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Chiral monodentate phosphorus ligands for rhodium-catalyzed asymmetric hydrogenation

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Abstract—This review reports the recent developments in the field of asymmetric hydrogenation in the presence of metal catalysts containing monodentate phosphorus ligands. Besides monophosphines, that have been used at the origin of asymmetric hydrogenation, it mainly includes the use of monophosphites and monophosphoramidites, which when associated to rhodium precursors have recently led to very efficient enantioselective catalytic systems.

Contents

1. Introduction

Since chirality has emerged as a key issue in industrial production, especially in the areas connected to life sciences (pharmaceutical, agrochemical, flavours and fragrance industries,...), the preparation of pure enantiomers has become a major objective for synthetic chemists.[1,2] Enantioselective catalysis is the tool of choice for producing enantiomerically pure or enriched compounds with the help of small amounts of selected chiral metal catalysts. The first successful attempts of homogeneous metal-catalyzed asymmetric transformations involving chiral phosphorus ligands were obtained in the hydrogenation of carbon–carbon double bonds. The coordination of mono- and then diphosphines to transition metal centres has opened up routes to a large number of examples of enantioselective hydrogenations of prochiral substrates containing C=C, C=O and C=N bonds.[3–5] After the introduction of the very efficient bidentate DIOP ligand by Kagan in 1971,[6] this field has mainly been driven by the use of bidentate ligands, especially C_2-symmetrical diphosphines associated to ruthenium, rhodium and iridium metal centres, which make possible the enantioselective hydrogenation of a variety of substrates such as dehydroamino acids, acrylic derivatives, ketones, imines, enamides, enecarbamates, etc... However, after sinking into almost complete oblivion for about thirty years, a revival of monodentate phosphorus ligands took place when easily prepared novel enantiopure ligands with P–O and/or

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P–N bonds revealed excellent properties for the enantioselective hydrogenation of dehydroamino acids, itaconic derivatives and enamides. This report will show the potential in enantioselective hydrogenation of rhodium catalysts bearing chiral monodentate phosphorus ligands including phosphines, phosphonites, phosphinites, phosphoramidites and phosphites.

2. Chiral monodentate phosphine ligands

Monodentate phosphines represent a class of widespread ligands both in stoichiometric coordination chemistry and in catalysis. Chiral monophosphines have found useful applications in asymmetric catalytic reactions including olefin codimerization, allylic substitution, hydrosilylation, hydroacylation and cross-coupling reactions.[7]

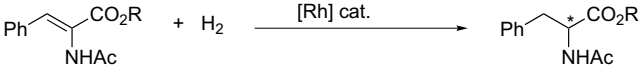
The first results on metal-catalyzed asymmetric hydrogenation were obtained with rhodium complexes bearing monodentate phosphines possessing a chirogenic phosphorus centre. Indeed, in 1968, Knowles and Sabacky[8] reported the hydrogenation of 2-phenylpropenoic acid and itaconic acid in the presence of a rhodium complex bearing two optically active methylphenyl-*n*-propylphosphine **1** ligands with low enantioselectivity (up to 15% enantiomeric excess). The same year, the hydrogenations of the nonfunctionalized olefins, α-ethyl and α-methoxystyrene were performed by Horner et al. with the same catalytic system but also with very low enantioselectivity (<8% ee).[9] An important breakthrough was performed in 1972 by Knowles who used rhodium complexes generated in situ from $[Rh(cod)Cl]_2$ (cod = 1,5-cyclooctadiene) and two equivalents of the monodentate *o*-anisylmethylphenylphosphine **3** (pamp) and *o*-anisylcyclohexylmethylphosphine **4** (camp) ligand for the enantioselective hydrogenation of α-dehydroamino acid derivatives.[10] Optically active *N*-acylamino acids were obtained in high yields and good enantioselectivities (up to 90% ee). A rhodium-camp catalyst was also used with moderate success to perform the hydrogenation of the endocyclic C=C bond of piperitone to produce pulegone in less than 38% ee.[11] The first asymmetric homogeneous hydrogenation of ketones (acetophenone and butan-2-one) was carried out at room temperature under 1 bar of hydrogen in ethanol in the presence of catalytic amounts of [Rh(nbd)(benzylmethylphenylphosphine **2**)$_2$][ClO_4] (nbd = norbornadiene) as catalyst and provided very low enantioselectivities.[12] A few other examples of the hydrogenation of ketones with monophosphine ligands have been reported with the best results being obtained for the enantioselective hydrogenation of methyl acetylacetate (71% ee) with [Rh(nbd)(**4**)$_2$] complexes[13] and for the transformation of a cyclopenta-1,3,4-trione into the corresponding 4-hydroxycyclopent-1,3-dione in methanol under 1 bar of hydrogen in the presence of [Rh(cod)(**3**)$_2$][BF_4].[14]

Rhodium complexes with two coordinated diastereomeric P-chiral phosphine **5** involving a menthyl or neomenthyl group as an additional chiral fragment were used to chemo- and enantioselectively hydrogenate the acrylic double bond of (*E*)-3,7-dimethylocta-2,6-dienoic acid (geranic acid) with 79% ee under mild conditions.[15] It is noteworthy that menthyldiphenylphosphines **6** with no chirality centered on the P atom have also shown interesting results for the rhodium-catalyzed hydrogenation of (*E*)-3-methylcinnamic and 2-methylcinnamic acid leading to enantiomeric excesses of 61% and 52%, respectively.[16]

Diastereomeric P-chiral heterocyclic phosphines such as phosphiranes **7** and **8** and phosphetanes **9** have been coordinated to rhodium and iridium centres to generate [M(cod)(L*)$_2$][PF_6] (L* = **7**–**9**) complexes. The phosphirane-containing rhodium complexes were tested for the hydrogenation of *N*-acetyldehydroamino acids: the *trans*-phosphiranes appeared to induce better enantioselectivities (up to 76% ee) than the *cis*-isomers.[17] Phosphetane **9** appeared to be difficult to coordinate to rhodium, while the iridium complex proved to be able to hydrogenate *N*-acetyldehydrophenylalanine methyl ester but with low enantioselectivity.[18]

C_2-Symmetrical chiral monophosphines, where the phosphorus atom is included in a four, five, six and seven-membered ring, have been investigated in the asymmetric hydrogenation of α-acetamidocinnamic acid derivatives under typical conditions (Table 1, ligands **10**–**14**).

