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Asymmetric Hydroformylation Using Rhodium

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Abstract Asymmetric hydroformylation is a powerful catalytic reaction that produces chiral aldehydes from inexpensive feedstock (alkenes, *syngas*) in a single step. The elucidation of the different steps of the catalytic cycle and the characterization of the resting state, together with the discovery of several types of ligands, have made possible that nowadays a variety of chiral products incorporating a formyl unit can be enantioselectively prepared by Rh-catalyzed asymmetric hydroformylation, and that this process is now considered as a useful tool in organic synthesis.

Keywords Aldehydes • Asymmetric • Chiral ligands • Enantioselectivity • Hydroformylation • Phosphorus • Regioselectivity • Rhodium

Contents

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1 Introduction

The hydroformylation of alkenes, which was originally discovered by Otto Roelen in 1938 [1–3], is nowadays one of the most important industrial applications of homogeneous catalysis (Scheme 1) [4–14]. Today, over 9 million tons of so-called oxo-products are produced per year, a number which is still rising. The majority of these oxo-products are obtained from the hydroformylation of propene **1**, which is a fraction of the steam-cracking process. The resulting products *iso*-butyraldehyde **2** and *n*-butanal **3** are important intermediates for the production of esters, acrylates, and 2-ethylhexanol [4, 5].

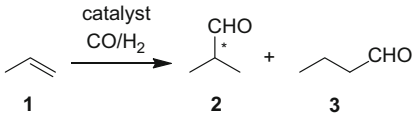
From a synthetic point of view, the reaction is a one-carbon chain elongation caused by the addition of carbon monoxide and hydrogen across the π system of a C=C double bond [15, 16]. As a pure addition reaction, the hydroformylation reaction meets all requirements of an atom-economic process [17]. Furthermore, the synthetically valuable aldehyde function is introduced, which allows subsequent skeleton expansion that may even be achieved in one-pot sequential transformations [18, 19].

In 1968, Wilkinson discovered that phosphine-modified rhodium complexes display a significantly higher activity and selectivity compared to the first generation of cobalt catalysts [20–22]. Since that time, ligand modification of the rhodium catalyst has been the method of choice in order to influence the catalyst activity and selectivity [23].

In the asymmetric hydroformylation of alkenes, the first examples of high level of enantioselectivity (*ee*'s up to 90%) were achieved by Stille and Consiglio using chiral Pt-diphosphine systems [24, 25]. However, these catalysts suffered several disadvantages such as low reaction rates, tendency to hydrogenate the substrates, and low regioselectivity to the branched products. Later, these issues were mainly overcome by the use of Rh-based catalysts [26, 27].

In the low-pressure hydroformylation of internal alkenes, the chemoselectivity (and simultaneously regioselectivity) is one of the remaining problems to be solved in industry. This issue originates from the exponential drop of alkene reactivity when

Scheme 1 Hydroformylation of propene

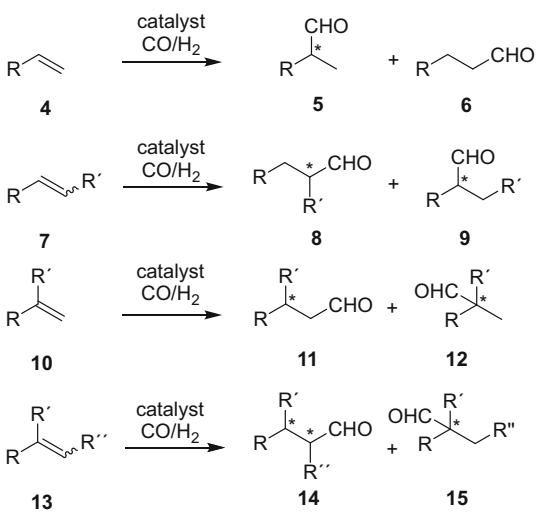


increasing the number of alkene substituents. The known hydroformylation catalysts for internal alkene hydroformylation operating under low-pressure conditions rely on the use of strong π-acceptor ligands, such as bulky phosphites and phosphobenzene systems [28–30]. However, the high activity of the corresponding rhodium catalysts is usually associated with a high tendency towards alkene isomerization, which renders a position-selective hydroformylation of an internal alkene extremely challenging, although over the last years, some examples started to appear in the literature.

The regioselectivity of the hydroformylation of alkenes is function of many factors and quantum chemical calculations have been frequently used to gain useful insights into its origin [31–50]. These include inherent substrate preferences, directing effects exerted by functional groups as part of the substrate, as well as catalyst effects. In order to appreciate substrate inherent regioselectivity trends, alkenes have to be classified according to the number and nature of their substituents (Scheme 2) [15, 16].

The regioselectivity issue usually only arises for terminal and 1,2-disubstituted alkenes **7**. For alkyl-substituted terminal alkenes **4** there is a slight preference for the linear product **6**. For terminal alkenes **4** containing an electron-withdrawing substituent, the formation of the branched product **5** is favored and is sometimes exclusive. This tendency is more or less unaffected by the catalyst structure. Both 1,1-disubstituted **10** and trisubstituted **13** alkenes generally provide only one regioisomer (**11** and **14**, respectively) based on Keuleman's rule, which states that the formyl group is usually added in order to avoid the formation of a quaternary carbon center [51].

Asymmetric hydroformylation is a very promising catalytic reaction that produces chiral aldehydes from inexpensive feedstock (alkenes, *syngas*) in a single step under essentially neutral reaction conditions. Even though asymmetric hydroformylation offers great potential for the fine chemical industry, this reaction has not yet been utilized on an industrial scale due to several technical challenges [4, 5]. Among the most

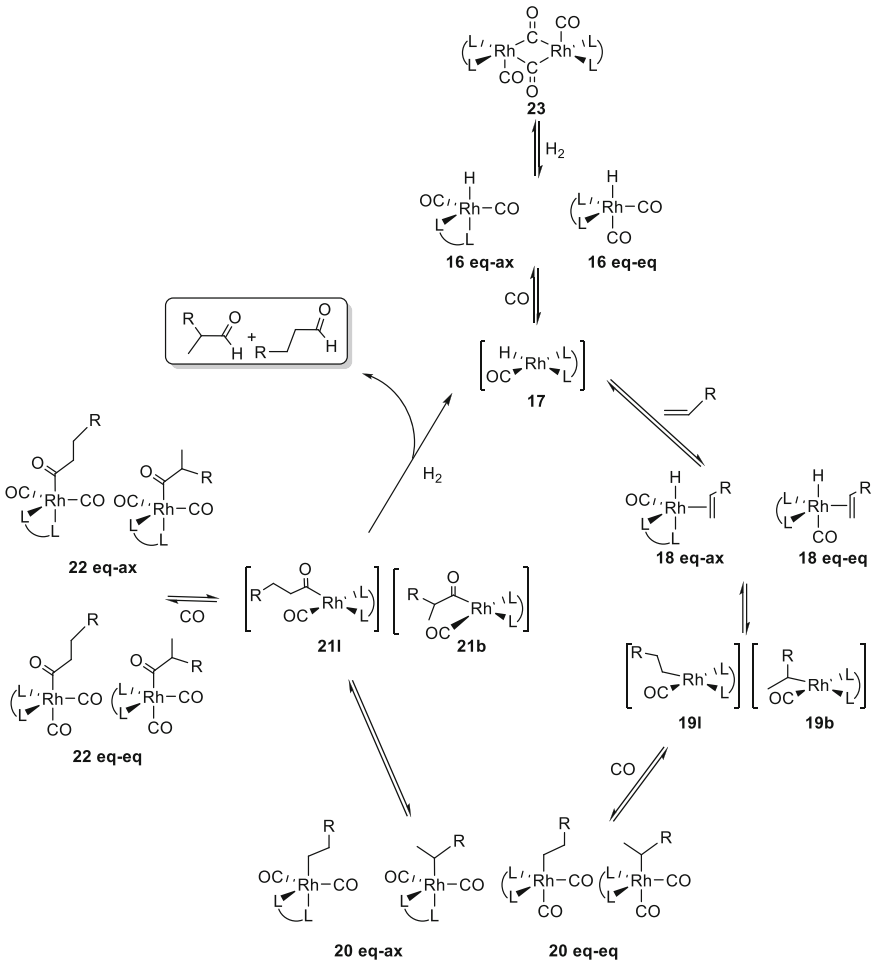


Scheme 2 Regioselective trends on hydroformylation of different alkenes

significant issues are (a) the low reaction rates at low temperature where good selectivities are usually observed, (b) the difficulty to control simultaneously the regio- and the enantioselectivity, and (c) the limited substrate scope for any single ligand.

2 Rh-Catalyzed Hydroformylation Mechanism

In Scheme 3, the well-known mechanism of the Rh-catalyzed hydroformylation mechanism proposed by Heck is described for bidentate ligands [52]. It corresponds to Wilkinson's so-called dissociative mechanism [20–22]. The associative mechanism



Scheme 3 Mechanism of the Rh-catalyzed asymmetric hydroformylation in the presence of bidentate ligand (L–L)

involving 20-electron intermediates for ligand/substrate exchange will not be considered. In this process, a great understanding of the mechanism has been possible due to the observation and structural characterization of the resting state of the catalyst by in situ spectroscopic techniques (HP-IR, HP-NMR) [23, 53]. For bidentate ligands (L–L), the common starting complex is the [RhH(L–L)$(CO)_2$] species **16**, containing the ligand coordinated in equatorial positions (denoted eq–eq throughout the scheme) or in an apical-equatorial positions (complexes denoted eq–ax).

Dissociation of equatorial CO from **16** leads to the square-planar intermediate **17**, which associates with alkene to give complexes **18**, where the ligand can again be coordinated in two isomeric forms eq–ax and eq–eq, having a hydride in an apical position and alkene coordinated in the equatorial plane. On the basis of experimental results and theoretical calculations, it has been proposed that the regioselectivity is determined by the coordination of the alkene to the square-planar intermediate **17** to give the pentacoordinate intermediates **18** [35]. This step is also crucial in determining the enantioselectivity since the enantioface discrimination occurs between **17** and **19**, and particularly from **17** to **18**. The CO dissociation from **16** was shown to be much faster than the overall hydroformylation process, indicating that the rate of the reaction is dominated by the reaction of **17** with either CO or the alkene to form **16** or **18** [39]. It has not been established experimentally whether alkene complexation is reversible or not; although in the Scheme 3, all steps are described as reversible except the final hydrogenolysis. Experiments using deuterated substrates suggest that alkene coordination and insertion into the Rh–H bond can be reversible, certainly when the pressures are low. Complexes **18** undergo migratory insertion to give the square-planar alkyl complex **19**. This species can undergo β-hydride elimination, thus leading to isomerization or can react with CO to form the trigonal bipyramidal (TBP) complexes **20**. Thus, under low pressure of CO more isomerization may be expected. At low temperatures ($<70°C$) and a sufficiently high pressure of CO (>10 bar) the insertion reaction is usually irreversible and thus the regioselectivity and the enantioselectivity in the hydroformylation of alkenes is determined at this point. Complexes **20** undergo the second migratory insertion (see Scheme 3) to form the acyl complex **21**, which can react with CO to give the saturated acyl intermediates **22** or with H_2 to give the aldehyde product and the unsaturated intermediate **17**. The reaction with H_2 involves presumably oxidative addition and reductive elimination, but for rhodium no trivalent intermediates have been observed [54]. At low hydrogen pressures and high rhodium concentrations, the formation of dirhodium dormant species such as **23** becomes significant [55].

Recently, the full catalytic cycle for mono- and bis-ligated monophosphine Rh complexes has been investigated using DFT calculations [56].

As mentioned above, the catalytic hydroformylation of alkenes is one of the largest applications of homogeneous transition metal catalysis today. Due to the robustness of the process and the wide availability of alkene substrates, enantioselective hydroformylation provides high possibilities to obtain a great variety of enantiomerically pure aldehydes. The first Rh-based systems that were reported in the asymmetric hydroformylation contained diphosphine ligands provided low to moderate enantioselectivities [26, 27]. With this type of ligand, the highest *ee* value was reported using styrene as substrate and bdpp (bis-diphenylphosphino pentane) as ligand

(*ee*'s up to 64%) [57]. Later, higher enantioselectivities were achieved using more sophisticated diphosphite and phosphine–phosphite ligands [6–16, 23]. The most successful ligands developed for this reaction were recently reviewed [58].

In the following sections, the most relevant results reported in the asymmetric Rh-catalyzed hydroformylation of alkenes are described. The reactions are classified by degree of substitution of the substrates in order to highlight the issue of the substrate/ligand compatibility in this process. For each family of substrates, the most successful ligands are described.

3 Rh-Catalyzed Asymmetric Hydroformylation of Monosubstituted Alkenes

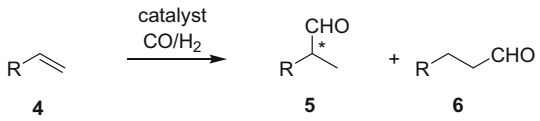
The hydroformylation of monosubstituted alkenes (Scheme 4) was extensively studied due to the interest in the synthesis of linear aldehydes (non-chiral) or the enantioselective synthesis of 2-substituted branched aldehydes using chiral hydroformylation catalysts [4–16].

