Top Curr Chem (2013) 342: 79–116
DOI: 10.1007/128_2013_429

Published online: 18 April 2013

Asymmetric Hydroformylation

Bernabé F. Perandones, Cyril Godard, and Carmen Claver

Abstract Rhodium is currently the metal of choice to achieve high enantioselectivities in the hydroformylation of a relatively wide 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.

For years, ligands containing phosphite moieties such as diphosphites and phosphine–phosphites were considered the most successful ligands to achieve high enantioselectivities for classical substrates such as styrene and vinyl acetate. In fact, the phosphite–phosphine BINAPHOS (**43**) and its derivatives are still today the most successful ligands in terms of selectivity and scope. For more substituted substrates, general trends can be extracted. However, recent studies showed that these general trends can be sometimes reversed by the use of the appropriate catalyst and choice of reaction conditions, clearly showing that these trends are only indicative and that there are still many challenges to be tackled in this area.

Keywords Asymmetric · Chiral ligands · Enantioselectivity · Hydroformylation · Phosphine · Phosphite · Phosphorus · Regioselectivity · Rhodium

Contents

B.F. Perandones, C. Godard (✉), and C. Claver
Departament de Química Física i Inorgánica, Universitat Rovira i Virgili, C/ Marcel.li Domingo s/n, 43007 Tarragona, Spain
e-mail: cyril.godard@urv.cat

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 [4–12]. However, the potential of this process in fine chemicals production is still to be exploited.

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 [13, 14 and references therein]. As a pure addition reaction, the hydroformylation reaction meets all the requirements of an atom economic process [15]. Furthermore, the synthetically valuable aldehyde function is introduced, which allows subsequent skeleton expansion that may even be achieved in one-pot sequential transformations [16, 17].

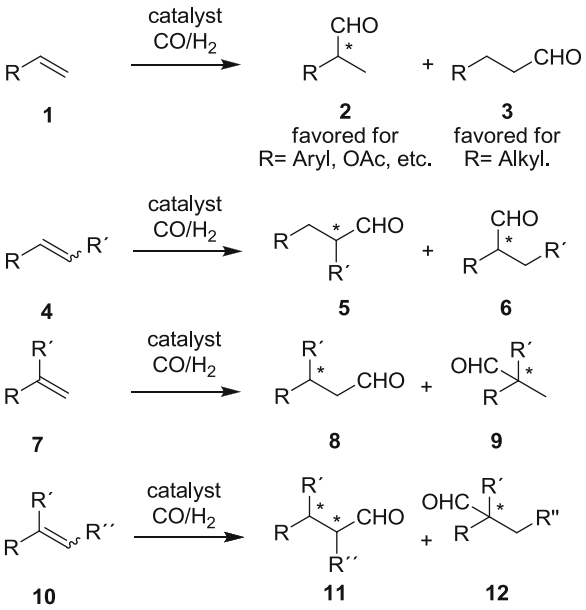
Since early studies, ligand modification of the rhodium catalyst has been the main strategy to influence the catalyst activity and selectivity [18–21 and references therein].

In the asymmetric hydroformylation of alkenes, the first examples of high level of enantioselectivity (ees up to 90%) were achieved by Stille and Consiglio using chiral Pt- diphosphine systems [22–24]. However, these catalysts suffered several disadvantages such as low reaction rates, tendency to hydrogenate the substrates, and low regioselectivity to the branched products.

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 rhodium-catalyzed hydroformylation a synthetically useful tool [25, 26].

In asymmetric hydroformylation of alkenes, the regioselectivity is key to providing chiral products and is a function of many factors. 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 substituent pattern (Scheme 1) [13, 14 and references therein].

Scheme 1 Regioselectivity trends in the hydroformylation of various alkenes

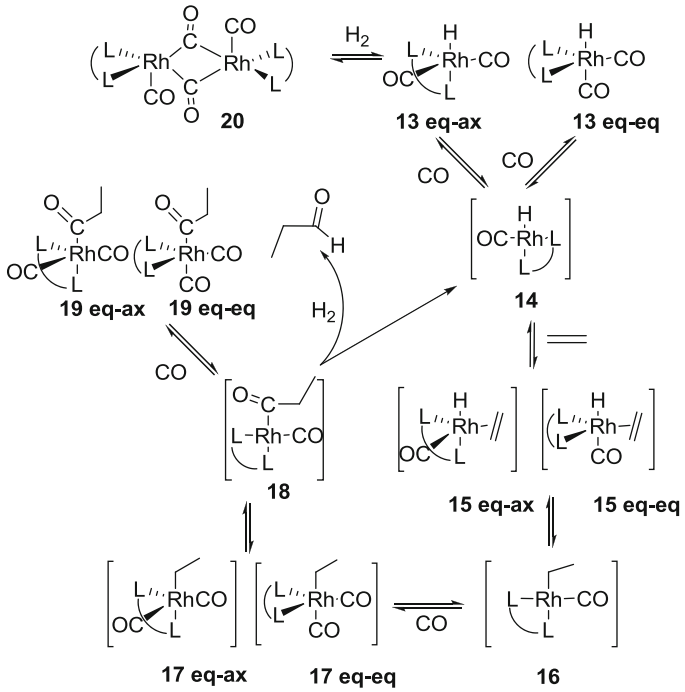


For the terminal alkenes **1** containing electron-withdrawing substituents, the formation of the branched product **2** is favored. The regioselectivity issue usually only arises for terminal and 1,2-disubstituted alkenes **4**, where isomerization usually leads to the formation of the linear products. For 1,1-disubstituted **7** and trisubstituted **10** alkenes, only one regioisomer is generally produced (**8** and **11**, respectively) with the formyl group being usually added so the formation of a quaternary carbon center is avoided [27].

However, recent studies showed that these general trends can sometimes be reversed by appropriate catalyst modifications and choice of reaction conditions, clearly showing that these trends are only indicative and that there are still many challenges to tackle in this area. Among the most significant issues are (1) the low reaction rates at low temperature where good selectivities are usually observed, (2) the difficulty to control simultaneously the regio- and the enantioselectivity, and (3) the limited substrate scope for any single ligand.

2 Rh-Catalyzed Hydroformylation Mechanism

In Scheme 2 the well accepted mechanism of the Rh-catalyzed hydroformylation proposed by Heck is described for bidentate ligands [28]. It corresponds to Wilkinson's so-called dissociative mechanism [18–20]. The associative mechanism involving 20-electron intermediates for ligand/substrate exchange will not be considered. In this process, a great understanding of the mechanism has been possible



Scheme 2 Mechanism of the Rh-catalyzed asymmetric hydroformylation in the presence of bidentate ligand (L–L)

due to the observation and structural characterization of the resting state of the catalyst by in situ spectroscopic techniques (HP-IR, HP-NMR) [21 and references therein]. For bidentate ligands (L–L), the common starting complex is the [RhH(L–L)$(CO)_2$] species **13**, containing the ligand coordinated in equatorial positions (denoted eq–eq throughout the scheme) or in an apical–equatorial position (complexes denoted eq–ax).

Dissociation of equatorial CO from **13** leads to the square-planar intermediate **14**, which associates with alkene to give complexes **15**, 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 **14** to give the pentacoordinate intermediates **15** [29]. This step is also crucial in determining the enantioselectivity since the enantioface discrimination occurs between **14** and **16**, and particularly between **14** and **15**. The CO dissociation from **13** was shown to be much faster than the overall hydroformylation process, indicating that the rate of the reaction is dominated by the reaction of **14** with either CO or the alkene to form **13** or **15** [30]. It has not been established experimentally whether alkene complexation is reversible or not, although in Scheme 2 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 **15** undergo migratory insertion to give the square-planar alkyl complex **16**. This species can undergo β-hydride elimination, thus leading to isomerization, or can react with CO to form the trigonal bipyramidal (TBP) complexes **17**. Thus, under low pressure of CO more isomerization may be expected. At low temperatures (<70°C) and 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 are determined at this point. Complexes **17** undergo the second migratory insertion (see Scheme 2) to form the acyl complex **18**, which can react with CO to give the saturated acyl intermediates **19** or with H_2 to give the aldehyde product and the unsaturated intermediate **14**. The reaction with H_2 presumably involves oxidative addition and reductive elimination, but for rhodium no trivalent intermediates have been observed [31]. At low hydrogen pressures and high rhodium concentrations, the formation of dirhodium dormant species such as **20** becomes significant [32].

As mentioned above, the catalytic hydroformylation of alkenes is one of the largest applications of homogeneous organotransition 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 that provided low to moderate enantioselectivities [25, 26]. With this type of ligand, the highest ee value was reported using styrene as substrate and bdpp (bis-diphenylphosphino pentane) as ligand (ees up to 64%) [33]. Later, higher enantioselectivities were achieved using more sophisticated diphosphite and phosphine–phosphite ligands [6–14 and references therein; 18–20].

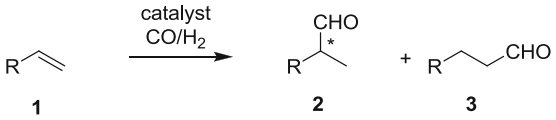
In the following sections, the most relevant results reported in the asymmetric Rh-catalyzed hydroformylation of alkenes are described. The reactions are classified by degree of substitution of the substrates in order to highlight the issue of the substrate/ligand compatibility in this process. Advances in supported chiral catalysts in this process are also described.

3 Rh-Catalyzed Asymmetric Hydroformylation of Monosubstituted Alkenes

The hydroformylation of monosubstituted alkenes (Scheme 3) 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 [4–14 and references therein].

For example, the hydroformylation of vinyl arenes (R = aryl) is used as a model for the synthesis of 2-aryl propionaldehydes, which are intermediates in the

Scheme 3 Asymmetric hydroformylation of monosubstituted alkenes



synthesis of 2-aryl propionic acids, the profen class of non-steroidal drugs. The Rh-catalyzed asymmetric hydroformylation of several other monosubstituted alkenes, such as allyl cyanide and vinyl acetate, was successfully carried out [6–14 and references therein]. In general, 1,3-diphosphite and phosphine–phosphite ligands provided the best results in these processes [18–20]. However, the use of bisphosphacyclic ligands has recently emerged as an efficient alternative [6–14 and references therein].

3.1 1,3-Diphosphite Ligands

The use of diphosphite ligands was intensively studied in this process as they provide high levels of selectivity with these substrates [34]. The initial success in the rhodium-catalyzed asymmetric hydroformylation of vinyl arenes came from Union Carbide with the discovery of the diphosphite ligand (2*R*, 4*R*)-pentane-2,4-diol **21** (Scheme 4) [35, 36].

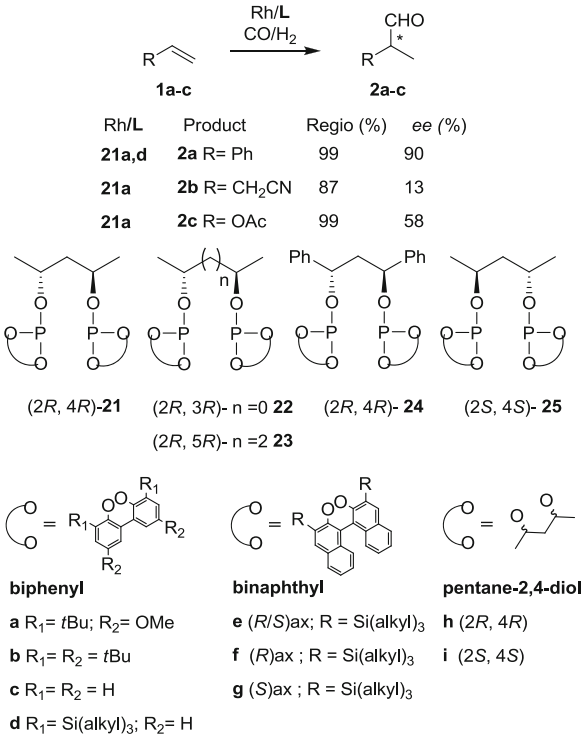
Good chemo-, regio-, and enantioselectivities (ee up to 90%) were obtained with (2*R*, 4*R*)-pentane-2,4-diol diphosphite derivatives (**21a–c**) but only when the reaction was performed around room temperature. Inspired by these excellent results, other research groups synthesized the series of diphosphite ligands **22–25** in order to study the effect of structural modifications on the Rh-catalyzed asymmetric hydroformylation of vinyl arenes (Scheme 4) [37–41].