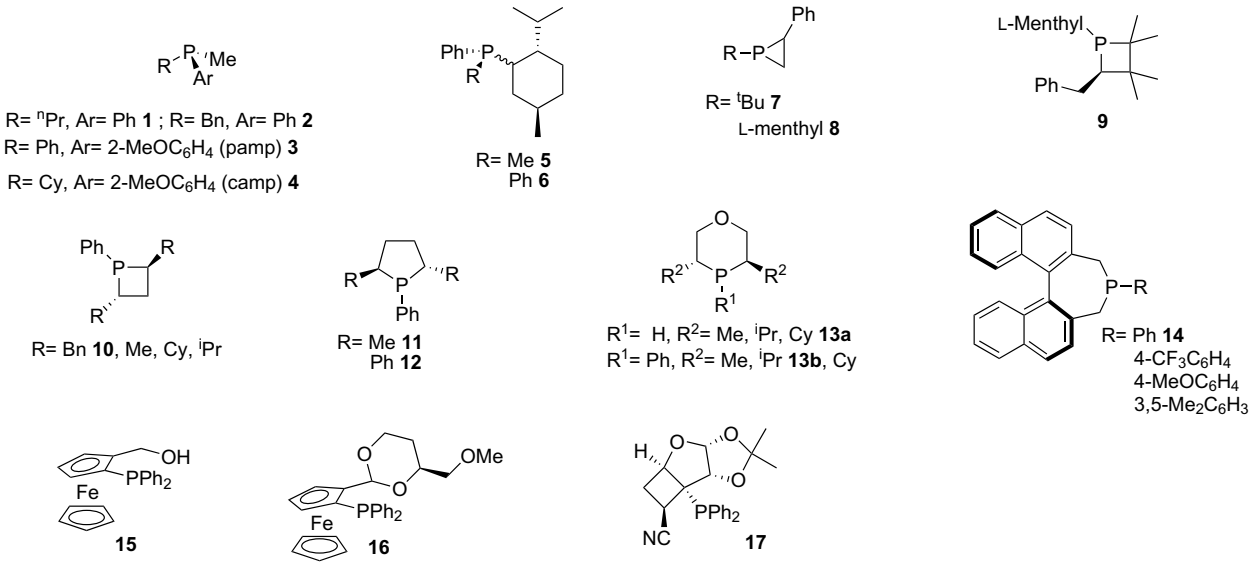
Table 1. Enantioselective hydrogenation of (*Z*)-PhCH=C(NHAc)(CO_2R) in the presence of rhodium catalysts containing monophosphine ligands



[Rh] cat.: chiral Rh catalyst containing monophosphine ligands

Ligand	R	Ee (%)	Ref.
10	H	86	19
11	Me	60	20
12	Me	93	21
13a	H	90	22
13b	H	46.5	22
14	Me	90	23
16	H	87	25

The enantiomeric excesses obtained with P-phenyl phosphetane ligands associated to rhodium strongly depend on the nature of the R group (13–86%), with the best ee being obtained with ligand **10**, which bore benzyl groups.[19] The in situ generation of an active catalyst by adding phospholane **12** to $[Rh(cod)_2]BF_4$ in methanol provided an efficient catalyst, which led to phenylalanine methyl ester at 20 °C under a hydrogen atmosphere in 93% ee.[21] This catalytic system also made possible the enantioselective hydrogenation of itaconic acid and dimethyl itaconate in 73% and 55% ee, respectively.[21a] Tertiary and secondary six-membered oxaphosphinanes of type **13** have recently been tested in the hydrogenation of *N*-acetyldehydroamino acids and itaconic



derivatives catalyzed by rhodium(I) complexes.[22] Total conversions were obtained in polar solvents such as methanol and isopropanol at room temperature with enantiomeric excesses up to 90% for the resulting amino acids and 96% for the saturated diacid. A new class of monophosphines, dinaphthophosphepines,[23,24] have led to very good enantioselectivities in the rhodium-catalyzed hydrogenation of α-acetamidocinnamic esters, under the condition that an aromatic group was directly attached to the P(III) atom.[23a,24] The best ligand **14** gave 90% ee when the reaction was performed in toluene at 25 °C under 1 bar of hydrogen pressure in the presence of 1 mol% of rhodium catalyst (Table 1).[23a]

Whereas the ferrocenyl monophosphine **15** gave an active but poorly enantioselective rhodium catalyst, the association of four equivalents of **16** with respect to $[Rh(cod)Cl]_2$ provided a good catalyst, which gave *N*-acetylphenylalanine in 87% enantiomeric excess (Table 1).[25] The functional phosphine **17**, derived from sugar, was used to hydrogenate α-acetamidocinnamic methyl ester (70.6% ee) and the corresponding acid in 91.6% ee.[26]

