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► **To cite this version:**

Joris Langlois, Martine Urrutigoïty, Cyril Godard. Comprehensive Chirality. Reference Module in Chemistry, Molecular Sciences and Chemical Engineering, Elsevier, 2022, 10.1016/B978-0-32-390644-9.00019-6 . hal-04543415

**HAL Id: hal-04543415**

**<https://hal.science/hal-04543415>**

Submitted on 17 Apr 2024

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## Comprehensive Chirality

Joris Langlois, Martine Urrutigoity and Cyril Godard\*

Laboratoire de Chimie de Coordination, LCC, Université de Toulouse, CNRS, 4 allée Emile Monso, 31030 Toulouse Cedex 4, France ;

joris.langlois@lcc-toulouse.fr, martine.urrutigoity@lcc-toulouse.fr.

Universitat Rovira i Virgili, Campus Sescelades, Department of Physical Chemistry and Inorganic Chemistry, C/ Marcel·li Domingo s/n 43007, Tarragona, Spain; joris.langlois@urv.cat, \*cyril.godard@urv.cat.

**Abstract:** The Rh-catalyzed asymmetric hydroformylation is an efficient catalytic reaction that produces chiral aldehydes from inexpensive feedstock (alkenes, syngas) in one step. The elucidation of the different steps of the catalytic cycle and the characterization of the resting state, simultaneously with the discovery of several types of ligands, permitted that nowadays, a variety of chiral products can be efficiently synthesized and this process is considered a useful tool in organic synthesis. Asymmetric hydroaminomethylation is a one-pot tandem reaction involving hydroformylation and reductive amination leading to chiral amines. The most relevant results concerning these reactions are depicted in this book chapter.

**Keywords:** asymmetric, hydroformylation, hydroaminomethylation, rhodium, chiral ligands, regioselectivity, enantioselectivity, phosphorus, aldehydes, amines.

**Acknowledgments:** The authors are grateful to the European Union's Horizon 2020 Research and Innovation Programme for funding (Marie Skłodowska-Curie grant agreement No. 860322 for the ITN-EJD “Coordination Chemistry Inspires Molecular Catalysis” (CCIMC)).

### Olefins hydrofunctionalization; hydroformylation and hydrocarboxyamination

#### 1. Introduction

The use of carbon monoxide as C1 building block via metal-catalyzed carbonylation processes has revealed an efficient tool for the functionalization of organic molecules; moreover, the atom-economy nature of this type of reaction has increased the interest of both academy and industry.<sup>1</sup> The production of acetic acid through the carbonylation of methanol<sup>2</sup>, and the

production of aldehydes by the hydroformylation of propene<sup>3</sup> are the two main homogeneous processes currently applied in industry. Nonetheless, metal-catalyzed carbonylations are not only limited to bulk chemistry and can also be applied for the synthesis of fine chemicals such as chiral molecules through enantioselective processes.<sup>4</sup>

Among the metals that catalyze carbonylation reactions, rhodium has been largely studied due to its intrinsic properties that provide high activity and selectivity for this type of reaction.<sup>5</sup> Recently, an attractive strategy combining the efficiency of rhodium catalysts in carbonylation and C-H activation reactions has emerged for the construction of more complex cyclic skeletons.<sup>6</sup>

Rhodium catalyzed hydroformylation constitutes an attractive strategy for the synthesis of aldehydes from readily available starting materials such as alkenes in a high atom economy process (Scheme 1.2).<sup>7</sup> The reaction consists in the addition of “synthesis gas” (syngas), a mixture of CO and H<sub>2</sub>, to olefins in the presence of a catalyst. Formyl group and hydrogen are added through the  $\pi$  system of the alkene for the formation of aldehydes.

