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Review

Progress in stereoselective catalysis by metal complexes with chiral ferrocenyl phosphines

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Contents

Abstract

This review covers recent achievements in homogeneous and single-site heterogeneous asymmetric catalysis by metal complexes containing stereohomogeneous ferrocenyl phosphine ligands. The processes reviewed include: reductions of various prochiral substrates, allylic substitutions, hydrosilylations, hydroformylations, hydroaminations and hydroborations. Particular attention has been paid to studies aimed at designing novel ligand architectures as well as identifying active catalytic species.

Keywords: C_1-symmetric diphosphines; Ferrocenyl phosphines; Asymmetric catalysis; Catalyst immobilization

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Abbreviations: Cyp, cyclopentyl; COD, 1,5-cyclooctadiene; COT, 1,3,5-cyclooctatriene; DMI, dimethyl itaconate; MAA, methyl 2-acetamidoacrylate; MAC, (Z)-α-methyl acetamidocinnamate; MCA, (Z)-α-methylcinnamic acid; NBD, bicyclo[2.2.1]hepta-2,5-diene; phobyl, 9-phospha-9H-bicyclo[3.3.1]nonane; OTF, trifluoromethanesulfonate; TOF, turnover frequency (mol product/mol cat x h); TON, turnover number

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1. Introduction

Asymmetric catalysis comprises all the stereoselective reactions whereby a catalyst promotes the transformation of a prochiral substrate into an enantio- or diastereopure compound [1–5]. Several industrial processes aimed at producing optically pure compounds—for instance, pharmaceuticals, agrochemicals, drugs and flavours—adopt this methodology as it can provide access to large quantities of optically pure products by using minimal amounts of chiral auxiliaries with apparent economical and environmental benefits [6–16].

An asymmetric catalyst is generally defined as an ensemble of a metal ion and an optically active ligand whose combined action promotes the transfer of chiral information from the catalyst to the substrate. Crucial elements in asymmetric catalysis are therefore the chiral ligands that can exist in many structural variations and symmetries [17–26]. This review article is exclusively concerned with chiral ferrocenyl ligands which have the peculiar property to combine the planar chirality of the substituted ferrocenyl moiety with the chirality of other centers in the ligand backbone. As a result, a class of stereoselective transition metal catalysts with unique properties is generated [27–33].

Some relevant characteristics that make ferrocenyl phosphine ligands more amenable to asymmetric catalysis than many other types of chiral ligands are given below [34–39]:

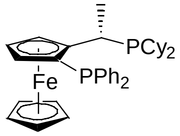
(a) Ferrocenyl phosphine ligands are usually stable, easy to handle, often isolable as both optical stereoisomers.
(b) Ferrocenyl phosphine ligands are modular and versatile, i.e. a large number of them, sharing the same primary structure but with different electronic and steric properties, can be easily obtained by relatively simple chemical modifications.
(c) Ferrocenyl phosphine ligands are able to form complexes with transition metals in a variety of coordination geometries and oxidation states, thus leading to efficient catalyst precursors for many chemical transformations.

In this paper, we have focused our attention exclusively on the ferrocenyl phosphines that have found application in asymmetric catalysis since 1997. In particular, we have considered ligands containing exclusively phosphorus donor atoms and used in both homogeneous and heterogeneous asymmetric catalysis. Review articles covering specific catalytic aspects of ferrocenyl ligands, including all mixed donor-atoms ferrocenes, have appeared elsewhere [40–45].

2. Asymmetric reduction reactions

2.1. Asymmetric hydrogenation reactions

Activated olefins, enamines, imines and β-keto esters are prochiral substrates of major interest in enantioselective hydrogenation catalysis [2,17,19]. For these reactions, innumerable stereohomogeneous phosphine ligands, especially chelating diphosphines with C_2 symmetry, have been designed to achieve good conversions and enantioselectivities [20,23,46]. Among the most efficient and selective ligands for the asymmetric hydrogenation of these prochiral substrates, chelating ferrocenyl diphosphines play a crucial role, generally in conjunction with ruthenium(II), rhodium(I), iridium(I) and palladium(II) ions [40,41,47].



(*R*)-(*S*)-*Josiphos*

Fig. 1. Sketch of the *Josiphos* ligand.

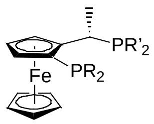
Chiral ferrocenyl diphosphines can be divided in two main structural classes depending on the mutual position (1,1′ or 1,2) of the phosphorus donor atoms, which may be attached to one or both cyclopentadienyl rings, directly or via a spacer [48,49].

2.1.1. Hydrogenation of alkenes

The progenitor of all chiral 1,2-substituted ferrocenyl diphosphines is Josiphos, which combines the typical planar chirality of these ligands with the central chirality of a carbon atom in a side arm (Fig. 1) [50]. Josiphos is a very versatile ligand that can be effectively tailored for many different transition metal-catalyzed stereoselective processes (vide infra), including the hydrogenation of alkenes, by simply varying the substituents on the phosphorus atoms [40].

Recent variations of Josiphos are the so-called *Solvias–Josiphos* ligands, which differ from the parent ligand essentially for the nature of the phosphorus substituents [39,51]. Fig. 2 summarizes the substituent variations reported so far for the *Solvias–Josiphos* family [52–54].

Several members of the *Solvias–Josiphos* family are being successfully employed, in conjunction with rhodium(I) fragments, to catalyze the enantioselective hydrogenation of prochiral olefins on both laboratory and industrial scale. Common model substrates for use as benchmarks to compare the catalytic performance of the various ligands are



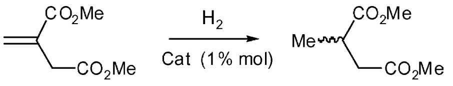
(*R*)-(*S*)-R_2PF-PR_2'

R = Ph, Cy, 4-MeOXyl, *p*-$CF_3C_6H_4$, *o*-Tol,
p-Tol, *p*-MeOPh, *m*-2$(CF_3)_2C_6H_3$, Xyl

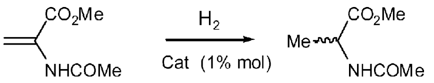
R ’ = Cy, *t*Bu, Cyp, 2-adamantyl, phobyl,
Ph, Xyl, *o*-Tol, *m*-Tol, *p*-Tol, *o*-Anisyl,
m-Anisyl, *p*-Anisyl, *p*-*t*BuPh

Fig. 2. The *Solvias–Josiphos* ligands.

itaconic acid and dehydroamino acid derivatives. Typical enantiomeric excesses (*ee*) obtained in the hydrogenation of dimethyl itaconate (DMI) (Eq. (1)) and methyl 2-acetamidoacrylate (MAA) (Eq. (2)) are in the range 90–99.9%. For example, under 1 bar H_2 at 25 °C, a catalyst, obtained by mixing equimolar amounts of $[Rh(NBD)_2]BF_4$ and Josiphos in methanol, can reduce DMI in 90–99.9% *ee* and a TOF 200 mol product (mol cat h)$^{-1}$, while MAA can be reduced in 97% *ee* and a TOF of 330 [23].

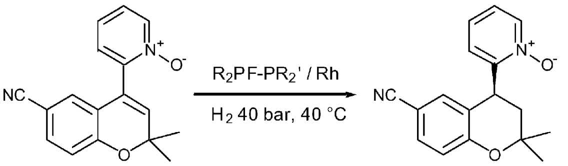


(1)



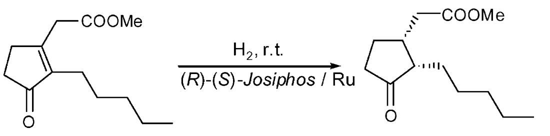
(2)

The enantioselective synthesis of chromanoylpyridine derivatives with *Solvias–Josiphos* catalysis is being performed at a pilot-plant stage in various solvents (hydrocarbons, chlorinated solvents, esters and mixtures thereof). The process involves the asymmetric hydrogenation at relatively high pressure of the *N*-oxide derivative with a rhodium catalyst prepared in situ from $[Rh(COD)_2]BF_4$ and $R_2PF\text{-}PR'_2$ ligands where R = Ph and R′ = 4-*t*BuC_6H_4, 2-Napthyl or 3,5-$Me_2C_6H_3$ (Eq. (3)). Catalyst/substrate ratios in the range 1000–6000 commonly lead to excellent *ee*'s (93–95%) with a moderate catalyst activity (TON 25, TOF 5 h^{-1}), however [55].



(3)

An industrial process based on *Solvias–Josiphos* ruthenium catalysts has been developed by Firmenich for the large scale production (tons/y) of (+)-*cis*-methyl dihydrojasmonate (Eq. (4)) [56–58]. The catalyst is conveniently generated in situ from (*R*)-(*S*)-*Josiphos*, [Ru(COD)(2-methylallyl)$_2$] and HBF_4 or [Ru(COD)(COT)] in CH_2Cl_2, while the reactions are carried at room temperature in hydrocarbon solvents or ethers at a hydrogen pressure between 35 and 90 bar in the presence of 0.05–0.2% catalyst. In these conditions, the reduced products were obtained in 76–86% *ee* and *cis*/*trans* ratios as high as 99:1. A relatively high TOF of 200 was observed at 25 °C under 90 bar H_2. Similar results have been obtained with a *Josiphos* derivative with the phenyl groups replaced by *p*-CF_3-C_6H_4 groups. In either case, the results are remarkable as tetra-substituted C=C double bonds are quite difficult to hydrogenate in high selectivity.



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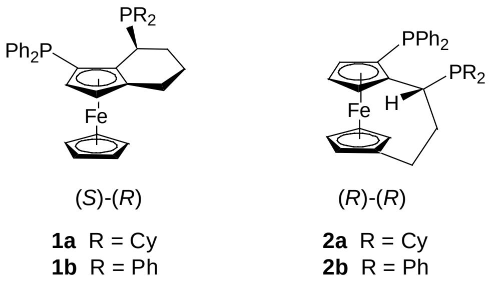
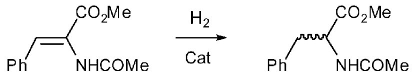


Fig. 3. The chelating diphosphine ligands described by Weissensteiner.

Recently, some *Josiphos*-related ligands have been described by Weissensteiner and Kagan. The former author has reported the synthesis of the four homo- and heteroannularly bridged diphosphines shown in Fig. 3 [59], which have been tested in the asymmetric hydrogenation of (Z)-α-methyl acetamidocinnamate (MAC) (Eq. (5)), (Z)-α-methylcinnamic acid (MCA) (Eq. (6)) and DMI (Eq. (1)).



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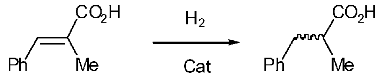


(6)

In all cases, the catalyst was prepared in situ by reacting an equimolecular amount of $[Rh(COD)_2]BF_4$ with the appropriate ligand. Typical conversion and *ee*'s obtained at 1–6 bar H_2, 18–40 °C and 16–66 h reaction time are: DMI, 100% yield and 43–98% *ee*; MAC, 95–100% yield and 7–84% *ee*; MCA, 20–100% yield and 2–55% *ee*

The ferrocenyl phosphines developed by Kagan (Fig. 4) differ from those of the *Solvias–Josiphos* family for displaying only the planar chirality [60]. These ligands have been screened in the hydrogenation of various alkenes under standard reaction conditions (1% in situ Rh catalyst, methanol, 1–20 bar H_2).

The best results in terms of enantioselectivity were obtained using the ligands with cyclohexyl or cyclopentyl substituents. In particular, the hydrogenation of DMI gave 98 and 92% *ee* for R = Cy and cyclopentyl, respectively. These results, being comparable with those of Josiphos, have suggested that the planar chirality may be of major importance in determining the extent of the asymmetric induction in hydrogenation reactions of prochiral olefins [60].

Another family of 1,2-ferrocenyl diphosphines with numerous applications in asymmetric catalysis is constituted by the *Walphos* ligands (Fig. 5) [61,62]. These differ from

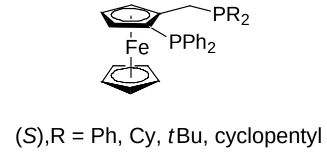
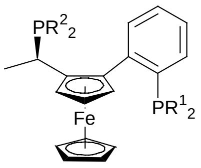


Fig. 4. The chelating ferrocenyl diphosphines developed by Kagan.



(*R*)-(*R*)-*Walphos*

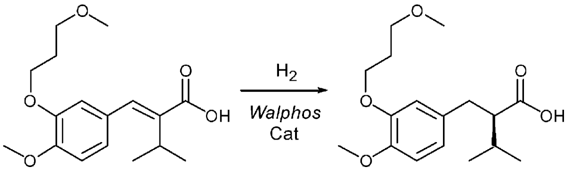
a R^1 = Ph R^2 = Cy
b R^1 = Ph R^2 = *t*Bu
c R^1 = Ph R^2 = 3,5-$(CH_3)_2$-4-$(CH_3O)C_6H_2$
d R^1 = Ph R^2 = Ph
e R^1 = Ph R^2 = 3,5-$(CF_3)_2C_6H_3$
f R^1 = 3,5-$(CH_3)_2$-4-$(CH_3O)C_6H_2$ R^2 = 3,5-$(CF_3)_2C_6H_3$

Fig. 5. The *Walphos* ligands.

Josiphos for the presence of a phenyl spacer between a phosphorus donor and a cyclopentadienyl unit, which may ultimately result in the formation of eight-membered chelate metallarings.

Selected results for the enantioselective hydrogenation of DMI (Eq. (1)), MAC (Eq. (5)) and MCA (Eq. (6)) by rhodium *Walphos* catalysis are reported in Table 1 [63].