3. Chiral monodentate phosphoramidite ligands

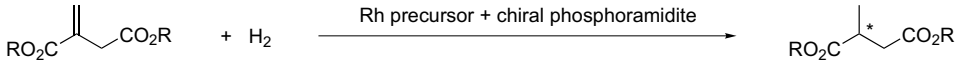
Whereas the search for new ligands concentrated on diphosphine systems, new chiral monodentate ligands (especially phosphoramidites and phosphites) derived from 2-binaphthyl-1,1′-diol (binol) emerged as efficient catalysts for the asymmetric hydrogenation of olefins. In this case, the chirality arose from the atropoisomeric binolate moiety. These ligands possess: (i) chirality close to the phosphorus atom and (ii) a rigid structure imposed by the binaphtyl group. The catalytic species, usually generated from $[Rh(cod)_2][BF_4]$ and two equivalents of the enantiomerically pure ligand are efficient hydrogenation catalysts and provide good enantioface differentiation during hydrogenation of prochiral carbon–carbon double bonds. In 2000, Feringa reported the hydrogenation of dehydroaminoacids and itaconic acid catalyzed by rhodium(I) complexes bearing the monophosphoramidite ligand MonoPHOS **20** and showed that this ligand exhibited faster reaction and better enantioselectivity than the corresponding bidentate ligand where the (binolate-P) ends are connected by an *N*,*N*′-dimethylethylene-1,2-diamino group.[27] Conversions were completed at room temperature under 1 bar of hydrogen in 20 h with enantioselectivities reaching 99% ee. The best enantiomeric excesses were obtained in nonprotic solvents such as dichloromethane and ethyl acetate (93–95% ee for the enantioselective hydrogenation of methyl 2-acetamidocinnamate at room temperature under 1 bar of hydrogen), whereas protic solvents, such as methanol, led to the hydrogenated products with a maximum enantiomeric excess of 75% ee under similar catalytic conditions. Further studies by different groups were then orientated towards the discovery of more efficient catalytic systems involving monophosphoramidite ligands. Three classes of compounds were used as test compounds: itaconic acids and esters, *N*-acylated dehydroamino acid derivatives and enamides. Selected examples in each of these families illustrate the performances of the rhodium-catalyzed catalytic systems (Tables 2–4).

Substitution on the binaphthyl moiety in **21** and **22** did not improve the enantioselectivities of the reactions but decreased the reaction rates, especially in the case of **22**, which required a long induction period.[28a]

An improvement in efficiency of these types of ligands via substitution of the dimethylamino group were attempted. Indeed, ligand **23** bearing a diethylamino group led to highly effective rhodium catalysts in the hydrogenation of *N*-acetyldehydroamino esters (up to 99.9 ee) and enamides (up to 99.6% ee).[29]

Other phosphoramidite ligands such as **27** and **28** derived from substituted anilines were also tested, combined with 0.5 equiv of $[Rh(cod)_2]BF_4$ precursor,

Table 2. Selected examples of rhodium-catalyzed hydrogenation of itaconic derivatives $RO_2CC(=CH_2)(CH_2CO_2R)$ in the presence of phosphoramidite ligands

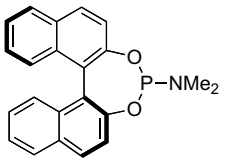


Ligand	R	Solvent	S/C	H_2 (bar)	Temp. (°C)	Reaction time (h)	Ee (%)	Ref.
20	H	CH_2Cl_2	20	1	25	20	96.6	27
20	Me	CH_2Cl_2	20	1	0	20	94.4	27
20	H	EtOAc	20	1	20	20	97	28a
27	Me	CH_2Cl_2	20	1	rt	20	91	30
28	Me	CH_2Cl_2	20	1	rt	20	76	30
31	H	CH_2Cl_2	20	1	rt		94.7	39
31	Me	CH_2Cl_2	100	1	rt		94	39

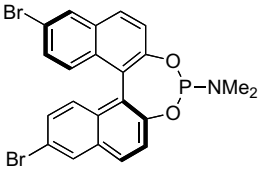
however they generally exhibited poorer enantioselectivities in the asymmetric hydrogenation of α-dehydroamino acids and methyl itaconate.[30] An enantiomeric excess of 91% obtained with the ligand **27** in the hydrogenation of methyl itaconate represents the best result obtained with these ligands. The ligands possessing a styrene moiety on the nitrogen atom were included in polymers by radical copolymerization. Hydrogenations of methyl acetamidocinnamate performed with the resulting supported rhodium(I) complexes gave encouraging results since conversions were completed in 4 h with enantiomeric excesses reaching 80%. Grafting the ligands made possible their recycling with no important changes of conversion and enantioselectivity being observed after 4 runs.

The best system for the hydrogenation of itaconic acid and methyl itaconate were based on MonoPHOS **20**, which made possible the preparation of the acid with 97% ee and the ester with 94.4% ee, but a relatively large amount of catalyst (5 mol%) and long reaction times were required (Table 2).

On the other hand, phosphoramide **26** exhibited a poor reactivity for the hydrogenation of methyl itaconate (5% conversion after 12 h at room temperature under 1.3 bar



(*S*)-Monophos **20**



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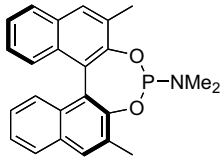

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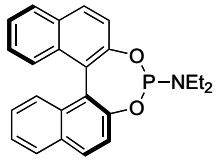

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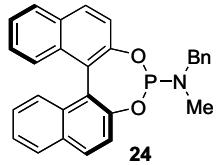

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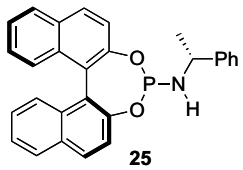

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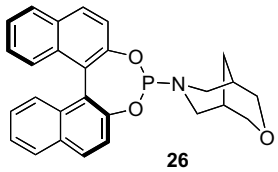

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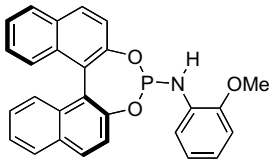