In this process, the first examples of high enantioselectivity (ee's up to 90%), were reported the same year by Stille and Consiglio using Pt diphosphite systems.<sup>8</sup> Nonetheless, such systems provided several disadvantages such as low reaction rates, tendency to hydrogenate substrates and low regioselectivity to branched products. Later, these issues were mainly overcome using Rh-based catalysts.<sup>9</sup>

From an organic point of view, chiral aldehydes are products of interest due to their potential in terms of subsequent functionalization, that can lead to the formation of new carbon-carbon and carbon-heteroatom bonds.<sup>10</sup> However, despite the clear potential of asymmetric hydroformylation for the synthesis of chiral aldehydes, the application of this process at a large scale has not yet been completed. Aldehydes are generally not isolated as final products, since the products of interest are usually derivatives. In this context, tandem processes with HF as the initial step constitute an interesting strategy. Indeed, the possibility to carry out several catalytic transformations in “one-pot” is even more attractive from an environmental and efficiency point of view. In this context, tandem catalytic processes are described as sequential catalytic transformations of the substrate through two, or even more, mechanistic pathways.<sup>11</sup>

When HF is the first step of such processes, alcohols can be prepared by in situ reduction of the aldehyde using the same hydrogen pressure present in the medium.<sup>12</sup> In the presence of a carbonyl compound such as an aldehyde and an organocatalyst, aldol reaction takes place to

expand the structure of the molecule.<sup>13</sup> It is also possible to create new C-C bonds if the aldehyde reacts with a phosphorus ylide via a Wittig reaction.<sup>14</sup> On the other hand, aldehydes can act as electrophiles and react with a nucleophile present in the media. If the nucleophile is an alcohol, then hemiacetals or acetals can be created.<sup>15</sup> In the presence of a primary or secondary amine, imines and enamines can be easily prepared.<sup>16</sup> When these imines or enamines are hydrogenated to create the corresponding amine, the reaction receives the name of hydroaminomethylation (HAM).

The efficient and selective synthesis of chiral amines using easily available and abundant precursors is a long-standing goal of chemical research since they are powerful building blocks for the synthesis of many chemicals such as pharmaceuticals.<sup>17</sup> In this context, the metal-catalyzed hydroaminomethylation reaction constitutes an attractive alternative to the classical multistep organic synthetic routes.

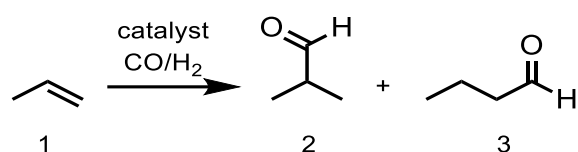
In this chapter, advances in the fields of asymmetric hydroformylation and enantioselective hydroaminomethylation of alkenes are described. After a brief introduction of these reactions, the mechanisms of these processes will be detailed and the most relevant catalytic results will be described according to the alkenes substrates.

## 2. Asymmetric hydroformylation of alkenes

### 2.1. Asymmetric hydroformylation using Rhodium

#### 2.1.1. Introduction

The hydroformylation of alkenes, formerly discovered by Otto Roelen,<sup>18</sup> is currently one of the most principal industrial applications of homogeneous catalysis.<sup>3-19</sup> Nowadays, several million tons of oxo-products are manufactured per year, mainly through the hydroformylation of propene **1** (Scheme 1). The products *iso*-butyraldehyde **2** and *n*-butanal **3** are important intermediates to synthesize esters, acrylates, and 2-ethylhexanol.<sup>3</sup>