The influence of the bite angle of these ligands was studied with diphosphite ligands (2*R*, 4*R*)-pentane-2,4-diol **21**, (2*R*, 4*R*)-butane-2,4-diol **22**, and (2*R*, 4*R*)-hexane-2,4-diol **23** [38]. In general, the ligand **21**, which contains a three-carbon-atoms bridge, provided higher enantioselectivities than ligands **22** and **23**, which have a two and four-carbon-atoms bridge, respectively.

The effect of different phosphite moieties was studied with ligands **21a–g** [37–39]. 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 also has 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 **21a** and **21d**.

The influence of the backbone was studied comparing the results obtained with the ligands **21** and **24** [37–39]. Surprisingly, ligand **24**, which contains a more sterically hindered phenyl group, provided lower enantioselectivity than ligand **21**.

Scheme 4 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligands **21**–**25**



A cooperative effect between the different chiral centers of the phosphite ligands **21f–i** and **25f–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 **21f**, **g** and **25f**, **g**. The hydroformylation results indicated a suitable combination for ligand **21g** (ees up to 86%) [37–39]. Later, Bakos and co-workers found a similar matched–mismatched effect between the chiral ligand bridge and the chiral phosphite moiety of the ligands **21h**, **i** and **25h**, **i** [40]. Interestingly, the hydroformylation results obtained with ligands **21a** and **21d**, which are conformationally flexible and contain axially chiral biphenyl moieties, are similar to those obtained with ligand **21g**. This indicated that diphosphite ligands containing these biphenyl moieties predominantly exist as a single atropoisomer in the hydridorhodium complexes [$RhH(CO)_2$(diphosphite)] when bulky substituents are present in *ortho* positions [37–39]. 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 = **21**, **25**) species formed under hydroformylation conditions by high pressure NMR techniques (HP-NMR) [14 and references therein; 18–20]. From these TBP complexes, two isomeric structures are possible, one containing the diphosphite

coordinated in a bis-equatorial (eq–eq) fashion and one 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 = **21**, **25**) species strongly depend on the configuration of the pentane-2,4-diol ligand backbone and on the chiral biaryl phosphite moieties. Thus, ligands **21a**, **21d,** and **21g**, which form well-defined stable bis-equatorial (eq–eq) complexes, lead to good enantiomeric excesses. In contrast, ligands **21i** and **25g**, which form mixtures of complexes, lead to low enantioselectivities [37–39, 42]. The ligand **21a** was also evaluated in the Rh-catalyzed asymmetric hydroformylation of allyl cyanide **1b** and vinyl acetate **1c** 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 (**26**, **29**) and 6-deoxy-1,2-*O*-isopropyliden-*α*-D-glucofuranose (**27**, **28**, **30**, **31**) were successfully applied in the Rh-catalyzed asymmetric hydroformylation of vinyl arenes (Scheme 5) [43–46].

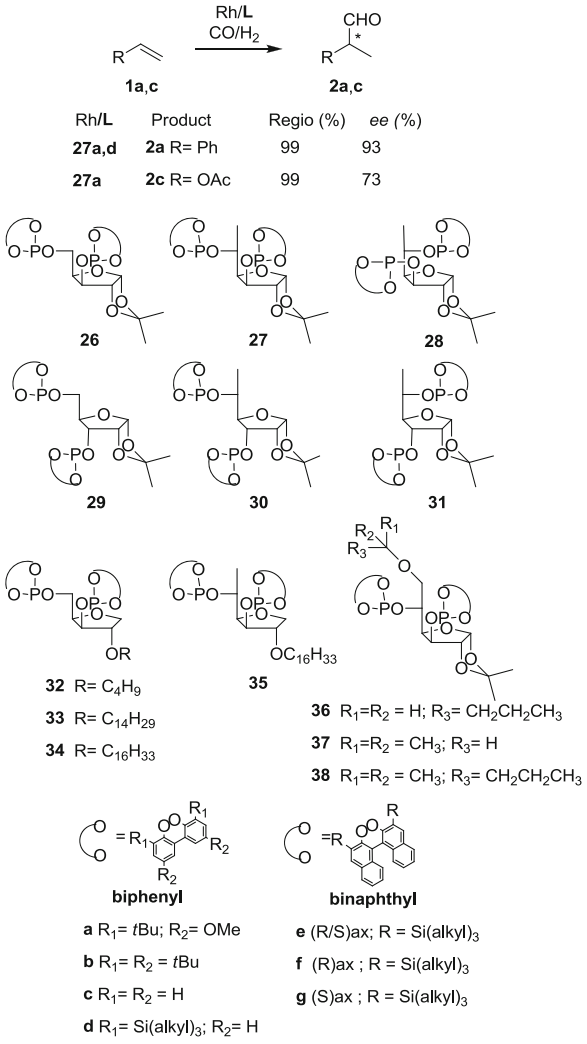
The use of diphosphite ligands **27a**, **d** and **31a**, **d** in the Rh-catalyzed asymmetric hydroformylation of styrene provided the *S*- and *R*-enantiomers of the product with high enantioselectivities (ee up to 93%) and excellent regioselectivity (Scheme 5) [45, 46]. The ligand **27b** was also tested in the hydroformylation of vinyl acetate, obtaining excellent regioselectivity (99%) with an enantioselectivity of 73% [47].

Recently, related C1-symmetry diphosphite ligands conformationally more flexible (**32–35**) or incorporating an increase in steric hindrance at the C-6 position (**36–39**) were synthesized (Scheme 5) [47, 48]. These ligands were probed in the hydroformylation of styrene **1a** and vinyl acetate **1c** with good regio- and enantioselectivity (up to 81% and 68%, respectively), but these selectivities turned out to be lower than with the ligand **27**. Therefore, the bicycle structure and the methyl substituent at C-5 position seem to be 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 (1) the absolute configuration of the product is governed by the configuration at the stereogenic centre C-3, (2) the level of enantioselectivity is influenced by the presence of stereocenters at C-3 and C-5 positions, where the phosphorus atoms are attached, (3) bulky substituents in *ortho* positions of the biaryl phosphite moieties are necessary to achieve high levels of enantioselectivity, and (4) pseudo-enantiomer ligands such as **27** and **31** afford the same level of enantioselectivity for both product enantiomers.

Interestingly, the ligands **27** and **31**, for which only [$RhH(CO)_2$(L-L)] species with eq–eq coordination were observed by HP-NMR techniques, provided higher enantioselectivity (ee up to 93%) than the related ligands **28** and **30** (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

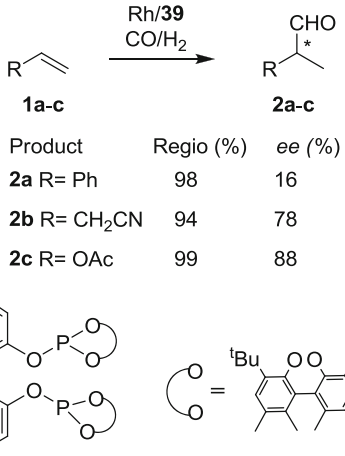
Scheme 5 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligands **26–38**



equatorial–equatorial (eq–eq) mode, was observed to produce high levels of enantioselectivity in the Rh-catalyzed asymmetric hydroformylation of styrene, as previously mentioned [45–48].

In contrast with the diphosphites previously mentioned, the KELLIPHITE ligand (**39**), which was developed by Dow Chemical Company, incorporates the chirality in the bisphenol unit, while the backbone is achiral (Scheme 6). 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 [49, 50].

Scheme 6 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligand KELLIPHITE (**39**)



KELLIPHITE (**39**)

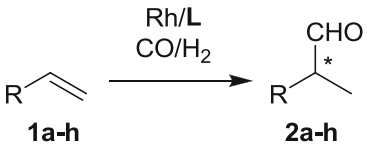
3.2 Phosphine–Phosphite Ligands

The discovery of the (*R*,*S*)-BINAPHOS (**40**) and (*S*,*R*)-BINAPHOS (**41**) ligands in 1993 by Takaya and Nozaki produced a real breakthrough in the Rh-catalyzed asymmetric hydroformylation reaction (Scheme 7) [51].

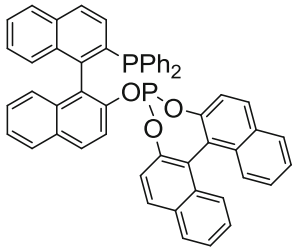
These ligands allowed, for the first time, an increase in the scope of this process since they provided high enantioselectivity in the Rh-catalyzed asymmetric hydroformylation of several classes of monosubstituted alkenes such as vinyl arenes, 1-heteroatom-functionalised alkenes, and disubstituted 1,3-dienes (Scheme 7), and are still currently references in this area [52 and references therein; 53–63]. 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 allyl cyanide and, although moderate regioselectivity was obtained (72%), the highest enantioselectivity (66%) by far was achieved using the ligand **40** [64]. As a general rule, the presence of electron-withdrawing substituents such as phenyl or heteroatoms in the alkene substrate leads to a control the regioselectivity in favor of the branched product, independently of the ligand used [6].

It is noteworthy that (*R*,*S*)-BINAPHOS (**40**) or the (*S*,*R*)-BINAPHOS (**41**) ligands yield the two enantiomers of the product with high enantioselectivity [65, 66]; however, the (*R*,*R*)- and (*S*,*S*)-BINAPHOS, diastereoisomers of ligands **40** and **41**, 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 centre in an eq–eq fashion, the BINAPHOS ligand was found to coordinate



Product	2a	2b	2c	2d$_1$	2e	2f	2g	2h
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 (**40**)

(*S,R*)-BINAPHOS (**41**)

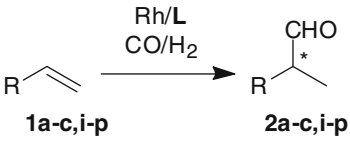
Scheme 7 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using (*R*,*S*)- and (*S*,*R*)-BINAPHOS (**40**) and (**41**)

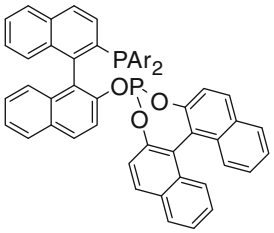
to Rh in an eq–ax mode as a single isomer in the resting state [$RhH(CO)_2$(L–L)] of the process [65, 66].

The second generation of BINAPHOS-type ligands (Scheme 8) was recently developed by the introduction of 3-methoxy substituents on the aryl phosphine units **42** [53, 54], and by replacement of the phosphite group by a phosphoramidite function, yielding the YANPHOS ligand (**43**) (Scheme 8) [67]. The Rh/**42** increased the regio- and enantioselectivity in the asymmetric hydroformylation of styrene, vinylfurans, and thiophenes (Scheme 8).