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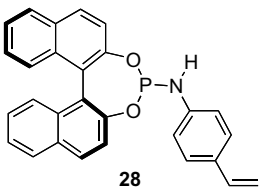

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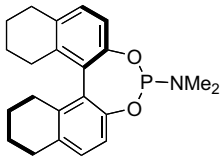
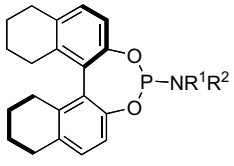
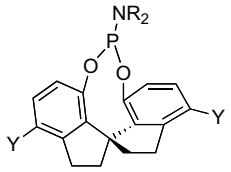


(R)-H_8-Monophos **29**

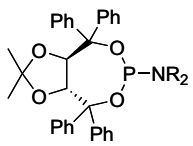


30

$R^1 = R^2 =$ Et
$R^1 =$ (R)CH(Me)Ph, $R^2 = H$
$R^1 =$ (R)CH(Me)Ph, $R^2 =$ Me
R^1-R^2 = -$(CH_2)_4$-

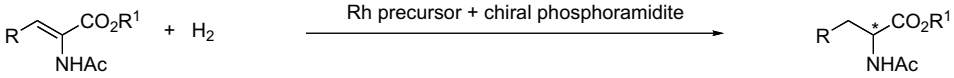


Y= H, R= Me **31**
Y= H, R= Et, ^{i}Pr
R= Me, Y= Br, Ph, MeO



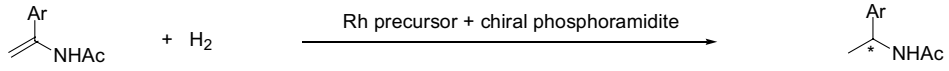
R= Bn, ^{i}Pr **32**

Table 3. Selected examples of rhodium-catalyzed hydrogenation of *N*-acetyldehydroamino acid derivatives (RCH=C(NHAc)(CO_2R^1) in the presence of phosphoramidite ligands



Ligand	R	R^1	Solvent	S/C	H_2 (bar)	Temp. (°C)	Reaction time	Ee (%)	Ref.
20	H	Me	CH_2Cl_2	20	1	25	20 h	99	27
20	Ph	Me	EtOAc	20	1	0	20 h	98.4	27
20	Ph	Me	EtOAc	20	1	25	20 h	93.2	27
20	H	H	EtOAc	20	1	25	20 h	98.7	27
20	Ph	H	EtOAc	20	1	25	20 h	97.1	27
21	Ph	Me	CH_2Cl_2	100	5	rt	28 min	94	28a
22	Ph	Me	CH_2Cl_2	100	5	rt	2 h	89	28a
23	Ph	Me	THF	100	20	rt	4 h	98	29
23	4-F–C_6H_4	Me	THF	100	20	rt	4 h	99.8	29
27	Ph	Me	CH_2Cl_2	20	1	rt	20 h	82	30
28	H	H	CH_2Cl_2	20	1	rt	20 h	73	30
28	Ph	H	CH_2Cl_2	20	1	rt	20 h	84	30
29	Ph	Me	CH_2Cl_2	100	20	rt	30 min	94.4	36
29	Ph	Me	^{i}PrOH	100	20	0	12.5 h	97	37
29	$PhCH_2$	Et	THF	100	20	rt	30 min	96.6	37
29	H	Me	Acetone	100	20	rt	30 min	99.9	37
29	4-NO_2–C_6H_4	Me	CH_2Cl_2	100	20	rt	5 h	96	37
29	4-MeO–C_6H_4	Me	Acetone	100	20	rt	30 min	94.4	37
31	Ph	Me	CH_2Cl_2	100	1	0	24 h	97.8	39
31	4-MeO–C_6H_4	Me	CH_2Cl_2	100	1	0	24 h	95.6	39
31	4-NO_2–C_6H_4	Me	CH_2Cl_2	100	1	0	24 h	99.1	39

Table 4. Selected examples of rhodium-catalyzed hydrogenation of enacetamides [ArC(=CH_2)(NHAc)] in the presence of phosphoramidite ligands



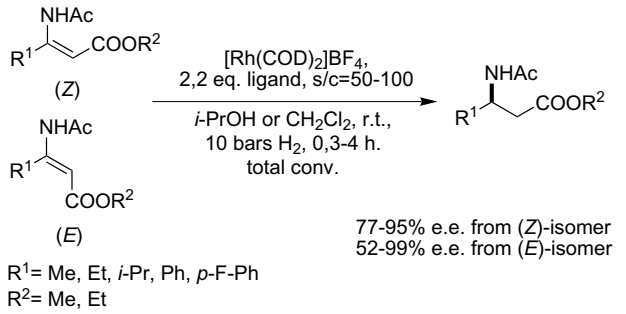
Ligand	Ar	Solvent	S/C	H_2 (bar)	Temp. (°C)	Reaction time (h)	Ee (%)	Ref.
20	4-Cl–C_6H_4	CH_2Cl_2	50	15	−5	20	92	28a
20	Ph	CH_2Cl_2	100	20	−20	8	95	32
20	4-CF_3–C_6H_4	CH_2Cl_2	100	20	−20	6	96	32
27	4-MeO–C_6H_4	CH_2Cl_2	100	20	−20	8	90	30
21	4-Cl–C_6H_4	CH_2Cl_2	50	15	rt	3.5	89	28a
23	Ph	THF	100	20	rt	4	95	29
23	4-CF_3–C_6H_4	THF	100	20	5	4	99.6	29
23	4-MeO–C_6H_4	THF	100	20	5	6	98	29
29	Ph	CH_2Cl_2	100	20	0	3	90.4	38
29	Ph	THF	100	20	0	3	91.2	38
29	Ph	THF	100	20	−10	8	96.2	38
29	4-CF_3–C_6H_4	THF	100	20	−10	6	99	38
29	4-MeO–C_6H_4	THF	100	20	−10	8	92	38
31	Ph	Toluene	100	50	0	24	98.0	41
31	4-CF_3–C_6H_4	Toluene	100	50	0	24	98.1	41
31	4-MeO–C_6H_4	Toluene	100	50	0	24	99	41

of hydrogen pressure) even though an enantiomeric excess of 78% was obtained.[31] This ligand could have behaved as a bidentate hemilabile ligand with weak coordination of the oxygen atom.