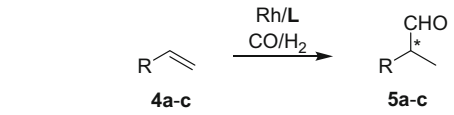
For example, the hydroformylation of vinylarenes (R=aryl) is used as a model for the synthesis of 2-aryl propionaldehydes, which are intermediates in the synthesis of 2-aryl propionic acids, the profen class of non-stereoidal drugs. Nowadays, the application of the Rh-catalyzed asymmetric hydroformylation to obtain enantiomerically pure chiral aldehydes is growing. The Rh-catalyzed asymmetric hydroformylation of several other monosubstituted alkenes was successfully carried out, such as allyl cyanide and vinyl acetate [6–16]. In general, 1,3-diphosphite and phosphine–phosphite ligands provided the best results in these processes [23]. However, the use of bisphosphacyclic ligands has recently emerged as an efficient alternative [6–16].

3.1 1,3-Diphosphite Ligands

The use of disphosphite ligands was intensively studied in this process as they provide high levels of selectivity with these substrates [59]. The initial success in the rhodium-catalyzed asymmetric hydroformylation of vinylarenes came from Union Carbide with the discovery of the diphosphite ligand (2*R*, 4*R*)-pentane-2,4-diol **24** (Scheme 5) [60, 61].

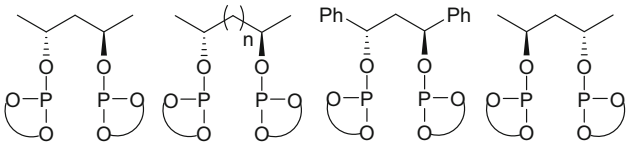
Scheme 4 Asymmetric hydroformylation of monosubstituted alkenes





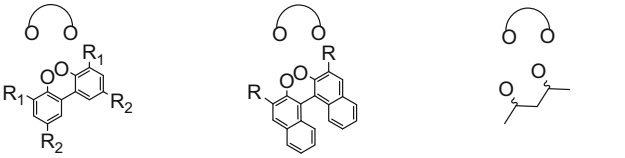
4a-c **5a-c**

Alkene	Rh/**L**	Product	Regio (%)	*ee* (%)
4a R= Ph	**24a,d**	**5a** R= Ph	99	90
4b R= CH_2CN	**24a**	**5b** R= CH_2CN	87	13
4c R= OAc	**24a**	**5c** R= OAc	99	58



(2*R*, 4*R*)-**24** (2*R*, 3*R*)- n =0 **25** (2*R*, 4*R*)- **27** (2*S*, 4*S*)- **28**

(2*R*, 5*R*)- n =2 **26**



biphenyl

a R_1= *t*Bu; R_2= OMe

b R_1= R_2 = *t*Bu

c R_1= R_2 = H

d R_1= $Si(alkyl)_3$; R_2= H

binaphthyl

e (*R*/*S*)ax; R = $Si(alkyl)_3$

f (*R*)ax ; R = $Si(alkyl)_3$

g (*S*)ax ; R = $Si(alkyl)_3$

pentane-2,4-diol

h (2*R*, 4*R*)

i (2*S*, 4*S*)

Scheme 5 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes **4a–c** using ligands **24–28**

Good chemo-, regio-, and enantioselectivities (*ee* up to 90%) were obtained with (2*R*, 4*R*)-pentane-2,4-diol diphosphite derivatives (**24a**,**d**) but only when the reaction was performed around room temperature. Other research groups synthesized the series of diphosphite ligands **25–28** in order to study the effect of structural modifications on the Rh-catalyzed asymmetric hydroformylation of vinylarenes (Scheme 5) [62–66].

The influence of the bite angle of these ligands was studied with diphosphite ligands (2*R*, 4*R*)-pentane-2,4-diol **24**, (2*R*, 3*R*)-butane-2,4-diol **25,** and (2*R*, 5*R*)-hexane-2,4-diol **26** [63]. In general, the ligand **24**, which contains a three carbon atoms bridge, provided higher enantioselectivities than ligands **25** and **26**, which have a two and four carbon atoms bridge, respectively.

The effect of different phosphite moieties was studied with ligands **24a–g** [62–64]. In general, sterically hindered phosphite moieties are necessary to achieve high enantioselectivities. The results indicated that varying the *ortho* and *para* substituents on the biphenyl and binaphthyl moieties has also a great effect on

the asymmetric induction. The highest enantioselectivity (*ee* up to 90% at 20 bar of syngas and 25°C) in the Rh-catalyzed asymmetric hydroformylation of styrene was obtained by using ligands **24a** and **24d**.

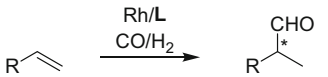
The influence of the backbone was studied comparing the results obtained with the ligands **24** and **27** [62–64]. Surprisingly, the ligand **27**, which contains a more sterically hindered phenyl group, provided lower enantioselectivity than ligand **24**.

A cooperative effect between the different chiral centers of the phosphite ligands **24f–i** and **28f–i** was demonstrated. Initially, van Leeuwen and co-workers studied the cooperative effect between the chiral ligand bridge and the axially chiral binaphthyl phosphite moieties by comparing ligands **24f**,**g** and **28f**,**g**. The hydroformylation results indicated a suitable combination for ligand **24g** (*ee*'s up to 86%) [62–64]. Later, Bakos and co-workers found a similar matched–mismatched effect between the chiral ligand bridge and the chiral phosphite moiety of the ligands **24h**,**i** and **28h**,**i** [65]. Interestingly, the hydroformylation results obtained with ligands **24a** and **24d**, that are conformationally flexible and contain axially chiral biphenyl moieties, are similar to those obtained with ligand **24g**. This indicated that diphosphite ligands containing these biphenyl moieties predominantly exist as a single atropisomer in the hydridorhodium complexes [$RhH(CO)_2$(diphosphite)] when bulky substituents are present in *ortho* positions [62–64]. It is therefore not necessary to use expensive conformationally rigid binaphthyl moieties.

To investigate whether a relationship exists between the solution structures of the [$RhH(CO)_2$(diphosphite)] species and catalytic performance, van Leeuwen and co-workers extensively studied the [$RhH(CO)_2$(diphosphite)] (diphosphite = **24**, **28**) species formed under hydroformylation conditions by high pressure NMR techniques (HP-NMR) [16, 23]. From these trigonal bipyramidal (TBP) complexes, two isomeric structures are possible: one containing the diphosphite coordinated in a bis-equatorial (eq–eq) fashion and one containing the diphosphite in an equatorial-axial (eq–ax) fashion (Scheme 3). The results indicated that the stability and catalytic performance of the [$RhH(CO)_2$(diphosphite)] (diphosphite = **24**, **28**) species strongly depend on the configuration of the pentane-2,4-diol ligand backbone and on the chiral biaryl phosphite moieties. Thus, ligands **24a**, **24d,** and **24g**, which form well-defined stable bis-equatorial (eq–eq) complexes, lead to good enantiomeric excesses. In contrast, the ligands **24i** and **28g**, which form mixtures of complexes, lead to low enantioselectivities [62–64, 67]. The ligand **24a** was also evaluated in the Rh-catalyzed asymmetric hydroformylation of allyl cyanide **4b** and vinyl acetate **4c** but low to moderate enantioselectivities (13 and 58%, respectively) were obtained with these substrates [6].

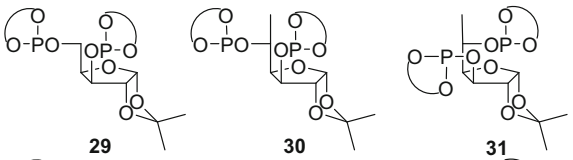
1,3-Diphosphite ligands derived from 1,2-*O*-isopropyliden-*α*-D-xylofuranose (**29**, **32**) and 6-deoxy-1,2-*O*-isopropyliden-*α*-D-glucofuranose (**30**, **31**, **33**, **34**) were successfully applied in the Rh-catalyzed asymmetric hydroformylation of vinylarenes (Scheme 6) [68–71].

The use of diphosphite ligands **30a**,**d** and **34a**,**d** in the Rh-catalyzed asymmetric hydroformylation of styrene provided the *S*- and *R*-enantiomers of the product with high enantioselectivies (*ee* up to 93%) and excellent regioselectivity (Scheme 6) [70, 71]. The ligand **30a** was also tested in the hydroformylation of vinyl acetate obtaining excellent regioselectivity (99%) with an enantioselectivity of 73% [72].

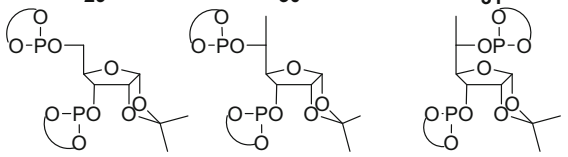


4a,**c** **5a**,**c**

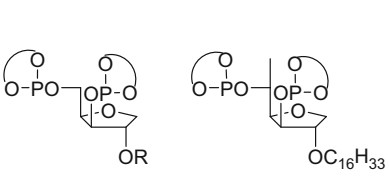
Alkene	Rh/**L**	Product	Regio (%)	*ee* (%)
4a R= Ph	**30a,d**	**5a** R= Ph	99	93
4c R= OAc	**30a**	**5c** R= OAc	99	73



29 **30** **31**



32 **33** **34**

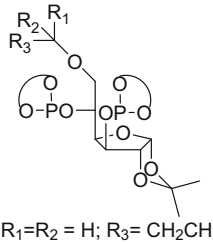


35 R= C_4H_9

36 R= $C_{14}H_{29}$

37 R= $C_{16}H_{33}$

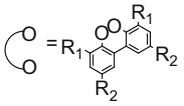
38



39 R_1=R_2 = H; R_3= $CH_2CH_2CH_3$

40 R_1=R_2 = CH_3; R_3= H

41 R_1=R_2 = CH_3; R_3= $CH_2CH_2CH_3$



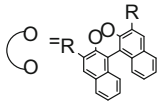
biphenyl

a R_1= *t*Bu; R_2= OMe

b R_1= R_2 = *t*Bu

c R_1= R_2 = H

d R_1= Si(alkyl)$_3$; R_2= H



binaphthyl

e (R/S)ax; R = Si(alkyl)$_3$

f (R)ax ; R = Si(alkyl)$_3$

g (S)ax ; R = Si(alkyl)$_3$

Scheme 6 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligands **29**–**41**

Recently, related C1-symmetry diphosphite ligands conformationally more flexible (**35**–**38**) or incorporating an increase in steric hindrance at the C-6 position (**39**–**41**) were synthesized (Scheme 6) [72, 73]. These ligands were probed in the hydroformylation of styrene **4a** and vinyl acetate **4c** with good regio- and enantioselectivity (up to 81% and 68%, respectively), but these selectivities resulted to be lower than with the ligand **30**. Therefore, the bicycle structure and the methyl substituent at C-5 position seem required to achieve high enantioselectivity in the hydroformylation of styrene and vinyl acetate when using 1,3-diphosphites derived from carbohydrates.

In summary, the results obtained in the Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes indicate that: (a) the absolute configuration of the product is governed by the configuration at the stereogenic center C-3; (b) the level of enantioselectivity is influenced by the presence of stereocenters at C-3 and C-5 positions, where the phosphorus atoms are attached; (c) bulky substituents in *ortho* positions of the biaryl phosphite moieties are necessary to achieve high levels of enantioselectivity; (d) pseudo-enantiomer ligands such as **30** and **34** afford the same level of enantioselectivity for both product enantiomers.

Interestingly, the ligands **30** and **34**, for which only [$RhH(CO)_2(L)$] species with eq–eq coordination were observed by HP-NMR techniques, provided higher enantioselectivity (*ee* up to 93%) than the related ligands **31** and **33** (*ee* up to 64%), for which an equilibrium between the isomeric eq–eq and eq–ax [$RhH(CO)_2(L)$] species was observed by HP-NMR and HP-IR techniques. Therefore, the presence of a single coordination isomer, in this case with ligand coordinated in an equatorial–equatorial (eq–eq) mode, was observed to produce high levels of enantioselectivity in the Rh-catalyzed asymmetric hydroformylation of styrene, as previously mentioned [70–73].

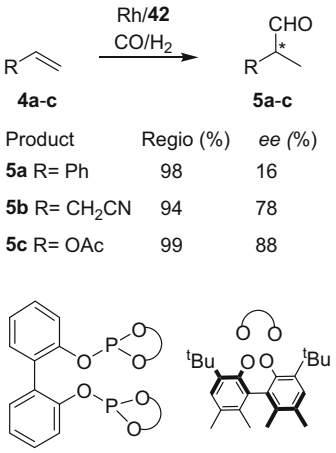
In contrast with the diphosphites previously mentioned, the KELLIPHITE ligand (**42**), which was developed by Dow Chemical Company, incorporates the chirality in the bisphenol unit, while the backbone is achiral (Scheme 7). The catalytic system containing this ligand afforded very good enantioselectivity in the rhodium-catalyzed hydroformylation of vinyl acetate and allyl cyanide, although low selectivities were obtained in the hydroformylation of styrene [74, 75].