YANPHOS (**43**) (Scheme 8) provided higher enantioselectivity than the BINAPHOS ligand **40** without altering the regioselectivity in the Rh-catalyzed asymmetric hydroformylation of styrene and vinyl acetate (ee up to 99% and 96%, respectively). Additionally, the ligand **43** provided higher enantioselectivity than KELLIPHITE (**39**) (Scheme 6), although a slight decrease in regioselectivity (80% vs 94%) was observed in the hydroformylation of allyl cyanide (ee up to 96% vs 78%) [68].

Recently, the efficiency of YANPHOS ligand **43** was again demonstrated in the Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes with *N*-allyl amides, *N*-allyl phthalamides, and *N*-allyl sulfonamides substituents with excellent

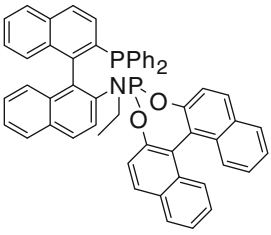




42 Ar = 3-MeOC$_6$H$_4$

Rh/**42**

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



(R,S)-YANPHOS (**43**)

Rh/**43**

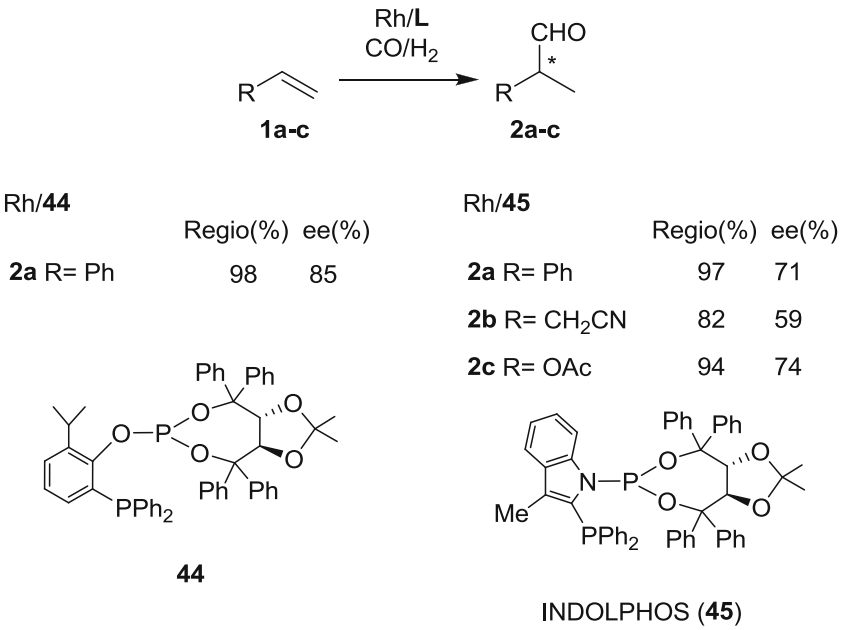
	Regio(%)	ee(%)
2a R= Ph	89	99
2b R= CH_2CN	80	96
2c R= OAc	93	96
2m R= CH_2NHBOC	66	94
2n R= CH_2NHBz	78	95
2o R= $CH_2NHPhthaloyl$	84	96
2p R= CH_2NHSO_2(p-MeOPh)	71	96

Scheme 8 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using the ligands **42** and **43**

ees (up to 96%), good regioselectivities (up to 84%), and a turn over number (TON) up to 9,700.

Inspired by the excellent results obtained using **40** and **41**, several new phosphine–phosphite ligands with different backbones have been developed over the last few years but the catalytic results using these ligands provided lower enantioselectivity (from 20% to 85%) than those previously achieved with the original BINAPHOS ligand [69–74]. Some of these ligands help to elucidate the correlation between the ee and the electron-withdrawing properties of the substitution in the alkene [75].

Based on the BINAPHOS structure, a new family of phosphine–phosphite and phosphine–phosphoramidite ligands was constituted using a Taddol-based backbone in the phosphite or phosphoramidite moiety, respectively (Scheme 9) [76, 77]. These ligands were applied in the Rh-catalyzed asymmetric hydroformylation of



Scheme 9 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using Taddol-based ligands (**44** and **45**)

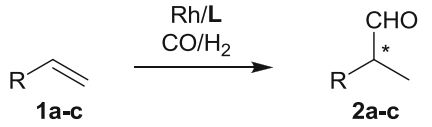
styrene, allyl cyanide, and vinyl acetate with excellent regioselectivities (up to 98%) and good ees (up to 85%).

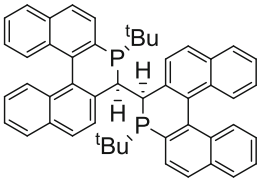
3.3 Bisphospholane Ligands

Several bisphospholane chiral ligands known as efficient ligands for asymmetric hydrogenation were recently evaluated in asymmetric hydroformylation (Scheme 10) [78].

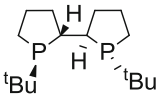
Two ligands, namely (*S*)-BINAPINE (**46**) and (*S*,*S*,*R*,*R*)-TANGPHOS (**47**), were found to give excellent enantioselectivities in the asymmetric hydroformylation of styrene, allyl cyanide, and vinyl acetate (Scheme 10) [79]. It is noteworthy that the enantioselectivities achieved for product **2b** with these ligands are the highest ever reported for the allyl cyanide substrate.

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 (**48**) (Scheme 10), 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

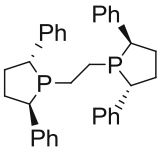




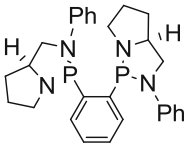
(R,S)-BINAPINE (**46**)



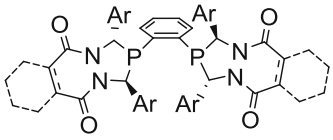
(S,S,R,R)-TANGPHOS (**47**)



(R,R)-Ph-BPE (**48**)



Esphos (**49**)



Bis-3,4-diazaphospholane (**50**)

Product	**2a**		**2b**		**2c**	
Rh/**L**	R= Ph		R= CH_2CN		R= OAc	
			Regio (%)	ee(%)		
46	90	94	87	94	97	87
47	93	90	88	93	97	83
48	98	94	88	90	99	82
49					94	89
50	97	89	83	87	98	96

Scheme 10 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using the diphosphine ligands **46**–**50**

this ligand [80]. Several spacers between the two phosphorus donor atoms were evaluated and the two-carbon bridge of **48** provided the highest selectivity for all three substrates [79].

A series of bis-2,5-diazaphospholane ligands was also probed in this process and the ESPHOS (**49**) proved to be optimal, with the best results being obtained in the hydroformylation of vinyl acetate (ee up to 89%) (Scheme 10) [81]. The bis-3,4-diazaphospholane ligand **50** also provided excellent regio- and enantioselectivity (ee up to 96%) in this reaction (Scheme 10) [82].

3.4 Bis-Phosphonite Ligands

The bis-phosphonite ligand **51** provided moderate selectivities in the hydroformylation of styrene and allyl cyanide (Scheme 11). However, this ligand provided an excellent 91% ee in the hydroformylation of vinyl acetate [83]. The related diphosphinite ligand derived from ferrocene **52** was also recently reported by Ding and co-workers 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) [84].

3.5 Phosphite–Phospholane Ligands

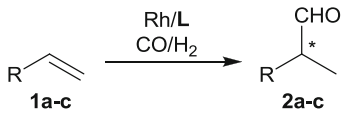
Very recently it was demonstrated that branched aldehydes can be produced by hydroformylation of terminal alkenes of formula $RCH_2CH{=}CH_2$ using a new hybrid ligand called "bobphos" (**53**) (Scheme 12) [85]. This ligand, result of the combination of KELLIPHITE and Ph-bpe, provided good to excellent conversions (between 64% and 99%), very good regioselectivities (between 71% and 91%), and excellent ees (up to 93%) for a series of terminal alkenes (Scheme 12).

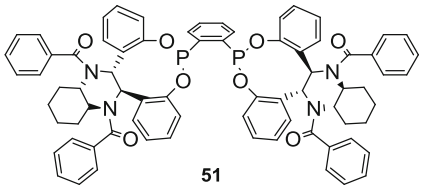
3.6 Monodentate Phosphorus-Based Ligands

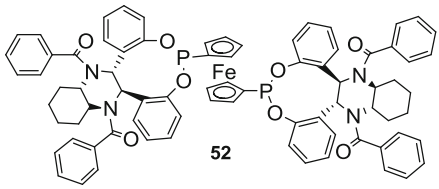
Nowadays, despite the successful use of monodentate ligands in many transition metal catalyzed processes, there are only a few reports concerning their use in asymmetric hydroformylation. Achieving high enantioselectivities in this process using those ligands remains a challenge.

Although the use of monodentate phosphorus donor ligands usually provides higher catalytic activity than their bidentate counterparts, only moderate to good enantioselectivities have been reported in asymmetric hydroformylation processes so far. For instance, the ligand **57** was tested in the Rh-catalyzed asymmetric hydroformylation of styrene and allyl cyanide and provided moderate enantioselectivities (Scheme 13). When vinyl acetate was the substrate, very poor ees were obtained (Scheme 13) [49, 50]. However, in 2004, Ojima and co-workers reported the use of the phosphoramidite ligand **55** (Scheme 13), related to monophosphite **54**, 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 [86]. These results, although still far from those obtained with bidentate ligands, clearly indicated that achieving high ees using monodentate ligands is possible.

Scheme 11 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes with ligands **51** and **52**







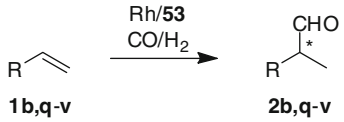
Product	2a		2b		2c	
Rh/**L**	R= Ph		R= CH_2CN		R= OAc	
			Regio (%)	*ee*(%)		
51	92	79	82	79	98	91
52	95	55			94	83

In 2005, Breit report 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 [87]. 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 14) [88, 89]. The templated heterobidentate ligand **56** induced much higher enantioselectivities (ee up to 72%) 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.

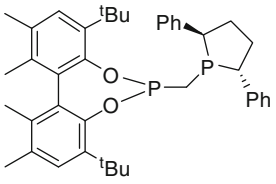
4 Rh-Catalyzed Asymmetric Hydroformylation of Disubstituted Alkenes

The Rh-catalyzed asymmetric hydroformylation of disubstituted alkenes has received much less attention than that of their monosubstituted counterparts. To the best of our knowledge, only a few examples of asymmetric Rh-catalyzed hydroformylation of

Scheme 12 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes with ligand **53**



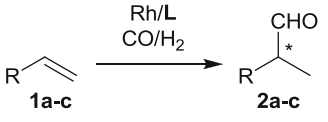
1b,q-v **2b,q-v**



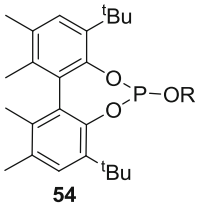
bobphos (**53**)

Product	Regio (%)	*ee* (%)
2b R= CH_2CN	91	81
2q R= Bz	80	90
2r R= $CH_2C_6F_5$	86	91
2s R= CH_2(*p*-^{t}BuPh)	75	92
2t R= CH_2CH_2Ph	71	75
2u R= Bu	75	93
2v R= $CH_2CON(Ph)(CH_3)$	81	92

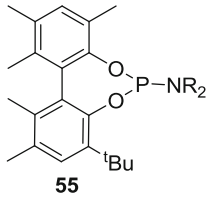
Scheme 13 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligands **54** and **55**



1a-c **2a-c**



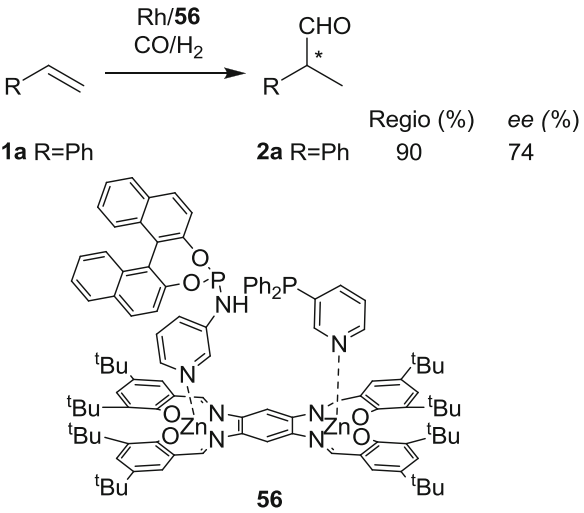
54



55

Product	**2a**	**2b**	**2c**
Rh/**L**	R= Ph	R= CH_2CN	R= OAc
		Regio (%) *ee*(%)	
54	94 38	84 43	93 8
55		96 80	

Scheme 14 Rh-catalyzed asymmetric hydroformylation of styrene using the templated ligand **56**



1,2-disubstituted and 1,1-disubstituted alkenes have been reported so far (Scheme 1) [25, 47, 90–110].