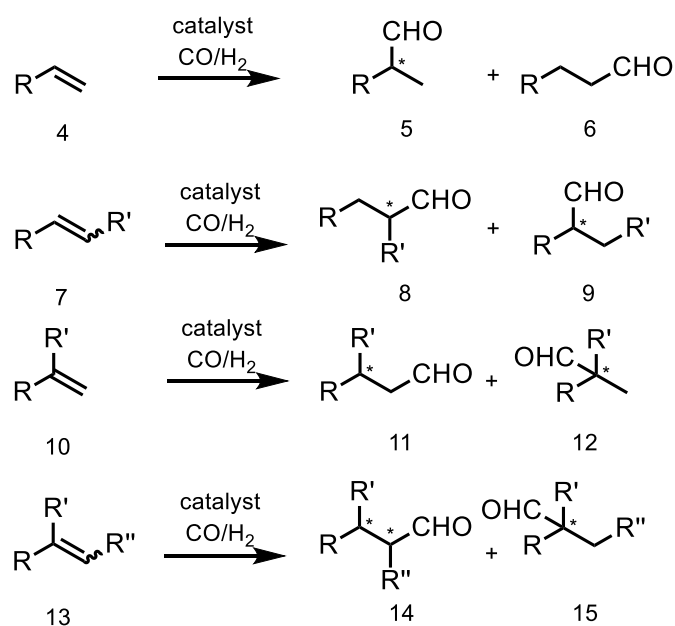
Scheme 1. Hydroformylation of propene.

Hydroformylation is a reaction consisting in the addition of carbon monoxide and hydrogen across the  $\pi$  system of a C=C double bond.<sup>7-20</sup> As such, hydroformylation constitutes an atom economic process<sup>10a</sup> that introduces the synthetically valuable aldehyde function, which can undergo subsequent transformations via tandem processes.<sup>10b,21</sup>

Since Wilkinson reported that phosphine-containing rhodium complexes could provide enhanced catalytic performance compared with the first generation of cobalt catalysts,<sup>22</sup> ligand tuning has constituted the main axis of research to improve the outcome of hydroformylation.<sup>23</sup>

In the low-pressure hydroformylation of internal alkenes, the chemoselectivity (and simultaneously regioselectivity) is one of the main issues in the industry due to the substantial decrease of substrate reactivity as the number of alkene substituents increases and usually rely on the use of strong  $\pi$ -acceptor ligands.<sup>24</sup> However, a high tendency towards alkene isomerization is usually observed and does not provide position-selective hydroformylation of internal alkenes, although recently, some examples started to appear in the literature.

The regioselectivity of the hydroformylation of alkenes depends on many aspects and insights into its origin often relied on quantum chemical calculations.<sup>25</sup> These include intrinsic substrate properties, directing effects caused by functional groups of the substrate, and catalyst effects. In order to better grasp substrate intrinsic regioselectivity trends, alkenes must be classified according to the number and nature of their substituents (Scheme 2)<sup>7-20</sup>.