Recently, Vidal-Ferran and co-workers reported the use of polyether binders as regulation agents (RAs) to enhance the enantioselectivity of rhodium-catalyzed transformations (Scheme 8) [76, 77]. Using rhodium complexes bearing α,ω-bisphosphite-polyether ligands, the enantiomeric excess was increased by up to 82% in the asymmetric hydroformylation of vinyl benzoate (96% ee), This ligand design enabled the regulation of enantioselectivity by generation of an array of catalysts that simultaneously preserve the advantages of a privileged structure and offer geometrically close catalytic sites.

3.2 Phosphine–Phosphite Ligands

The discovery of the (*R*,*S*)-BINAPHOS (**44**) and (*S*,*R*)-BINAPHOS (**45**) ligands in 1993 by Takaya and Nozaki produced a real breakthrough in the Rh-catalyzed asymmetric hydroformylation reaction (Scheme 9) [78].

Scheme 7 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligand KELLIPHITE (**42**)

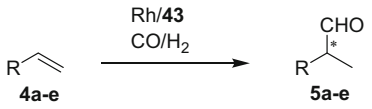


These ligands allowed for the first time an increase in the scope of this process since they provided high enantioselectivity in the Rh-catalyzed asymmetric hydroformylation of several classes of monosubstituted alkenes such as vinyl arenes, 1-heteroatom-functionalized alkenes, and disubstituted 1,3-dienes (Scheme 9), and is still currently a reference in this area [79–90]. Excellent regio- and enantioselectivity were achieved with most of these substrates, although the formation of the branched product (21%) was disfavored when but-1-ene was the substrate. In 2003, De Vries and co-workers reported the first Rh-catalyzed asymmetric hydroformylation of allylcyanide and although moderate regioselectivity was obtained (72%), the highest enantioselectivity (66%) by far was achieved using the ligand **44** [91]. As a general rule, the presence of electron-withdrawing substituents such as phenyl or heteroatoms in the alkene substrate leads to control the regioselectivity in favor of the branched product, independently of the ligand used [6].

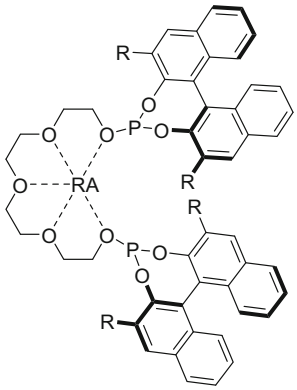
It is noteworthy that (*R*,*S*)-BINAPHOS (**44**) or the (*S*,*R*)-BINAPHOS (**45**) ligands yield the two enantiomers of the product with high enantioselectivity; [92, 93] however, the (*R*,*R*)- and (*S*,*S*)-BINAPHOS, diastereoisomers of ligands **44** and **45**, yielded much lower enantioselectivity in this process, thus demonstrating the importance of the combination of opposite configurations at the phosphine and phosphite moieties.

In contrast with the previously mentioned diphosphite ligands which coordinate to the Rh center in an eq–eq fashion, the BINAPHOS ligand was found to coordinate to Rh in an eq–ax mode as a single isomer in the resting state [$RhH(CO)_2$(L-L)] of the process [92, 93]. Recently, DFT calculations on this system demonstrated that the coordination of the ligand with the phosphite moiety in apical position is crucial for the stereoselectivity of this reaction and that the presence of a second chiral center plays a role in determining the *R* or *S* configuration of the aldehyde product [94]. They also showed that for styrene, in the stereoselectivity determining

Scheme 8
Supramolecularly regulated bisphosphite ligands with a distal regulation site reported by Vidal and co-workers



Product	Regio %	ee %
5a R = OAc	>99	99
5b R = $EtCO_2$	>99	99
5c R = $PhCO_2$	>99	96
5d R = Ph	80	5
5e R = CH_2OSiMe_3	18	25

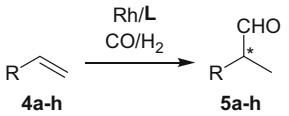


43 RA = RbBArF

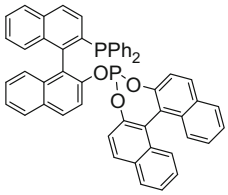
transition state, the key substrate–ligand interactions occur between the styrene and the phosphite moiety and that these interactions are repulsive in nature.

The second generation of BINAPHOS-type ligands (Scheme 10) was developed by the introduction of 3-methoxy substituents on the aryl phosphine units **46** [80, 81], and by replacement of the phosphite group by a phosphoramidite function, yielding the YANPHOS ligand (**47**) (Scheme 10) [95]. The Rh/**46** increased the regio- and enantioselectivity in the asymmetric hydroformylation of styrene, vinylfurans and thiophenes (Scheme 10). Recently, the use of (*S*,*R*)-Bn-YANPHOS was reported in the asymmetric hydroformylation of vinyl-heteroarenes such as pyrroles and provided excellent regio- and enantioselectivities (up to 96%) [96].

YANPHOS (**47**) (Scheme 10) provided higher enantioselectivity than the BINAPHOS ligand **44** without altering the regioselectivity in the Rh-catalyzed asymmetric hydroformylation of styrene and vinyl acetate (*ee* up to 99 and 98%, respectively). Additionally, the ligand **47** provided higher enantioselectivity than KELLIPHITE



Product	5a	5b	5c	5d	5e	5f	5g	5h
R	Ph	CH_2CN	OAc	C_6F_5	CF_3	Et	Phth	S(4-tolyl)
Regio (%)	90	72	86	96	95	21	89	96
ee (%)	94	66	92	98	93	83	85	74



(*R,S*)-BINAPHOS (**44**)
(*S,R*)-BINAPHOS (**45**)

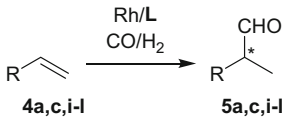
Scheme 9 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using (*R*,*S*)- and (*S*,*R*)-BINAPHOS (**44**) and (**45**)

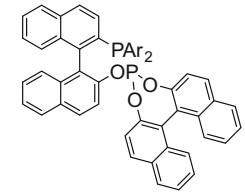
(**42**) (Scheme 7), although a slight decrease in regioselectivity (80 vs 94%) was observed in the hydroformylation of allyl cyanide (ee up to 96 vs 78%) [97].

Recently, the efficiency of YANPHOS ligand **47** was again demonstrated in the Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes with *N*-allylamides, *N*-allylphthalamides, and *N*-allylsulfonamides substituents with excellent ee's (up to 96%), good regioselectivies (up to 84%), and a turnover number (TON) up to 9,700 [98].

DFT calculations on a series of chiral Rh catalysts proposed an explanation for the high enantioinduction observed for Rh–CHIRAPHITE, –BINAPINE, –diazaphospholane, and YANPHOS systems [99]. For BINAPINE and YANPHOS ligands, the main contribution to the selectivity was assigned to the naphthyl groups, while for CHIRAPHITE and diazaphospholane ligands, the ^{t}Bu and chiral amine groups were highlighted as the key enantioinducting moieties. Importantly, in all cases, the effective placement of these groups to interact with the substrate is achieved through the coordination of phosphane moieties in the apical site of the complex.

Inspired by the excellent results obtained using **44** and **45**, several new phosphine–phosphite ligands with different backbones were developed over the last years but the catalytic results using these ligands provided lower enantioselectivity (from 20 to 85%) than those previously achieved with the original BINAPHOS ligand [100–105]. Some of these ligands help to elucidate the correlation between the ee and the electronic withdrawing properties of the substituent on the alkene [106].

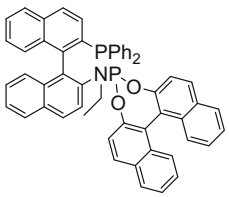




46 Ar = 3-MeOC$_6$H$_4$

Rh/**46**

	Regio(%)	ee(%)
5a R= Ph	95	97
5i R= 2-vinylfuran		79
5j R= 3-vinylfuran		99
5k R= 2-vinylthiophene		93
5l R= 3-vinylthiophene		91



(R,S)-YANPHOS (**47**)

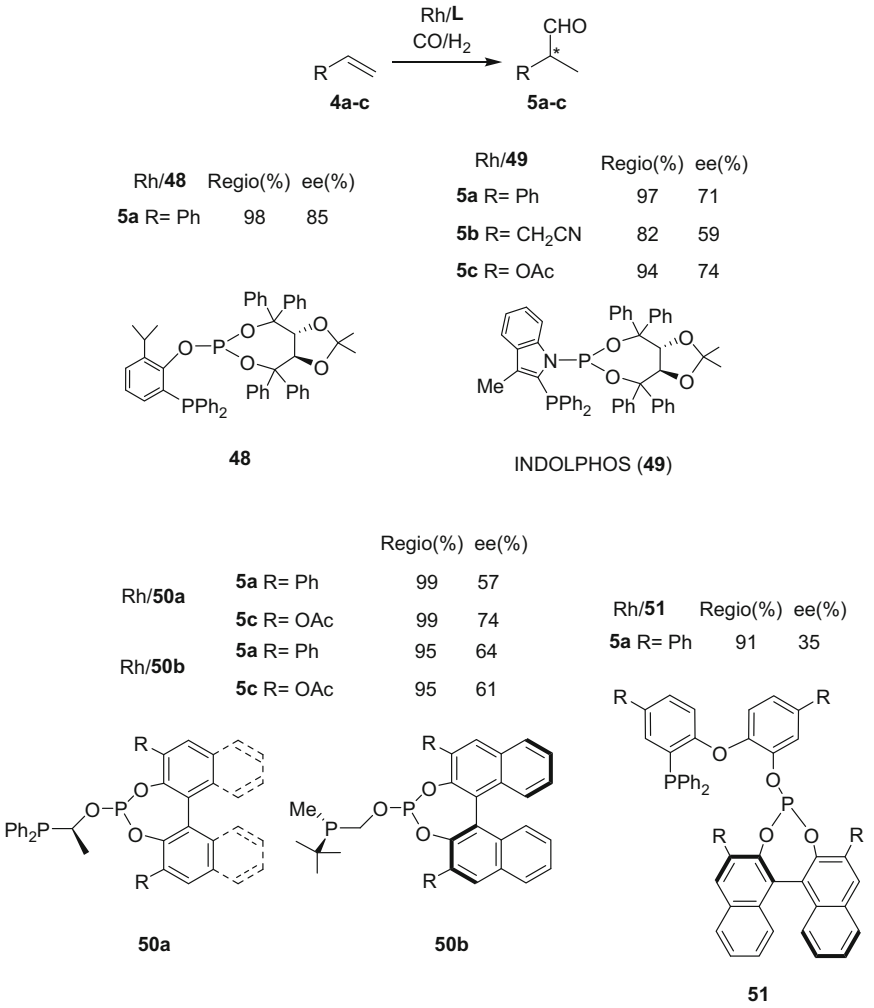
Rh/**47**

	Regio(%)	ee(%)
5a R= Ph	89	99
5b R= CH_2CN	80	96
5c R= OAc	93	98
5m R= CH_2NHBOC	66	94
5n R= CH_2NBz	78	95
5o R= $CH_2NHPhthaloyl$	84	96
5p R= CH_2NHSO_2(p-MeOPh)	71	96

Scheme 10 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using the ligands **46** and **47**

A new family of phosphine–phosphite and phosphine–phosphoramidite ligands was constituted using a Taddol-based backbone in the phosphite or phosphoramidite moiety, respectively (ligands **48** and **49**, Scheme 11) [107, 108]. These ligands were applied in the Rh-catalyzed asymmetric hydroformylation of styrene, allyl cyanide, and vinyl acetate with excellent regioselectivities (up to 98%) and good ee's (up to 85%). Recently, the group of Vidal-Ferran reported the use of two families of small bite angle phosphine–phosphite ligands **50a** and **50b** in the hydroformylation of styrene and vinyl acetate, obtaining excellent regioselectivity but with moderate ee's (up to 74%) [109, 110]. Interestingly, the introduction of P-stereogenic center in ligands **50b** slightly increased the ee when styrene was the substrate but resulted in a lower enantioinduction in the case of vinyl acetate. The use of the large bite angle ligands **51** containing a diphenylether backbone only provided moderate ee's (up to 35%) in the Rh-catalyzed hydroformylation of styrene [111]. The synthesis of phosphine–phosphite ligands built on an α-cyclodextin scaffold was also reported recently and provided moderate regioselectivity (ca. 75%) and ee (50%) in the Rh-catalyzed hydroformylation of styrene [112].