4.1 Linear 1,2-Disubstituted Alkenes

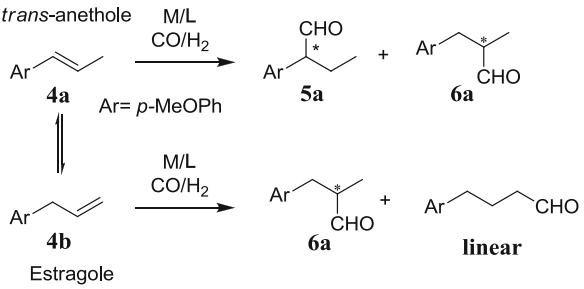
The asymmetric hydroformylation of propenylbenzenes was originally studied by Kollár using $PtCl_2$(bdpp)/$SnCl_2$ as catalyst [90]. The reaction was performed using *trans*-anethole and estragole as substrate in order to synthesize the branched chiral aldehydes **5a** and **6a** (Scheme 15). However, the formation of the linear aldehyde was observed due to *trans*-anethole isomerization into terminal monosubstituted estragole. Furthermore, moderate to low enantioselectivities were obtained (ee up to 27%). The 1,3-diphosphite ligand **26** was used in the Rh-catalyzed asymmetric hydroformylation of *trans*-anethole **4a** and estragole **4b** (Scheme 15) but moderate to low enantioselectivities were achieved (ee up to 15%) [91].

Nozaki et al. reported the asymmetric Rh-catalyzed hydroformylation of *trans*-anethole **4a** into **5a** using the BINAPHOS ligand **40** with excellent regioselectivity (98%) and a remarkable 80% ee [92, 93].

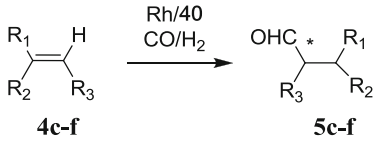
In the Rh-catalyzed asymmetric hydroformylation of 1,2-alkyl-disubstituted alkenes (Scheme 16) as substrates, the BINAPHOS ligand **40** provided the highest ee values [92, 93]. Interestingly, it was reported that the *E*-isomers **4d** and **4f** yielded lower enantioselectivity than their *Z*-counterparts **4c** and **4e**.

A monodentate phosphoramidite template ligand was developed by Reek et al. and used in the asymmetric Rh-catalyzed hydroformylation of *E*-2-octene (**5i**) (Scheme 17). This ligand (**57**) exhibits a supramolecular control over the Rh center, due to the presence of two pyridine functions in the bis(naphthol) skeleton that are

Scheme 15 Isomerization processes and asymmetric hydroformylation of *trans*-anethole and estragole



Scheme 16 Rh-catalyzed asymmetric hydroformylation of disubstituted alkenes



Product	*ee* (%)
5c R_1= H, R_2=R_3= Me	85
5d R_1= Me, R_2= H, R_3= Me	48
5e R_1= H, R_2=R_3= Et	79
5f R_1= Et, R_2= H, R_3= Et	69

bound to zinc(II) porphyrins. With this ligand, useful conversions (up to 56%) with moderate ees (up to 45%) were achieved. When the BINAPHOS ligand **40** was used in the same reaction, similar conversion (55%) was obtained although without significant enantioselective induction [94].

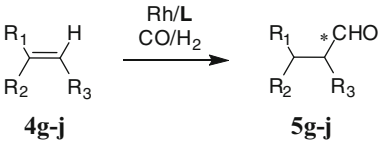
Very recently the same author described the use of this ligand (**57**) in the asymmetric Rh-catalyzed hydroformylation of internal alkenes like *E*-2-hexene (**4g**), *E*-2-heptene (**4h**), and *E*-2-nonene (**4j**), achieving conversions up to 65% and moderate ees (up to 47%) [95].

The same research group formerly reported the use of encapsulated catalysts for the selective hydroformylation of unfunctionalized alkenes [96]. The ligand (**58**) (Scheme 18) acts as a supramolecular "box" with the bis-[Zn(salphen)] moiety as a template and two chiral phosphoramidite ligands as the pillars. In the asymmetric Rh-catalyzed hydroformylation of internal alkenes, the inner aldehydes with *R* configuration were preferably formed (with the exception of 3-hexene for which the *S*-aldehyde was produced).

4.2 Monocyclic 1,2-Disubstituted Alkenes

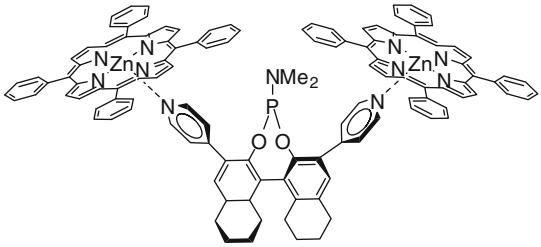
Among monocyclic 1,2-disubstituted alkene substrates, five-membered ring heterocycles such as dihydrofurans and dihydropyrroles have been the most studied.

Scheme 17 Rh-catalyzed asymmetric hydroformylation of disubstituted alkenes with ligands (**40**) and (**57**)



4g-j **5g-j**

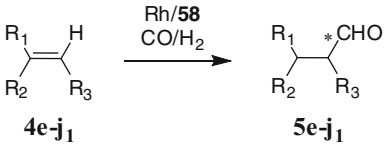
Product		
	5g	R_1= Me, R_2=H, R_3= Pr
	5h	R_1= Me, R_2=H, R_3= Bu
	5i	R_1= Me, R_2=H, R_3= Pent
	5j	R_1= Me, R_2=H, R_3= Hex



57

Rh/**40**	Conv (%)	*ee*(%)	Rh/**57**	Conv (%)	*ee*(%)
			5g	65	46
			5h	43	44
5i	55	0	**5i**	56	45
			5j	52	47

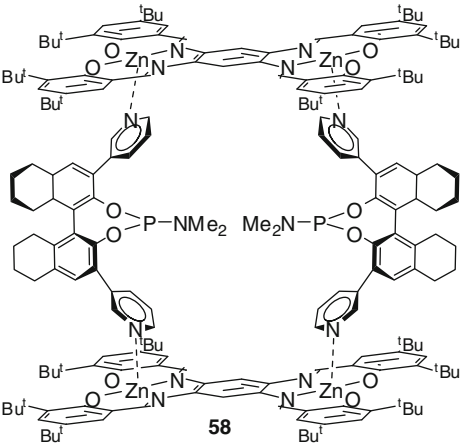
With these substrates, the simultaneous control of the chemo-, regio-, and enantioselectivity is a key issue since the presence of a heteroatom in the cycle favors in some cases an isomerization process in the presence of a metal-hydride species. Previous studies using achiral ligands demonstrated that the reaction conditions greatly affected the chemo- and regioselectivity of this reaction [97, 98]. Indeed, allyl ethers were shown to isomerize rapidly into their vinyl analogues under hydroformylation conditions (Scheme 19). This isomerization process is of critical importance since it has a direct influence on the regioselectivity of the reaction, but also on the enantioselectivity since the opposite enantiomers of tetrahydro-3-carbaldehyde are formed from the allylic **4k–m** and vinylic **4n–p** isomers of the substrate [99]. It is therefore required to limit the isomerization in order to obtain high selectivities. In the Rh-catalyzed asymmetric hydroformylation of 2,5-dihydrofuran **4k**, Nozaki et al. reported the first successful results using the BINAPHOS ligand **40** which yielded total regioselectivity to the tetrahydro-3-carbaldehyde **5k** with 68% ee (*R*) (Scheme 21) [92, 93, 100]. However, when the 2,3-dihydrofuran **4n** was tested with the same catalyst, no regioselectivity was observed and the ee obtained for the



4e-j$_1$ **5e-j$_1$**

Product

5e	R_1= H, R_2=Et, R_3= Et	**5i**	R_1= Me, R_2=H, R_3= Pent
5f	R_1= Et, R_2= H, R_3= Et	**5i$_1$**	R_1= H, R_2=Me, R_3= Pent
5h	R_1= Me, R_2=H, R_3= Bu	**5j**	R_1= Me, R_2=H, R_3= Hex
5h$_1$	R_1= H, R_2=Me, R_3= Bu	**5j$_1$**	R_1= H, R_2=Me, R_3= Hex



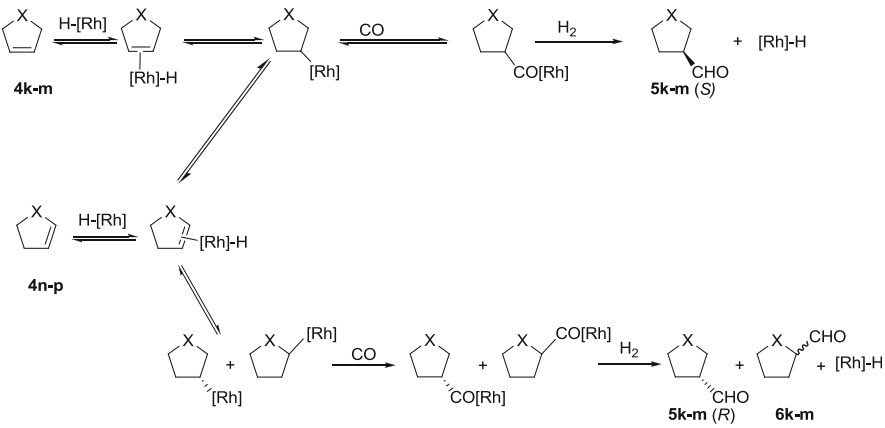
58

Rh/**58**	Conv(%)	Inner(%)	*ee*(%)		Conv(%)	Inner(%)	*ee*(%)
5e	11	na	78 (S)	**5i**	10	60	86 (R)
5f	19	na	81 (S)	**5i$_1$**	20	70	93 (R)
5h	9	55	83 (R)	**5j**	13	52	81 (R)
5h$_1$	24	67	91 (R)	**5j$_1$**	26	61	90 (R)

Scheme 18 Rh-catalyzed asymmetric hydroformylation of internal alkenes with the ligand **58**

aldehyde **5k** decreased to 38% with *S* configuration. This catalytic system was thus suitable to avoid isomerization of **4k** into **4n** but not selective for the hydroformylation of **4n**. In the same study, the amine analogues **4l**, **4m,** and **4o** were also tested as substrates using the same catalytic system (Scheme 19) and similar results were obtained.