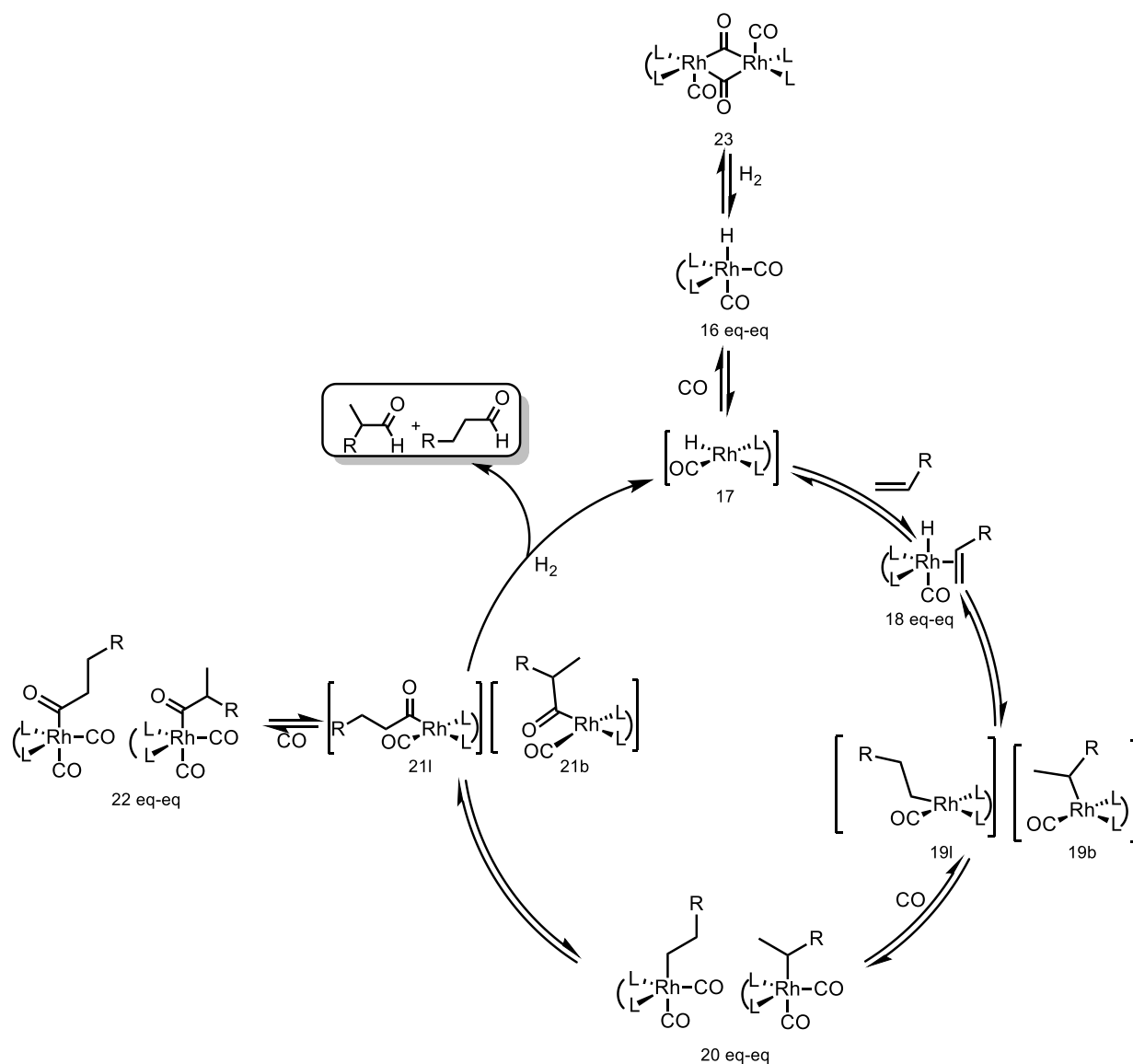
**Scheme 2. Regioselective trends on hydroformylation of different alkenes.**

Terminal and 1,2-disubstituted alkenes **7** are the substrates that present the most important regioselectivity issues. For alkyl-substituted terminal alkenes **4**, a slight preference is usually observed in favor of the linear product **6**. In contrast, when the reaction is performed using terminal alkenes **4** bearing an electron-withdrawing substituent, high selectivity to the branched product **5** can be achieved, independently of the catalyst used. When the substrates are 1,1-disubstituted alkenes **10** and trisubstituted **13**, only one regioisomer is usually obtained (**11** and **14**, respectively) in agreement with Keuleman's rule, which states that the addition of the formyl group usually avoids the formation of a quaternary carbon center.<sup>26</sup>

Although chiral aldehydes can be obtained in a single step via asymmetric hydroformylation, this reaction has not yet been applied at industrial scale due to several technical issues such as the low reaction rates under the conditions required for high selectivity and the difficulty to control simultaneously the regio- and the enantioselectivity.<sup>3</sup>

### 2.1.2. Rh-catalyzed hydroformylation mechanism

The mechanism of the Rh-catalyzed hydroformylation mechanism proposed by Heck is described for bidentate ligands,<sup>27</sup> which corresponds to Wilkinson's dissociative mechanism (Scheme 3)<sup>9</sup> In this process, a great understanding of the mechanism was made possible by the structural characterization of the catalyst resting state using *in situ* spectroscopic techniques (HP-IR, HP-NMR).<sup>10,28</sup> In this mechanism, the coordination mode of the bidentate ligands (L-L) can be equatorial-equatorial (eq-eq) or apical-equatorial (eq-ax), depending on the ligand structural properties such as their bite angle.