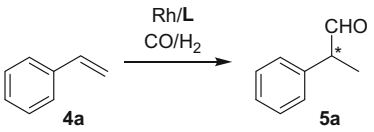
Reek and co-workers reported the use of supramolecular phosphine–phosphoramidite hybrid ligands in the Rh-catalyzed hydroformylation of styrene derivatives (Scheme 12)



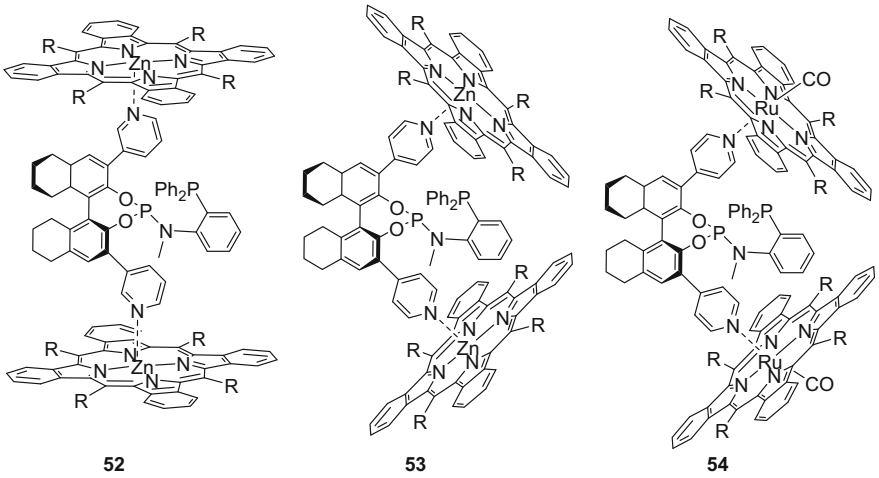
Scheme 11 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using Taddol-based ligands (**48** and **49**) and phosphine–phosphite ligands (**50**) and (**51**)

[113]. They observed that the electronic and steric properties of the M(II) (M = Zn, Ru) templates had a significant influence on the activity and selectivity of the catalytic reaction. Using styrene as substrate, ee's up to 59% were obtained using ligand **54**.

The production of chiral aldehyde from simple terminal alkyl olefins of formula $RCH_2CH{=}CH_2$ with high regio- and enantioselectivity has been aimed for many years and a large set of ligands was probed in this reaction. However, poor regioselectivity was usually obtained, the linear aldehyde is preferably formed in most cases, although interesting ee's were achieved, for instance, using the BINAPHOS



Rh/**L**	Regio (%)	ee(%)
52	94	52
53	99	51
54	92	59



Scheme 12 Asymmetric hydroformylation of styrene using supramolecular phosphine–phosphoramidite ligands

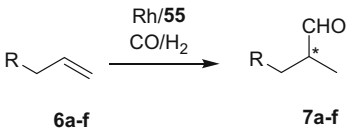
ligand [87]. However, the phosphine–phosphite ligand BOBPHOS (Scheme 13) was recently reported to be efficient in the production of branched aldehydes from alkyl alkenes with high regioselectivity and ee's (Scheme 13) [114].

3.3 Bisphosphacyclic Ligands

Several bisphospholane chiral ligands known as efficient ligands for asymmetric hydrogenation were recently evaluated in asymmetric hydroformylation (Scheme 14) [115].

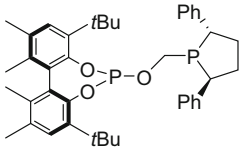
Two ligands, namely (*S*)-BINAPINE (**56**) and (*S*,*S*,*R*,*R*)-TANGPHOS(**57**), were found to give excellent enantioselectivities in the asymmetric hydroformylation of styrene, allyl cyanide, and vinyl acetate (Scheme 14) [98]. It is noteworthy that the enantioselectivities achieved for product **5b** with these ligands are the highest ever

Scheme 13 Rh-catalyzed asymmetric hydroformylation of terminal alkyl alkenes using the BOBPHOS ligand **55**



6a-f **7a-f**

Rh/**55**	regio (%)	ee (%)
7a R= Ph	80	90
7b R= C_6F_5	86	91
7c R= 4-*t*-BuC_6H_4	75	92
7d R= Bn	70	75
7e R= Pr	75	93
7f R= CN	89	71
7g R= CONPh(Me)	82	92

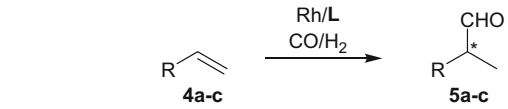


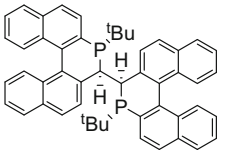
($S_{ax}S,S$)-BOBPHOS (**55**)

reported for the allyl cyanide substrate. Recently, the ligand BIBOP **58** was reported to provide excellent results in the asymmetric hydroformylation of vinyl acetate and allylic substrates [116].

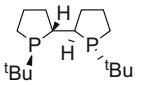
The discovery of the biphospholane scaffold as a new privileged structure for asymmetric alkene hydroformylation has triggered new research efforts for novel and improved bisphospholane-type ligands. In this context, the (*R*,*R*)-Ph-BPE ligand (**59**) (Scheme 14), derivative of DuPhos, was identified as an outstanding ligand for asymmetric hydroformylation since excellent regio- and enantioselectivities were achieved for styrene, allyl cyanide, and vinyl acetate as substrates with this ligand [117]. Several spacers between the two phosphorus donor atoms were evaluated and the two carbon bridge of **59** provided the highest selectivity for all three substrates [118]. Recently, both enantiomers of ligand were also utilized in the Rh-catalyzed asymmetric hydroformylation of vinylarenes using formaldehyde as a substitute of syngas providing excellent regioselectivity and enantioselectivity (up to 95%) [119]. This ligand also provided excellent results in the branched selective asymmetric hydroformylation of a wide range of 1-alkenes, including 1-dodecene, with regioselectivity up to 93% and enantioselectivity up to 96% [120].

A series of bis-2,5-diazaphospholane ligands was also probed in this process and the ESPHOS (**60**) proved to be optimal, with the best results being obtained in the hydroformylation of vinyl acetate (*ee* up to 89%) (Scheme 14) [121]. The bis-3,4-diazaphospholane ligand **61a** also provided excellent regio- and enantioselectivity (*ee* up to 96%) in this reaction (Scheme 14) [122]. Immobilization of ligand **61a**

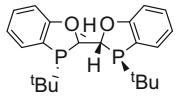




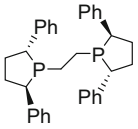
(R,S)-BINAPINE (**56**)



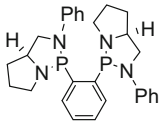
(S,S,R,R)-TANGPHOS (**57**)



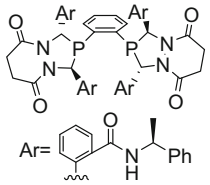
(R)-BIBOP (**58**)



(R,R)-Ph-BPE (**59**)



Esphos (**60**)



Bis-3,4-diazaphospholane (**61a**)

Product	**5a**		**5b**		**5c**	
Rh/**L**	R= Ph		R= CH_2CN		R= OAc	
			Regio (%)	ee(%)		
56	90	94	87	94	97	87
57	93	90	88	93	97	83
58					96	82
59	98	94	88	90	99	82
60					94	89
61a	97	82	83	87	98	96

Scheme 14 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using the diphosphine ligands **56**–**61**

onto resins and silica supports was also recently reported and provided similar performances to those of the homogenous systems with high regio- and enantioselectivity for the Rh-catalyzed hydroformylation of styrene and vinyl acetate [123]. Using these systems, excellent recyclability with only trace levels of Rh leaching was observed in batch and flow reactor conditions. It is noteworthy that silica supported systems provided poorer enantioselectivities that resin-supported catalysts. Recently, a detailed spectroscopic characterization of catalytic Rh intermediates bearing ligand **61a** was reported for the hydroformylation of octene, vinyl acetate, allyl cyanide, and 1-phenyl-1,3-butadiene [124].

This catalytic system was recently used for the continuous flow asymmetric hydroformylation of 2-vinyl-6-methoxynaphthalene during 8h of reaction using a

reactor consisting of 20 vertical bubble pipe-in-series connected by small tubing jumpers [125, 126].

Two derivatives of the ligand **61a** were also used in the synthesis of the Prelog–Djerassi Lactone via an asymmetric hydroformylation/crotylation tandem sequence in which the hydroformylation step provided 93% ee (Scheme 15).

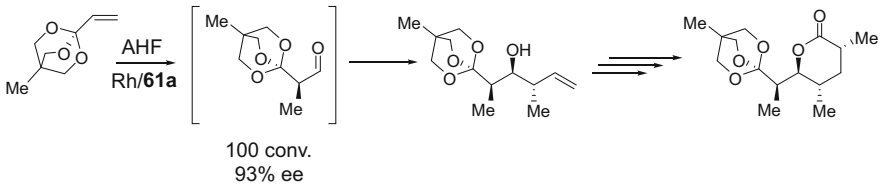
The sequential asymmetric hydroformylation/aerobic aldehyde oxidation was recently reported using the same ligand, providing an access to α-chiral carboxylic acids without racemization [127].

3.4 Bis-Phosphonite Ligands

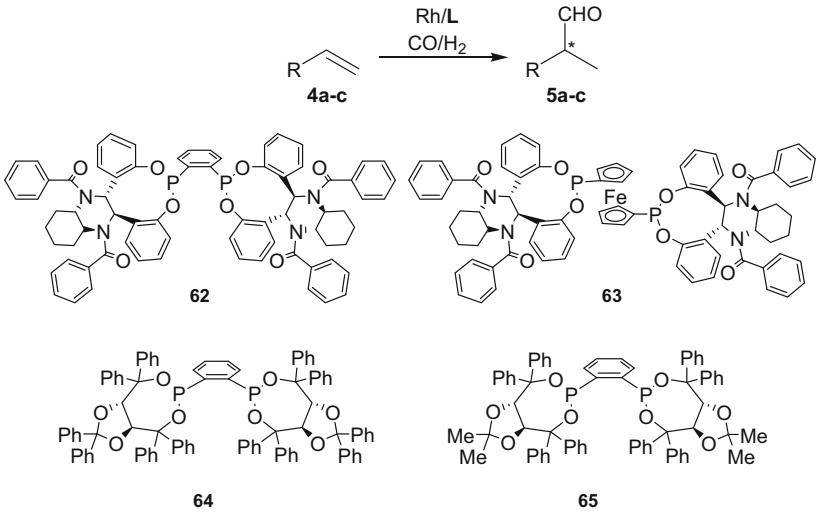
The bis-phosphonite ligand **62** provided moderate selectivities in the hydrofomylation of styrene and allyl cyanide (Scheme 16). However, this ligand provided an excellent 91% *ee* in the hydroformylation of vinyl acetate [128]. The related diphosphinite ligand derived from ferrocene **63** was also reported by Ding and coworkers and its application in the Rh-catalyzed asymmetric hydroformylation of styrene and vinyl acetate provided good conversion but lower enantioselectivities in the hydroformylation of styrene and vinyl acetate (up to 55% and 83%, respectively) [129] More recently, a family of TADDOL-derived bis-phosphonite ligands was reported, among which the ligands **64** and **65** provided excellent enantioselectivity in the asymmetric hydroformylation of styrene and derivatives [130].

3.5 Bis-Phosphinite Ligands

The diastereogenic bis-phosphinite ligands **66** and **67** were recently reported by Leitner and co-workers (Scheme 17) [131]. The Rh-catalysts bearing these binol-based ligands containing chiral phospholane units provided good regioselectivity for the branched products but only low to moderate selectivities in the hydrofomylation of styrene and vinyl acetate. It is noteworthy that the diastereoisomer **67** provided higher ee than **66** while the opposite trend was observed in the asymmetric hydrogenation of dimethyl itaconate.



Scheme 15 Synthesis of the Prelog–Djerassi Lactone via asymmetric hydroformylation/crotylation tandem sequence in the presence of derivatives of ligand **61a**



Product	5a		5b		5c	
Rh/**L**	R= Ph		R= CH_2CN		R= OAc	
			Regio (%)	*ee*(%)		
62	92	79	82	79	98	91
63	95	55			94	83
64	84	90				
65	84	91				

Scheme 16 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes with ligands **62–65**

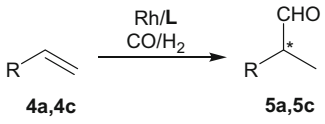
3.6 Monodentate Phosphorus-Based Ligands

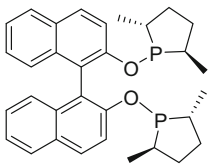
Nowadays, despite the successful use of monodentate ligands in many transition metal-catalyzed processes, there are only a few reports concerning their use in asymmetric hydroformylation and achieving high enantioselectivities in this process using those ligands remains a challenge.

Recently, an Rh complex bearing the monodentate phosphoramidite ligand encapsulated in a self-assembled molecular cage **68** (Scheme 18) provided the highest enantioselectivity (74%) in the asymmetric hydroformylation of styrenes using monoligated catalyst [132]. The presence of the cage was shown to enhance the enantioinduction of the catalyst and can therefore be considered as a second coordination sphere that is reminiscent of enzymatic active sites.