Rhodium *Walphos* catalysts have been also employed for the preparation of (*R*)-2-alkyl-3-phenylpropionic acid derivatives via enantioselective hydrogenation of the corresponding prochiral olefin [64]. In particular, a key intermediate for the synthesis of the renin inhibitor SPP100 (Eq. (7)) has been obtained by means of a *Walphos* ligand with R^1 = Ph and R^2 = 3, 5-$(CF_3)_2C_6H_3$. The saturated acid was isolated in 95% *ee* and 100% yield after 21 h at room temperature under 50 bar H_2 (TON 5000, TOF 800 h^{-1}) with an in situ prepared catalyst (1 mol% Rh).

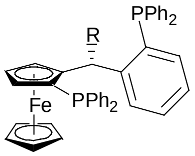


(7)

Table 1
Enantioselective hydrogenation of alkenes catalyzed by Walphos-rhodium complexes

Substrate	Ligand		Conv. (%)	*ee* (%)
	R^1	R^2		
MAC	Ph	3,5-$(CH_3)_2$-4-$(CH_3O)C_6H_2$	>99	95
	Ph	Ph	>98	87
	Ph	Ph	>99	90
MCA	Ph	Ph	>99	82
DMI	Ph	Ph	>99	90
	Ph	3,5-$(CF_3)_2C_6H_3$	>99	91

$[Rh(NBD)_2]BF_4$/ligand = 1/1, substrate/catalyst = 200, methanol, H_2 1–10 atm, 0–25 °C, 16–22 h.



Taniaphos

a R = H, (*S*)
b R = Me, (*R*)-(*S*)
c *R* = *i*Pr, (*R*)-(*S*)

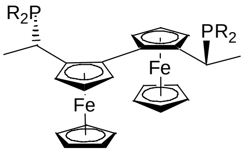
Fig. 6. Structure of the Taniaphos diphosphine ligands.

Eight-membered metallacycles are also formed by the chiral 1,2 disubstituted ferrocenyl ligands *Taniaphos*, a family that comprises both phosphine and mixed-donor ligands [65,66]. The main structure of the *Taniaphos* diphosphines is sketched in Fig. 6.

The *Taniaphos* ligands have proved excellent chiral auxiliaries for the enantioselective hydrogenation of various functionalized double bonds in alkenes, β-ketoesters, 1,3-diketones and hydrazones (see Paragraph 2.1.2). Typical *ee*'s obtainable by *Taniaphos*-rhodium catalysis for the hydrogenation of DMI (Eq. (1)) and MAC (Eq. (5)) are 97.9 and 96.6%, respectively (quantitative conversion, 1 bar H_2, room temperature, 1.5–4 h, MeOH or MeOH/toluene = 1/1, in situ $[Rh(NBD)_2]BF_4$/ligand = 1/1) [67].

A quite original structural variation of 1,2-disubstituted ferrocenyl diphosphines is represented by the well-known TRAP ligands [68–70]. In these ligands, two chiral ferrocenyl units are linked together by a direct Cp–Cp bond. Each ferrocenyl unit contains a carbon stereocenter on an alkyl-phosphino side chain (Fig. 7).

The TRAP ligands have been synthesized many years ago, yet only recently have begun to attract interest in asymmetric catalysis for their remarkable activity in the hydrogenation of prochiral olefins such as acetamidoacrylates (Eq. (8)) [71–73], 1,4,5,6-tetrahydropyrazine-2-carboxamide derivatives (Eq. (9)) [74] and indoles (Eq. (10)) [75].



(*R*,*R*)-(*S*,*S*)-TRAP ligands

R = Me, MeTRAP
R = Et, EtTRAP
R = Pr, PrTRAP
R = Bu, BuTRAP
R = *i*Bu, *i*BuTRAP
R = *i*Pr, *i*PrTRAP
R = Ph, PhTRAP
R = 2-Furyl, FurTRAP
R = *p*-MeOPh, *p*-MeOPhTRAP

Fig. 7. Sketch of the TRAP ligands.

Table 2
Enantioselective hydrogenation of acetamidoacrylates (Eq. (8)) catalyzed by TRAP-rhodium complexes[a]

Substrate		Ligand	Conv. (%)	*ee* (%)	Config.
R^1	R^2				
H	H	EtTRAP	100	96	R
H	Me	EtTRAP	100	92	R
H	Ph	iBuTRAP	100[b]	92	S
CbzNH	Me	PrTRAP	93[c]	82	(2S,3R)
CbzNH	Et	PrTRAP	100[c]	81	(2S,3R)
Me	TBDMSO	PrTRAP	98	95	(2S,3S)
$MeOCH_2$	TBDMSO	PrTRAP	89	97	(2S,3R)
*t*BuCOO	Me	PrTRAP	99[d]	97	(2S,3R)

[a] $[Rh(COD)_2]X$/ligand = 1/1 (X=ClO_4, BF_4), substrate/catalyst = 100, H_2 0.5–1 atm, 15–60 °C, 24 h, 1,2 dichloroethane.

[b] Dichloromethane.

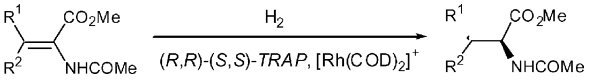
[c] Methanol.

[d] 2-Propanol.

Table 3
Enantioselective hydrogenation of tetrahydropyrazine derivatives (Eq. (9)) catalyzed by TRAP-rhodium complexes

Substrate		Ligand	Conv. (%)	*ee* (%)	Config.
R^1	R^2				
*t*BuO	PhO	*i*BuTRAP	85	96	S
*t*BuO	PhO	MeTRAP	32	62	R
BnO	*t*BuO	*i*BuTRAP	40	94	S
BnO	*t*BuO	MeTRAP	85	85	R

$[Rh(COD)_2]SbF_6$/ligand = 1/1, substrate/catalyst = 100, H_2 1 atm, 50 °C, 1,2 dichloroethane, 24 h.



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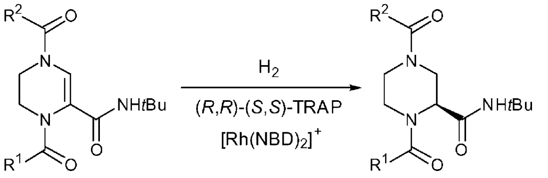

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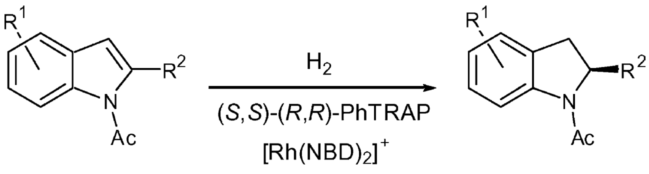


(10)

Selected results obtained with these substrates are reported in Tables 2–4.

In most cases were observed good *ee*'s under mild reaction conditions, which is not a trivial result as the asymmetric hydrogenation of heteroaromatic compounds and cyclic olefins is still a difficult task [76,77]. Noteworthy, the optically active 2-substituted piperazines shown in Eq. (9) are important intermediates for the synthesis of several pharmaceuticals [78].

Table 4
Enantioselective hydrogenation of indoles (Eq. (10)) catalyzed by TRAP-rhodium complexes

Substrate		Ligand	Conv. (%)	*ee* (%)	Config.
R^1	R^2				
H	CO_2Me	PhTRAP	95	95	S
5-Me	Bu	PhTRAP	94	94	R
6-MeO	Bu	PhTRAP	98	94	R

$[Rh(NBD)_2]SbF_6$/ligand/Cs_2CO_3 = 1/1/10, substrate/catalyst = 100, H_2 5.0 MPa, 60 °C, 2-propanol.

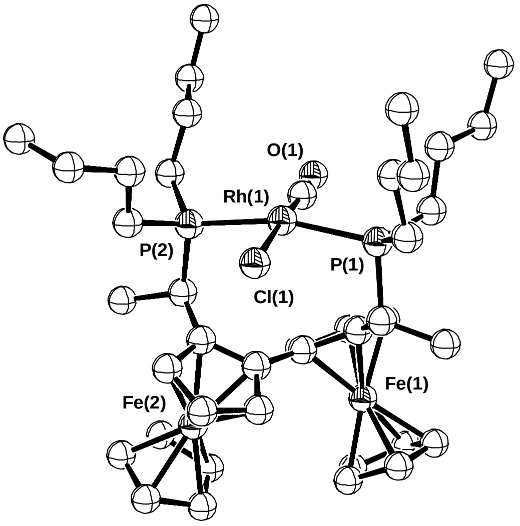
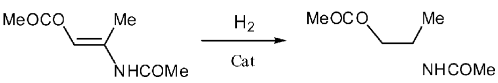


Fig. 8. ORTEP view of the complex *trans*-[RhCl(CO)((*R*,*R*)-(*S*,*S*)-BuTRAP)].

The TRAP ligands represent a rare example of chiral bidentate phosphines capable of binding a metal center in *trans* fashion. Fig. 8 shows the X-ray crystal structure of the rhodium(I) complex *trans*-[RhCl(CO)((*R*,*R*)-(*S*,*S*)-BuTRAP)] [79].

Apart from *Josiphos* and *Solvias–Josiphos* ligands, the most intensively studied 1,1′ disubstituted ferrocenyl phosphines in recent years are probably those belonging to the FerroTANE family, synthesized independently by Burk and Genêt [80–83]. In these ligands, the optical activity is brought about by the central chirality associated with the stereogenic carbon atoms at the 2,5 positions of the phosphetanyl fragments (Fig. 9).

The catalytic efficiency of FerroTANE-rhodium(I) precursors in the hydrogenation of activated olefins has been demonstrated for many substrates, including MAC (Eq. (5)) [84], (*E*)-methyl-3-acetamidobutenoate (Eq. (11)) [85], itaconates (Eq. (12)) [81], acrylates and cinnamates [80] (Table 5).



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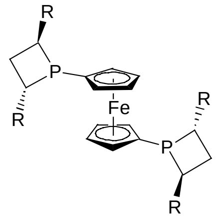


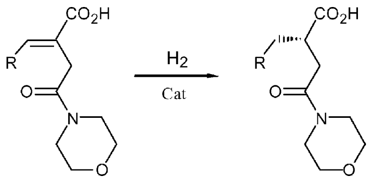
R = Me, (*R*)-(*R*)-Me-FerroTANE
R = Et, (*S*)-(*S*)-Et-FerroTANE
R = Pr, (*R*)-(*R*)-Pr-FerroTANE
R = *i*Pr, (*S*)-(*S*)-*i*Pr-FerroTANE
R = *t*Bu, (*S*)-(*S*)-*t*Bu-FerroTANE

Fig. 9. Sketch of the FerroTANE ligands.

Table 5
Enantioselective hydrogenation of alkenes catalyzed by FerroTANE-rhodium complexes

Substrate	R	Ligand	*ee* (%)
DMI		(*S*)-(*S*)-Et-FerroTANE	98
		(*R*)-(*R*)-Pr-FerroTANE	97
Eq. (12)	Ph	(*S*)-(*S*)-Et-FerroTANE	98
	*t*Bu	(*S*)-(*S*)-Et-FerroTANE	99
MAA		(*R*)-(*R*)-Me-FerroTANE	94
MAC		(*R*)-(*R*)-Me-FerroTANE	96
Eq. (11)		(*R*)-(*R*)-Et-FerroTANE	99

Typical reaction conditions: Rh/ligand = 1/1, substrate/catalyst = 100–200, methanol, H_2 0.5–4 atm, 25–50 °C, 1–18 h.



(12)

The hydrogenation of MAC has been accomplished using preformed precursors of the formula [((*S*,*S*)-L)Rh(COD)] OTf, where L = (*S*,*S*)-*i*Pr-FerroTANE or (*R*,*R*)-Me-FerroTANE. The crystal structure of the (*S*,*S*)-*i*Pr-FerroTANE complex is reported in Fig. 10.

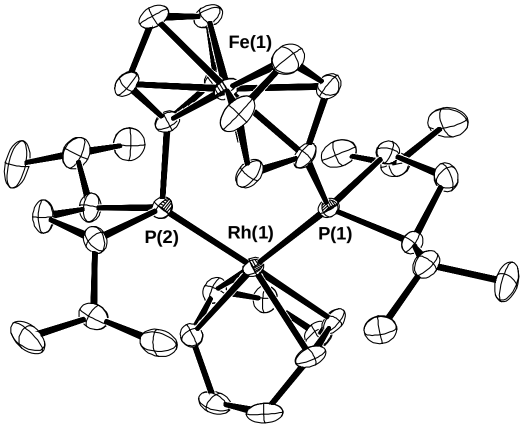


Fig. 10. ORTEP view of the complex [((*S*,*S*)-*i*Pr-FerroTANE)Rh(COD)] OTf.

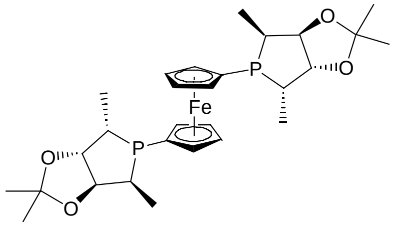


Fig. 11. The 1,1′ ferrocenyl diphosphine ligand **3** described by Zhang [86].

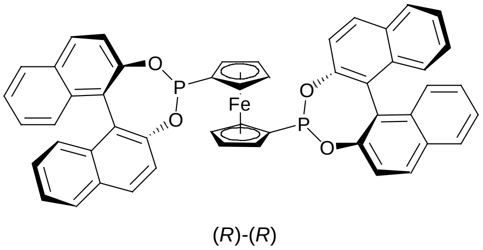


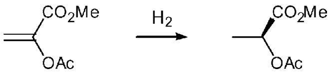
Fig. 12. The 1,1′ ferrocenyl diphosphine ligand **4** described by Reetz [87].

1,1′-Ferrocenyl diphosphines, either with central carbon or with axial chirality (ligand **3**, Fig. 11; ligand **4** Fig. 12) have been recently employed as chiral auxiliaries in rhodium(I)-catalyzed asymmetric hydrogenation of MAA (Eq. (2)), DMI (Eq. (1)) and various α-acetamidocinnamic acid derivatives [86,87].