**Scheme 3. Mechanism of the Rh-catalyzed hydroformylation in the presence of bidentate ligand (L-L) coordinated in eq-eq mode.**

The common starting complex is the  $[\text{RhH}(\text{L-L})(\text{CO})_2]$  species **16** from which dissociation of the equatorial CO provides the square-planar intermediate **17**. Coordination of the alkene substrate gives 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. 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**.<sup>25c</sup> This step is also enantioselectivity-determining since the enantioface discrimination occurs between **17** and **19**, and particularly from **17** to **18**. The rate of the reaction is usually governed by the reaction of **17** with either CO or the alkene to form **16** or **18**.<sup>25i</sup> Experiments using

deuterated substrates suggest that alkene coordination and insertion into the Rh-H bond can be reversible, especially at low pressure and all steps are usually described as reversible except the final hydrogenolysis. Complexes **18** undergo migratory insertion to give the square-planar alkyl complexes **19**. This species can undergo  $\beta$ -hydride elimination, thus leading to isomerization, or can react with CO to form the trigonal bipyramidal (TBP) complexes **20**. Under low pressure of CO, a higher degree of isomerization may thus be expected. At low temperatures ( $< 70^\circ\text{C}$ ) and high pressure of CO ( $> 10$  bar), the insertion reaction is usually irreversible and the regioselectivity and the enantioselectivity of the overall process are therefore determined at this point. Complexes **20** undergo the second migratory insertion to form the acyl complex **21**, which can react with CO to form the 18-electron acyl intermediates **22** or with  $\text{H}_2$  to give the aldehyde product and the unsaturated intermediate **17**. The reaction with  $\text{H}_2$  could involve oxidative addition and subsequent reductive elimination, but no Rh (III) intermediates were detected.<sup>29</sup> It is noteworthy that at low hydrogen pressures and high rhodium concentrations, the formation of dirhodium dormant species such as **23** becomes significant.<sup>30</sup> Recently, the full catalytic cycle for monophosphine Rh complexes has been investigated using DFT calculations.<sup>31</sup>

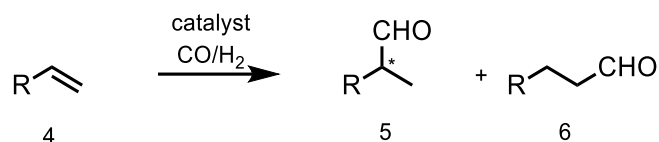
As previously mentioned, enantioselective hydroformylation presents a high potential to obtain a great variety of enantiomerically pure aldehydes. The first Rh-based systems reported in the asymmetric hydroformylation contained diphosphine ligands and provided *ee*'s up to 64% using styrene as substrate.<sup>32</sup> Later, the use of diphosphite and phosphine-phosphite ligands led to higher enantioselectivities.<sup>19-20,23</sup>

In the following sections, the most relevant results reported in the asymmetric Rh-catalyzed hydroformylation of alkenes are described. The reactions are classified by the degree of substitution of the substrates and for each family of substrates, the most successful chiral ligands are described.

## **2.2. Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes**

The asymmetric hydroformylation (AHF) of monosubstituted alkenes (Scheme 4) was lengthily investigated due to the interest in the enantioselective synthesis of 2-substituted branched aldehydes such as 2-aryl propionaldehydes, which are intermediates in the synthesis of 2-aryl propionic acids, the profen class of non-steroidal drugs.