The previously mentioned 1,3-diphosphites **27**–**38** derived from carbohydrates were successfully applied in the Rh-catalyzed hydroformylation of these substrates [47, 101, 102]. The results indicated that ligands **27**, **35**–**38**, which have a glucose



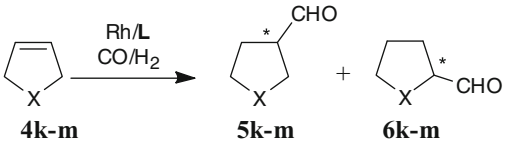
Scheme 19 Isomerization processes observed during the Rh-asymmetric hydroformylation of five-membered heterocyclic alkenes

configuration, are the most appropriate to obtain high enantioselective induction in the hydroformylation of these substrates. In the case of the 2,5-dihydrofuran **4k**, the highest enantioselectivity in the aldehyde **5k** was obtained using ligand **35b** (88% *S*). Using this ligand, no isomerization was observed under hydroformylation conditions. Interestingly, the presence of bulky substituents at C-5, such as in ligands **36b**–**38b**, was shown to increase the degree of isomerization. When the 2,3-dihydrofuran (**4n**) was used as substrate, ees up to 84% (*R*) in aldehyde **5k** were achieved using ligands **36b**–**37b**, together with a regioselectivity of 80%. The 2,5-dihydropyrrole **4l** was also tested with the Rh/**27b** system, achieving comparable results to those previously reported using ligand **40** (71% and 66%, respectively).

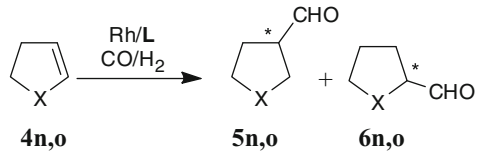
Formerly, Reek and co-workers described the synthesis and application of the ligand **59** in the Rh-catalyzed asymmetric hydroformylation of the cyclic olefins **4k**–**o** (Scheme 20). This system provided regioselectivities up to 99% and excellent ees (up to 91%). It should be noted that the highest enantioselectivities (91%) reported to date for the substrates **4k** and **4n** were achieved with this ligand [96, 103].

Interestingly, in the Rh-catalyzed asymmetric hydroformylation of the cyclic alkene **4n** (Scheme 20), which usually selectively produces the aldehyde **5n**, high regioselectivity (68%) to the aldehyde **6n** was recently reported, together with good ees (62%) using the ligand **60** (the highest reported to date) [96].

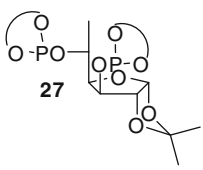
The asymmetric Rh-catalyzed hydroformylation of dioxapines **4q**, **r** was reported using the BINAPHOS ligand **40** and 1,3-diphosphite ligands derived from carbohydrates **61b** (Scheme 21) [92–100, 102]. Using the ligand **40**, total regioselectivity to **5q**, **r** was achieved, together with ees up to 76%. Among the carbohydrate derived ligands that were tested, the ligand **61b** provided the best results (Scheme 21), affording total regioselectivity to **5q**, **r** and up to 68% ee, thus indicating that no isomerization of **4q**, **r** had occurred.

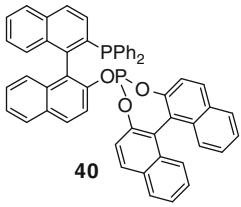


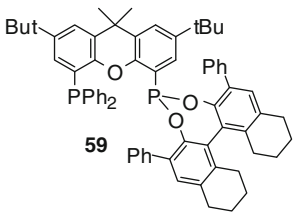
Product	5k		5l		5m	
Rh/L	X=O		X=NBoc		X=NAc	
	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)
27b	99	75 (*S*)			99	71 (-)
35b	99	88 (S)				
40	99	68 (*R*)	99	73 (*R*)	99	66 (+)
59	99	91 (*S*)	90	86 (+)	99	85

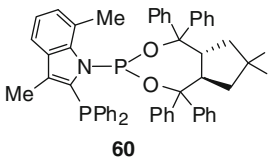


Product	5n		5o		6n	
Rh/L	X=O		X=NBoc		X=O	
	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)
27b	76	75 (*R*)				
36b	78	83 (*R*)				
37b	78	84 (*R*)				
40	50	38 (*S*)	33	71 (*S*)		
59	80	91 (*R*)				
60	32	73 (*R*)			68	62 (*R*)





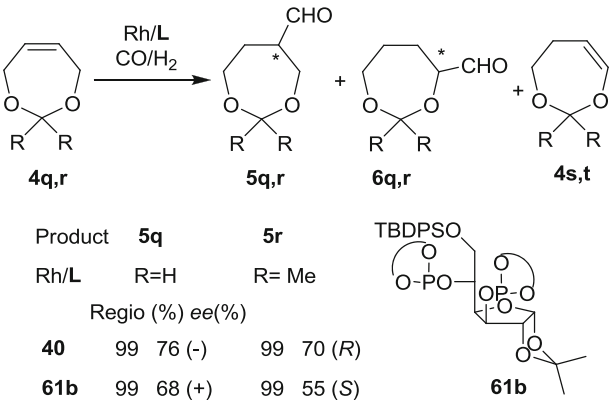




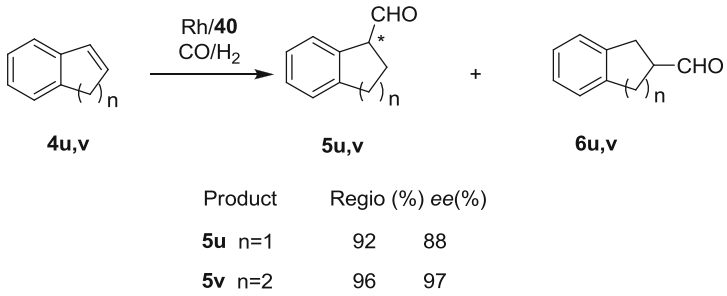
Scheme 20 Rh-catalyzed asymmetric hydroformylation of five-membered heterocyclic alkenes **4k–o**

4.3 Bicyclic 1,2-Disubstituted Alkenes

The Rh-catalyzed asymmetric hydroformylation of substrates **4u** and **4v** was reported by Nozaki et al. using the ligand **40** (Scheme 22) [92, 93]. The results are really remarkable, in particular with substrate **4v**, for which compound **5v** was obtained with practically total regio and enantioselectivity (Scheme 22). The corresponding products **5u** and **5v** are of interest since the aldehyde **5u** can be converted in a single step into the corresponding amine which exhibits hypotensive activity and the product **5v** is a synthetic intermediate to produce a vasoconstrictor tetrahydrozoline [104].



Scheme 21 Rh-catalyzed asymmetric hydroformylation of **4q**, **r**

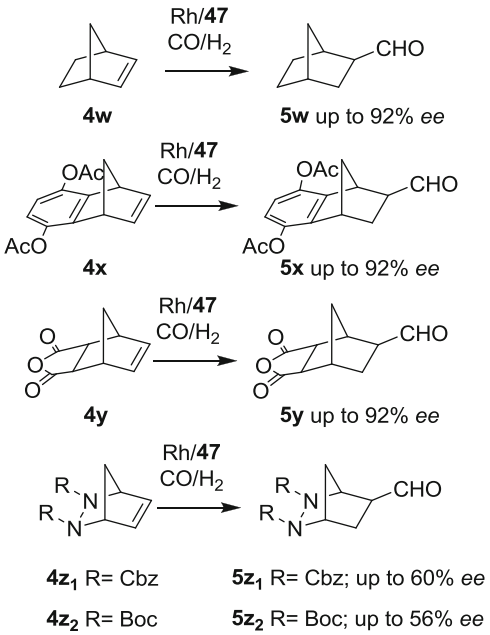


Scheme 22 Rh-catalyzed asymmetric hydroformylation of bicyclic alkenes using (*R*,*S*)-BINAPHOS ligand **40**

Another bicyclic alkene substrate of interest for carbonylation reactions is the norbornene **4w** and its derivatives. The first reports on the asymmetric Rh-catalyzed hydroformylation of norbornene afforded low enantiomeric induction with ees below 25% [105, 106]. In 2005, Bunel and co-workers reported the first highly enantioselective Rh-catalyzed hydroformylation of norbornene into the *exo* aldehyde with ees up to 92% using the diphospholane ligands **47** and **48** [107]. Using these ligands, they also reported the hydroformylation of several derivatives of this substrate with similar enantioselectivities (Scheme 23).

Recently, the hemispherical diphosphite ligands **62** (Fig. 1) with a conical calixarene skeleton was used in the asymmetric Rh-catalyzed hydroformylation of norbornene, achieving enantioselectivities up to 61% with the *exo* aldehyde being the major product [108].

More recently, the KELLIPHITE ligand (**39**) was employed in the Rh-catalyzed asymmetric hydroformylation of the bicyclic lactam azababicyclo-[2.2.1]hept-



Scheme 23 Rh-catalyzed asymmetric hydroformylation of norbornene derivatives using the diphospholane ligand **47**

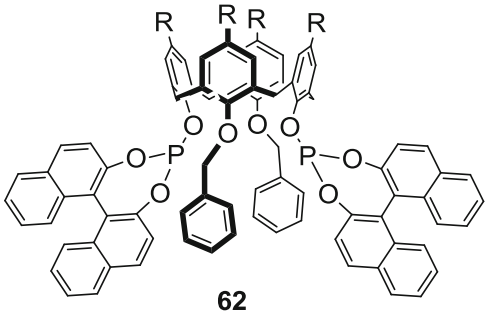
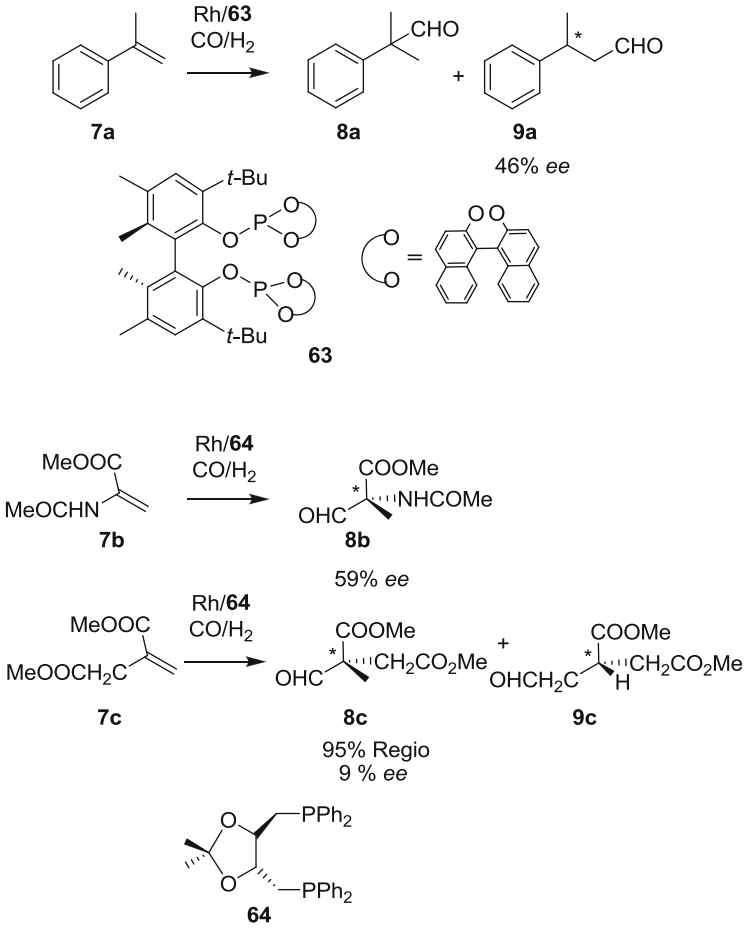


Fig. 1 Hemispherical diphosphite ligands **62** with a conical calixarene skeleton

5-en-3-one with very good results. The reaction was completely *exo*-selective, yielding total conversions and excellent regioselectivities (up to 91%) [109].