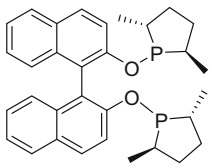
The monophosphite ligand **69** was tested in the Rh-catalyzed asymmetric hydroformylation of styrene and allyl cyanide and provided moderate enantioselectivities (Scheme 19). When vinyl acetate was the substrate, very poor *ee*'s were obtained

Scheme 17 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes with ligands **66** and **67**





(*R*$_a$, *R*, *R*, *R*)-**66**



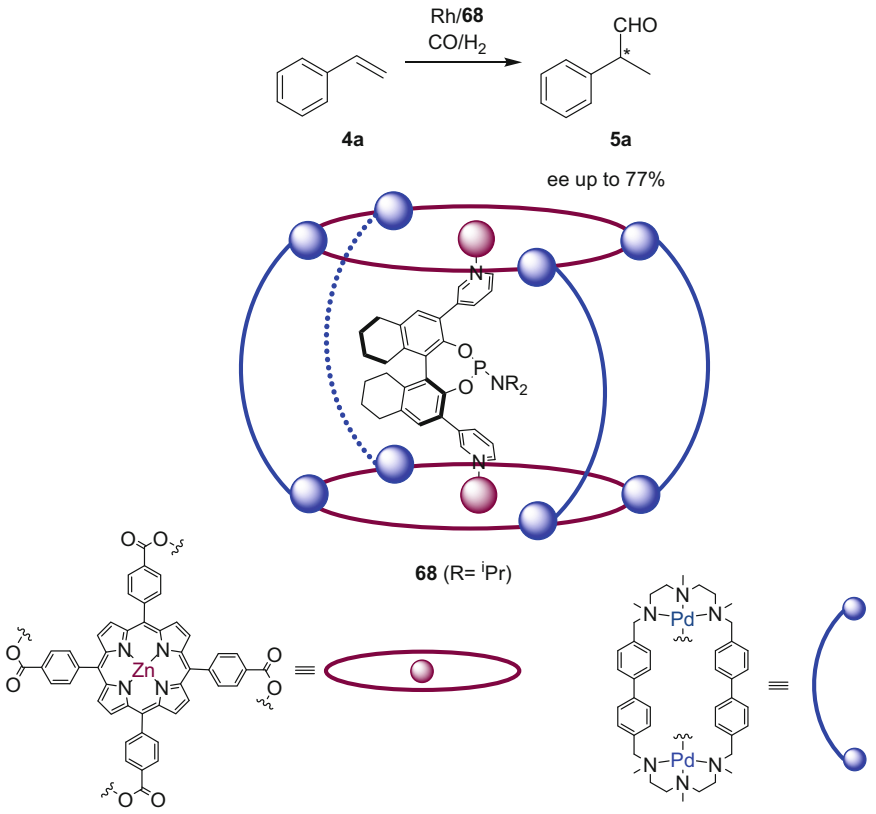
(*S*$_a$, *R*, *R*, *R*)-**67**

Product	**5a**		**5c**	
Rh/**L**	R= Ph		R= OAc	
	regio (%)/ ee(%)			
66	84	4		
67	75	40	96	33

(Scheme 19) [74, 75]. However, in 2004, Ojima and co-workers reported the use of the phosphoramidite ligand **70** (Scheme 19), related to monophosphite **69**, in the Rh-catalyzed asymmetric hydroformylation of allyl cyanide and achieved excellent regioselectivities together with the highest enantiomeric excess (80%) ever reported for this reaction with a monodentate ligand [133].

These results, although still far from those obtained with bidentate ligands, clearly indicated that achieving high *ee*'s using mondentate ligands is possible. Later, Alexakis, Pamies, Dieguez, and co-workers reported the testing of monodentate phosphoramidite and aminophosphine libraries in the asymmetric hydroformylation of styrene derivatives [134]. However, only ee's up to 50% could be achieved.

In 2005, Breit reports an alternative approach to the classical synthesis of bidentate ligands for hydroformylation by using the self-assembly of bidentate ligands based on an A-T base-pair model [135]. This method presents the advantage of allowing the rapid screening of various pairs of available monodentate ligands to obtain the most suitable combination for each substrate, overcoming the typical synthetic limitations for new bidentate ligands. Later, van Leeuwen and Reek reported the template-induced formation of chelating heterobidentate ligands by the self-assembly of two distinct monodentate ligands on a rigid bis-zinc(II)-salphen template with two identical binding sites (Scheme 20) [136, 137]. The templated heterobidentate ligand **71** induced much higher enantioselectivities (*ee* up to 74%) than any of the corresponding homobidentate ligands or non-templated mixed ligand combinations (*ee* up to 13%) in the Rh-catalyzed asymmetric hydroformylation of styrene.



Scheme 18 Rh-catalyzed asymmetric hydroformylation of styrene using Rh/monodentate phosphoramidite catalyst encapsulated in a self-assembled molecular cage

4 Other Monosubstituted Alkene Substrates

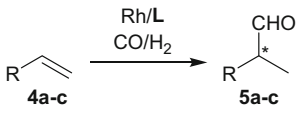
In this section, recent reports on the Rh-catalyzed asymmetric hydroformylation of "non-common" monosubstituted alkene substrates using chiral phosphorus donor ligands are presented.

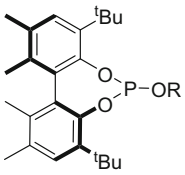
The substrate scope for the hydroformylation of dialkylacrylamides **4d$_1$–d$_4$** has so far been limited to methacrylamide, acrylamide, or *N*-benzylacrylamide, with low enantioinduction (20–50% ee's) [138, 139].

However, the use of a bis-diazaphospholane ligand (**61a**) in the Rh-catalyzed asymmetric hydroformylation of *N*,*N*-dialkylacrylamides was recently described achieving nearly total regioselectivity and ee's up to 82% (Scheme 21) [140].

The use of the bis-3,4-diazaphospholane type ligands has also been reported in the rhodium-catalyzed hydroformylation of several 1,3-diene substrates (1,3-dienes, *N*-vinyl carboxamides, allyl carbamates, and allyl ethers) with excellent regio- and

Scheme 19 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligands **69** and **70**





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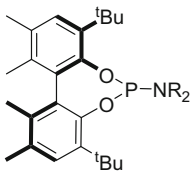

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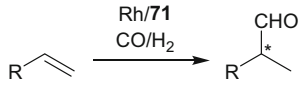
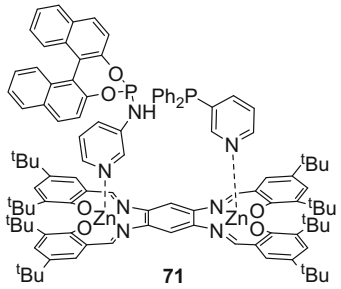
Product	**5a**	**5b**	**5c**
Rh/**L**	R= Ph	R= CH_2CN	R= OAc
		Regio (%) *ee*(%)	
69	94 38	84 43	93 8
70		96 80	

Scheme 20 Rh-catalyzed asymmetric hydroformylation of styrene using the templated ligand **71**



		Regio (%)	*ee* (%)
4a R=Ph	**5a** R=Ph	90	74

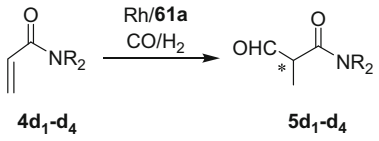


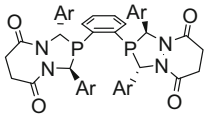
71

enantioselectivities by Landis et al. [141, 142]. Total conversions with good regioselectivities (>88%) and excellent enantioselectivities (91–97%) were achieved (Scheme 22).

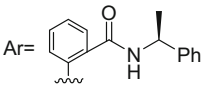
The ligand **61a** was also successfully employed in the Rh-catalyzed asymmetric hydroformylation of other alkene substrates containing amine (**4f**) and ether (**4g**) substituents, with ee's up to 99% and 97%, respectively [142] (Scheme 23).

Recently, Leitner, Francio, and co-workers reported the highly regio- and enantioselective hydroformylation of vinyl esters using the bidentate phosphine, P-chiral



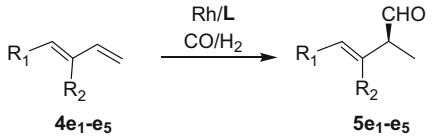


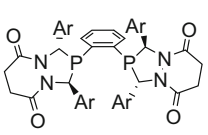
Bis-3,4-diazaphospholane (**61a**)



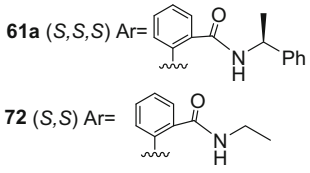
Rh/**61a**		Regio (%)	ee(%)
5d$_1$	R= Me	98	68
5d$_2$	R= Et	97	82
5d$_3$	R= *i*-Pr	98	74
5d$_4$	NR_2=NMe(OMe)	98	71

Scheme 21 Rh-catalyzed asymmetric hydroformylation of *N*,*N*-dialkylacrylamides





Bis-3,4-diazaphospholane

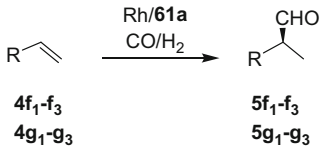


Rh/**61a**		Regio (%)	ee(%)
4e$_1$	R_1= Ph, R_2= H	99	91
4e$_2$	R_1= 2-furan, R_2= H	99	97
4e$_3$	R_1= MeO, R_2= H	99	94

Rh/**72**		Regio (%)	ee(%)
4e$_4$	R_1= Ph, R_2= Me	88	93
4e$_5$	R_1= 2-furan, R_2= Me	98	93

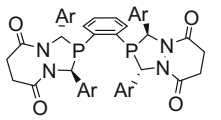
Scheme 22 Rh-catalyzed asymmetric hydroformylation of 1,3-dienes with ligands **61a** and **72**

phosphoramidate ligands [143]. The BettiPhos ligand **73** was particularly efficient and provided total regioselectivity and ee's up to 97% for a number of these substrates (Scheme 24).

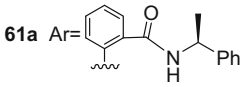


4f$_1$-f$_3$
4g$_1$-g$_3$

5f$_1$-f$_3$
5g$_1$-g$_3$



Bis-3,4-diazaphospholane



Rh/**61a**

		Regio (%)	ee(%)
5f$_1$	R= NH-COOBn	99	94
5f$_2$	R= NHCOO^{t}Bu	97	99
5f$_3$	R= NHCOCF$_3$	98	99
5g$_1$	R= CH$_2$OTMS	67	97
5g$_2$	R= CH$_2$OPh	72	96
5g$_3$	R= CH(OAc)$_2$	82	93

Scheme 23 Rh-catalyzed asymmetric hydroformylation of monosubstituted enamides and other allylic substrates with the ligand **61a**

5 Rh-Catalyzed Asymmetric Hydroformylation of Disubstituted Alkenes

The Rh-catalyzed asymmetric hydroformylation of disubstituted alkenes has received much less attention than their monosubstituted counterparts. To the best of our knowledge, only a few examples of asymmetric Rh-catalyzed hydroformylation of 1,2-disubstituted and 1,1-disubstituted alkenes have been reported so far (Scheme 2) [26, 143–180].

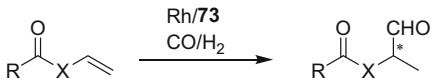
5.1 Linear 1,2-Disubstituted Alkenes

The 1,3-diphosphite ligand **29** was used in the Rh-catalyzed asymmetric hydroformylation of *trans*-anethole **8a** and estragole **8b** (Scheme 25) but moderate to low enantioselectivities were achieved (*ee* up to 15%) [145].

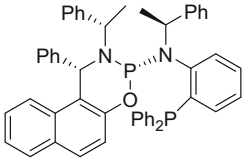
Nozaki and co-workers reported the asymmetric Rh-catalyzed hydroformylation of *trans*-anethole **8a** into **9a** using the BINAPHOS ligand **44** with excellent regioselectivity (98%) and a remarkable 80% *ee* [146, 147].

In the Rh-catalyzed asymmetric hydroformylation of 1,2-alkyl-disubstituted alkenes (Scheme 26) as substrates, the BINAPHOS ligand **44** provided high *ee* values [146, 147]. Interestingly, it was reported that the *E*-isomers **11b** and **11d** yielded lower enantioselectivity than their *Z*-counterparts **11a** and **11c**.