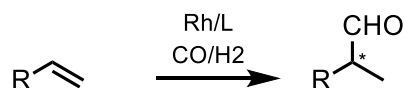


**Scheme 4. Asymmetric hydroformylation of monosubstituted alkenes.**

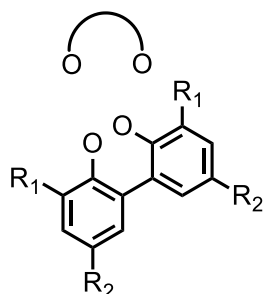
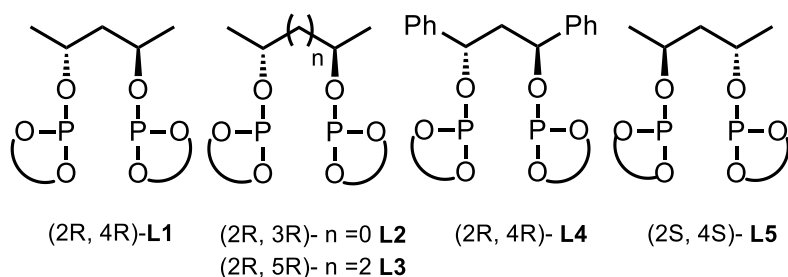
Several other monosubstituted alkenes such as allyl cyanide and vinyl acetate were also successfully converted.<sup>19-20</sup> 1,3-diphosphite and phosphine-phosphite ligands gave excellent results in these processes,<sup>23</sup> although bisphosphacyclic ligands have recently emerged as an efficient alternative.<sup>19-20</sup>

### 2.2.1. 1,3-Diphosphite ligands

Disphosphite ligands were intensively used in this process as they provide high levels of selectivity.<sup>33</sup> The initial success in the rhodium-catalyzed asymmetric hydroformylation of vinylarenes came from Union Carbide with the application of the (2*R*, 4*R*)-pentane-2,4-diol **24** diphosphite ligand (Scheme 5).<sup>34</sup>



| L            | Product               | Regio (%) | ee (%) |
|--------------|-----------------------|-----------|--------|
| <b>L1a,d</b> | R= Ph                 | 99        | 90     |
| <b>L1a</b>   | R= CH <sub>2</sub> CN | 87        | 13     |
| <b>L1a</b>   | R= OAc                | 99        | 58     |