Selected results obtained in asymmetric hydrogenation reactions using ligands **3** and **4** are reported in Table 6. In most instances, remarkably high *ee*'s were observed using either preformed or in situ prepared catalysts.

The family of chiral C_2 symmetrical ligands FERRIPHOS (FerroPHOS), containing ferrocenyl units with both 1,1′ and 2,2′ substituents, have been described by Knochel and Kang (Fig. 13).

Both FERRIPHOS and FerroPHOS ligands have been tested in the rhodium-catalyzed hydrogenation of α-(acylamino)acrylic acid derivatives [88,89] and enol acetates (Eq. (13)) [90], yielding quite remarkable *ee*'s (Table 7).

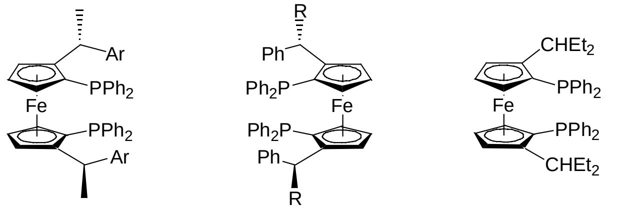


(13)

Table 6
Enantioselective rhodium-catalyzed hydrogenation of alkenes with 1,1′ disubstituted ferrocenyl diphosphines

Substrate	Ligand	Solvent	H_2 (atm)	*t* (h)	*ee* (%)
DMI	4	CH_2Cl_2	1.3	20	99.5
	3	MeOH	5.5	12	89.9
MAA	4	CH_2Cl_2	1.3	20	99.5
	3	THF	1.0	0.5	99.9
MAC	3	THF	3.1	1	99.5

All data reported are at 100% conversion, r.t. and with substrate/catalyst ratio ranging from 100 to 1000.



FERRIPHOS (S)-(S)-FerroPHOS

Ar = Ph R = *i*Pr
Ar = o-Tolyl R = Me
Ar = 2-Naphthyl

Fig. 13. Sketch of the FERRIPHOS and FerroPHOS ligands.

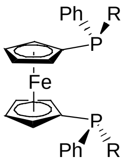
Table 7
Enantioselective hydrogenation of alkenes catalyzed by FERRIPHOS-rhodium complexes

Substrate	Ligand	Solvent	*ee* (%)
Eq. (13)	FERRIPHOS, R = *i*Pr	Acetone	94.9
MAC	FERRIPHOS, Ar = Ph	MeOH	98.6
	FERRIPHOS, Ar = *o*-Tolyl	MeOH	98.1
	FerroPHOS	EtOH	97.6
MAA	FERRIPHOS, Ar = Ph	MeOH	97.9
	FERRIPHOS, Ar = *o*-Tolyl	MeOH	97.7
	FerroPHOS	MeOH	97.5

$[Rh(COD)_2]BF_4$/ligand = 1/1, H_2 1-2 bar, r.t.

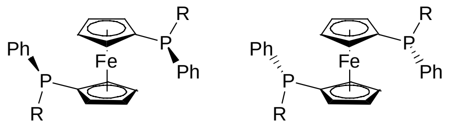
All reactions were performed using in situ prepared catalysts under mild reaction conditions. In some cases, the enantioselectivities obtained with these ligands are even better than those reported for 1,2-disusbtituted ferrocenyl diphoshines. For example, the hydrogenation of (Z)-α-acetamidocinnamic acid occurs with 97.3–97.6 *ee*% using the Ar FERRIPHOS ligands [88], whereas, in comparable experimental conditions, a modest 84% *ee* is obtained with Josiphos [50].

A particular class of 1,1′-bis(phosphino)ferrocenes is that featured by the presence of stereogenic phosphorus atoms as the only chirality source (Figs. 14 and 15). Ligands of this type have been independently developed by Mezzetti [91,92] and van Leeuwen [93].



5a R = *o*-anisyl (*S*)-(*S*)
5b R = 1-naphthyl (*S*)-(*S*)

Fig. 14. *P*-Stereogenic 1,1′-bis(phosphino)ferrocenes **5** reported by Mezzetti.



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

6a R = 1-naphthyl, R = 2-naphthyl
6b = 2-anisyl
6c = 2-biphenylyl
6d = 9-phenanthryl

Fig. 15. *P*-Stereogenic 1,1′-bis(phosphino)ferrocenes **6** reported by van Leeuwen.

Table 8
Enantioselective rhodium-catalyzed hydrogenation of alkenes with *P*-stereogenic ferrocenyl diphosphines

Substrate	Ligand	R	H_2 (atm)	*ee* (%)
MAC	5[a]	*o*-Anisyl	1	96
	5[b]	*o*-Anisyl	1	91
	6[b]	9-Phenanthryl	2	98.7
	6[b]	1-Naphthyl	2	97.3
N-Methyl MAC	5[a]	*o*-Anisyl	5	97

Substrate/catalyst = 100–200, methanol, 25–60 °C, 95–100% conversion, 2–20 h.

[a] Preformed catalyst $[Rh(COD)(Ligand)]BF_4$.

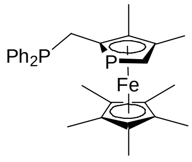
[b] In situ catalyst $[Rh(NBD)_2]X$/ligand = 1/1 (X=ClO_4, BF_4).

The enantioselectivities induced by these *P*-stereogenic ligands in rhodium-catalyzed hydrogenation reactions of dehydramino acid derivatives under standard reaction conditions were rather good, in general comparable to those reported for several efficient chiral ferrocenyl diphosphines (Table 8). With the Mezzetti ligands, the chiral transfer is more efficient using preformed catalyst precursors (96% *ee*) than using catalysts prepared in situ (91% *ee*) (Table 8, rows 1 and 2). In all cases, the *ee*'s provided by the *P*-stereogenic 1,1′-ferrocenyl diphosphines have been found to increase with the bulkiness of the phosphorus substituents (Table 8, rows 3 and 4).

These *P*-stereogenic ligands have been also tested in the ruthenium(II)-catalyzed hydrogenation of DMI, MAC and MCA in combination with the precursors $[RuCl_2(PPh_3)(ligand)]$, $[RuCl_2(ligand)]$ or $[Ru(\eta^2\text{-}O_2CCF_3)(ligand)]O_2CCF_3$. However, the *ee*'s were lower than those reported for comparable rhodium catalysts [91].

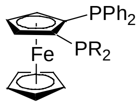
Over the last 5 years, a number of miscellaneous chiral ferrocenyl phosphines have been employed to form efficient enantioselective catalysts for olefin hydrogenation. Fu has described the first application of a planar-chiral phosphorus heterocycle **7** in asymmetric catalysis (Fig. 16), obtaining *ee*'s as high as 96% in the reduction of several dehydroamino acids derivatives (87% *ee* for MAC, 95% yield, 1 bar H_2, room temperature, 12 h, EtOH, in situ $[Rh(COD)_2]PF_6$/ligand = 1/1) [94].

1,2-Disubstitued ferrocenes (8) bearing two different phosphine groups and exhibiting only planar chirality have been used by Kagan to hydrogenate various types of C=C bonds (Fig. 17) [95]. Only moderate to good *ee*'s were



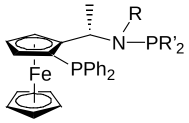
(-) **7**

Fig. 16. Phosphacyclopentadiene ligand with planar chirality reported by Fu.



8 R = Cy, Me

Fig. 17. Ferrocenyl diphosphine ligands reported by Kagan.



(*R*)-(*S*)-*BoPhoz*

a R = H, R’ = Ph
b R = CH_3, R’ = Ph
c R = Et, R’ = Ph
d R = *n*Pr, R’ = Ph
e R = CH_3, R’ = cy-C_6H_{11}

Fig. 18. *BoPhoz* ligands.

achieved, however. The best result was that with DMI (95% *ee*).

Excellent results have been obtained with the phosphine-aminophosphine ligands *BoPhoz* (Fig. 18) in the rhodium(I)-catalyzed asymmetric hydrogenation of itaconic acid and dehydroamino acid derivatives (Table 9) [96].

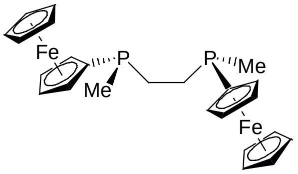
Remarkably, very high reaction rates were observed (initial TOF 30,000 h^{-1}) even at low catalyst loading (substrate/catalyst up to 10,000).

Dehydroamino acid derivatives have been used as model substrates to test the efficiency of the bis-ferrocenyl *P*-chirogenic diphosphine (9) shown in Fig. 19 and synthesized by Imamoto [97]. This ligand generally gives moderate to good enantioselectivities; the best reported result is probably that obtained with the cyclic alkene of Eq. (8) in which $R^1 = R^2 = -(CH_2)_4-$ (77% *ee*, 99% yield, 6 bar H_2, 50 °C, 3 h, MeOH, in situ $[Rh(COD)Cl]_2$/ligand = 1/2).

Table 9
Asymmetric hydrogenation catalyzed by *BoPhoz*-rhodium complexes

Ligand		Substrate	*ee* (%)
R	R′		
CH_3	Ph	MAA	98.5
CH_3	Ph	MAC	99.1
H	Ph	MAC	97.2
Et	Ph	MAC	94.3
CH_3	Ph	DMI	94.0

$[Rh(COD)_2]OTf$/ligand = 1/1, H_2 1-21 atm, r.t., 1–6 h, THF or MeOH.



(*S*)-(*S*) **9**

Fig. 19. *P*-Chirogenic diphosphine **9** reported by Imamoto.

2.1.1.1. Supported single-site catalysts. Due to the cost of the sophisticated chiral ligands, often exceeding that of the noble metal employed, catalyst recovery is of paramount importance for the application of enantioselective metal catalysis to large scale processes. In order to easily recover and recycle asymmetric catalysts, successful approaches involve the immobilization of molecular precursors either onto a support material or into an appropriate phase system so that the catalyst can be quantitatively separated from both product(s) and unreacted reagents by filtration or phase separation [98,99]. For this purpose, various methodologies and materials have been developed over the last 20 years [100].

The immobilization of *Josiphos* has been achieved by Togni by appropriately modifying the parent ligand in such a way to form a covalent bond to peripheral amino groups of dendrimers containing phosphazene [101], benzene or adamantane cores [102] (Fig. 20). Using this procedure, dendrimers containing up to sixteen ferrocenyl diphosphine units have been obtained.

Remarkably, the reaction of “dendritic *Josiphos*” with $[Rh(COD)_2]BF_4$ converts all the ligand sites into effective rhodium catalysts for the asymmetric hydrogenation of alkenes [103]. For example, a second-generation dendrimer, containing 16 ferrocenyl units, converts DMI into (*S*)-dimethyl methylsuccinate in 98% *ee* (78% yield, MeOH, r.t., 1 bar H_2, 30 min), which is only slightly lower than the *ee* obtained with the corresponding monomeric Josiphos catalyst in equivalent metal concentration (see Section 2.1.1).

2.1.2. Hydrogenation of ketones

The asymmetric hydrogenation of functionalized ketones is a process that many rhodium(I) and ruthenium(II) complexes of chiral phosphines bring about in very high yields and *ee*’s [17,21]. Excellent results in the hydrogenation of prochiral ketones, 1,3-diketones, β-keto esters can be obtained also with the use of many chiral ferrocenyl diphosphines described in Section 2.1.1 (Fig. 21). Selected catalytic results are given in Table 10.

The ligands of the *Walphos* family can yield *ee*’s as high as 97% (Table 10, entries 1, 2) with TON of ca. 1.000 and TOF of 200 h^{-1} [63]. A fine tuning of the ligands properties,

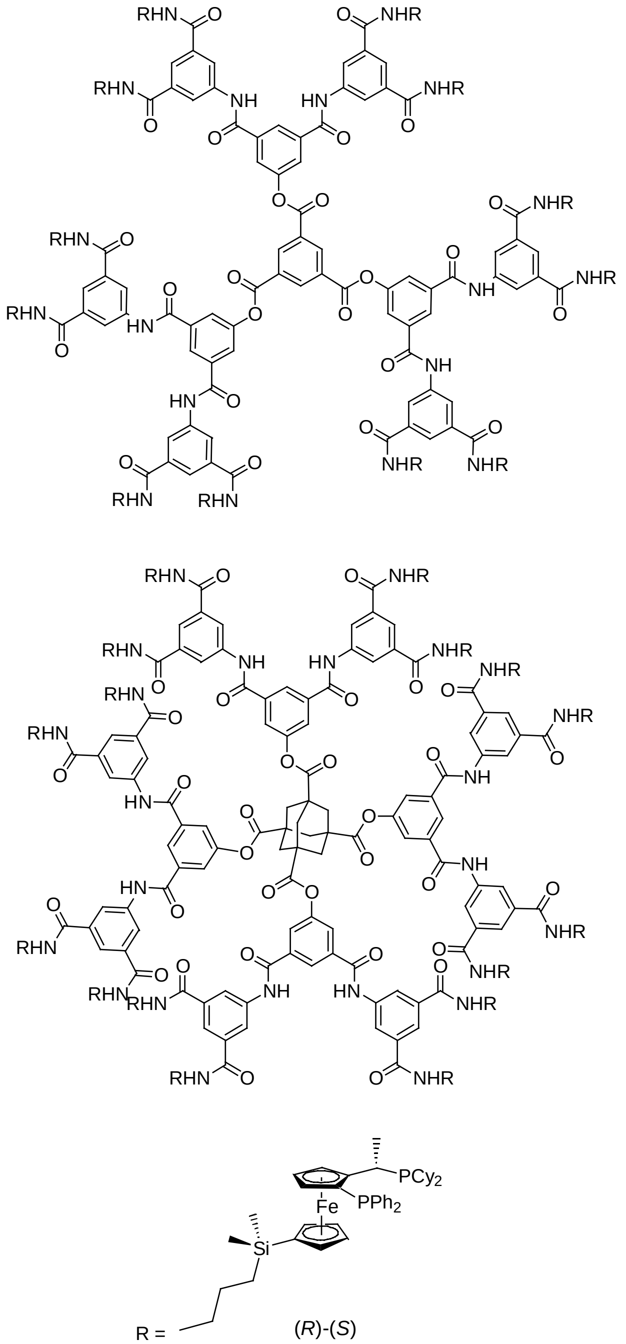


Fig. 20. *Josiphos*-containing dendrimers.

hence of the asymmetric performance, has been achieved by varying the substituents either on the phosphino groups or on the carbon side-arm (*e.g Taniaphos* ligands, entries 3–5) [67]. It is worth noticing that the asymmetric inductions provided by the *Taniaphos* ligands can be reached only by some atropoisometric and phospholane-type ligands or by chiral diphosphine-diamine systems [104–107].