The hydrogenation of *N*-(1-arylethenyl)acetamides was performed with very high enantioselectivities in the presence of in situ generated [Rh(cod)(MonoPHOS)$_2$][BF_4] as the catalyst precursor.[28,29,32] Dichloromethane and tetrahydrofuran were the solvents of choice for this reaction (Table 4). As a general rule, the presence of an electron-withdrawing group at the *para*-position of the phenyl ring enhanced the enantioselectivity.[29,32]

The extension to the hydrogenation of nonfunctionalized cyclic enamides has allowed fast conversions in dichloromethane and enantiomeric excesses up to 84% to be reached at −20 °C.[32]

The first hydrogenation of β-aminoacrylates catalyzed by cationic rhodium complexes generated in situ from [Rh(cod)$_2$]BF_4 and two equivalents of MonoPHOS **20** or ligands **24** and **25** was described by Feringa in 2002.[33]



The (*E*)- and (*Z*)-β-acylaminoacrylate isomers showed different behaviours during their asymmetric hydrogenation. Indeed, with the (*Z*)-isomer, the best enantioselectivities (77–95% ee) were obtained in isopropanol under 10 bars of hydrogen in the presence of 1 mol % of precatalyst, with substrates bearing an aliphatic R^1 group.[33,34] Conversions were total after 16 h and in some cases after 20 min. The same reaction conditions allowed 92–94% ee to be reached during the hydrogenation of β-amino β-aryl acrylates, which is one of the best ee's obtained with rhodium complexes. The use of an aprotic solvent, such as ethyl acetate, decreased the enantioselectivity down to 3% ee. With the (*E*)-isomer, total conversions and better enantiomeric excesses (83–99% ee) were obtained in dichloromethane, whatever the ligand used. Hydrogenations performed in isopropanol gave lower conversions (49–52%) and enantiomeric excesses (52–64%). The ligand with a methyl and a benzyl substituent on the nitrogen atom **24** seemed to be the best alternative for the hydrogenation of these (*E*)-substrates since the enantiomeric excesses varied from 98% ee to 99% ee under 10 bars of hydrogen.

Partial hydrogenation of the binaphthyl moiety constituted another way to modify the chiral backbone of these monophosphoramidite ligands. Indeed, H_8-MonoPHOS was quantitatively obtained from enantiomerically pure binol, after reduction of one aromatic ring of the naphthyl groups in the presence of platinum oxide under 3 bars of hydrogen and reaction with HMPA in refluxing toluene.[35]

With ligand **29**, which is in fact a biphenol derivative, associated with the rhodium(I) precursor, good conversions and excellent enantiomeric excesses (up to 99%+ ee) were reached during the hydrogenation of enamides in tetrahedrofuran[38] and α-dehydroaminoacids, whatever the nature of the solvent (Table 2).[36,37]

In 2002, new phosphoramidite ligands possessing a spirophosphine skeleton, SiPHOS **31**, were tested in asymmetric hydrogenation.[39] The ligands have a C_2-symmetry with a stereogenic centre, which is the common carbon of the two indanyl groups. These ligands are air-stable. The rate of hydrogenation of arylenamides is low but excellent enantiomeric excesses (up to 99% ee) were obtained during the hydrogenation of nonfunctionalized enamides (Table 4). The best ees were reached in nonprotic solvents such as toluene, dichloromethane or ethyl acetate.[40,41] The same catalytic system also gave very good selectivities in the hydrogenation of dehydroamino acids and itaconic derivatives since conversions were completed in 20 h with 1 mol % of catalyst in dichloromethane under 1 bar of hydrogen. High enantiomeric excesses up to 99% ee (Table 3) and 94% ee (Table 2), were obtained, respectively.

When the chiral backbone consists of an aliphatic C_2-symmetrical skeleton derived from tartaric acid, such as **32**, the enantiomeric excesses reported for the hydrogenation of dehydroamino esters are modest (<37% ee).[28a]

The most general features, which emerge from these studies on monophosphoramidite in asymmetric hydrogenation with Rh-monophosphoramidite catalysts are the following:

- the preferred solvents are nonprotic solvents even though ^{i}PrOH can be used with specific substrates[33]
- high hydrogen pressure accelerates the reaction but has little effect on the enantioselectivity
- lower temperatures enhance the enantioselectivity but also decrease the reaction rates
- these ligands compete with diphosphine ligands in terms of enantioselectivity.

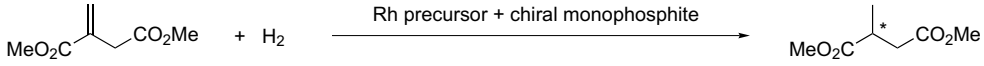
In addition, the prevailing advantages of these ligands are their stability and ease of preparation. This can be exemplified by the quantitative preparation of MonoPHOS **20** from chiral Binol and HMPA in refluxing toluene in 1 h.