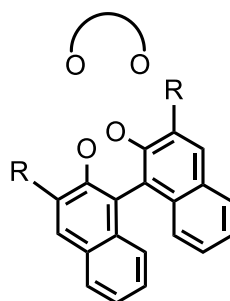
biphenyl

**a** R<sub>1</sub>= tBu; R<sub>2</sub>= OMe

**b** R<sub>1</sub>= R<sub>2</sub>= tBu

**c** R<sub>1</sub>= R<sub>2</sub>= H

**d** R<sub>1</sub>= Si(alkyl)<sub>3</sub>; R<sub>2</sub>= H

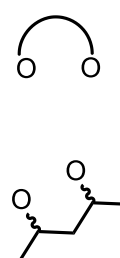


binaphthyl

**e** (R/S)ax; R = Si(alkyl)<sub>3</sub>

**f** (R)ax; R = Si(alkyl)<sub>3</sub>

**g** (S)ax; R = Si(alkyl)<sub>3</sub>



pentane-2,4-diol

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

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

**Scheme 5. Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligands L1-L5.**

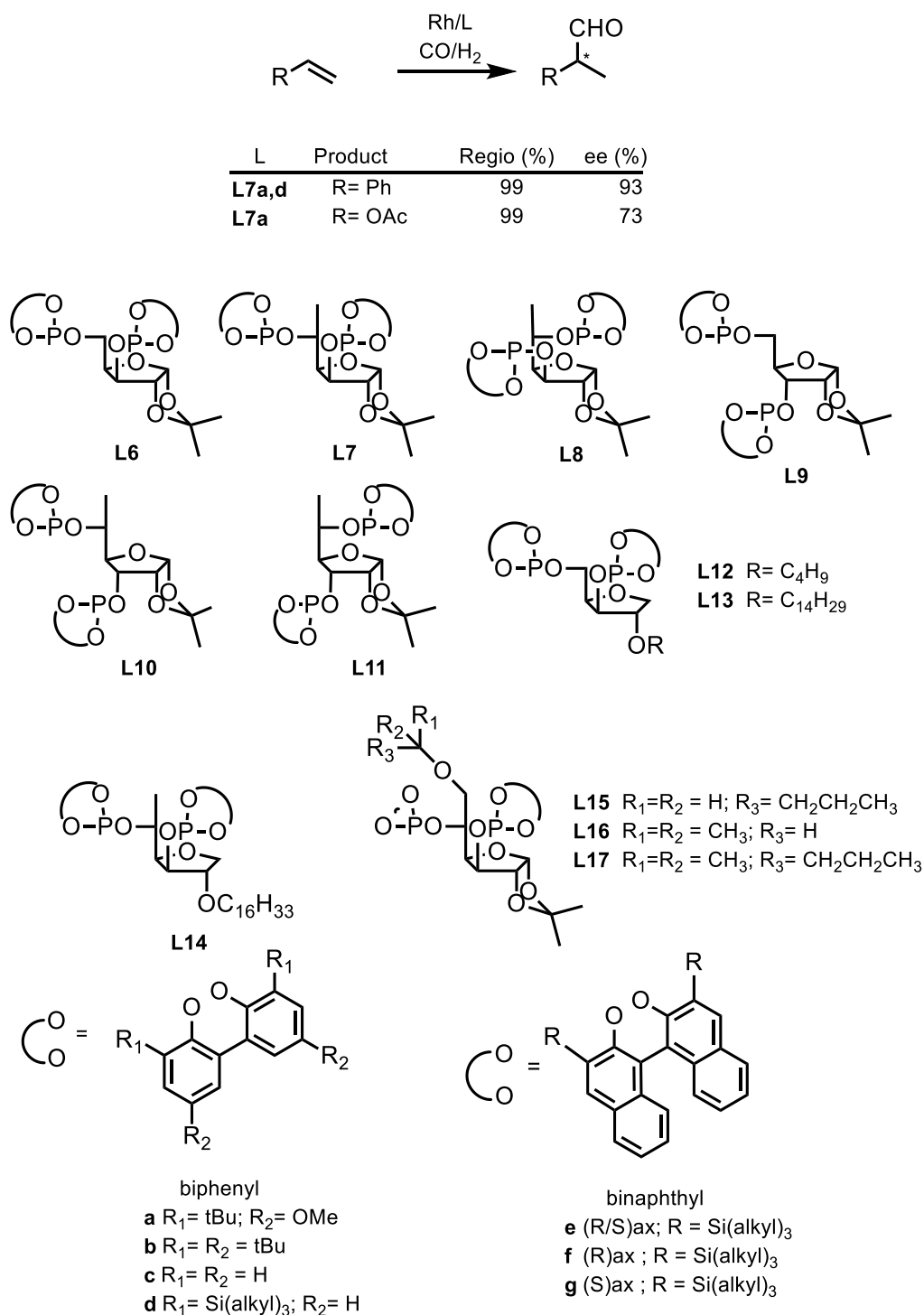
Good selectivities (*ee* up to 90%) were obtained with (2*R*,4*R*)-pentane-2,4-diol diphosphite derivatives **L1a** and **L1d** but only at temperatures close to room temperature. The series of **L2-L5** diphosphite ligands were later tested to examine the effect of structural variations for the Rh-catalyzed asymmetric hydroformylation of vinylarenes (Scheme 5).<sup>35</sup>

The influence of the bite angle of (2*R*, 4*R*)-pentane-2,4-diol **L1**, (2*R*, 3*R*)-butane-2,4-diol **L2** and (2*R*, 5*R*)-hexane-2,4-diol **L3** diphosphite ligands was studied and the highest enantioselectivities were obtained with the **L1** ligand.<sup>35b</sup> Reactions using **L1a-g** ligands indicated that the sterically hindered phosphite moieties are necessary to achieve high enantioselectivities, and the *ortho* and *para* substituents on the biphenyl and binaphthyl moieties also greatly affect the asymmetric induction.<sup>36</sup> 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 using **L1a** and **L1d** ligands .