Josiphos-type ligands have been scarcely investigated as chiral auxiliaries for the hydrogenation of ketones. The small number of experiments carried out, however, shows that high

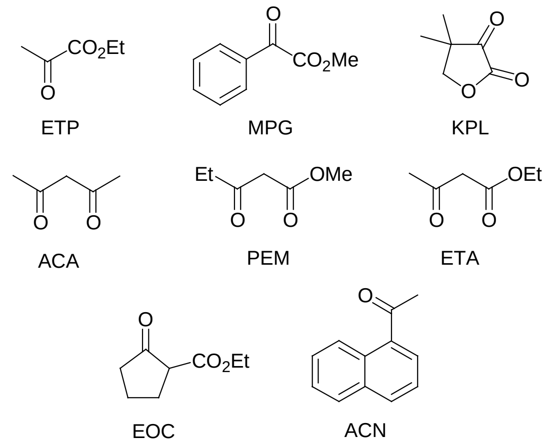


Fig. 21. Common ketones hydrogenated by ferrocenyl phosphine-metal catalysts.

ee's can be obtained, but the activities are invariably lower than those provided by other chiral diphosphines, including *Walphos*, *Taniaphos* and Binap.

For example, the preformed precursor *trans*-[RuCl$_2$(*Josiphos*)(py)$_2$] (Fig. 22) required 48 h to give 2400 turnovers (entry 6) [108].

The C_2-symmetrical 2,2″-phosphino-1,1″-biferrocenes **10** developed by Xiao (Fig. 23) have proved less efficient than *Taniaphos* for the asymmetric hydrogenation of ethyl acetylacetate (entry 7) [109], yet much better than ferrocenyl ligands containing stereogenic phosphorus atoms (entry 8) [91].

A few examples of asymmetric hydrogenation of ketones with rhodium complexes have been reported (Table 11). In particular, the homo- and heteroannularly bridged ligands **1** and **2** described by Weissensteiner gave quite low conversions and *ee*'s (5–57%) in the hydrogenation of keto esters by rhodium catalysis (Table 11, entries 1 and 2) [59]. The *BoPhoz* ligand was more active (entry 3), yet far from the

Table 10
Asymmetric hydrogenation recations of ketones catalyzed by ruthenium complexes with chiral ferrocenyl phoshines

Entry	Ligand	Subst.	H_2 (bar)	T (°C)	t (h)	Conv. (%)	*ee* (%)
$1^{a,b}$	Walphos e	ACA	100	80	17	99	97
$2^{a,b}$	Walphos f	PEM	5	80	16	99	95
$3^{c,d}$	Taniaphos c	ETA	50	50	9	100	96
$4^{c,d}$	Taniaphos b	. EOC	50	r.t.	21	90	92
$5^{c,d}$	Taniaphos c	ACA	50	50	9	94	99
$6^{e,f}$	Josiphos	ACN	4	60	48	96	98
$7^{a,d}$	10a	ETA	80	80	16	99	82
$8^{d,g}$	5b	ETA	80	70	16	99	53

[a] In situ catalyst [RuI$_2$(*p*-cymene)]$_2$/ligand = 1/2.2.

[b] In MeOH.

[c] In situ catalyst [Ru(COD)(C$_4$H$_7$)$_2$]/HBr/ligand = 1/3/1.

[d] In EtOH.

[e] In 2-propanol.

[f] Preformed catalyst trans-[RuCl$_2$(Josiphos)(py)$_2$].

[g] Preformed catalyst [RuCl$_2$(PPh$_3$)Ligand].

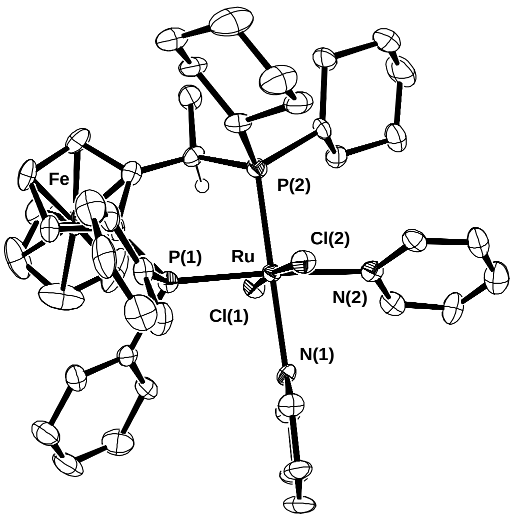
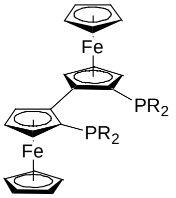


Fig. 22. Molecular structure of the complex trans-[$RuCl_2$(*Josiphos*)$(py)_2$].



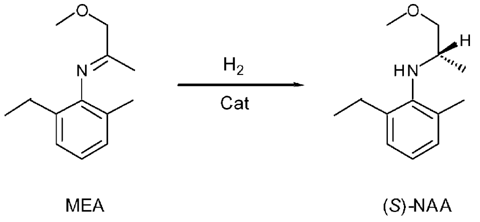
10a R = Ph (*S*)-(*S*)
10b R = 3,5-$(CH_3)_2$Ph (*S*)-(*S*)

Fig. 23. Bis-ferrocenyl diphosphines described by Xiao.

performance obtainable with other ruthenium(II) catalysts [96].

2.1.3. Hydrogenation of imines

The asymmetric hydrogenation of imines is a powerful tool to produce several important industrial intermediates [17,110]. Chiral ferrocenyl phosphines, particularly in conjunction with iridium, show a great potential in the hydrogenation of imines. A typical example is reported in Eq. (14) for the conversion of the imine *N*-(2′-methyl-6′-ethyl-phen-1′-yl)-*N*-(1-methoxymethyl)-ethylimine (MEA) to the amine (*S*)-NAA, which is a key precursor to commercial herbicides based on (*S*)-metolachlor [111,112].

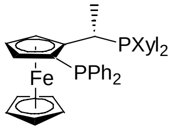


(14)

Table 11
Asymmetric hydrogenation reactions of ketones catalyzed by rhodium complexes with chiral ferrocenyl phoshines

Entry	Ligand	Subst.	H_2 (bar)	*T* (°C)	*t* (h)	Conv. (%)	*ee* (%)
1[a,b]	**2a**	ETP	40	25	18	50	50
2[c,b]	**2a**	KPL	50	25	16	70	57
3[d,e]	BoPhoz	ETP	20	r.t.	6	95	91

[a] In situ catalyst [Rh(NBD)(OTFA)]/ligand = 1/1.
[b] In toluene.
[c] In situ catalyst [Rh(NBD)(OAc)]/ligand = 1/1.
[d] In THF.
[e] In situ catalyst $[Rh(COD)_2]OTf$/ligand = 1/1.



(*R*)-(*S*)-*Xyliphos*

Fig. 24. Sketch of (*R*)-(*S*)-*Xyliphos*.

Some ligands of the *Josiphos* family are very efficient for the reaction illustrated in Eq. (14) [39,113]. For example, the combination of $[Ir(COD)Cl]_2$ and *Xyliphos* (Fig. 24) has been found to produce the desired product in ca. 80% *ee*. Complete conversion was obtained in 4 h at 50 °C under 80 bar H_2 with an initial TOF of 1,800,000 h^{-1} at a substrate/catalyst ratio of 1,000,000.

Remarkably, comparable *ee*'s have been obtained in heterogeneous phase using *Xyliphos* covalently immobilized onto both inorganic (SiO_2) and organic (polystyrene) supports via linkers obtained by functionalization of the 1′ position (Fig. 25) [114].

The immobilized single-site catalysts are slightly less active than the homogeneous counterparts, with the advantage, however, of being recovered (up to 95%) by simple filtration at the end of the reactions. The best catalyst, with *TON's* > 100,000 and TOF's up to 20,000 h^{-1}, is the silica-bound derivative with a loading of 0.042 mmol ligand/g support [115–117].

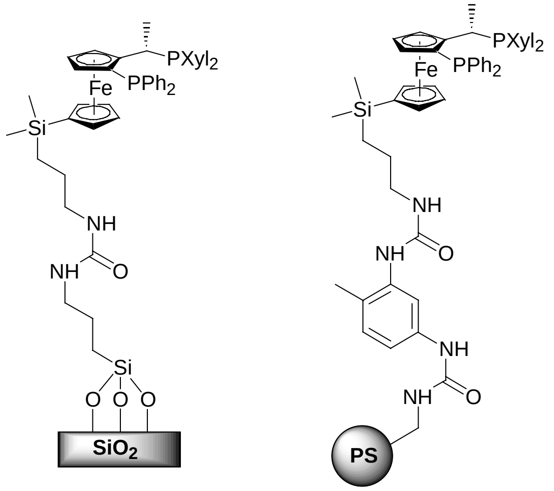


Fig. 25. *Xyliphos* tethered to silica (left) and polystyrene (right).

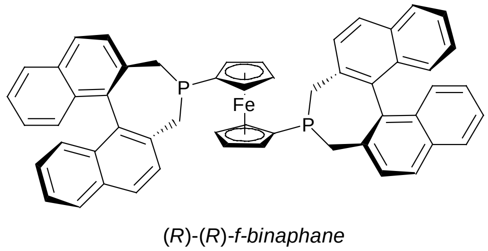


Fig. 26. Sketch of the f-*binaphane* ligand.

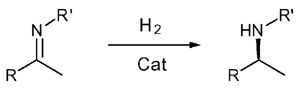
Table 12
Asymmetric hydrogenations of imines catalyzed by iridium f-*binaphane* complexes

Entry	Substrate		*ee* (%)
	R	R′	
1	Ph	Ph	84
2	Ph	2,6-$(CH_3)_2$-C_6H_3	99
3	Ph	2-(CH_3)-6-(CH_3O)-C_6H_3	98
4	1-Naph	2-(CH_3)-6-(CH_3O)-C_6H_3	96

In situ catalyst $[Ir(COD)Cl]_2$/ligand = 1/1.1; CH_2Cl_2, r. t., H_2 1000 psi.

The hydrogenation of MEA has been also achieved with the Weissensteiner' s ligands **1** and **2** (Fig. 3) by means of an in situ catalyst obtained by mixing the ligands with $[Ir(COD)Cl]_2$ in toluene. Up to 100% conversion and 73% *ee* were obtained after 18 h at 80 bar H_2 and 25 °C.

Excellent results (up to 99% *ee*) in the enantioselective hydrogenation of acyclic *N*-arylimines (Eq. (15)) have been reported for reactions catalyzed by the $[Ir(COD)Cl]_2$/(*R*)-(*R*)-f-*binaphane* system (Fig. 26) [118]. Table 12 summarizes some representative data.

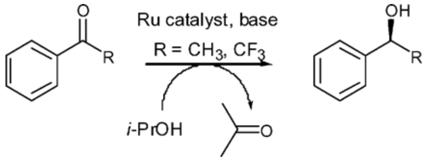


(15)

2.2. Asymmetric hydrogen-transfer reduction of ketones

In the case of prochiral ketones, ruthenium-catalyzed hydrogen transfer reductions represent a valid alternative to hydrogenation reactions (see Section 2.1.2) [17,19,119]. Various reagents can be used as hydrogen source, including alcohols and formic acid, and many chiral ligands can effectively assist these reactions, which may require the use of basic co-catalysts as initiators [120,121].

Chiral tridentate ferrocenyl phoshines have been recently employed in base-assisted hydrogen-transfer reactions from 2-propanol to prochiral ketones such as acetophenone or trifluoroacetophenone (Eq. (16)).



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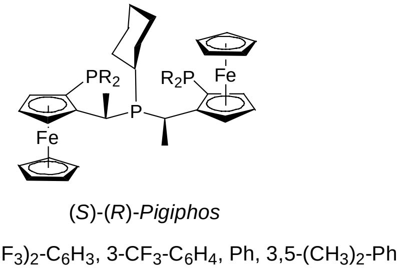


Fig. 27. Sketch of the tridentate phosphine ligand (*S*)-(*R*)-*Pigiphos*.

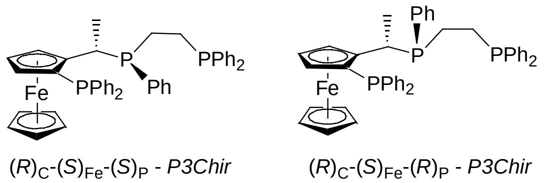


Fig. 28. Sketch of the triphosphine ligands $(R)_C$-$(S)_{Fe}$-$(S)_P$-*P3Chir* and $(R)_C$-$(S)_{Fe}$-$(R)_P$-*P3Chir*.

Several ruthenium(II) complexes of the formula $[(L)RuCl_{2-x}(CH_3CN)_{x+n}]^{x+}$ ($x = 1, 2$; $n = 0, 1$) with the tridentate ligands *Pigiphos* (Fig. 27) and *P3Chir* (Fig. 28) have been isolated and then used to reduce prochiral ketones in 2-propanol as solvent and hydrogen source [122,123].