4. Chiral monodentate phosphite ligands

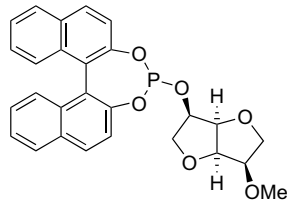
During the same period, Reetz developed new cationic rhodium complexes bearing chiral monophosphite ligands (*R*)-**33** and (*S*)-**33** including a binaphthyl (*R*)- or (*S*)-moiety and a chiral group derived from 1,4:3,6-dianhydro-D-mannite, for the successful asymmetric hydrogenation of dehydroaminoacids and dimethyl itaconate (Table 5).[42] A variety of (Binol)P-OR ligands **34**–**39**, where R is a chiral or achiral group, were then tested for the hydrogenation of dimethyl itaconate (Table 5).[42–44] Enantiomeric excesses varied from 90% to 94% ee in dichloromethane under a low pressure of hydrogen. The best enantiomeric excesses were obtained with the monophosphite ligand **37** bearing the chiral 1-phenylethyl moiety (up to 99%+ ee).[42,43] Variation of the alkoxy group of the phosphite ligand has allowed the optimization of the reaction conditions and reach total conversions in 20 h with enantiomeric excesses up to 96% ee during the hydrogenation of α-arylenamides at 30 °C with 0.2 mol % of catalyst under 60 bars of hydrogen in dichloromethane.[45]

Then, with the binaphtholate core always attached to the phosphorus atom, other types of chiral groups derived from terpenes **40**[46,47] or sugar derivatives **41**–**43**[48–50] were condensed to the phosphorus centre to

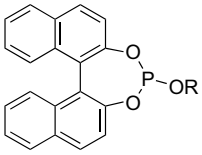
Table 5. Selected examples of rhodium-catalyzed hydrogenation of dimethyl itaconate ($MeO_2CC(=CH_2)(CH_2CO_2Me)$) in the presence of monophosphite ligands in CH_2Cl_2



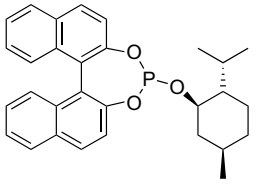
Ligand	S/C	H_2 (bar)	Temp. (°C)	Reaction time	Ee (%)	Ref.
(*S*)-**33**	1000	1.3	rt	20 h	97.8	42
(*R*)-**33**	1000	1.3	rt	20 h	95.2	42
34	1000	1.3	20	20 h	89.2	42
35	1000	1.3	20	20 h	97.6	42
35	1000	20	23	20 min	96.3	44
36	1000	1.3	20	20 h	96.6	42
(*S*,*S*)-**37**	1000	1.3	20	20 h	98.2	42
(*S*,*R*)-**37**	200	1.1	20	12 h	99.6	43
(*S*,*R*)-**37**	1000	20	23	15 min	97.6	44
(*S*,*S*)-**39**	200	1.1	20	12 h	93.9	43
(*S*,*L*)-**40**	2000	10	rt	12 h	95.2	46
(*R*,*L*)-**40**	2000	10	rt	12 h	90.5	46
43	100	10	20	12 h	98.5	49
47	400	1.5	0	2 h	99.0	53
50	1000	1	23	2 h	98.7	44
50	40000	20	23	20 min	96.9	44



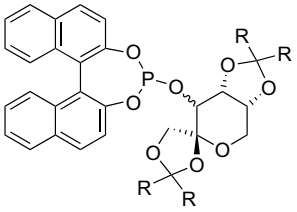
(*S*)-33 and **(*R*)-33**



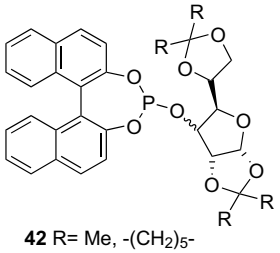
34 R= Me ; **35** R= ^{i}Pr
36 R= Ph ; **37** R= CH(Me)Ph
38 R= $CH_2{}^{t}Bu$; **39** R= $CHPh(CH_2OMe)$



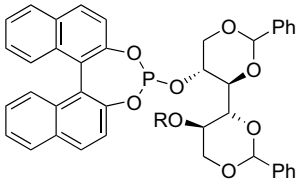
(*R*,*L*)-40
and **(*S*,*L*)-40**



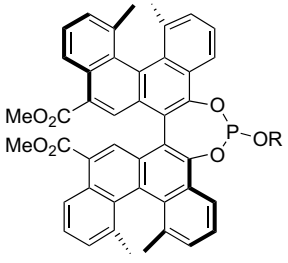
41 R= Me, $-(CH_2)_5-$



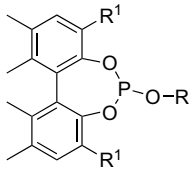
42 R= Me, $-(CH_2)_5-$



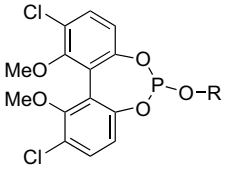
43 R= alkyl, Bn, $CHPh_2$,
1-CH_2Naphthyl



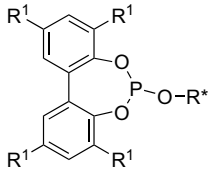
44 R= menthyl, 1-phenethyl



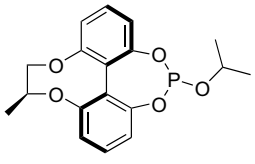
45 R^1= H , R= Ph, 2-naphthyl, menthyl
46 R^1= ^{t}Bu, R= Ph, 2-naphthyl, menthyl



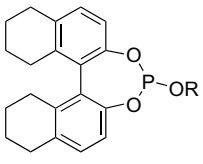
R= ^{i}Pr, C_6H_{11},
(*R*)-CH(Me)Ph **47**,
Ph, 2,6-$Me_2C_6H_3$