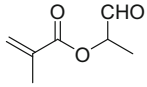
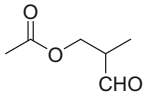
More recently, a monodentate phosphoramidite template ligand was used in the asymmetric Rh-catalyzed hydroformylation of *trans*-2-octene (Scheme 27). This



4h-r **5h-r**



BettiPhos **(73)**

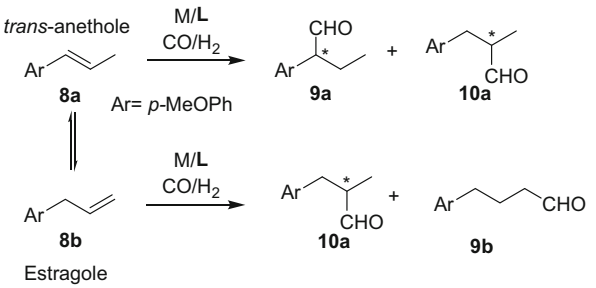
Product	Regio %	ee %
5h R = Et; X = O	>99	94
5i R = ^{t}Bu; X = O	>99	95
5j R = Ph; X = O	>99	94
5k R = 4-MeOC_6H_4; X = O	>99	91
5l R = 4-FC_6H_4; X = O	>99	92
5m R = naphthyl; X = O	98	88
5n R = $CH_3(CH_2)_{10}$; X = O	>99	95
5o 	>99	96
5p 	-	5
5q R = CH_3; X = NH	96	82
5r R = CH_3; X = NCH_3	86	83

Scheme 24 Rh-catalyzed asymmetric hydroformylation of vinyl esters using the BettiPhos ligand **73**

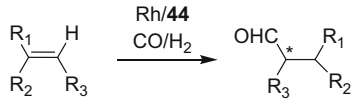
ligand (**74**) exhibits a supramolecular control over the Rh center, due to the presence of two pyridine functions in the bis(naphthol) skeleton that are bounded to zinc(II) porphyrins. With this ligand, useful conversions (up to 56%) with moderate ee's (up to 45%) were achieved. When the BINAPHOS ligand **44** was used in the same reaction, similar conversion (55%) was obtained although without significant enantioinduction [148]. More recently, a new supramolecular ligand **75** (Scheme 27) containing two phosphoramidite moieties was reported, providing remarkable enantioselectivities in the asymmetric hydroformylation of internal alkenes [149].

Very recently, Landis and co-workers showed that the diazaphospholane ligand **61a** could provide high enantioselectivity in the hydroformylation of Z-enamides and enol esters, providing excellent enantioselectivities for a broad range of these substrates (Scheme 28) [150].

Scheme 25 Isomerization processes and asymmetric hydroformylation of *trans*-anethole and estragole



Scheme 26 Rh-catalyzed asymmetric hydroformylation of disubstituted alkenes



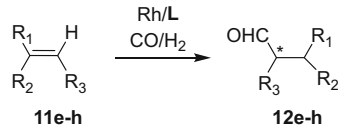
Product	*ee* (%)
12a R_1= H, R_2=R_3= Me	85
12b R_1= Me, R_2= H, R_3= Me	48
12c R_1= H, R_2=R_3= Et	79
12d R_1= Et, R_2= H, R_3= Et	69

Using the same ligand **61a**, Burke and Risi reported the total synthesis of (+)-patulolide C, which exhibits both antifungal and antibacterial activities [151, 152], through a methodology based upon Rh-catalyzed asymmetric hydroformylation (Scheme 29) [153]. This synthetic method included an Rh-catalyzed hydroformylation/intramolecular Wittig olefination to set the C_4-hydroxyl stereochemistry and *E*-olefin geometry and form the macrolactone, which afforded a very short, high-yielding synthesis of this compound, which usually required over 14 steps. The hydroformylation substrate is therefore an *E*-1,2-disubstituted alkene bearing an acetate and an alkyl substituent.

More recently, the same authors also employed this ligand in the synthesis of other biologically relevant molecule using asymmetric hydroformylation as the key step [55, 154].

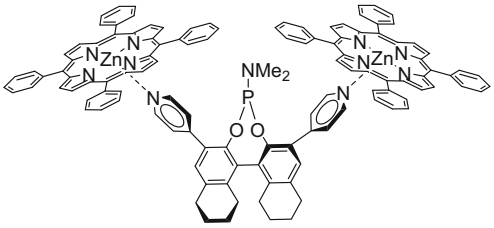
5.2 Scaffolding [156] Ligands

The term "catalyst-directing groups" was defined for organocatalysts that are able to form simultaneously covalent bonds with a substrate and dative bonds with a metal catalyst, which allow them to direct metal-catalyzed transformations [157]. In general, these "scaffolding ligands" were named by analogy with scaffolding proteins, which promote biological processes [158].



e: R_1= Me, R_2=H, R_3= Pent
f: R_1= Me, R_2=H, R_3= hex
g: R_1= H, R_2=Me, R_3= Pent
h: R_1= H, R_2=Me, R_3= Bu

	ee(%)			
Product	**12e**	**12f**	**12g**	**12h**
Rh/**L**				
44	0			
74	45			
75	72	62	80	82



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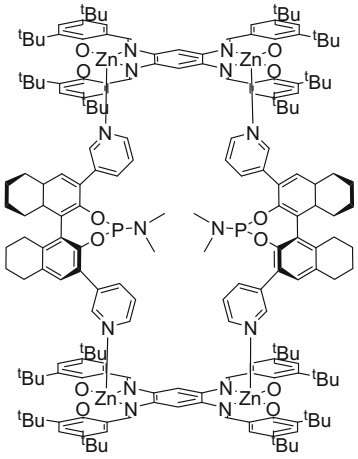


75

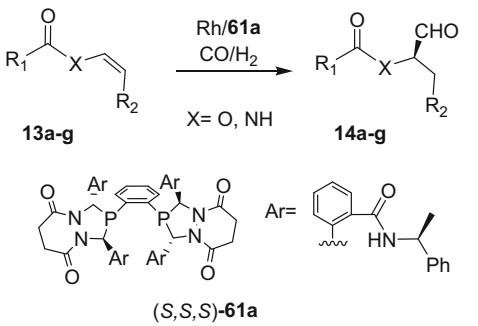
Scheme 27 Rh-catalyzed asymmetric hydroformylation of internal alkenes with the ligands **44**, **74,** and **75**

Using such methodology, the groups of Tan and Breit reported the highly regioselective Rh-catalyzed hydroformylation of homoallylic alcohols [157, 159]. Tan et al. designed the alkoxy benzoazaphophole ligand **76** derived from *N*-methylaniline that undergo facile exchange with other alcohols or secondary amines (Scheme 30) [141, 142].

The asymmetric hydroformylation of several alkene substrates was performed by Tan and co-workers using scaffolding ligands containing a tetrahydroisoquinoline group on the alkoxy benzoazaphosphole yielding the scaffolding ligand **78** (Scheme 31).

More recently, the group of Tan reported the use of ligands containing an oxazoline moiety able to bind alcohols (Scheme 32) [160]. They applied these ligands

Scheme 28 Rh-catalyzed asymmetric hydroformylation of Z-enamides and enol esters with the (*S*,*S*,*S*)-bis diazaphos ligand **61a** reported Landis and co-workers



(*S*,*S*,*S*)-**61a**

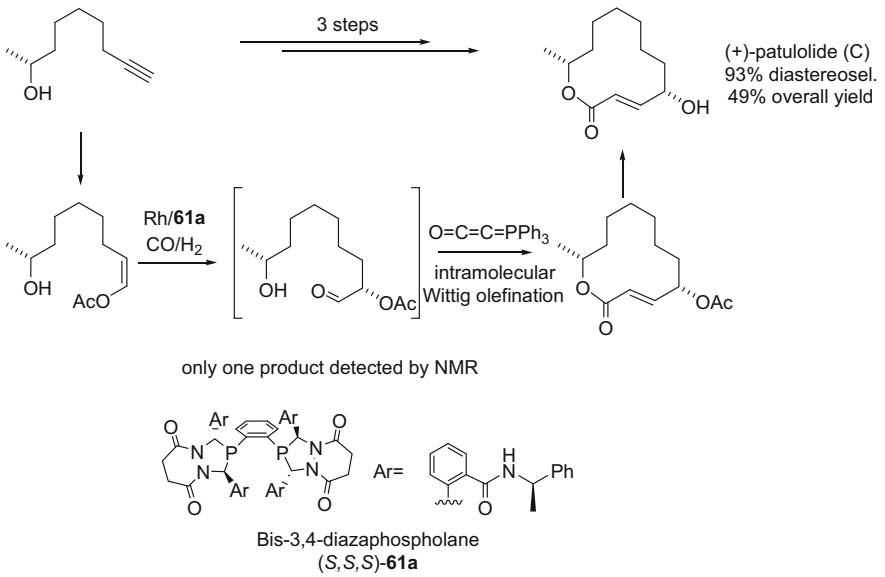
Product	Regio(%)	ee(%)
14a X=O, R_1= Ph, R_2= Bu	>99	97
14b X=O, R_1= *p*-C_6H_4-OH, R_2= Bu	>99	99
14c X=O, R_1= Me, R_2= CH_2-CH_2-Ph	>99	93
14d X=NH, R_1= Ph, R_2= Bu	>99	85
14e X=NH, R_1= Ph, R_2= CH_2-CH_2Ph	>99	90
14f X=NH, R_1= Ph, R_2= CH_2-CH_2Cl	93	92
14g X=NH, R_1= Ph, R_2= CH_2-CH_2CN	>99	94
14h X=NH, R_1= Ph, R_2= CH_2-C_6H_{11}	>99	84
14i X=NH, R_1= Ph, R_2= Ph	86	98
14j X=NH, R_1= CF_3, R_2= Ph	92	90

in the diaseteroselective hydroformylation of homoallylic alcohols to afford β-lactams with excellent regio- and diastereoselectivities.

The Breit research group demonstrated that Ph_2POMe was a suitable catalytic directing group for hydroformylation [157]. Notably, the functionalization of 1,2-disubstituted olefins and other substrates containing stereocenters proceeded with excellent regio- and stereoselectivity. Additionally, the chemoselective hydroformylation of homoallylic alcohols over unactivated alkenes was observed.

5.3 Monocyclic 1,2-Disubstituted Alkenes

Among monocyclic 1,2-disubstituted alkene substrates, 5-membered ring heterocycles such as dihydrofurans and dihydropyrroles have been the most studied. With these substrates, the simultaneous control of the chemo-, regio-, and enantioselectivity is a key issue since the presence of a heteroatom in the cycle favors in some cases an isomerization process in the presence of a metal-hydride species. Previous studies using achiral ligands demonstrated that the reaction conditions highly affected the chemo- and regioselectivity of this reaction [161, 162]. Indeed, allyl

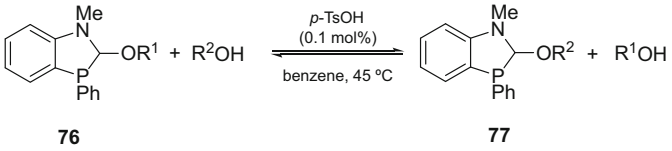


Scheme 29 Synthesis of (+)-patulolide C via Rh-catalyzed asymmetric hydroformylation/macrocyclization cascade using ligand **61a**

ethers were shown to rapidly isomerize into its vinyl analogue under hydroformylation conditions (Scheme 33). This isomerization process is of critical importance since it has a direct influence not only on the regioselectivity of the reaction, but also on the enantioselectivity since the opposite enantiomers of tetahydro-3-carbaldehyde are formed from the allylic **17a** and vinylic **17b** isomers of the substrate [163]. It is therefore required to limit the isomerization in order to obtain high selectivities.

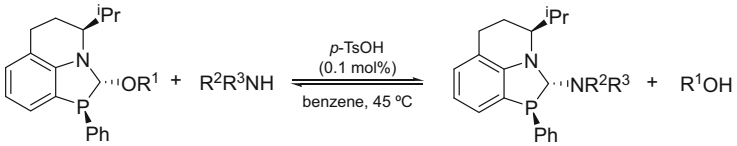
In the Rh-catalyzed asymmetric hydroformylation of 2,5-dihydrofuran **17a**, Nozaki and co-workers reported the first successful results using the BINAPHOS ligand **44** which yielded total regioselectivity to the tetahydro-3-carbaldehyde **18a** with 68% *ee* (*R*) (Scheme 34) [146, 147, 164]. However, when the 2,3-dihydrofuran **17b** was tested with the same catalyst, no regioselectivity was observed and the *ee* obtained for the aldehyde **18b** decreased to 38% with *S* configuration. This catalytic system was thus suitable to avoid isomerization of **17a** into **17b** but not selective for the hydroformylation of **17b**. In the same study, the amine analogues **17c**,**d** and **17e** were also tested as substrates using the same catalytic system (Scheme 34) and similar results were obtained.