4.4 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 1).

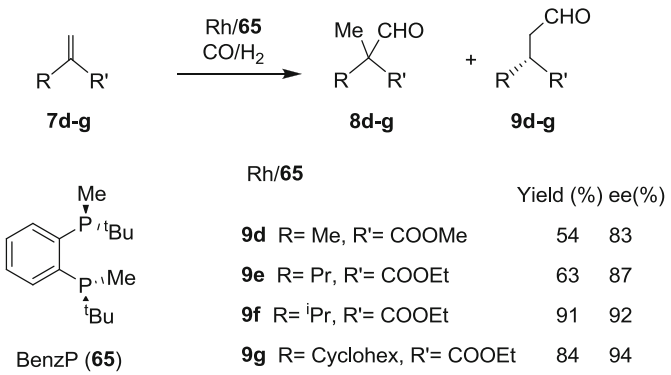


Scheme 24 Rh-catalyzed asymmetric hydroformylation of 1,1′-disubstituted alkenes

Indeed, the Rh-catalyzed asymmetric hydroformylation of 1,1-methyl styrene (**7a**) using diphosphite ligand **63** (Scheme 24) to form the linear product **9a** was recently patented. The enantioselectivity was, however, moderate (ee up to 46%) [110].

Interestingly, however, when dehydro amino acid derivatives **7b** and dimethyl itaconate **7c** were used as substrates (Scheme 24) in the presence of [RhH(CO)$(PPh_3)_3$] and 1–6 equiv. of the (*R*,*R*)-DIOP ligand **64**, the formation of the branched products was largely favored with moderate enantioselectivity (ees 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 **7c** are hydroformylated in the presence of the [$PtCl(SnCl_3)$], the only hydroformylation product obtained was the linear aldehyde with ees up to 82% [25].

Very recently, Buchwald et al. reported the Rh-catalyzed asymmetric hydroformylation of 1,1-disubstituted alkenes (α-alkyl acrylates) using the 1,3-diphosphine



Scheme 25 Rh-catalyzed asymmetric hydroformylation of α-alkyl acrylates

ligand BenzP (**65**). With this ligand, good regio- (up to 91%) and enantioselectivities (up to 94%) were achieved (Scheme 25) [111]. 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).

4.5 Other Substrates

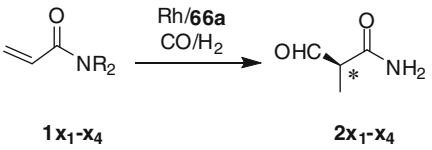
In this section, recent reports on the Rh-catalyzed asymmetric hydroformylation of "non common" alkene substrates using chiral phosphorus donor ligands and scaffolding [112] ligands (metal-organic cooperative catalysts) are presented.

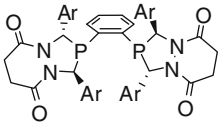
4.5.1 α,β-Unsaturated Amides, 1,3-Dienes, *N*-Vinyl Carboxamides, Allyl Carbamates, and Allyl Ethers

The substrate scope for the hydroformylation of dialkyl acrylamides $\mathbf{1x_{1-4}}$ has so far been limited to methacrylamide, acrylamide or *N*-benzyl acrylamide, with low enantioselective induction (20–50% ees) [113, 114].

However, the use of a bis-diazaphospholane ligand (**66a**) in the Rh-catalyzed asymmetric hydroformylation of *N*,*N*-dialkyl acrylamides was recently described, achieving nearly total regioselectivity and ees up to 82% (Scheme 26) [115].

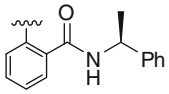
The use of the bis-3,4-diazaphospholane type ligands (**66**) has also been reported in the rhodium catalyzed hydroformylation of several 1,3-diene substrates (1,3-dienes, *N*-vinyl carboxamides, allyl carbamates, and allyl ethers) with excellent regio- and enantioselectivities by Landis et al. [116, 117]. Total conversions with good regioselectivities (>88%) and excellent enantioselectivities (91–97%) were achieved (Scheme 27).





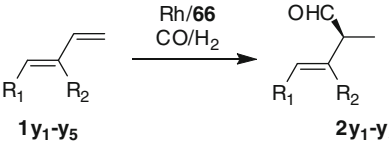
Bis-3,4-diazaphospholane (**66a**)

Ar=

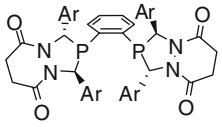


Rh/**66a**		Regio (%)	ee(%)
2x$_1$	R= Me	98	68
2x$_2$	R= Et	97	82
2x$_3$	R= *i*-Pr	98	74
2x$_4$	NR_2=NMe(OMe)	98	71

Scheme 26 Rh-catalyzed asymmetric hydroformylation of *N*,*N*-dialkyl acrylamides

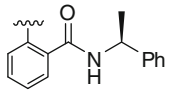


1y$_1$-y$_5$ **2y$_1$-y$_5$**

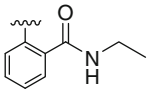


Bis-3,4-diazaphospholane

66a (S,S) Ar=



66b (S) Ar=

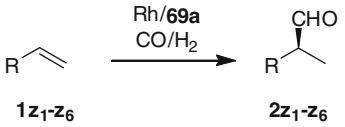


Rh/**66a**		Regio (%)	ee(%)
1y$_1$	R_1= Ph, R_2= H	99	91
1y$_2$	R_1= 2-furan, R_2= H	99	97
1y$_3$	R_1= MeO, R_2= H	99	94

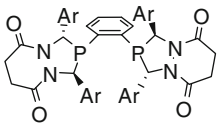
Rh/**66b**		Regio (%)	ee(%)
1y$_4$	R_1= Ph, R_2= Me	88	93
1y$_5$	R_1= 2-furan, R_2= Me	98	93

Scheme 27 Rh-catalyzed asymmetric hydroformylation of 1,3-dienes with ligands **66a** and **66b**

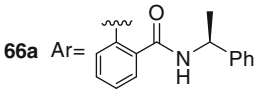
The ligand **66a** was also successfully employed in the Rh-catalyzed asymmetric hydroformylation of other alkene substrates containing amide (**1z$_1$**–**z$_3$**) and ether (**1z$_4$**–**1z$_6$**) substituents, with ees up to 99% and 82%, respectively (Schemes 26 and 28) [117].



1z$_1$-z$_6$ **2z$_1$-z$_6$**



Bis-3,4-diazaphospholane



Rh/**66a**		Regio (%)	ee(%)
2z$_1$	R= NHCOOBn	99	94
2z$_2$	R= NHCOO^{t}Bu	97	99
2z$_3$	R= $NHCOCF_3$	98	99
2z$_4$	R= CH_2OTMS	67	97
2z$_5$	R= CH_2OPh	72	96
2z$_6$	R= $CH(OAc)_2$	82	93

Scheme 28 Rh-catalyzed asymmetric hydroformylation of monosubstituted enamides and other allylic substrates with the ligand **66a**

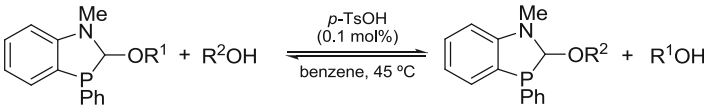
4.5.2 Scaffolding Ligands

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 [118]. In general, these "scaffolding ligands" were named by analogy with scaffolding proteins, which promote biological processes [119].

Using such methodology, the groups of Tan and Breit reported the highly regioselective Rh-catalyzed hydroformylation of homoallylic alcohols [118, 120]. Tan et al. designed the alkoxy benzoazaphosphole ligand **67** derived from *N*-methyl aniline that undergoes facile exchange with other alcohols or secondary amines (Scheme 29) [120].

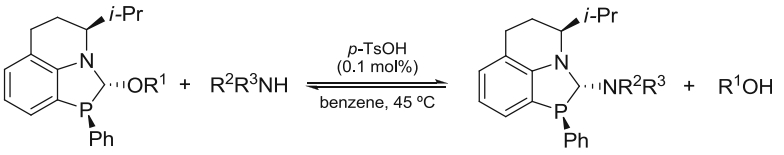
The asymmetric hydroformylation of several alkene substrates was performed by Tan and co-workers using scaffolding ligands containing a tetrahydroisoquinoline group on the alkoxy benzoazaphosphole yielding the scaffolding ligand **69** (Scheme 30).

The Breit research group demonstrated that Ph_2POMe was a suitable catalytic directing group for hydroformylation [118]. Notably, the functionalization of 1,2-disubstituted olefins and other substrates containing stereocenters proceeded with excellent regio- and stereo- selectivity. Additionally, the chemoselective hydroformylation of homoallylic alcohols over unactivated alkenes was observed.



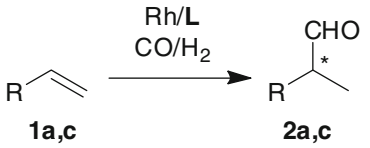
67 68

Scheme 29 Alkoxy benzoazaphosphole catalytic directing group



69 70

Scheme 30 Tetrahydroisoquinoline alkoxy benzoazaphosphole scaffolding ligand

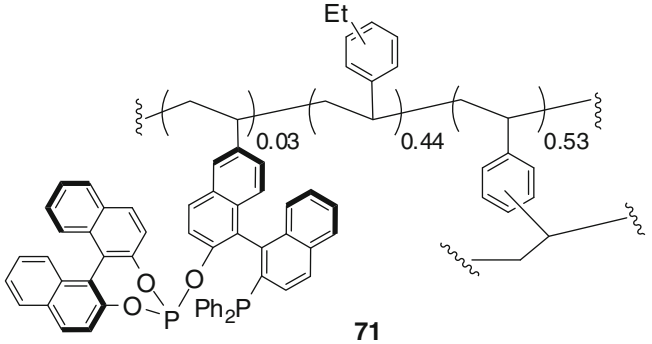


1a,c 2a,c

Product

2a R=Ph

2c R=OAc

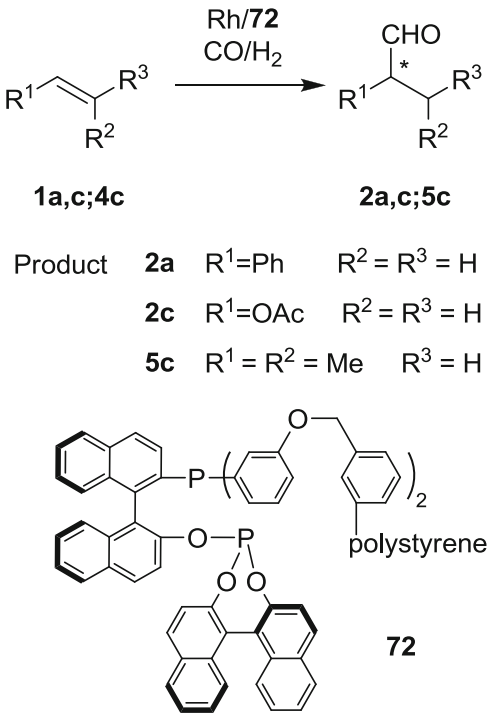


71

Rh/**40**	Regio(%)	*ee*(%)	Rh/**71**	Regio(%)	*ee*(%)
2a	89	92	**2a**	85	90
2c	84	92	**2c**	90	93