48 R^1=H , R*= (*L*)-menthyl,
49 R^1= ^{t}Bu, R*=(*L*)- menthyl



50



R= ^{i}Pr **51**, CH(Me)Ph

generate active monophosphite–rhodium catalysts. Thus, Xiao reported the enantioselective hydrogenation of dimethyl itaconate with high efficiency (Table 5), and dehydroaminoacids with modest enantioselectivities [75% ee with (*S*,*L*)-**40** and 85% ee with (*R*,*L*)-**40**], with 0.05 mol% of precatalyst generated in situ from $[Rh(cod)_2]BF_4$ and two equivalents of chiral monophosphite ligand.[46] We have shown that the hydrogenation of ethyl (*E*)-β-acylaminobut-2-enoate went to completion at 25 °C under 15 bars of hydrogen pressure, with the saturated ethyl β-acylaminobutanoate being obtained in 94% ee.[47] It is noteworthy that these ligands **40** are air stable and can be easily prepared from racemic binaphthol after successive recrystallizations in ether at room temperature and at 0 °C. Rhodium complexes containing the optically active ligands **41**–**43** were also very efficient catalysts as they performed with excellent enantioselectivities complete hydrogenation of dimethyl itaconate,[48,49] *N*-acetyl-α-arylenamides,[48,49] α-dehydroamino esters,[49] in dichloromethane at room temperature under 10 bars of hydrogen pressure with a substrate/catalyst ratio of 100, and also hydrogenated enol esters ($R^1CO_2CHR{=}CH_2$) with high enantioselectivity.[50] Ligands **44**, which were prepared from bihelicenol, menthol (or 1-phenylethanol), also provided catalysts for the hydrogenation of dimethyl itaconate.[51] Under 90 bars, conversions were total in the range of −78 to 20 °C, with enantiomeric excesses reaching 96%. This catalytic system is very pressure sensitive, with only 37% ee obtained under 40 bars of hydrogen. In these ligands, matched and mismatched pairs were observed between the helical and axial chiralities.

New monophosphite ligands **45**–**51** with an atropoisomeric biphenyl skeleton have recently been developed for rhodium-catalyzed asymmetric hydrogenation. Total conversions of dimethyl itaconate and good enantioselectivities were obtained in dichloromethane or 1,2-dichloroethane under 6.3 bars of hydrogen with ligands **45**–**46**.[52] Whereas $[Rh(cod)_2]BF_4$, used as the source of rhodium led to low to modest conversions and enantioselectivities, the use of in situ generated precatalysts synthesized from $[Rh(cod)_2]SbF_6$ allowed total conversions to be reached whatever the ligands with much higher enantiomeric excesses (up to 99%).[52] Other phosphite ligands based on the 5,5′-dichloro-6,6′-dimethoxy-1,1′-biphenyl-2,2′-diyl structure of type **47** have shown their potential to perform the enantioselective hydrogenation of dimethyl itaconate and α-dehydroamino acid derivatives.[53]

The incorporation of bulky groups upon reaction of achiral biphenylchlorophosphites with an enantiomerically pure alcohol derived from terpenes, such as menthol, borneol or fenchol, has led to rhodium catalysts containing two diastereomeric forms of the ligands **48** and **49**.[54]

These species are active for the hydrogenation of dimethyl itaconate in dichloromethane at −15 to 20 °C under 10 bars of hydrogen, but the enantioselectivities do not exceed 75% ee. Following the concept of chirality induced by an atropoisomeric biphenyl structure, monophosphite **50** featuring a chiral diphenyl framework was used to hydrogenate the itaconic acid and α-dehydroamino acids. Under 3 bars of hydrogen in dichloromethane, conversions went to completion in 24 hours in the presence of 2% of rhodium catalyst, with 96% ee and 93% ee, respectively.[55]

Monophosphites ligands **51** bearing a H_8-Binol moiety have been shown to be very efficient for the asymmetric hydrogenation of dimethyl itaconate in dichloromethane catalyzed by 0.1 mol% of cationic rhodium(I) complexes prepared from $[Rh(cod)_2]BF_4$ and two equivalents of monodentate ligands under 20 bars of hydrogen.[44] These catalysts are very efficient since conversions were completed at room temperature within a short reaction time (5–180 min) and excellent enantiomeric excesses (up to 98% ee). This catalytic system was still active with a substrate/catalyst ratio of 40.000. Under these conditions, 95% conversion and 97% ee were reached after 20 min.

Very recently, rhodium complexes bearing monoacylphosphite or pyrophosphite ligands, which also contain three P–O bonds, have been used to catalyze the hydrogenation of the usual model compounds.[56] They introduced new steric and electronic effects while monoacylphosphites have made possible the enantioselective hydrogenation of dimethyl itaconate in 80% ee.[56a]

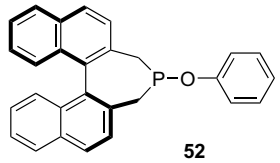
From these studies on monophosphite–rhodium catalysts in asymmetric hydrogenation, the following points seem to be general:

- the preferred solvent is dichloromethane
- high hydrogen pressure accelerates the reaction but has little effect on enantioselectivity
- lower temperatures enhance the enantioselectivity but also decrease the reaction rates
- the absolute configuration of the hydrogenated compound is usually imposed by the absolute configuration of the Binol structure,[44–47] except when the third alkoxy group is bulky and contains several stereogenic centres as is the case in sugar derivatives.[48,50] This rule cannot be applied to phosphite ligands containing the atropoisomeric biphenol framework.[52]
- In most cases, matched and mismatched pairs, including the catalyst, for example, the monodentate ligands and the substrate are formed, which has a drastic influence on the efficiency and enantioselectivity of the hydrogenation reactions.

