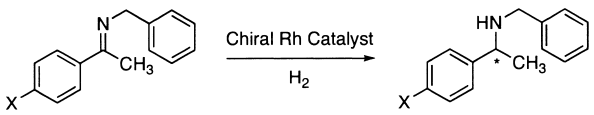
1.3.3 Asymmetric Hydrogenation of Imines

The paramount significance of chiral amines in pharmaceutical and agrochemical substances drives the development of efficient catalytic asymmetric methods for their formation. In contrast to the high enantioselectivities observed in asymmetric reduction of both alkenes and ketones, only limited success has been achieved in the enantioselective hydrogenation of imines [118]. Currently, there are few efficient chiral catalytic systems available for the asymmetric hydrogenation of imines.

1.3.3.1 Acyclic *N*-Alkylimines

Several chiral rhodium, iridium, titanium, and zirconium catalysts have been applied to the asymmetric hydrogenation of acyclic *N*-alkylimines, with limited success. While the chiral titanocene catalyst has a broad substrate scope for the reduction of *N*-alkylimines [119], affording the secondary amines with moderate to good enantioselectivity, the corresponding rhodium and iridium catalysts are limited to acetophenone *N*-benzylimine derivatives. The substrates are generally mixtures of *E*- and *Z*-isomers, of which several examples are outlined in Tab. 1.12. The asymmetric hydrogenation of acetophenone *N*-benzylimine derivatives using the neutral CycPhos–Rh complex in the presence of potassium iodide affords moderate to good enantioselectivity (up to 91% *ee*) [120]. (*S*,*S*)-BDPP is also an effective ligand for the reduction of acetophenone *N*-benzylimine, in which enantioselectivities of up to 83% *ee* have been observed at 0 °C, albeit with low conversion [117 b]. The selectivity in this transformation was improved (89% *ee*) through the addition of reversed aggregated micelles of sodium bis(2-ethylhexyl)sulfosuccinate (AOT) and 15-crown-5 [121]. The optimum enantioselectivity (94% *ee*) for hydrogenation of acetophenone *N*-benzylimine was obtained with a neutral monosulfonated (*S*,*S*)-BDPP–Rh complex in a mixed solvent system ($EtOAc/H_2O$) [122]. The *para*-chloro- and *para*-methoxy-substituted derivatives also provide good enantioselectivity (≥90% *ee*). Interestingly, the di-, tri-, and tetrasulfonated (*S*,*S*)-BDPP ligands are much less selective for this particular transformation [123].

Tab. 1.12



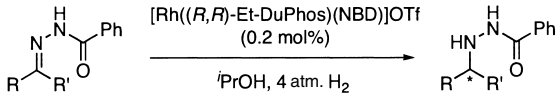
Catalyst	*X*	*Additive*	*Yield [%]*	*% ee (config.)*	*Ref.*
$[Rh(nbd)Cl]_2$+ (*R*)-CycPhos [a)]	H	KI	>99	79 (*S*)	120
$[Rh(nbd)Cl]_2$+ (*R*)-Cycphos [a)]	OMe	KI	>99	91 (*S*)	120
$[Rh(cod)Cl]_2$+ (*S,S*)-BDPP [b)]	H	NEt_3	55	83 (*R*)	117b
$[Rh(cod)Cl]_2$+ (*S,S*)-BDPP [b)]	H	_	96	84 (*R*)	122
$[Rh(cod)Cl]_2$+ monosulfonated (*S,S*)-BDPP [c)]	H	_	>98	94 (*R*)	122
$[Rh(cod)Cl]_2$+ monosulfonated (*S,S*)-BDPP [c)]	OMe	_	>98	92 (*R*)	122
$[Rh(cod)Cl]_2$+ monosulfonated (*S,S*)-BDPP [c)]	Cl	_	>98	92 (*R*)	122
$[Rh(S,S)$-BDPP$(nbd)]ClO_4$ [d)]	H	15-crown-5	98	89 (*R*)	121
$[Rh(S,S)$-BDPP$(nbd)]ClO_4$ [d)]	OMe	–	96	92 (*R*)	121

Reaction conditions:
a) PhH/MeOH (1:1), 1000 psi H_2.
b) MeOH, 70 atm. H_2.
c) EtOAc/H_2O, 20 °C, 70 atm. H_2.
d) AOT/PhH, 70 atm. H_2.

1.3.3.2 C=N–X Substrates

The presence of a heteroatom directly connected to the nitrogen atom of the imine activates it toward hydrogenation, while creating a second coordination site for the catalyst. Indeed, some successful results have been achieved for the hydrogenation of *N*-acylhydrazone, sulfonimide, and *N*-diphenylphosphinyl ketimines. The Et-DuPhos–Rh complex is an efficient catalyst for the asymmetric hydrogenation of a variety of *N*-acylhydrozone derivatives [124], as outlined in Tab. 1.13, with up to 97% *ee*.

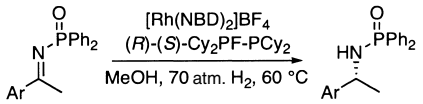
Tab. 1.13



R	*R'*	*Temp (°C)*	*Time (h)*	*% ee (config.)*
Ph	Me	–10	24	95 (*S*)
4-MeOPh	Me	0	24	88 (*S*)
4-EtO_2CPh	Me	0	12	96 (*S*)
4-NO_2Ph	Me	0	12	97 (*S*)
Ph	Et	–10	24	85 (*S*)
2-NP	Me	0	12	95 (*S*)
COOEt	Et	0	24	91 (*S*)
$PO(OEt)_2$	Ph	–10		90

The asymmetric hydrogenation of *N*-diphenylphosphinyl ketimines was achieved using the (*R*)-(*S*)-Cy2PF-PCy2–Rh complex as the catalyst (Tab. 1.14) [125], in which *N*-diphenylphosphinyl acetophenone imine was reduced with up to 99% *ee* at 60 °C under 70 atm. of hydrogen. Interestingly, the reaction temperature is crucial for achieving high levels of enantioselectivity.

Tab. 1.14



R	*S/C ratio*	*Time (h)*	*% ee (config.)*
H	500	1	99 (*R*)
OMe	100	19	62 (*R*)
Me	100	21	97 (*R*)
CF_3	100	18	93 (*R*)
Cl	100	53	30 (*R*)

1.4 Conclusion

Asymmetric catalytic hydrogenation is unquestionably one of the most significant transformations for academic and industrial-scale synthesis. The development of tunable chiral phosphorous ligands, and of their ability to control enantioselectivity and reactivity, has allowed asymmetric catalytic hydrogenation to become a reaction of unparalleled versatility and synthetic utility. This is exemplified in the ability to prepare enantiomerically enriched intermediates from prochiral olefins, ketones, and imines through asymmetric hydrogenation, which has been exploited in industry for the synthesis of enantiomerically enriched drugs and fine chemicals.

Despite the many advances there remain many unresolved challenges in the field of asymmetric hydrogenation, in which excellent enantioselectivity and high turnover numbers remain elusive with certain substrates. Asymmetric hydrogenation of imines and aromatic rings, for example, remain challenging. Hence, the development of new chiral phosphorous ligands and of their application to asymmetric hydrogenation reactions remains an important and significant area of endeavor.

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