With either ligand, the conversions to alcohols are generally good, but the *ee*'s never exceed 70%. The tris(acetonitile) Ru(II) $[(L)Ru(CH_3CN)_3](PF_6)_2$ precursors form the most efficient catalysts; for example *fac*-[((*S*)-(*R*)-*Pigiphos*)$Ru(CH_3CN)_3](PF_6)_2$ promotes the reduction of acetophenone to (*R*)-1-phenylethanol in 99% yield and 72% *ee* (2-propanol solvent, 68 °C, 2 h, substrate/catalyst ratio 100). The crystal structure of the dichlororuthenium precursor with (*S*)-(*R*)-*Pigiphos* is reported in Fig. 29. The geometry of this complex approxi-

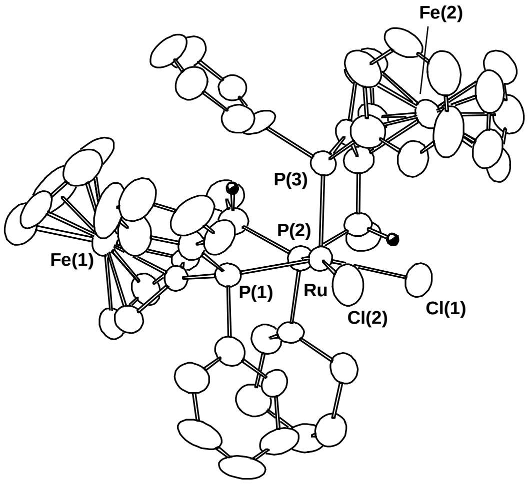


Fig. 29. ORTEP drawing of the complex [(*S*)-(*R*)-*Pigiphos*]$RuCl_2 \cdot 2CH_2Cl_2$.

mates a square-pyramid in which the tridentate ligand is *fac*-coordinated to the metal, with the (Ph)P(3) atom in the apical position and the Cl(1) and Cl(2) atoms *trans* to the (Ph)P(1) and (Cy)P(2) groups, respectively.

It is worth noticing that the *P3Chir* ligands combine planar, phosphorus and carbon chirality in the same molecular framework [124]. Despite this unique assembly of chirality elements, the ruthenium catalysts with *P3Chir* are less enantioselective (*ca*. 41% *ee*) than any analogous *Pigiphos* derivative, which highlights the inherent difficulty in rationalizing and predicting the origin of the chiral transfer.

3. Enantioselective allylic substitution reactions

Transition metal-catalyzed allylic substitution reactions employing soft carbon nucleophiles and/or amines represent one of the most useful synthetic protocols to generate C–C and C–N bonds [125]. Since Tsuji's pioneering work [126], allylic substitution reactions, commonly catalyzed by palladium complexes, have experienced an extraordinary growth in terms of variety of applications and effective synthetic procedures [127]. The main features that distinguish allylic substitution reactions from other C–C and/or C–N bond-making methods are: the mild conditions required, the large variety of employable nucleophiles and electrophiles, the tolerance to many functional groups and the high regio- and stereo-selectivity commonly achieved [128].

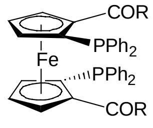
3.1. Allylic alkylation reactions

Several chiral, enantiomerically pure, bis(phosphine) ligands exhibiting only planar chirality have been successfully investigated in the last years as effective systems for transition-metal mediated asymmetric allylic alkylations with soft nucleophiles (Eq. (17)). The ability of these ligands to promote asymmetric allylic alkylations with soft nucleophiles has been recently investigated by Kagan [60,95] (Table 13). Only moderate *ee*'s have been obtained with the chelating 1,2-bis-phosphines 8 (entries 1,2), while the 1,3-bis-phosphines shown in Fig. 4 have provided better results (entries 3–5) However, the *Solvias–Josiphos* ligands still form the best enantioselective catalysts for this kind of reactions (entries 6 and 7).

Table 13
Pd-catalyzed allylic alkylations of racemic 1,3-diphenyl-2-propenyl acetate with dimethyl malonate.

Entry	Ligand type	R	*ee* (%)	Abs.conf.
1	**8**	Cy	34	*R*
2	**8**	Me	47	*S*
3	1,3-Bis-phosphines	Ph	12	*S*
4	1,3-Bis-phosphines	Cy	62	*S*
5	1,3-Bis-phosphines	*t*Bu	83	*S*
6	*Solvias–Josiphos*	Cy	93	*S*
7	*Solvias–Josiphos*	*t*Bu	81	*S*

1 mmol% catalyst; BSA 2 eq./AcOK cat., THF (ca. 0.3 M); all the isolated yields are >98%.



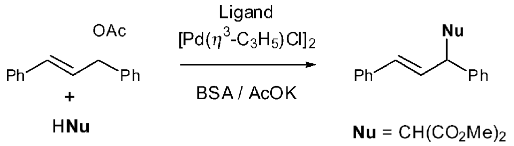
11 a R = OMe
11 b = OEt
11 c = O*i*-Pr

Fig. 30. Sketch of ligand **11**.

Table 14
Pd-catalyzed allylic alkylations of prochiral allylic acetates with dimethyl malonate using ligand **11**

Entry	Ligand	Subst.	*T* (°C) /*t* (h)	*ee* (%)/Abs.Conf.
1	**11a**	A	25/1	86/S
2	**11c**	A	25/8	92/S
3	**11c**	A	0/10	94/S
4	**11a**	B	0/<0.17	81/R
5	**11a**	B	−25/0.33	82/R
6	**11a**	B	−50/1	83/R

1 mmol of substrate, 3 mmol of dimethyl malonate, 3 mmol of base (BSA), 20 μmol of AcOK, 30 μmol of ligand and 12.5 μmol of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in 3 mL of CH_2Cl_2.



(17)

The C_2-symmetrical *P,P*-chelating ligands **11a–c**, exhibiting only the planar chirality of the ferrocenyl moiety, have been recently used by Ikeda [129] to form very efficient Pd catalysts for the allylic alkylation of sterically hindered allylic substrates (Fig. 30). Ligands **11a–c** afforded good to excellent *ee*'s in the allylation of 1,3-diphenyl-2-propenyl acetate (A) (Table 14, entries 1–3) and of the less sterically hindered cyclohex-2-en-1-yl acetate (B) (entries 4–6).

As a general trend, the enantioselectivity increases with the bulkiness of the ester groups in the 2,2′-positions (entries 1–3) and is not significantly affected by the temperature (entries 4–6).

New types of chiral ligands, based on the planar chirality of the phosphaferrocene moiety, have been developed independently by Ganter [130] and Fu [131]. The enantiomerically pure (*S*,*S*)-bis(phospaferrocene) ligand **12** shown in Fig. 31 has been tested by Ganter in the allylic substitution of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, affording good yields and *ee*'s as high as 79%.

Hayashi has prepared mixed phosphino-phosphaferrocene ligands [132] in which one Cp ring of a ferrocenyl unit is replaced by a phosphacyclopentadienyl ring (Fig. 32). A palladium complex generated in situ from $[Pd(\eta^3\text{-}C_2H_5)Cl]_2$ has been reported to be very efficacious in the asymmetric allylic alkylation of racemic 1,3-diphenyl-2-propenyl

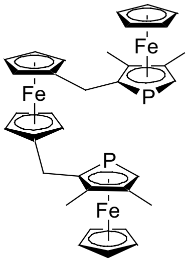


Fig. 31. Sketch of ligand **12**.

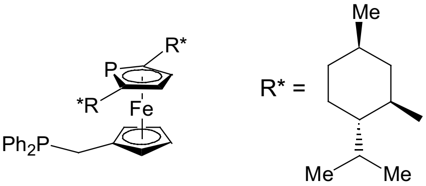


Fig. 32. The phosphino-phosphaferrocene ligand **13** developed by Hayashi.

acetate with dimethyl malonate in the presence of BSA/AcOK.

The different binding affinity of the two phosphorus donor atoms to palladium has been exploited to tune the catalytic activity of the phosphino-phosphaferrocenyl ligands. At high ligand/metal molar ratios, the ligand is presumably monodentate with a free phosphaferrocene arm, which may account for the relatively low *ee*'s (Table 15, entries 1–2).

Accordingly, a sub-stoichiometric amount of ligand would favor the formation of chelating chiral ligands, hence leading to an increase in the enantioselectivity (entries 3–4. No improvement in the enantioselectivity has been obtained by decreasing the temperature (entries 3 and 4).

Dendrimers derived from 1′-functionalized (*R*)-(*S*)-*Josiphos* ligands (Fig. 20, Section 2.1.1.1) have been employed by Köllner and Togni [103] to alkylate 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The *ee*'s obtained are slightly lower than those provided by *Josiphos* in homogeneous phase (Table 16, entries 1–5), and show a surprising dependence on the number of available ligands (hence by the dendrimer generation): with eight peripheral ferrocenyl units the *ee* is between 85 and 91% (entries 1–3), while an ee of only 54% is obtained with the second-generation dendrimers (entry 4), probably due to their lower solubility however.

Table 15
Allylic alkylations of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of phosphino-phosphaferrocenyl palladium catalysts

Entry	Ligand/Pd mol/mol	*T* (°C)/*t* (h)	Yield (%)	*ee* (%)/abs.Conf.
1	4/1	20/24	97	87/*R*
2	8/1	20/24	99	77/*R*
3	0.75/1	20/24	97	98/*R*
4	0.75/1	−20/96	99	99/*R*

1 mmol of substrate, 3 mmol of dimethyl malonate, 3 mmol of base (BSA—N,O-bis(trimethylsylil)acetamide), 20 μmol of AcOK, 40 μmol [Pd(η^3-C_3H_5)Cl]$_2$ in 2 mL of CH_2Cl_2.

Table 16
Allylic alkylations of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate by *Josiphos*-dendrimers palladium catalysis

Entry	Dendrimer generation	Ferrocene units	Yield (%)	*ee* (%) /abs.Conf.
1	0	4	96	91/*S*
2	1	6	85	90/*S*
3	1	8	91	90/*S*
4	2	16	–	54/*S*
5	–	*Josiphos*	97–99	93/*S*

1 mmol of substrate, 2 mmol of dimethyl malonate, 2 mmol of base (BSA), 47 μmol of AcOK, 12.8 μmol Pd(dba)$_2$ in 5 mL of CH_2Cl_2 and the chiral dendrimer ligand (14.1 μmol divided by the number of the ferrocene units in the molecule), r.t. 20 h.

Table 17
Pd-catalyzed allylic alkylations of 1,3-diphenyl-2-propenyl acetate using ligand **9**

Entry	*t* (h)	Solvent	*ee* (%)	Abs.Conf.
1	24	CH_3CN	29	*S*
2	24	DMF	95	*S*
3	5	CH_2Cl_2	94	*S*
4	3	Toluene	95	*S*
5	1	THF	95	*S*

1 mol % catalyst; 1 mL/mmol of solvent; r. t.

Recent applications of ferrocenyl ligands bearing optically active phosphorus atoms in allylic alkylation reactions have been reported by van Leeuwen [133] and Imamoto [97].

Moderate to good enantioselectivities have been obtained by van Leeuween in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate using a Pd-**6a** catalyst (73–88% yield, up to 73% *ee*), whereas the parent ligand **6b** gives a very low asymmetric induction (Fig. 15).

Imamoto has reported that **9** (Fig. 19), in conjunction with palladium, forms effective catalysts for the alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, leading to almost quantitative yields and *ee*'s as high as 95% (Table 17).

3.2. Allylic amination reactions

Asymmetric allylic amination reactions have been less studied than allylic alkylations, yet the growing interest in optically pure allyl amines is boosting research aimed at developing efficient catalyst for the former reactions.

Over the last few years, a number of palladium catalysts with mixed bidentate *P,N*-ferrocenyl ligands have been reported to catalyze asymmetric allylic amination reactions. In contrast, ferrocenyl phosphines have been much less investigated. The only relevant example has been described by Johnson and Thomas [134] who were able to immobilize the ferrocenyl-based ligand (*S*)-1-

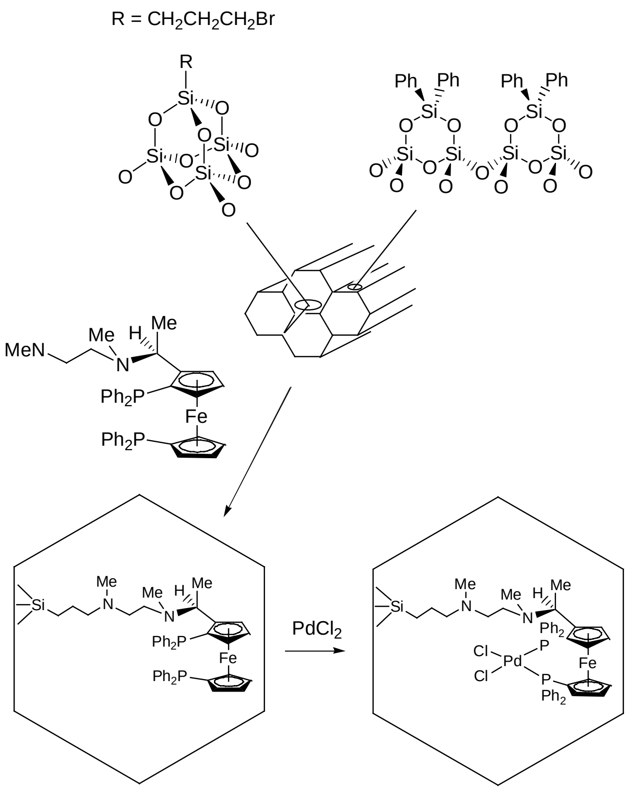


Fig. 33. Immobilization of a ferrocenyl diphosphine ligand on the inner walls of MCM-41.

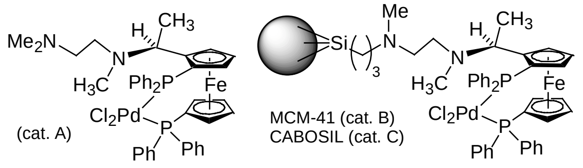
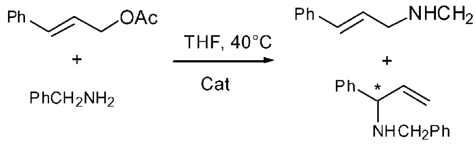


Fig. 34. Homogeneous, Cabosil and MCM-41 palladium catalysts.