5. Chiral monodentate phosphonite and phosphinite ligands

Monodentate phosphinites have not been used extensively as ligands for asymmetric hydrogenation. The few examples, which have been reported on the asymmetric hydrogenation of α-dehydroamino acids catalyzed by rhodium complexes bearing the chiral monophosphinite ligands **52**,[24] **53** and **54**[57] generated from $[Rh(cod)_2]SbF_6$ or $[RhCl(cod)]_2$ have shown poor enantioselectivi-

ties.[24,57] On the other hand, an excellent result has been obtained for the hydrogenation of dimethyl itaconate in the presence of the $[RhCl(cod)]_2$-**54** catalyst.[57] Much better results were reached in the hydrogenation of α-dehydroamino esters with the aminophosphinites of type **55** as enantioselectivities up to 96% were obtained in toluene at room temperature under 1 bar of hydrogen.[58]



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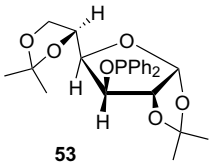
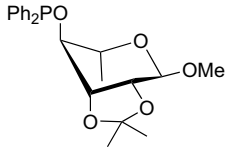
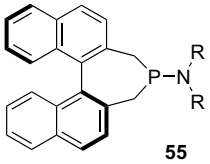


53

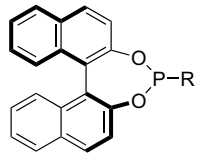


54



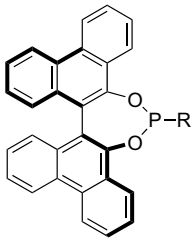
55

R= Me, Et, ^{i}Pr
R-R = -$(CH_2)_3$-, -$(CH_2)_5$-, -$(CH)_4$-



R= Me, Et, ^{t}Bu, Ph

56



R= Me, ^{t}Bu, Ph **57**

The hydrogenation of dehydroamino acid derivatives catalyzed by a rhodium(I) precursor bearing monodentate **56** or **57** or bidentate phosphonite ligands, prepared from enantiomerically pure binol derivatives have also been tested.[59,60] With 0.2 mol% of catalyst, complete hydrogenations were achieved within 3 h in the case of methyl acetamidoacrylate and in 20 h for methyl acetamidocinnamate; the enantiomeric excesses reached 92% and 80% ee, respectively. Moreover, it was shown that the catalytic systems involving monodentate ligands **56** and **57** were more selective than the systems with bidentate analogues.[59] Asymmetric hydrogenations of dimethyl itaconate and α-dehydroaminoacids were also performed within 20 h in dichloromethane at room temperature under 1.3 bar H_2 with 0.1% of rhodium(I) catalyst bearing the monophosphonite ligands **56** with enantiomeric excesses reaching 90% ee and 94% ee, respectively.[60]

6. Combinatorial asymmetric hydrogenation

From all these results, it clearly appears that monodentate phosphorus ligands associated to the rhodium at least, represent an excellent alternative to bidentate ligands in asymmetric hydrogenation. It is also now acknowledged that two monodentate ligands can coordinate to the rhodium centre to generate an active catalytic species able to induce enantioface differentiation. A large number of coordination complexes is thus expected from the variety of monophosphorus ligands that can be imagined and prepared. Thus, the high throughput techniques are the tools of choice for investigating new efficient catalytic systems, explaining the appearance of combinatorial catalysis in this field. Indeed, until recently, most of the catalysts used for asymmetric hydrogenation were prepared from a single ligand (homocombination). A new strategy based on the combination of two different ligands at the metal centre (heterocombination) has been recently developed.

The asymmetric hydrogenation of dimethyl itaconate catalyzed by rhodium(I) complexes bearing two different chiral monophosphite ligands has been reported with a substrate/catalyst ratio of 200 under 10 bars of hydrogen in dichloromethane.[54] Good conversions were attained within 0.5 h at room temperature. However the enantiomeric excesses did not improve when compared to homocombinations and they remained modest (27–58% ee).

The first examples, which clearly showed that selected heterocombinations of chiral P-ligands provided more reactive and enantioselective catalytic systems were reported by Reetz et al.[61] This new concept was applied to the combination of chiral monodentate phosphinite and/or phosphite ligands. Higher enantiomeric excesses (up to 98% ee) were obtained with heterocombinations rather than with homocombinations (up to 94% ee) of monodentate ligands during the hydrogenation of α-acetamidoacrylates catalyzed by rhodium(I) complexes.[61,62] The catalysts were generated in situ from $[Rh(cod)_2]BF_4$ and one equivalent of each ligand. The best enantiomeric excesses (up to 98% ee) were attained with heterocombinations of monophosphonite and monophosphite or with mixtures of monophosphite ligands. Catalytic systems based on heterocombinations of phosphonite ligands were also efficient for the asymmetric hydrogenation of nonfunctionalized enamides (97.4% ee) and dimethyl itaconate (96.4% ee).[61] Enantioselective hydrogenations of α-dehydroamino acids with heterocombinations of chiral and achiral monodentate ligands were also attempted.[63] Good conversions and enantioselectivities could be attained while these systems also offered the possibility to reverse enantioselectivity. Similarly, it was clearly demonstrated that some selected heterocombinations of phosphoramidite ligands were much more active and selective than their homocombinations during the rhodium-catalyzed hydrogenation of (*Z*)-β-(acylamino)-acrylates.[64]

7. Conclusion

The results presented in this review show a significant and unexpected development of rhodium(I) precursors bearing monodentate phosphorus ligands for asymmetric hydrogenation of prochiral olefins. Not only monophosphines, but also P–O and P–N bond containing

compounds, which exhibit excellent performances in terms of reactivity and enantioselectivity, have contributed to this rapid development. The excellent results obtained with monodentate ligands should provide the incentive for the search of efficient ligands based on new principles to reach the highest enantioselectivities.[65] Moreover, the stability of these ligands and their straightforward syntheses in enantiomerically pure form provide easy fine tuning of their catalytic properties. Finally, their monodentate coordination allows the development of new strategies in combinatorial asymmetric catalysis, which was impossible with bidentate ligands.

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