Recently, the previously mentioned 1,3-diphosphites **30**, **40** (Scheme 6) derived from carbohydrates were successfully applied in the Rh-catalyzed hydroformylation of these substrates [72, 165, 166]. The results indicated that ligands **30**, **38**–**40**, which have a glucose configuration, are the most appropriate to obtain high enantioselective induction in the hydroformylation of these substrates. In the case of the 2,5-dihydrofuran **17a**, the highest enantioselectivity in the aldehyde **18a** was obtained using ligand **38b** (88% *S*). Using this ligand, no isomerization was



76 77

Scheme 30 Alkoxy benzoazaphosphole catalytic directing group



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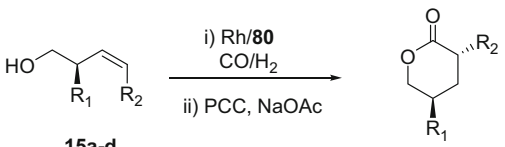
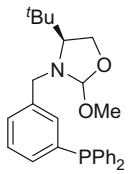
Scheme 31 Tetrahydroisoquinoline alkoxy benzoazaphosphole scaffolding ligand



15a-d 16a-d

	regio(%)	anti/syn
16a: R_1= Me; R_2= Bu	91	87/13
16b: R_1= iPr; R_2= Bu	95	91/9
16c: R_1= Me; R_2= Ph	88	83/17
16b: R_1= TBSO; R_2= Pent	85	89/11



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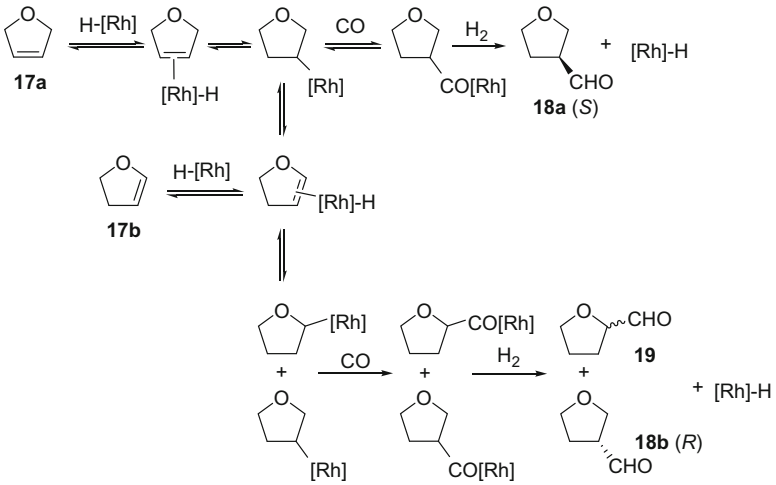
Scheme 32 Rh-catalyzed diaseteroselective hydroformylation of homoallylic alcohols using the scaffolding ligand **80**

observed under hydroformylation conditions. Interestingly, the presence of bulky substituents at C-5 such as in ligands **39b–40b** was shown to increase the degree of isomerization. When the 2,3-dihydrofuran (**17b**) was used as substrate, *ee*'s up to 84% (*R*) in aldehyde **18b** were achieved using ligands **39b–40b**, together with a regioselectivity of 80%. The 2,5-dihydropyrrole **17d** was also tested with the Rh/**30b** system, achieving comparable results to those previously reported using ligand **44** (71 and 66%, respectively) (Scheme 9).



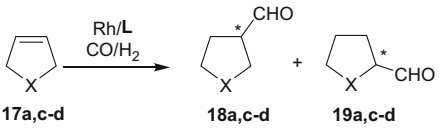
Scheme 33 Isomerization processes observed during the Rh-asymmetric hydroformylation of five-membered heterocyclic alkenes

Reek and co-workers described the synthesis and application of the ligand **81**, containing a skeleton related to the Xantphos diphosphine ligand, in the Rh-catalyzed asymmetric hydroformylation of the dihydrofurans **17a** and **17b** (Scheme 34). This system provided regioselectivities of 99 and 80%, respectively, and very high enantioselectivities (up to 91%) for these substrates [167, 168]. Recently, Zhang and co-workers reported the Rh-asymmetric hydroformylation of five-membered heterocyclic alkenes using a derivative of the diazaphospholane ligand **82** developed by Landis (Scheme 34) [169]. This system provided excellent regio- and enantioselectivities (up to 92%) for several of these substrates. Vidal-Ferran and co-workers also reported the use of the small bite angle phosphine phosphite ligand **50a** (Scheme 11) in the same reaction [109]. When the dihydrofuran **17a** was the substrate, they obtained total regioselectivity and ee's up to 72%, while moderate regioselectivity and ee's up to 76% were obtained when **17b** was tested.

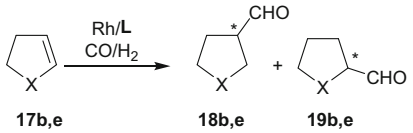
More recently, the same authors reported the use of conformationally transformable α,ω-bisphosphite ligands combined with an alkali metal BArF salt as a regulation agent (RA) [77]. These ligands provide enantioselectivities up to 82% in the asymmetric hydroformylation of 2,5-dihydrofuran **17a** and 2,3-dihydrofuran **17b**.

The asymmetric Rh-catalyzed hydroformylation of dioxapines **20a**,**b** was reported using the BINAPHOS ligand **44** and 1,3-diphosphite ligands derived from carbohydrates **83** (Scheme 35) [146–166]. Using the ligand **44**, total regioselectivity to **21a**,**b** was achieved, together with *ee*'s up to 76%. Among the carbohydrate derived ligands that were tested, the ligand **83** provided the best results (Scheme 35), affording total regioselectivity to **21a**,**b** and up to 68% *ee* and thus indicating that no isomerization of **20a**,**b** had occurred. More recently, Vidal-Ferran and co-workers reported the highest *ee* in the asymmetric hydroformylation of the dioxapines **20a** by using an Rh-complex bearing the disphosphite **84** (Scheme 35) [77].

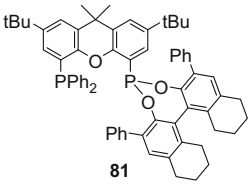
Scheme 34 Rh-catalyzed asymmetric hydroformylation of five-membered heterocyclic alkenes **17a–e**



Product	**18a**		**18c**		**18d**	
Rh/**L**	X=O		X=NBoc		X=NAc	
	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)
30b	99	75 (*S*)			99	71 (-)
38b	99	88 (S)				
44	99	68 (*R*)	99	73 (*R*)	99	66 (+)
81	99	91 (*S*)				
50a	99	72 (*R*)				
82	99	84 (*S*)	99	92 (*S*)		



Product	**18b**		**18e**	
Rh/**L**	X=O		X=NBoc	
	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)
30b	76	75 (*R*)		
39b	78	83 (*R*)		
40b	78	84 (*R*)		
44	50	38 (*S*)	33	71 (*S*)
81	80	91 (*R*)		
50a	45	76 (*S*)		
82	50	92 (*R*)	85	86 (*R*)



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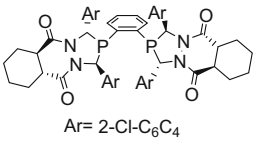

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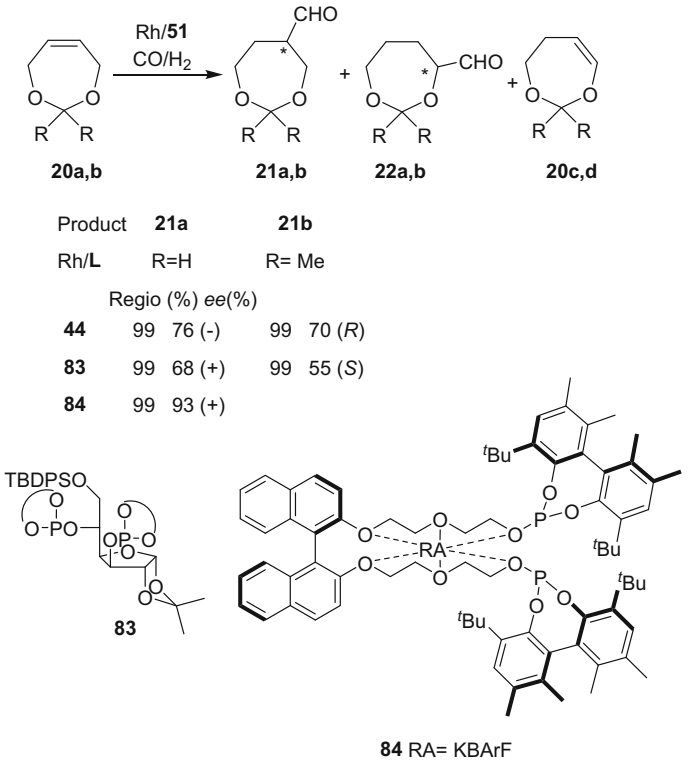
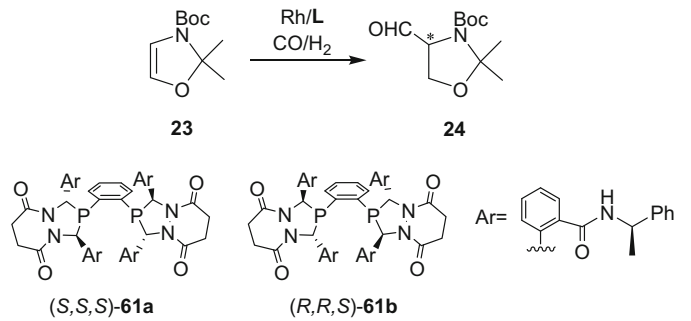
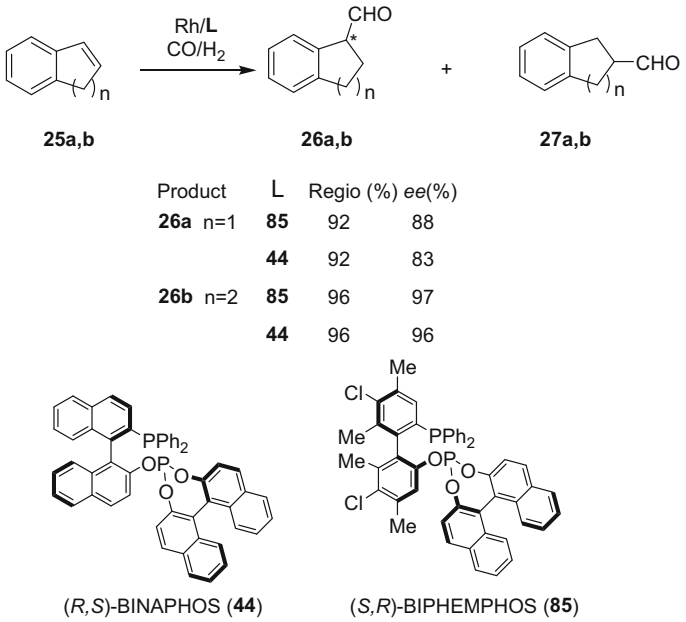
In 2012, the application of the asymmetric hydroformylation of cyclic disubstituted olefins was employed to provide useful chiral molecules like the Garner's aldehyde, a popular building block [170, 171]. Both enantiomers of this molecule were prepared through this reaction using catalytic systems bearing the diastereoisomeric bis-diazaphospholane ligands **61a** and **61b** (Scheme 36) [172]. The *S* enantiomer can



Scheme 35 Rh-catalyzed asymmetric hydroformylation of **20a**,**b**



Scheme 36 Synthesis of Garner's aldehyde through Rh-catalyzed asymmetric hydroformylation of the cyclic disubstituted olefin *N*-Boc-2,2-dimethyl-2,3-dihydrooxazole **23**



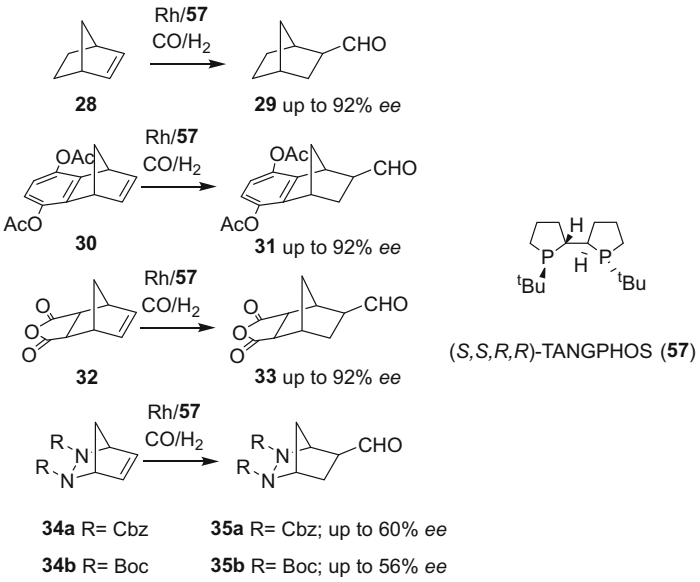
Scheme 37 Rh-catalyzed asymmetric hydroformylation of bicyclic alkenes using the ligands (R, S)-BINAPHOS (**44**) and BIPHEMPHOS (**85**)

be produced in 97% ee in the presence of (*S*,*S*,*S*)-**61a** while the *R* product is formed with a slightly lower ee's (94%), using the ligand (*R*,*R*,*S*)-**61b**. The reactions were run on a *ca*. 5 mmol scale at 55°C under 10 bar of syngas (1:1) using 2 mol% Rh catalyst.

5.4 Bicyclic 1,2-Disubstituted Alkenes

The Rh-catalyzed asymmetric hydroformylation of substrates **25a** and **25b** was reported by Nozaki and co-workers using the ligands **44** and **85** (Scheme 37) [146, 147]. The results are really remarkable, in particular with substrate **25b**, for which compound **26b** was obtained with practically total regio- and enantioselectivity (Scheme 37). The corresponding products **26a** and **26b** are of interest since the aldehyde **26a** can be converted in a single step into the corresponding amine which exhibits hypotensive activity and the product **26b** is a synthetic intermediate to produce a vasoconstrictor tetrahydrozoline [173].