[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl-*N*,*N*′-dimethylethylenediamine to the inner walls of MCM-41 (Fig. 33).

The tethered catalyst was then employed to catalyze, in conjunction with palladium(II), the amination of cinnamyl acetate with benzylamine (Eq. (18)).

 (18)

For comparative purposes, this allylic amination reaction was also performed either in homogeneous phase with the unsupported catalyst (*S*)-1-[(*R*)-1′,2-bis(diphenylphosphino) ferrocenyl]ethyl-*N*,*N*′-trimethylethylendiamine/$PdCl_2$ or in heterogeneous phase with the palladium catalyst tethered to a non-porous silica support (Cabosil) (Fig. 34).

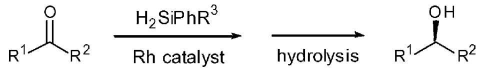
Table 18
Pd-catalyzed allylic aminations of cinnamyl acetate with benzylamine

Entry	Cat.	Linear prod.(%)	Branched prod.(%)	Conv. (%)	*ee* (%)
1	A	>99	–	76	–
2	B	49	51	99	99
3	C	98	2	98	43

The mesopore-confined catalyst showed an enantioselectivity (100% *ee*, 51% of branched product) far superior to those of both homogeneous (only linear product) and Cabosil-tethered analogues (2% branched product with 43% *ee*) (Table 18).

4. Asymmetric hydrosilylation reactions

Only a few examples of asymmetric hydrosilylation reactions assisted by chiral ferrocenyl phosphine metal complexes have been reported so far. Simple ketones have been reduced using either in situ or preformed rhodium(I) catalyst precursors to give the corresponding optically active secondary alcohols, after hydrolysis (Eq. (19)). Representative results are reported in Table 19.

 (19)

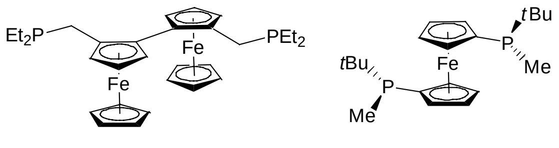
The EtTRAP-H ligand, featured by planar chirality (Fig. 35), affords high enantioselectivities (up to 94% *ee*, Table 19 entry 1,2) in the hydrosilylation of a variety of ketones using in situ prepared rhodium catalysts [135].

Excellent results in the reduction of aryl-akyl ketones with the silylation agent 1-naphthylphenyilsilane (Table 19, entries 3,4) have been reported by Imamoto who made use of

Table 19
Asymmetric hydrosilylations of ketones catalyzed by rhodium complexes with chiral ferrocenyl phoshines

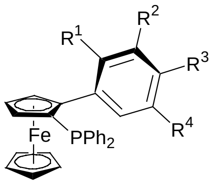
Entry	Ligand	Ketone		Silane, R^3	Conv. (%)	*ee* (%)
		R^1	R^2			
$1^{a,b}$	EtTRAP-H	Ph	Me	Ph	89	94
$2^{a,c}$	EtTRAP-H	$Ph(CH_2)_2$	Me	Ph	94	81
$3^{d,e}$	**14**	Ph	Me	1-naphth.	96	92
$4^{d,e}$	**14**	2-naphth.	Me	1-naphth.	99	85

[a] In situ catalyst $[Rh(COD)_2]BF_4$/ligand = 1/1.1.
[b] In THF at −40 °C.
[c] In THF at −50 °C.
[d] Preformed catalyst $[(Ligand)Rh(NBD)]BF_4$.
[e] In THF at −20 °C.



(*S*,*S*)-EtTRAP-H (*S*,*S*) **14**

Fig. 35. Sketches of the ligands EtTRAP-H (left) and **14** (right).

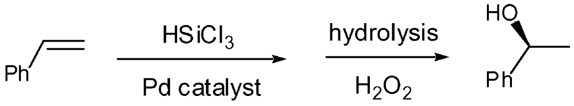


15

Fig. 36. Sketch of the atropoisomeric ferrocenyl phosphine ligand 15.

the (*S*)-(*S*)-1,1′-ferrocenyl diphosphine ligand **14** shown in Fig. 35 [136].

The atropisomeric and chiral planar ferrocene ligands **15** shown in Fig. 36 have been reported to form efficient palladium catalysts for the asymmetric hydrosilylation of styrene (Eq. (20)) with *ee*'s as high as 90% and TOF's exceeding 180000 h^{-1} [137].

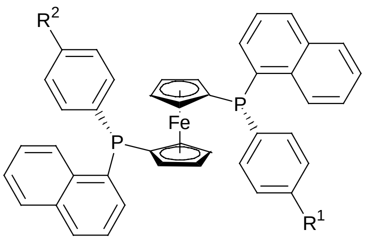


(20)

5. Enantioselective hydroformylation reactions

The hydroformylation of alkenes is one of the largest scale industrial reactions in homogeneous phase [138]. Despite the interest in optically pure aldehydes and, eventually, in the corresponding alcohols, asymmetric hydroformylation is still at a laboratory stage. In fact, a very efficient catalyst has not yet been discovered and the fast epimerization of aldehydes still represents a serious obstacle to obtain high *ee*'s.

Van Leeuwen has studied the performance of rhodium complexes with the chiral ferrocenyl diphosphines **16** (Fig. 37) (see Section 2.1.1) in the hydroformylation of various styrenes (Eq. (21)) [139]. In line with previous results, rather low productivities and branched/linear ratios were obtained (Table 20). As a general trend, both the TOF and the *ee* increased with the electron-withdrawing character of the *P*-aryl substituent.



16a $R^1 = R^2 = H$
16b $R^1 = R^2 = OCH_3$
16c $R^1 = R^2 = CF_3$
16d $R^1 = OCH_3$, $R^2 = CF_3$

Fig. 37. Scheme of ligand **16** developed by van Leeuwen.

Table 20
Hydroformylation of (substituted) styrenes using diphosphine **16**/Rh $(CO)_2$acac catalysts

Entry	Ligand	Substrate R	*T* (°C)	b/l[a]	TOF (h^{-1})	*ee* (%)
1	**b**	4-$MeOC_6H_4$	60	1.2	24	51
2	**c**	4-$MeOC_6H_4$	60	1.1	71	36
3	**d**	4-$MeOC_6H_4$	60	1.1	55	29
4	**b**	Ph	40	1.7	6	46
5	**c**	Ph	40	1.5	12	50
6	**d**	Ph	40	1.7	11	41

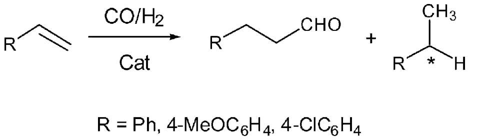
$CO/H_2 = 1$; pressure 20 bar, 2.2/1 ligand/rhodium, 500/1 styrene/rhodium; [Rh] = 2.30 mM in toluene.

[a] Branched/linear product ratio.

Table 21
Hydroformylation of styrene using different rhodium-*Solvias–Josiphos* ligands

Entry	Ligand		*T* (°C)	Conv. (%)	*ee* (%)
	R	R′			
1	Ph	Cy	60	3	63
2	Ph	Cy	90	31	57
3	Ph	Cy	120	84	45
4	*o*-Anisyl	Ph	40	3	76
5	*o*-Anisyl	Ph	60	26	51
6	*o*-Anisyl	Ph	75	78	31

$Rh(CO)_2$(acac)/ligand/styrene: 1/2/300; 10 MPa H_2–CO (1:1 mixture). Reaction time 16 h. Branched/linear ratios were between 9 and 15 in all cases.



(21)

Styrene hydroformylation with high optical induction (up to 76% *ee*) (Eq. (21)), albeit with low conversion, has been achieved by Herrmann with the use of rhodium(I)-*Solvias–Josiphos* ferrocenylethyl diphosphine precursors (see Fig. 2) [140]. The substituents on the phosphorus atoms have been found to affect both the activity and the selectivity (Table 21). In particular, dialkylaryl-alkyldiaryl diphosphines provided good enantioselectivities even at high temperature (entries 1–3), yet higher *ee*'s were obtained with diphenylaryl-alkyldiaryl diphosphines (entries 4–6). The hydroformylation of styrene by platinum complexes of heteroannularly bridged ferrocenyl diphosphine ligands of type **2** (Fig. 3, section 2.1.1) has been investigated by Weissensteiner (Table 22), who discovered a remarkable temperature dependence. For example, (*R*)-2-phenyl-propanal was obtained at low temperature, while (*S*)-2-phenyl-propanal was produced at high temperature [141].

Table 22
Hydroformylation of styrene using heteroannularly bridged ferrocenyl diphosphine ligands[a]

Entry	Catalyst	R_B[b] (%)	T (°C)	Conv. (%)	*ee* (%)	Config.
1[c]	$PtCl_2$ (**2b**)	46	60	41	38	*R*
2	$PtCl_2$ (**2b**)	50	100	99	2	*S*
3	$PtCl_2$ (**2a**)	32	40	77	19	*R*
4	$PtCl_2$ (**2a**)	36	100	83	37	*S*

[a] Reaction conditions: 0.025 mmol of $PtCl_2$(1 or 2), 0.05 mmol of $SnCl_2$, 30 ml Toluene. $P = 80$ bar (1:1 CO/H_2).
[b] % Branched aldehyde.
[c] $P = 100$ bar, $CO/H_2 = 1:1$.

Table 23
Enantioselective addition of aniline to norbornene catalyzed by the *Solvias–Josiphos* Ir complexes in Eq. (22)

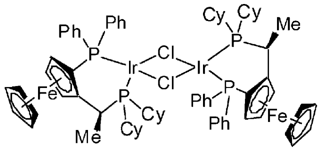
Entry	$[F^-]/[Ir]$	Yield (%)	TOF (h^{-1})	*ee* (%)	Conf.
1	0	12	0.17	51	S
2	1	81	1.11	50	R

The iridium complex was isolated as an inseparable mixture of cis/trans isomers. Catalyst (1 mol% Ir) + commercially available $(Me_2N)_3P{=}N^+{=}P(NMe_2)_3F^-$ (0.5 M in benzene), no solvent, 50 °C.

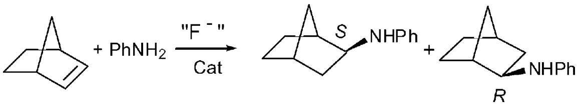
6. Asymmetric hydroamination reactions of alkenes

The metal-catalyzed coupling of primary and secondary amines to unsaturated C–C bonds is known as hydroamination reaction. Such reactions, especially in asymmetric fashion, constitute an area of great interest due to the large availability of amines as well as the ubiquity of double bonds in natural products, pharmacological agents and fine chemicals [142]. Besides alkenes, the hydroamination can be performed on alkynes and allenes in the presence of lanthanide [143] and transition metal catalysts [144].

The first example of enantioselective addition of aniline to the double bond of norbornene was carried out by Togni with the use of (*R*)-(*S*)-*Solvias–Josiphos* iridium catalysts (Eq. (22)) [145]. *ee*'s up to 60% were obtained upon addition of co-catalytic amounts of "naked" fluoride ions from phospazenium fluoride-P_2. In the absence of fluoride ions, the catalytic activity and the enantioselectivity were remarkably lower, and, also, the opposite enantiomer was formed (entry 2)(Table 23).



cat = *trans* + *cis*



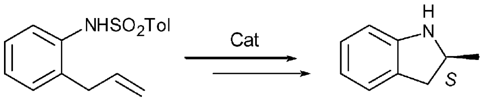
(22)

Table 24
Hydroamination of activated olefins catalyzed by nickel- *Pigiphos* complexes

Entry	R^1	R^2	R^3	Yield (%)	*ee* (%)
1	CH_3	H	Ph	91	22
2	H	CH_3	Ph	85	18
4	H	CH_3	$O(CH_2CH_2)_2$	99	69
5	H	CH_3	$(CH_2)_5$	99	20

THF, r.t., 24 h, 5 mol% cat. generated in situ $[Ni(\textit{Pigiphos})(THF)](ClO_4)_2$.

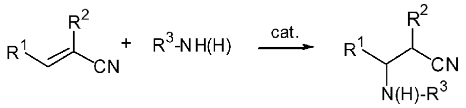
The *Solvias–Josiphos* iridium catalyst is also efficient to promote the intramolecular hydroamination of 2-(propen-3-yl)aniline derivatives to give the corresponding cyclic product in 40% yield and 67% *ee* (Eq. (23)) [43].



(23)

More recently, Togni has reported that nickel(II) complexes containing the chiral tridentate ferrocenyl phosphine *Pigiphos* (Fig. 27, Section 2.2) form efficient catalyst precursors for the hydroamination of activated olefins (Eq. (24)) [146].

Both anilines and cyclic aliphatic amines have been found to react with olefins in the presence of nickel(II)-*Pigiphos* precursors to give the corresponding secondary amines in high yields and *ee*'s (Table 24). In particular, the hydroamination of methacrylonitrile with morpholine yielded the *anti*-Markovnikoff product with 69% *ee*. Interestingly, the bidentate phosphine *Josiphos* did not form any active catalyst for this reaction.

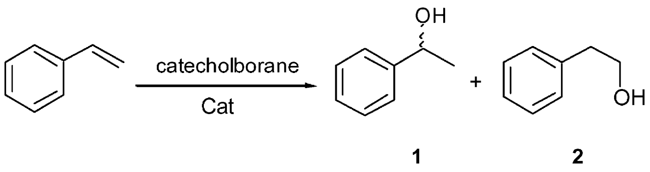


(24)

7. Miscellaneous reactions

7.1. Asymmetric hydroboration of alkenes

An interesting example of asymmetric hydroboration of alkenes, followed by oxidative workup of the organoboron intermediate (Eq. (25)), has been recently reported by Togni using Josiphos-rhodium dendrimers (Fig. 20, Section 2.1.1.1) [103]. In comparison with the homogeneous *Josiphos* system (Table 25, entry 5), the dendritic catalysts proved less regioselective but slightly more enantioselective (entries 1–4).