Scheme 31 Rh-catalyzed asymmetric hydroformylation of styrene and vinylacetate catalyzed with the ligand (*R*,*S*)-BINAPHOS (**40**) and the polystyrene supported ligand (**71**)

Scheme 32 Rh-catalyzed asymmetric hydroformylation with the polystyrene supported ligand (*R*,*S*)-BINAPHOS (**72**)



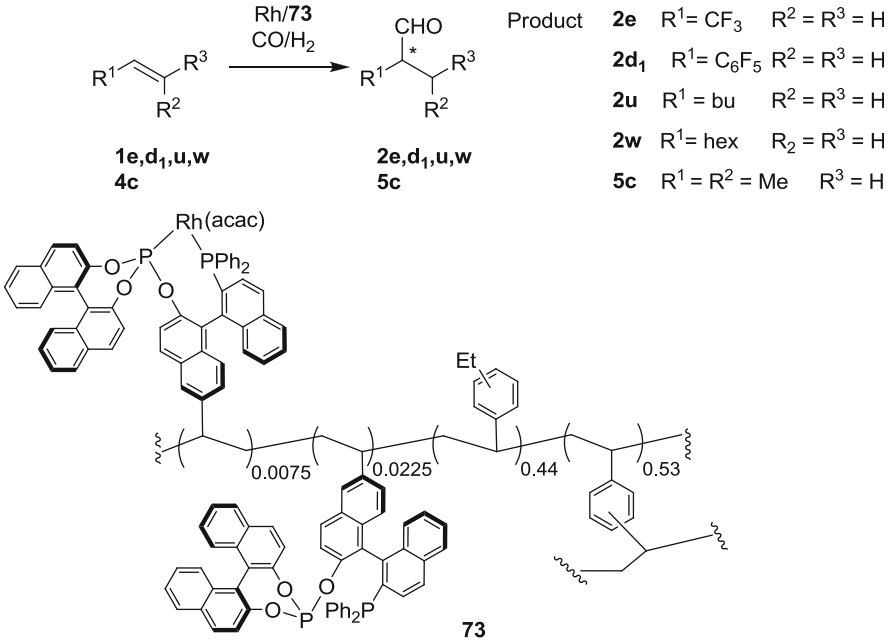
Rh/**72**	Regio(%)	*ee*(%)	TOF(h^{-1})
2a	89	92	
2b	87	92	
5c		80	27

5 Heterogenized Catalytic Systems for Asymmetric Hydroformylation of Alkenes

The development of supported chiral catalysts to facilitate its separation from the products and its recycling or its integration into continuous flow systems, is still a challenge in the field of asymmetric catalysis.

In the field of asymmetric hydroformylation, most of the results with heterogenized catalytic systems were reported by the group of Nozaki et al. using BINAPHOS derived systems.

In the late 1990s, the (*R*,*S*)-BINAPHOS ligand (**71**) was immobilized by covalent bonding to a high cross-linked polystyrene and studied the Rh-catalyzed asymmetric hydroformylation of styrene and vinyl acetate [121]. This catalytic system provided



Rh/**73**	Regio(%)	*ee*(%)	TOF(h^{-1})
2e	95	90	9
2d$_1$	89	88	
2u	21	60	
2w	21	73	
5c		82	10

Scheme 33 Rh-catalyzed asymmetric hydroformylation with the polystyrene supported catalyst **73**

good conversions (up to 83%), excellent regioselectivities (up to 90%), and ees up to 93% (Scheme 31).

A few years later, the new class of polymer-supported (*R*,*S*)-BINAPHOS (**72**) was reported in the asymmetric hydroformylation of styrene and vinyl acetate under batch conditions and in the transformation of *Z*-2-butene under continuous-flow conditions [57]. The results obtained in the hydroformylation of styrene and vinyl acetate were similar to those previously reported, but the most remarkable results were achieved in the continuous-flow asymmetric hydroformylation of *Z*-2-butene for which a TOF value of 27 h^{-1} and ee of 80% were obtained (Scheme 32).

In 2003, the use of the (*R*,*S*)-BINAPHOS-Rh(I) catalyst (**73**) (Scheme 33), which is covalently anchored to a highly cross-linked polystyrene support, was reported in the asymmetric hydroformylation of several alkenes in the absence of organic solvents [55]. In the hydroformylation of *Z*-2-butene this system provided total regioselectivity with ees up to 82%. The heterogenized catalysts were also employed

Table 1 Sequential conversion of various olefins using a continuous $scCO_2$ flow system

Cycle	Olefin	Conversion (%)	*b*/*l*	ee (%)
1	**1a**	49	82/18	77
2	**1c**	5	70/30	74
3	**1w**	47	21/79	73
4	**1u**	40	21/79	60
5	**1a**	36	81/19	82
6	$\mathbf{1d_1}$	27	89/11	88
7	$\mathbf{1d_2}$	21	91/9	78
8	**1a**	54	80/20	80

in a continuous vapor-flow column reactor to transform 3,3,3-trifluoropropene to the corresponding branched aldehyde with regioselectivity up to 95% and ee of 90%. Less volatile olefins such as 1-hexene, 1-octene, and pentafluoro styrene were successfully converted into the corresponding branched aldehydes with high ee through a flow column reactor with supercritical CO_2 as the mobile phase (Scheme 33). Under these conditions sequential injection of styrene (**2a**) into the $scCO_2$ flow reactor was analyzed, and the authors reported that even after 7 cycles, no loss of activity nor selectivity was observed.

Additionally, the sequential injections of various olefins were analyzed under $scCO_2$ flow and the results are summarized in Table 1. The alkenes studied were styrene (**1a**), vinyl acetate (**1c**), 1-octene (**1w**), 1-hexene (**1u**), 2,3,4,5,6-pentaflourostyrene ($\mathbf{1d_1}$), and $CF_3(CF_2)_5CH{=}CH_2$ ($\mathbf{1d_2}$) and all of them were successfully hydroformylated with high ees (Table 1).

6 Conclusions

Rhodium is currently the metal of choice to achieve high enantioselectivities in the hydroformylation of a relatively large variety of alkene substrates. Several breakthroughs in this field led to the discovery of several catalytic systems that can nowadays provide high levels of regio- and enantioselectivity for benchmark substrates such as styrene, vinyl acetate, and allyl cyanide.

Furthermore, recent advances have shown that challenging substrates such as alkyl alkenes and internal alkenes can also be converted into the corresponding branched aldehydes with high enantioselectivity by the appropriate choice of catalysts and reaction conditions. However, higher regio- and enantioselectivity can still be achieved when one of the substituents direct the regioselectivity, as is the case of 2,3-dihydrofuran, dihydropyrrol, indene, or 1,2-dihydronaphthalene (Schemes 20 and 22). In the case of symmetrically substituted alkenes such as 2,5-dihydrofuran and norbornene **4o**, **p**, no regiocontrol is required and high activities and enantioselectivities have been achieved in asymmetric hydroformylation (Schemes 20, 21, 23).

1,1-Disubstituted or 1,1,2-trisubstituted substrates are more challenging. 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. However, both types of products were formed by Rh-catalyzed hydroformylation with high enantioselectivity and there is still much to learn on the parameters that favor the formation of one regioisomer over another.

In terms of ligands, compounds containing phosphite moieties such as diphosphites and phosphine–phosphites were considered for many years as the most successful ligands to achieve high enantioselectivities. For instance, the phosphite–phosphine BINAPHOS (**40**) or its derivatives **42** and **43** are still today the most successful ligands in terms of selectivity and scope. Recently, however, diphosphines in which the P atoms are incorporated into a ring (**42**–**46**) were also shown to induce high levels of enantioselectivity in this process. 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.

A variety of chiral products incorporating a formyl unit can be enantioselectively prepared by Rh-catalyzed asymmetric hydroformylation and this process is nowadays considered a powerful tool in organic synthesis and is still a growing area of research. There are still many challenges to be tackled in this area and, for instance, only a few studies including the recovery and recycling of the chiral catalyst have been reported, which could further improve the sustainability of this process and lead to new applications.

Acknowledgements The authors are grateful to the Spanish Ministerio de Economía y Competitividad (CTQ2010-15835, *Juan de la Cierva* Fellowship to B.F.P., *Ramon y Cajal* Fellowship to C.G.) and the Generalitat de Catalunya (2009SGR116) for financial support.

References

1. Roelen O (1994) Chem Abstr 38:550
2. Roelen O (1938/1952) Chemische Verwertungsgesellschaft, mBH Oberhausen. DE Patent 849-584
3. Roelen O (1943) US Patent 2,317,066
4. Wiese K-D, Obst D (2010) In: Beller M (ed) Catalytic carbonylation reactions. Springer, Heidelberg, pp 1–33
5. Weissermel K, Arpe H-J (2008) Industrial organic chemistry. Wiley-VCH Verlag GmbH, Weinheim, pp 127–144
6. Klosin J, Landis CR (2007) Acc Chem Res 40:1251–1259
7. Breit B (2007) Top Curr Chem 279:139–172
8. Ungvári F (2007) Coord Chem Rev 251:2087–2102
9. Ungvári F (2007) Coord Chem Rev 251:2072–2086
10. Wiese KD, Obst D (2006) Top Organomet Chem 18:1–33
11. Gual A, Godard C, Castillón S, Claver C (2010) Tetrahedron Asymmetry 21:1135–1146
12. van Leeuwen PWNM, Kamer PCJ, Claver C, Pàmies O, Diéguez M (2011) Chem Rev 111:2077–2118