Another bicyclic alkene substrate of interest for carbonylation reactions is the norbornene **28** and its derivatives. The first reports on the asymmetric Rh-hydroformylation of norbornene afforded low enantiomeric induction with *ee*'s below 25% [174, 175]. In



Scheme 38 Rh-catalyzed asymmetric hydroformylation of norbornene derivatives using the diphospholane ligand **57**

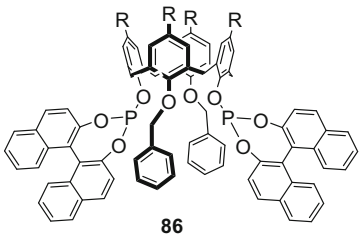
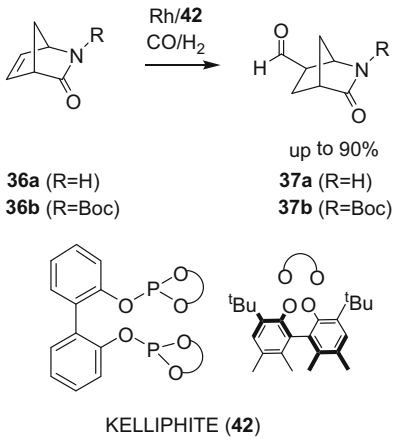


Fig. 1 Hemispherical diphosphite ligands **86** with a conical calixarene skeleton

2005, Bunel and co-workers reported the first highly enantioselective Rh-catalyzed hydroformylation of norbornene into the *exo* aldehyde using diphospholane ligands, reaching *ee*'s up to 92% with the TANGPHOS ligand **50** [176]. Using the same ligand, they also reported the hydroformylation of several derivatives of this substrate with similar enantioselectivities (Scheme 38).

Recently, the hemispherical diphosphite ligands **86** (Fig. 1) with a conical calixarene skeleton was used in the asymmetric Rh-hydroformylation of norbornene, achieving enantioselectivities up to 61% with the *exo* aldehyde being the major product [177].

More recently, the KELLIPHITE ligand (**42**) was employed in the Rh-catalyzed asymmetric hydroformylation of bicyclic lactam azababicyclo-[2.2.1]hept-5-en-3-



Scheme 39 Rh-catalyzed asymmetric hydroformylation of bicyclic lactam azababicyclo-[2.2.1]hept-5-en-3-ones using the KELLIPHITE ligand **42**

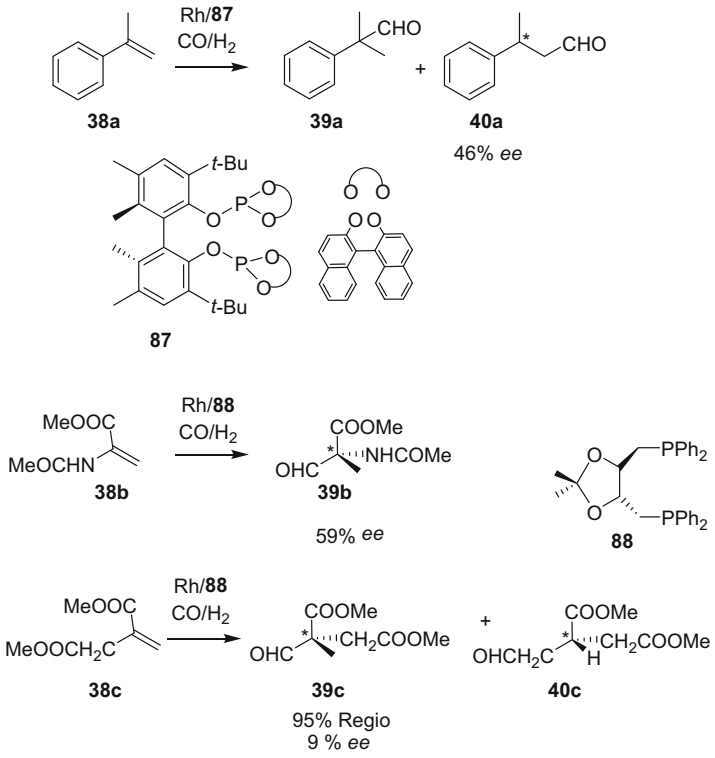
ones with very good results. The reaction was completely *exo*-selective, yielding total conversions and excellent regioselectivities (up to 90%) [178] (Scheme 39).

5.5 *1,1′-Disubstituted Alkenes*

The asymmetric hydroformylation of 1,1′-disubstituted alkenes differs from the classical asymmetric hydroformylation of monosubstituted terminal alkenes since the desired product is the linear aldehyde (Scheme 2) [179].

Indeed, the Rh-catalyzed asymmetric hydroformylation of 1,1-methylstyrene (**38a**) using diphosphite ligand **87** (Scheme 40) to form the linear product (**40a**) was recently patented. The enantioselectivity was, however, moderate (*ee* up to 46%) [180].

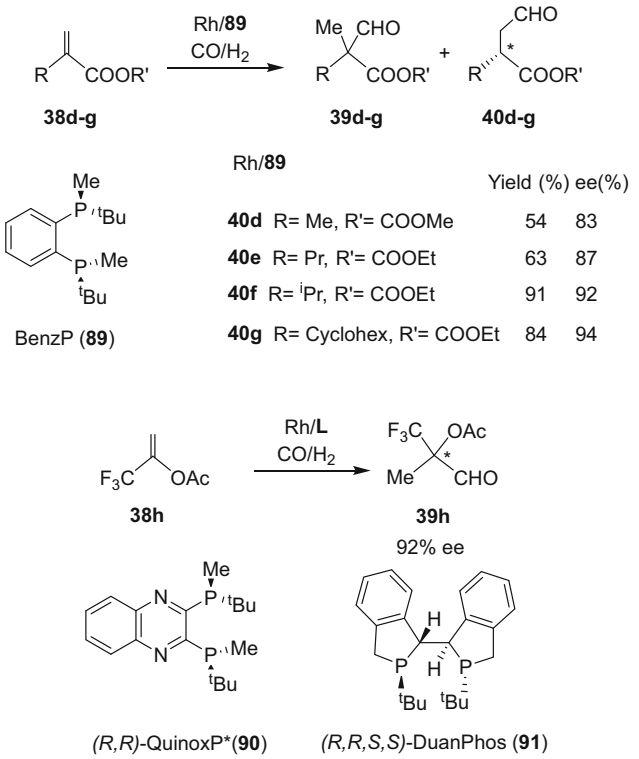
Interestingly, when dehydro amino acid derivatives **38b** and dimethyl itaconate **38c** were used as substrates (Scheme 40) in the presence of $[RhH(CO)(PPh_3)_3]$ and 1–6 equivalents of the (R,R)-DIOP ligand **88**, the formation of the branched products was largely favored with moderate enantioselectivity (*ee*'s up to 59%). In this process highly functionalized quaternary carbons are easily obtained from common products. This interesting reaction deserves more attention by researchers in the field. It should be noted that when the α,β-unsaturated carboxylic compounds such as **38c** are hydroformylated in the presence of the $[PtCl(SnCl_3)]$, the only hydroformylation product obtained was the linear aldehyde with *ee*'s up to 82% [26].



Scheme 40 Rh-catalyzed asymmetric hydroformylation of 1,1′-disubstituted alkenes

Recently, Buchwald et al. reported the Rh-catalyzed asymmetric hydroformylation of 1,1-disubstituted alkenes (α-alkylacrylates) using the 1,3-diphosphine ligand BenzP (**89**). With this ligand, good regio- (up to 91%) and enantioselectivities (up to 94%) were achieved (Scheme 41) [181]. The fine-tuning of the partial pressures of CO/H_2 minimizes the problem of the side reactions; in fact, the mild reaction conditions make it safe for general laboratory use (10 bar 1:5 CO/H_2, 100°C).

More recently, the same authors reported the asymmetric hydroformylation of 3,3,3-trifluoroprop-1-en-2-yl acetate **39h** using the P-stereogenic ligands QuinoxP (**90**) and DuanPhos (**91**) with 92% ee [182]. After oxidation of the resulting aldehyde and hydrolysis, crystallization provided enantiomerically pure 2-trifluoromethylallylic acid.



Scheme 41 Rh-catalyzed asymmetric hydroformylation of α-alkylacrylates

6 Conclusions

Rhodium is currently the metal of choice to achieve high enantioselectivities in the hydroformylation of a relatively large variety of alkene substrates. The elucidation of the different steps of the catalytic cycle and the characterization of the resting state, together with the discovery of several types of ligands that are able to provide high enantioselectivities, have made the rhodium-catalyzed hydroformylation a synthetically useful tool.

In the catalytic cycle, the complex **16** has been identified as the resting state of the process. An important feature for bidentate ligands is their possible coordination to the rhodium center in eq–eq or eq–ax fashions. Indeed, although the enantioface discrimination occurs at the alkene coordination step from the square-planar species **17**, experimental observations showed that high enantioselectivity in asymmetric hydroformylation of alkenes is obtained using ligands that lead to the formation of only one isomer of the resting state **16**. This fact could be attributed to the similitude in the structures of the Rh hydride species **16** and **18**. The co-existence of the two possible isomers in solution was shown to always provide lower enantioselectivity.

Commonly, the synthesis of a chiral compound by asymmetric hydroformylation involves the introduction of a formyl group in a substituted olefinic carbon. This process has been widely studied mainly for monosubstituted alkenes. However, since the favored process is usually the introduction of this group in the less substituted carbon, this transformation is only useful for substrates containing electron-withdrawing group(s) (R = Ph, heteroatom) which direct the introduction of the formyl group in the most substituted carbon. Consequently, a regioselectivity problem must be first considered. The presence of a functional group at the allylic position, which contributes to stabilize the double bond, always supposes an additional issue, since isomerization takes place easily. This isomerization can be controlled by the appropriate choice of ligand and reaction conditions. For instance, increasing the CO pressure and/or decreasing the reaction temperature reduce the degree of isomerization.

Furthermore, low temperatures ($<70^{\circ}C$) are usually required to achieve high enantioselectivities although under these conditions, the reaction rate is usually low. A way to partially circumvent this problem is increasing the H_2 pressure thus shifting the equilibrium from the inactive complex **23** towards the active species **16**.

1,2-Disubstituted substrates are particularly challenging when similar substituents such as alkyl substituents are present in both positions. However, higher regio- and enantioselectivity can be achieved when one of the substituents direct the regioselectivity, as is the case of 2,3-dihydrofuran, dihydropyrrol, indene, or 1,2-dihydronaphthalene. In the case of symmetrically substituted alkenes such as 2,5-dihydrofuran and norbornene, no regiocontrol is required and high activities and enantioselectivities have been achieved in asymmetric hydroformylation.

1,1-Disubstituted or 1,1,2-trisubstituted are more challenging substrates. The general trend is the introduction of the formyl group onto the less substituted carbon, thus creating the chiral center at the more substituted carbon atom. This trend is respected in the hydroformylation of such substrates using Pt catalysts, achieving high regio- and enantioselectivities. Interestingly, it is also possible to introduce the formyl group at the more substituted carbon using Rh catalysts, thus creating a highly functionalized chiral quaternary center.

For years, ligands containing phosphite moieties such as diphosphites and phosphine–phosphites were considered as the most successful ligands to achieve high enantioselectivies. For instance, diphosphite ligands **24**, **30**, and **42** are highly effective in the asymmetric Rh-catalyzed hydroformylation of several alkene substrates and the phosphite–phosphine BINAPHOS (**44**) or its derivatives **46** and **47** have been very successful ligands in terms of selectivity and scope. Recently, however, diphosphines in which the P atoms are incorporated in a ring (**56–59**) have also shown to induce high levels of enantioselectivity in this process. Furthermore, diazaphospholane ligands **61a**, **61b,** and **72** are currently the most efficient ligand in the asymmetric hydroformylation of alkenes, with exceptional results in terms of regio- and enantioselectivity. These ligands have also been successfully immobilized onto solid support in order to recycle and reuse the corresponding catalysts and employ them under continuous conditions. Over the last years, these ligands were also applied in the enantioselective hydroformylation of specific substrates for the synthesis of various organic molecules of biological and/ or synthetic interest.

It can consequently be concluded that the key to achieve high enantioselectivities is not the type of phosphorus function involved in the coordination to the metal, but the particular spatial arrangement of the coordinated ligand. Furthermore, recently, supramolecular strategies have also been very successful in asymmetric hydroformylation, clearly indicating that the control of the second coordination sphere could be key to reach selectivity for challenging substrates.

Nowadays, a variety of chiral products incorporating a formyl unit can be enantioselectively prepared by Rh-catalyzed asymmetric hydroformylation and this process can therefore be considered as a powerful and useful tool in organic synthesis.

Recently, an Rh catalyst was reported to convert alkenes to aldehydes without the need of gases through transfer hydroformylation [183, 184]. In this promising process, the catalyst transfers the equivalent of H_2 and CO between a sacrificial aldehyde and an alkene under mild conditions without evolving gases. Although this reaction is still at a very early stage, the development of efficient catalysts for the control of the selectivity could provide a general method for the formation of chiral aldehydes without the need of syngas.

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