(25)

Table 25
Rh-catalyzed hydroboration of styrene using *Josiphos*-dendrimers

Entry	Dendr. Gener.	Ferrocene units	Yield (%)	**1**:**2** ratio	*ee* **1** (%)	Conf. **1**
1	0	3	87	96:4	68	*S*
2	0	4	86	98:2	68	*S*
3	1	8	63	95:5	67	*S*
4	2	16	97	89:11	64	*S*
5	–	*Josiphos*	65	99:1	60–65	*S*

1.91 mmol of styrene, 2.10 mmol of catecholborane, 19.1 μmol $[Rh(COD)_2]BF_4$ in 2 mL of CH_2Cl_2 and the chiral dendrimer ligand (21.0 μmol divided by the number of the ferrocene units in the molecule), r.t. 5 h.

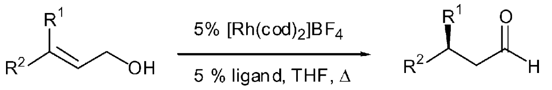
Table 26
Catalytic enantioselective isomerization of allylic alcohols with in situ prepared Rh-phosphaferrocenyl catalyst

Entry	R^1	R^2	Yield (%)	*ee* (%)
1[a]	Ph	*i*-Pr	91	83
2[a]	*p*-ClC_6H_4	*i*-Pr	74	86
3[b]	*p*-Tol	*i*-Pr	64	80

[a] Reaction temperature 70 °C.
[b] Reaction temperature 100 °C.

7.2. Enantioselective isomerization of allylic alcohols

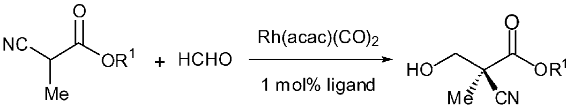
The enantioselective isomerization of allylic alcohols to aldehydes can be effectively achieved with the chiral phosphaferrocenyl ligand **7** shown in Fig. 16 [131]. Indeed, this ligand forms an excellent rhodium(I) catalyst for the production of aldehydes in high yields and *ee*'s as high as 86% (Eq. (26)), Table 26).



(26)

7.3. Asymmetric aldol reactions

The only relevant example of asymmetric aldol reaction which is pertinent to this review has been reported by Ito who made use of rhodium complexes with TRAP-type diphosphine ligands to produce chiral alcohols in good yields and excellent *ee*'s (up to 93%) [147]. The most outstanding result is provided by the reactions of 2-cyanopropionates with formaldehyde in the presence of either preformed (*S*,*S*)-(*R*,*R*)-(PhTRAP)/Rh(acac)(CO)$_2$ or (*S*,*S*)-(*R*,*R*)-(*p*-MeOC$_6$H$_4$TRAP)/Rh(acac)(CO)$_2$ (Eq. (27)) that gave *ee*'s as high as 93% (Table 27).



(27)

Table 27
Catalytic asymmetric aldol catalyzed by TRAP–Rh complexes

Entry	TRAP	R^1	Yield (%)	*ee* (%)
1[a]	Ph	Et	85	74
2	Ph	CHi-Pr$_2$	82	91
3	Ph	CHt-Bu$_2$	86	93
4	*p*-MeOC$_6$H$_4$	CHi-Pr$_2$	87	92

All the reaction were carried out in Bu$_2$O at −10 °C. 2-Cyanopropionate:HCHO:Rh(acac)(CO)$_2$:TRAP ligand = 1:1.3:0.01:0.011.
[a] At −30 °C.

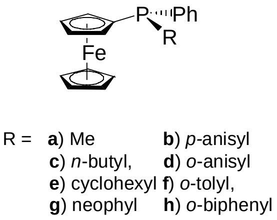
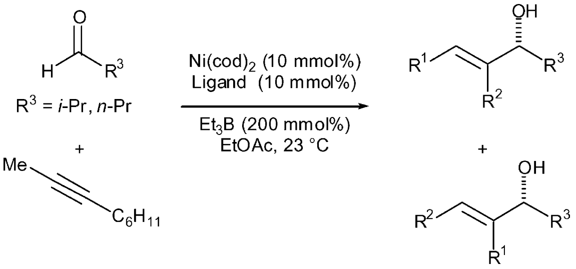


Fig. 38. *P*-Stereogenic ferrocenyl phosphines reported by Jamison.

7.4. Asymmetric carbon-carbon bond forming reactions

Jamison and Colby have recently reported the use of iridium precursors stabilized by *P*-stereogenic ferrocenyl phosphines (Fig. 38) to produce optically active allylic alcohols via intermolecular reductive coupling of alkynes and aldehydes (Eq. (28)) [148]. The products were obtained in moderate yields, but with excellent regioselectivity (>98% *E* conformation) and up to 68% enantioselectivity.



(28)

8. Conclusions

Since its origin, asymmetric catalysis has been haunted by the research of universal ligands, i.e. ligands capable of creating effective chiral pockets with all metals and, therefore, potentially employable in the known chemical transformations as well as in the design of new reactions. For the diversity of applications and the excellent results provided, there is little doubt that atropoisomeric ligands of the Binap family and ferrocenyl phosphines of the *Josiphos* family are the ligand systems which most approach this model.

In this paper, we have reviewed recent applications of different families of chiral ferrocenyl phoshine ligands in asymmetric catalysis. The increasingly large number and variety of chemical processes that make use of ferrocenyl phoshines prove the enormous potential of this type of chiral auxiliaries in asymmetric catalysis.

The success of ferrocenyl phoshines is largely attributable to their flexible molecular structure that allows one to easily change the position and number of the donor atoms as well as vary the steric and electronic properties and even the phase system of the catalytic process. Chiral ferrocenyl phosphines are generally expensive due the high cost of many key reagents and the complicated synthetic protocol. However, recent advances in organic synthesis aimed at reducing the number of steps and the quality of reagents, lead us to think that ferrocenyl phosphines will have a growing relevance also in large-scale industrial processes.

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References

[1] M.E. Davis, S.L. Suib (Eds.), Selectivity in Catalysis, ACS Symposium Series, vol. 517, American Chemical Society, Washington, 1993.
[2] J.D. Morrison (Ed.), Asymmetric Synthesis, vol. 5, Academic Press, Orlando, FL, 1985.
[3] B. Bosnich, M.D. Fryzuk, in: G.L. Geoffroy (Ed.), Topics in Inorganic and Organometallics Stereochemistry, Topics in Stereochemistry Series, vol. 12, Interscience Publications, New York, 1981.
[4] D.J. Berrisford, C. Bolm, K.B. Sharpless, Angew. Chem. Int. Ed. Engl. 34 (1995) 1059.
[5] R.E. Gawley, J. Aube, Principles of Asymmetric Synthesis, Pergamon, London, 1996.
[6] J. Crosby, Tetrahedron 47 (1991) 4789.
[7] S.C. Stinson, Chem. News Eng. 21 (1998) 83.
[8] A. Richards, R. McCague, Chem. Ind. June 2 (1997) 422.
[9] H.U. Blaser, F. Spindler, Top. Catal. 4 (1997) 275.
[10] S.C. Stinson, Chem. Eng. News 41 (1999) 101.
[11] S.C. Stinson, Chem. Eng. News 43 (2000) 55.
[12] S.C. Stinson, Chem. Eng. News 40 (2001) 79.
[13] H.U. Blaser, B. Pugin, F. Spindler, in: B. Cornils, W.A. Herrmann (Eds.), Applied Homogeneous Catalysis by Organometallic Complexes, VCH, Weinheim, 1996.
[14] R.A. Sheldon, Chirotechnology, Marcel Dekker Inc., New York, NY, 1993.
[15] A.N. Collins, G.N. Sheldrake, J. Crosby (Eds.), Chirality in Industry, Wiley, New York, NY, 1992.
[16] H.U. Blaser, Chem. Commun. (2003) 293.
[17] I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., VCH Publishers, New York, 2000.
[18] H. Brunner, W. Zettlmeier, Handbook of Enantioselective Catalysis with Transition Metal Compounds, vols. 1 and 2, VCH, Weinheim, 1993.
[19] R. Noyori, Asymmetric Catalysis in Organic Synthesis, Wiley, New York, 1994.
[20] W. Tang, X. Zhang, Chem. Rev. 103 (2003) 3029.
[21] E.N. Jacobsen, A. Pfaltz, H. Yamamoto, Comprehensive Asymmetric Catalysis, vols. 1–3, Springer, Berlin, 1999.
[22] M.P. Doyle (Ed.), Advances in Catalytic Processes, vol. 1, JAI, London, 1995.
[23] H.U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, Adv. Synth. Catal. 345 (2003) 103.
[24] E.N. Jacobsen, Acc. Chem. Res. 33 (2000) 421.
[25] H. Tye, P.J. Comina, J. Chem. Soc., Perkin Trans. 1 (2001) 1729.
[26] M. Burk, Acc. Chem. Res. 33 (2000) 363.
[27] Y. Ito, M. Sawamura, T. Hayashi, J. Am. Chem. Soc. 108 (1986) 6405.
[28] A. Togni, R. Häusel, Synlett (1990) 633.
[29] A. Togni, G. Rihs, R.E. Blumer, Organometallics 11 (1992) 613.
[30] A. Togni, Chimia 50 (1996) 86.
[31] M. Sawamura, Y. Ito, Chem. Rev. 92 (1992) 857.
[32] T. Hayashi, Pure Appl. Chem. 60 (1988) 7.
[33] T. Hayashi, M. Kumada, Acc. Chem. Res. 15 (1982) 395.
[34] A. Togni, Angew. Chem. Int. Ed. Engl. 35 (1996) 1475.
[35] S.C. Stinson, Chem. Eng. News 38 (1997) 28.
[36] J. McGarrity, F. Spindler, R. Fuchs, M. Eyer, (LONZA AG), Eur. Pat. Appl. EP 624 587 A2, Chem. Abstr. 1995. 122, P81369q.
[37] F. Spindler, B. Pugin, H.P. Jalett, H.P. Buser, U. Pittelkow, H.U. Blaser, in: R.E. Malz Jr. (Ed.), Catalysis of Organic Reactions (Chem. Ind.), vol. 68, Dekker, New York, 1996, pp. 153–166.
[38] F. Spindler, B. Pugin, EP-A 0256982 (1988) (Ciba-Geigy AG).
[39] H.U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, Top. Catal. 19 (2002) 3.
[40] T. Hayashi, in: A. Togni, T. Hayashi (Eds.), Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Materials Science, VCH, Weinheim, 1995, pp. 105–142.
[41] T.J. Colacot, Chem. Rev. 103 (2003) 3101.
[42] A. Togni, L.M. Venanzi, Angew. Chem. Int. Ed. Engl. 33 (1994) 497.
[43] A. Togni, N. Bieler, U. Burckhardt, C. Köllner, G. Pioda, R. Schneider, A. Schnyder, Pure Appl. Chem. 71 (1999) 1531.
[44] C.J. Richards, A. Locke, Tetrahedron: Asymmetry 9 (1998) 2377.
[45] L.X. Dai, T. Tu, S.L. You, W.P. Deng, X.L. Hou, Acc. Chem. Res. 36 (2003) 659.
[46] J.K. Whitesell, Chem. Rev. 89 (1989) 1581.
[47] T. Hayashi, K. Yamamoto, M. Kumada, Tetrahedron Lett. (1974) 4405.
[48] T. Hayashi, T. Mise, M. Fukushima, M. Kagotani, N. Nagashima, Y. Hamada, A. Matsumoto, S. Kawakami, M. Konishi, K. Yamamoto, M. Kumada, Bull. Chem. Soc. Jpn. 53 (1980) 1138.
[49] K. Inoguchi, S. Sakuraba, K. Achiwa, Synlett (1992) 169.
[50] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, J. Am. Chem. Soc. 116 (1994) 4062.
[51] The *Solvias–Josiphos* ligands are patent-protected and are all produced by Solvias in technical quantities as either single ligands or ligand kits. See: http://www.ligands.solvias.com/data/html/all/enter_page.html. Family members are available in research quantities from Strem and Fluka.
[52] B. Pugin, EP 0728768 (1996) (Ciba-Geigy).
[53] B. Pugin, WO 96/32400 (1996) (Novartis).
[54] B. Pugin, H. Landert, WO 98/01457 (1998) (Novartis).
[55] E. Broger, Y. Crameri, P. Jones, WO 99/01453 (1997) (Hoffmann-La Roche).
[56] D.A. Dobbs, K.P.M. Vanhessche, E. Brazi, V. Rautenstrauch, J.Y. Lenoir, J.P. Genêt, J. Wiles, S.H. Bergens, Angew. Chem. Int. Ed. Engl. 39 (2000) 1992.
[57] D.A. Dobbs, K.P.M. Vanhessche, V. Rautenstrauch, WO 98/52687 (1999) (Firmenich). Chem. Abstr. 130 (1999) 40076p.
[58] V. Rautenstrauch, J.P. Genêt, J.Y. Lenoir, WO 97/18894 (1997) (Firmenich). Chem. Abstr. 127 (1997) 83071p.
[59] T. Sturm, W. Weissensteiner, F. Spindler, K. Mereiter, A.M. López-Agenjo, B.R. Manzano, F.A. Jalón, Organometallics 21 (2002) 1766.
[60] G. Argouarch, O. Samuel, H.B. Kagan, Eur. J. Org. Chem. (2000) 2885.
[61] T. Sturm, L. Xiao, W. Weissensteiner, Chimia 55 (2001) 688.
[62] The Walphos ligand family is produced in technical scale by Solvias and sold in research quantities by Strem.
[63] T. Sturm, W. Weissensteiner, F. Spindler, Adv. Synth. Catal. 345 (2003) 160.
[64] P. Herold, S. Stutz, WO 02/02500 A1 (2002) (Speedel Pharma AG).