13. Breit B (2007) Aldehydes: synthesis by hydroformylation of alkenes. In: Brückner R (ed) Science of synthesis, vol 25. Thieme, Stuttgart
14. van Leeuwen PWNM (2004) Homogeneous catalysis: understanding the art. Chapter 8. Kluwer, Dordrecht
15. Trost BM (1991) Science 254:1471–1477
16. Breit B (2003) Acc Chem Res 36:264–275
17. Eilbracht P, Schmidt AM (2006) Top Organomet Chem 18:65–95
18. Evans DA, Osborn JA, Wilkinson G (1968) J Chem Soc 3133–3142
19. Evans D, Yagupsky G, Wilkinson G (1968) J Chem Soc A 2660–2665
20. Young JF, Osborn JA, Jardine FH, Wilkinson G (1965) J Chem Soc Chem Commun 131–132
21. van Leeuwen PWNM, Claver C (2000) Rhodium catalysed hydroformylation. Kluwer, Dordrecht
22. Consiglio G, Nefkens SCA, Borer A (1991) Organometallics 10:2046–2051
23. Stille JK, Su H, Brechot P, Parrinello G, Hegedus LS (1991) Organometallics 10:1183–1189
24. Janosi L, Kegl T, Kollar L (2008) J Organomet Chem 693:1127–1135
25. Agbossou F, Carpentier JF, Mortreux A (1995) Chem Rev 95:2485–2506
26. Gladiali S, Bayón JC, Claver C (1995) Tetrahedron Asymmetry 6:1453–1474
27. Keulemans AIM, Kwantes A, van Bavel T (1948) Rec Trav Chim Pays Bas 67:298–308
28. Heck RF (1969) Acc Chem Res 2:10–16
29. van der Veen LA, Boele MDK, Bregman FR, Kamer PCJ, van Leeuwen PWNM, Goubitz K, Fraanje J, Schenk H, Bo C (1998) J Am Chem Soc 120:11616–11626
30. van der Veen LA, Keeven PH, Schoemaker GC, Reek JNH, Kamer PCJ, van Leeuwen PWNM, Lutz M, Spek AL (2000) Organometallics 19:872–883
31. Deutsch PP, Eisenberg R (1990) Organometallics 9:709–718
32. Castellanos-Páez A, Castillón S, Claver C, van Leeuwen PWNM, de Lange WGJ (1998) Organometallics 17:2543–2552
33. Masdeu-Bultó AM, Orejon A, Castillón S, Claver C (1996) Tetrahedron Asymmetry 7:1829–1834
34. Diéguez M, Pàmies O, Claver C (2004) Tetrahedron Asymmetry 15:2113–2122
35. Babin JE, Whiteker GT (1993) Asymmetric synthesis. Patent No. WO 9303839
36. Whiteker GT, Briggs JR, Babin JE, Barne GA (2003) Asymmetric catalysis using biphosphite ligands in chemical industries, vol 89. Marcel Dekker, New York
37. van Leeuwen PWNM, van Roy A, Jongma T, Orij EEN, Kramer PCJ (1992) 203rd Meeting of the American Chemical Society, New York, 1992 Abstract I&EC 104
38. Buisman GJH, Vos EJ, Kamer PCJ, van Leeuwen PWNM (1995) J Chem Soc Dalton Trans 409–417
39. Buisman GJH, van der Veen LA, Klootwijk A, de Lange WGJ, Kamer PCJ, van Leeuwen PWNM, Vogt D (1997) Organometallics 16:2929–2939
40. Cserépi-Szûcs S, Tóth I, Párkanyi L, Bakos J (1998) Tetrahedron Asymmetry 9:3135–3142
41. Abdallah R, Breuzard JAJ, Bonet MC, Lemaire M (2006) J Mol Catal A Chem 249:218–222
42. Buisman GJH, van der Veen LA, Kamer PCJ, van Leeuwen PWNM (1997) Organometallics 16:5681–5687
43. Buisman GJH, Martin ME, Vos EJ, Klootwijk A, Kamer PCJ, van Leeuwen PWNM (1995) Tetrahedron Asymmetry 6:719–738
44. Pàmies O, Net G, Ruiz A, Claver C (2000) Tetrahedron Asymmetry 11:1097–1108
45. Diéguez M, Pàmies O, Ruiz A, Castillón S, Claver C (2001) Chem Eur J 7:3086–3094
46. Diéguez M, Pàmies O, Ruiz A, Claver C (2002) New J Chem 26:827–833
47. Gual A, Godard C, Castillón S, Claver C (2010) Adv Synth Catal 352:463–477
48. Gual A, Godard C, Claver C, Castillón S (2009) Eur J Org Chem 1191–1201
49. Cobley CJ, Klosin J, Qin C, Whiteker GT (2004) Org Lett 6:3277–3280
50. Cobley CJ, Gardner K, Klosin J, Praquin C, Hill C, Whiteker GT, Zanotti-Gerosa A (2004) J Org Chem 69:4031–4040
51. Sakai N, Mano S, Nozaki K, Takaya H (1993) J Am Chem Soc 115:7033–7034

52. Nozaki K (2005) Chem Rec 5:376–384
53. Tanaka R, Nakano K, Nozaki K (2007) J Org Chem 72:8671–8676
54. Nakano K, Tanaka R, Nozaki K (2006) Helv Chim Acta 89:1681–1686
55. Shibahara F, Nozaki K, Hiyama T (2003) J Am Chem Soc 125:8555–8560
56. Nozaki K, Matsuo T, Shibahara F, Hiyama T (2003) Organometallics 22:594–600
57. Shibahara F, Nozaki K, Matsuo T, Hiyama T (2002) Bioorg Med Chem Lett 12:1825–1827
58. Nozaki K, Matsuo T, Shibahara F, Hiyama T (2001) Adv Synth Catal 343:61–63
59. Horiuchi T, Ohta T, Shirakawa E, Nozaki K, Takaya H (1997) Tetrahedron 53:7795–7804
60. Nozaki K, Nanno T, Takaya H (1997) J Organomet Chem 527:103–108
61. Nozaki K, Li WG, Horiuchi T, Takaya H (1996) J Org Chem 61:7658–7659
62. Horiuchi T, Ohta T, Nozaki K, Takaya H (1996) Chem Commun 155–156
63. Nanno T, Sakai N, Nozaki K, Takaya H (1995) Tetrahedron Asymmetry 6:2583–2591
64. Lambers-Verstappen MMH, de Vries JG (2003) Adv Synth Catal 345:478–482
65. Nozaki K, Sakai N, Nanno T, Higashijima T, Mano S, Horiuchi T, Takaya H (1997) J Am Chem Soc 119:4413–4423
66. Nozaki K, Ito Y, Shibahara F, Shirakawa E, Otha T, Takaya H, Hiyama T (1998) J Am Chem Soc 120:4051–4052
67. Yan Y, Zhang X (2006) J Am Chem Soc 128:7198–7202
68. Zhang X, Cao B, Yan Y, Yu S, Ji B, Zhang X (2010) Chem Eur J 16:871–877
69. Deeremberg S, Kamer PCJ, van Leeuwen PWNM (2000) Organometallics 19:2065–2072
70. Pàmies O, Net G, Ruiz A, Claver C (2001) Tetrahedron Asymmetry 12:3441–3445
71. Arena CG, Faraone F, Graiff C, Tiripicchio A (2002) Eur J Inorg Chem 711–716
72. Rubio M, Suárez A, Álvarez E, Bianchini C, Oberhauser W, Peruzzini M, Pizzano A (2007) Organometallics 26:6428–6436
73. Robert T, Abiri Z, Wassenaar J, Sandee AJ, Meeuwissen J, Sandee AJ, de Bruin B, Siegler MA, Spek AL, Reek JNH (2010) Organometallics 29:2413–2421
74. Arribas I, Vargas S, Rubio M, Suárez A, Domene C, Alvarez E, Pizzano A (2010) Organometallics 29:5791–5804
75. Doro F, Reek JNH, Leeuwen PWNM (2010) Organometallics 29:4440–4447
76. Robert T, Abiri Z, Wassenaar J, Sandee AJ, Romanski S, Neudörfl J-M, Schmalz H-G, Reek JNH (2010) Organometallics 29:478–483
77. Wassenaar J, de Bruin B, Reek JNH (2010) Organometallics 29:2767–2776
78. Axtell AT, Klosin J, Abboud KA (2006) Organometallics 25:5003–5009
79. Axtell AT, Klosin J, Whiteker GT, Cobley CJ, Fox ME, Jackson M, Abboud KA (2009) Organometallics 28:2993–2999
80. Axtell AT, Colbey CJ, Klosin J, Whiteker GT, Zanotti-Gerosa A, Abboud KA (2005) Angew Chem Int Ed 44:5834–5838
81. Clarkson GJ, Ansell JR, Cole-Hamilton DJ, Pogorzelec PJ, Whittell J, Wills M (2004) Tetrahedron Asymmetry 15:1787–1792
82. Clark TP, Landis CR, Freed SL, Klosin J, Abboud KA (2005) J Am Chem Soc 127:5040–5042
83. Zhao B, Peng X, Wang W, Xia C, Ding K (2008) Chem Eur J 14:7847–7857
84. Peng X, Wang Z, Xia C, Ding K (2008) Tetrahedron Lett 49:4862–4864
85. Noonan GM, Fuentes JA, Cobley CJ, Clarke ML (2012) Angew Chem Int Ed 51:2477–2480
86. Hua Z, Vassar VC, Choi H, Ojima I (2004) Proc Natl Acad Sci USA 101:5411–5416
87. Breit B, Seiche W (2005) Angew Chem Int Ed 44:1640–1643
88. Kuil M, Goudriaan PE, van Leeuwen PWNM, Reek JNH (2006) Chem Commun 4679–4681
89. Kuil M, Goudriaan PE, Kleij AW, Tooke DM, Spek AL, van Leeuwen PWNM, Reek JNH (2007) Dalton Trans 2311–2320
90. Kollar L, Farkas E, Batiu J (1997) J Mol Catal A Chem 115:283–288
91. Axet MR, Castillón S, Claver C (2006) Inorg Chim Acta 359:2973–2979
92. Nozaki K, Takaya H, Hiyama T (1997) Top Catal 4:175–185
93. Sakai N, Nozaki K, Takaya H (1994) J Chem Soc Chem Commun 395–396

94. Bellini R, Chikkali SH, Berthon-Gelloz G, Reek JNH (2011) Angew Chem Int Ed 50:7342–7345
95. Bellini R, Reek JNH (2012) Chem Eur J 18:7091–7099
96. Gadzikwa T, Bellini R, Dekker HL, Reek JNH (2012) J Am Chem Soc 134:2860–2863
97. Polo A, Real J, Claver C, Castillón S, Bayón JC (1990) J Chem Soc Chem Commun 600–601
98. Polo A, Claver C, Castillón S, Ruiz A, Bayón JC, Real J, Mealli C, Masi D (1992) Organometallics 11:3525–3533
99. del Río I, van Leeuwen PWNM, Claver C (2001) Can J Chem 79:560–565
100. Horiuchi T, Otha T, Shirakawa E, Nozaki K, Takaya H (1997) J Org Chem 62:4285–4292
101. Diéguez M, Pàmies O, Claver C (2005) Chem Commun 1221–1223
102. Mazuela J, Coll M, Pàmies O, Diéguez M (2009) J Org Chem 74:5440–5445
103. Chikkali SH, Bellini R, Berthon-Gelloz G, Van der Vlugt JI, de Bruin B, Reek JNH (2010) Chem Commun 46:1244–1246
104. Botteghi C, Paganelli S, Schionato A, Marchetti M (1991) Chirality 3:355–369
105. Consiglio G, Rama F (1991) J Mol Catal 66:1–5
106. Lu S, Li X, Wang A (2000) Catal Today 63:531–536
107. Huang J, Bunel E, Allgeier A, Tedrow J, Storz T, Preston J, Correl T, Manley D, Soukup T, Jensen R, Syed R, Moniz G, Larsen R, Martinelli M, Reider PJ (2005) Tetrahedron Lett 46:7831–7834
108. Sémeril D, Matt D, Toupet L (2008) Chem Eur J 14:7144–7155
109. Noonan GM, Cpbley CJ, Lebl T, Clarke ML (2010) Chem Eur J 16:12788–12791
110. Ojima I, Takai M, Takahashi T (2006) Patent No. WO 078766
111. Wang X, Buchwald SL (2011) J Am Chem Soc 47:19080–19083
112. Yeung CS, Dong VM (2011) Angew Chem Int Ed 50:809–812
113. Consiglio G, Kollar L, Kolliker R (1990) J Organomet Chem 396:375–383
114. García L, Claver C, Dieguez M, Masdeu-Bulto AM (2006) Chem Commun 191–193
115. Noonan GM, Newton D, Cobley CJ, Suárez A, Pizzano A, Clarke ML (2010) Adv Synth Catal 352:1047–1104
116. Watkins AL, Landis CR (2011) Org Lett 13:164–167
117. McDonald RI, Wong GW, Neupane RP, Stahl SS, Landis CR (2010) J Am Chem Soc 132:14027–14029
118. Grünanger CU, Breit B (2008) Angew Chem Int Ed 47:7346–7349
119. Hardie RC (2007) Nature 450:37–39
120. Lightburn TE, Dombrowski MT, Tan KL (2008) J Am Chem Soc 130:9210–9211
121. Nozaki K, Itoi Y, Shibahara F, Shirakawa E, Ohta T, Takaya H, Hiyama T (1998) J Am Chem Soc 120:4051–4052