[65] T. Ireland, G. Grossheimann, K. Wieser-Jeunesse, P. Knochel, Angew. Chem. Int. Ed. Engl. 38 (1999) 3212.
[66] M. Lotz, K. Polborn, P. Knochel, Angew. Chem. Int. Ed. Engl. 41 (2002) 4708.
[67] T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, Chem. Eur. J. 8 (2002) 843.
[68] R. Kuwano, M. Sawamura, S. Okuda, T. Asai, Y. Ito, M. Redon, A. Krief, Bull. Chem. Soc. Jpn. 70 (1997) 2807.
[69] M. Sawamura, R. Kuwano, Y. Ito, J. Am. Chem. Soc. 117 (1995) 9602.
[70] M. Sawamura, H. Hamashima, Y. Ito, J. Am. Chem. Soc. 114 (1992) 8295.
[71] R. Kuwano, S. Okuda, Y. Ito, Tetrahedron: Asymmetry 9 (1998) 2773.
[72] R. Kuwano, S. Okuda, Y. Ito, J. Org. Chem. 63 (1998) 3499.
[73] R. Kuwano, M. Sawamura, Y. Ito, Bull. Chem. Soc. Jpn. 73 (2000) 2571.
[74] R. Kuwano, Y. Ito, J. Org. Chem. 64 (1999) 1232.
[75] R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, J. Am. Chem. Soc. 122 (2000) 7614.
[76] C. Bianchini, P. Barbaro, G. Scapacci, E. Farnetti, M. Graziani, Organometallics 17 (1998) 3308.
[77] K. Rossen, P.J. Pye, L.M. DiMichele, R.P. Volante, P.J. Reider, Tetrahedron Lett. 39 (1998) 6823.
[78] R.M. Klabe, L.T. Bacheler, P.J. Ala, S. Erickson-Viitanen, J.L. Meek, Biochemistry 37 (1998) 8735.
[79] R. Kuwano, M. Sawamura, S. Okuda, T. Asai, Y. Ito, M. Redon, A. Krief, Bull. Chem. Soc. Jpn. 70 (1997) 2807.
[80] A. Marinetti, F. Labrue, J.P. Genêt, Synlett 12 (1999) 1975.
[81] U. Berens, M.J. Burk, A. Gerlach, W. Hems, Angew. Chem. Int. Ed. Engl. 39 (2000) 1981.
[82] The FerroTANE ligands are available from Chirotech Technology Ltd.
[83] U. Berens, WO 99/24444 (Chirotech Technology Ltd.). Chem. Abstr. 130 (2000) 338253.
[84] A. Marinetti, F. Labrue, B. Pons, S. Jus, L. Ricard, J.P. Genêt, Eur. J. Inorg. Chem. (2003) 2583.
[85] D. Heller, H.J. Drexler, J. You, W. Baumann, K. Drauz, H.P. Krimmer, A. Börner, Chem. Eur. J. 8 (2002) 5196.
[86] D. Liu, W. Li, X. Zhang, Org. Lett. 4 (2002) 4471.
[87] M.T. Reetz, A. Gosberg, R. Goddard, S.H. Kyung, Chem. Commun. (1998) 2077.
[88] J.J. Almena Perea, A. Börner, P. Knochel, Tetrahedron Letters 39 (1998) 8073.
[89] J. Kang, J.H. Lee, S.H. Ahn, J.S. Choi, Tetrahedron Lett. 39 (1998) 5523.
[90] M. Lotz, T. Ireland, J.J. Almena Perea, P. Knochel, Tetrahedron: Asymmetry 10 (1999) 1839.
[91] F. Maienza, F. Santoro, F. Spindler, C. Malan, A. Mezzetti, Tetrahedron: Asymmetry 13 (2002) 1817.
[92] F. Maienza, M. Wörle, P. Steffanut, A. Mezzetti, F. Spindler, Organometallics 18 (1999) 1041.
[93] U. Nettekoven, P.C.J. Kamer, P.W.N.M. van Leeuwen, M. Widhalm, A.L. Spek, M. Lutz, J. Org. Chem. 64 (1999) 3996.
[94] S. Qiao, G.C. Fu, J. Org. Chem. 63 (1998) 4168.
[95] G. Argouarch, O. Samuel, O. Riant, J.C. Daran, H.B. Kagan, Eur. J. Org. Chem. (2000) 2893.
[96] N.W. Boaz, S.D. Debenham, E.B. Mackenzie, S.E. Large, Org. Lett. 4 (2002) 2421.
[97] N. Oohara, K. Katagiri, T. Imamoto, Tetrahedron: Asymmetry 14 (2003) 2171.
[98] H.U. Blaser, B. Pugin, in: G.J. James, V. Dubois (Eds.), Chiral Reactions in Heterogeneous Catalysis, Plenum Press, New York, 1995.
[99] D.E. De Vos, I.F.J. Vankelecom, P.A. Jacobs (Eds.), Chiral Catalyst Immobilization and Recycling, Wiley-VCH, Weinheim, 2000.
[100] C. Bianchini, P. Barbaro, Top. Catal. 19 (2002) 17.
[101] R. Schneider, C. Köllner, I. Weber, A. Togni, Chem. Commun. (1999) 2415.
[102] C. Köllner, B. Pugin, A. Togni, J. Am. Chem. Soc. 120 (1998) 10274.
[103] C. Köllner, A. Togni, Can. J. Chem. 79 (2001) 1762.
[104] T. Chiba, A. Miyashita, H. Nohira, H. Takaya, Tetrahedron Lett. 34 (1993) 2351.
[105] M. Burk, G. Harper, C. Kalberg, J. Am. Chem. Soc. 117 (1995) 4423.
[106] T. Ohkuma, M. Koizumi, K. Muñiz, G. Hilt, C. Kabuto, R. Noyori, J. Am. Chem. Soc. 124 (2002) 6508.
[107] R. Noyori, Angew. Chem. Int. Ed. Engl. 41 (2002) 2008.
[108] C.G. Leong, O.M. Akotsi, M.J. Ferguson, S.H. Bergens, J.M. Brown, Chem. Commun. (2003) 750.
[109] K. Xiao, F. Mereiter, W. Spindler, Weissensteiner, Tetrahedron: Asymmetry 12 (2001) 1105.
[110] S. Kobayashi, H. Ishitani, Chem. Rev. (1999) 1069.
[111] R.R. Bader, H.U. Blaser, Stud. Surf. Sci. Catal. 108 (1997) 17.
[112] H.U. Blaser, H.P. Buser, K. Coers, R. Hanreich, H.P. Jalett, E. Jelsch, B. Pugin, H.D. Schneider, F. Spindler, A. Wegmann, Chimia 53 (1999) 275.
[113] H.U. Blaser, H.P. Buser, H.P. Jalett, B. Pugin, F. Spindler, Synlett (1999) 867.
[114] B. Pugin, US 005783715, EP 0729969 A1 (1996) (Novartis).
[115] B. Pugin, H. Landert, F. Spindler, H.U. Blaser, Adv. Synth. Catal. 344 (2002) 974.
[116] B. Pugin, WO 96/32400 (1996) (Novartis).
[117] B. Pugin, WO 97/02232 (1997) (Ciba-Geigy AG).
[118] D. Xiao, X. Zhang, Angew. Chem. Int. Ed. Engl. 40 (2001) 3425.
[119] G. Zassinovich, G. Mestroni, S. Gladiali, Chem. Rev. 92 (1992) 1051.
[120] Y. Jiang, Q. Jiang, G. Zhu, X. Zhang, Tetrahedron Lett. 38 (1997) 215.
[121] M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, Org. Synth. 71 (1993) 1.
[122] P. Barbaro, C. Bianchini, A. Togni, Organometallics 16 (1997) 3004.
[123] P. Barbaro, C. Bianchini, G. Giambastiani, A. Togni, Eur. J. Inorg. Chem. (2003).
[124] P. Barbaro, C. Bianchini, G. Giambastiani, A. Togni, Chem. Commun. (2002) 2672.
[125] (a) L.S. Hegedus, in: M. Schlosser (Ed), Organometallics in Synthesis, Wiley, Chichester, 1994, pp. 385-459 (Chapter 5);
(b) J. Tsuji, Palladium Reagents and Catalysts, Innovation in Organic Synthesis, Wiley, Chichester, 1995;
(c) R.F. Heck, Palladium Reagents in Organic Synthesis, Academic Press, New York, 1985;
(d) J.P. Collman, L.S. Hegedus, J.R. Norton, R.G. Finke, Principles and Applications of Organotransition Metal Chemistry, University Sciences Books, Mill Valley, CA, 1987;
(e) P.J. Harrington in: E.W. Abel, F.G.A. Stone, G. Wilkinson (Eds.), Comprehensive Organometallic Chemistry II, vol. 12, Pergamon, Oxford, UK, 1995, pp. 798–903 (Chapter 8.2);
(f) M. Moreno-Mañas, R. Pleixats, Adv. Het. Chem. 66 (1996) 73;
(g) A. Heumann, M. Réglier, Tetrahedron 51 (1995) 975;
(h) S.A. Godleski, in: I. Fleming, B.M. Trost (Eds), Comprehensive Organic Synthesis, vol. 4, Pergamon, Oxford, UK, 1991, pp. 585–661;
(i) G. Consiglio, M. Waymouth, Chem. Rev. 89 (1989) 257.
[126] J. Tsuji, H. Takahashi, M. Morikawa, Tetrahedron Lett. (1965) 4387.
[127] L.S. Hegedus, Transition Metals in the Synthesis of Complex Molecules, University Science Books, Mill Valley, CA, 1994, pp. 261–305 (Chapter 9).
[128] (a) B.M. Trost, D.L. Van Vranken, Chem. Rev. 96 (1996) 395;
(b) B.M. Trost, Acc. Chem. Res. 29 (1996) 355;
(c) C.G. Frost, J. Howarth, J.M.J. Williams, Tetrahedron: Asymmetry 3 (1992) 1089;
(d) J.M.J. Williams, Synlett (1996) 705.

[129] W. Zhang, T. Shimanuki, T. Kida, Y. Nakatsuji, I. Ikeda, J. Org. Chem. 64 (1999) 6247.

[130] C. Ganter, C. Kaulen, U. Englert, Organometallics 18 (1999) 5444, and references cited herein.

[131] K. Tanaka, S. Qiao, M. Tobisu, M.M.-C. Lo, G.C. Fu, J. Am. Chem. Soc. 122 (2000) 9870, and references cited herein.

[132] M. Ogasawara, K. Yoshida, T. Hayashi, Organometallics 20 (2001) 3913.

[133] U. Nettekoven, M. Widhalm, P.C.J. Kamer, P.W.N. M. van Leeuwen, Tetrahedron: Asymmetry 8 (1997) 3185.

[134] B.F.G. Johnson, S.A. Raynor, D.S. Shephard, T. Mashmeyer, J.M. Thomas, G. Sankar, S. Bromley, R. Oldroyd, L. Gladden, M.D. Mantle, Chem. Commun. (1999) 1167.

[135] R. Kuwano, T. Uemura, M. Saitoh, Y. Ito, Tetrahedron Letters 40 (1999) 1327.

[136] H. Tsuruta, T. Imamoto, Tetrahedron: Asymmetry 10 (1999) 877.

[137] H. Lodberg Pedersen, M. Johannsen, J. Org. Chem. 67 (2002) 7982.

[138] (a) C.H. Frohning, C.W. Kohlpaintner, in: B. Cornils, W. Herrmann (Eds.), Applied Homogeneous Catalysis with Organometallic Compounds, VCH, Weinheim, 1996, p. 29.(b);
F. Ungváry, Coord. Chem. Rev. 228 (2002) 61.

[139] U. Nettekoven, P.C.J. Kamer, M. Widhalm, P.W.N.M. van Leeuwen, Organometallics 19 (2000) 4596.

[140] F.A. Rampf, W.A. Herrmann, J. Organomet. Chem. 601 (2000) 138.

[141] T. Sturm, W. Weissensteiner, K. Mereiter, T. Kégl, G. Jeges, G. Petõlz, L. Kollár, J. Organomet. Chem. 595 (2000) 93.

[142] T.E. Müller, M. Beller, Chem. Rev. 98 (1998) 675.

[143] (a) M.A. Giardello, V.P. Conticello, L. Brard, M.R. Gagné, T.J. Marks, J. Am. Chem. Soc. 116 (1994) 10241;
(b) Y.W. Li, T.J. Marks, Organometallics 15 (1996) 3770;
(c) S. Tian, V.M. Arredondo, C.L. Stern, T.J. Marks, Organometallics 18 (1999) 2568;
(d) M.R. Douglass, M. Ogasawara, S. Hong, M.V. Metz, T.J. Marks, Organometallics 21 (2002) 283, and references within.

[144] (a) L. Ackermann, R.G. Bergman, Org. Lett. 4 (2002) 1475;
(b) J.S. Johnson, R.G. Bergman, J. Am. Chem. Soc. 123 (2001) 2923;
(c) D. Fairfax, M. Stein, T. Livinghouse, M. Jensen, Organometallics 16 (1997) 1523;
(d) Y.K. Kim, T. Livinghouse, J.E. Bercaw, Tetrahedron Lett. 42 (2001) 2933;
(e) E. Haak, I. Bytschkov, S. Doye, Angew. Chem. Int. Ed. Engl. 38 (1999) 3389;
(f) A. Heutling, S. Doye, J. Org. Chem. 67 (2002) 1961, and references within.

[145] R. Dorta, P. Egli, F. Zürcher, A. Togni, J. Am. Chem. Soc. 119 (1997) 10857.

[146] L. Fadini, A. Togni, Chem. Commun. (2003) 30.

[147] R. Kuwano, H. Miyazaki, Y. Ito, Chem. Commun. (1998) 71.

[148] E.A. Colby, T.F. Jamison, J. Org. Chem. 68 (2003) 156.