The influence of the backbone was also studied and **L4**, which contains a more sterically hindered phenyl group, provided lower enantioselectivity than **L1**.<sup>35</sup>

van Leeuwen and co-workers studied the cooperative effect between the chiral ligand bridge and the axially chiral binaphthyl phosphite moieties by comparing **L1f**, **L1g** and **L5f**, **L5g** ligands. The hydroformylation results indicated a suitable combination for ligand **L24g** (*ee*'s up to 86%).<sup>35</sup> Later, Bakos and co-workers found a similar matched-mismatched effect between the chiral ligand bridge and the chiral phosphite moiety of the **L1h**, **L1i** and **L5h**, **L5i** ligands.<sup>36a</sup> To investigate the potential relationship between the solution structures of the [RhH(CO)<sub>2</sub>(diphosphite)] species and catalytic performance, van Leeuwen and co-workers extensively studied the [RhH(CO)<sub>2</sub>(diphosphite)] (diphosphite= **L1**, **L5**) species formed under hydroformylation conditions by high-pressure NMR techniques (HP-NMR).<sup>20,23</sup> The results indicated that the stability and catalytic performance of these systems strongly depend on the configuration of the pentane-2,4-diol ligand backbone and the chiral biaryl phosphite moieties. Thus, the **L1a**, **L1d** and **L1g** ligands, which form well-defined stable bis-equatorial (eq-eq) complexes, lead to good *ee*'s. In contrast, the **L1i** and **L5g** ligands, which form mixtures of complexes, generated low enantioselectivities.<sup>35,37</sup> The ligand **L1a** was also tested in the Rh-catalyzed asymmetric hydroformylation of allyl cyanide and vinyl acetate although low to moderate enantioselectivities (13 and 58%, respectively) were obtained.<sup>19a</sup>



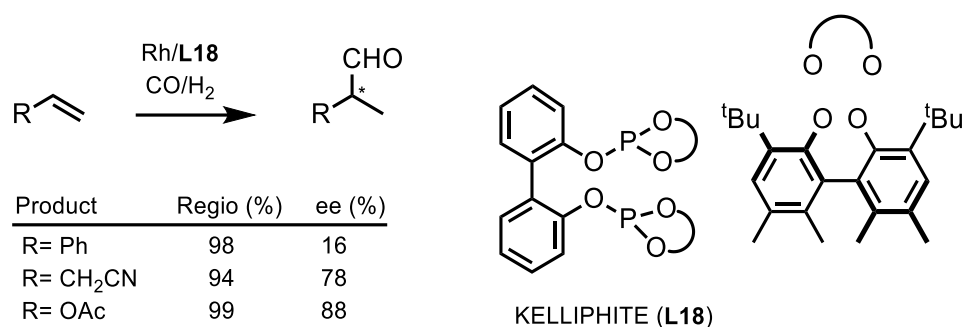
**Scheme 6.** Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligands **L6-L17**.

The use of diphosphite ligands **L6-L11** containing a sugar-based backbone was also successful in the Rh-catalyzed asymmetric hydroformylation of vinylarenes (Scheme 6).<sup>38</sup>

Indeed, the reaction of styrene and vinyl acetate with the diphosphite ligands **L7a**, **L7d** and **L11a**, **L11d** provided the *S*- and *R*-enantiomers of the products with excellent regioselectivity and *ee*'s up to 93% and 73%, respectively (Scheme 6).<sup>38c-d,39b</sup>

Interestingly, the use of related C1-symmetry diphosphite ligands conformationally more flexible (**L12-L14**) or increasing the steric hindrance at the C-6 position (**L15-L17**) afforded lower enantioselectivity than with the ligand **L7**.<sup>39</sup> Therefore, the bicyclic structure and the presence of a methyl substituent at C-5 position revealed crucial to achieving high enantioselectivity in these reactions using 1,3-diphosphites derived from carbohydrates.

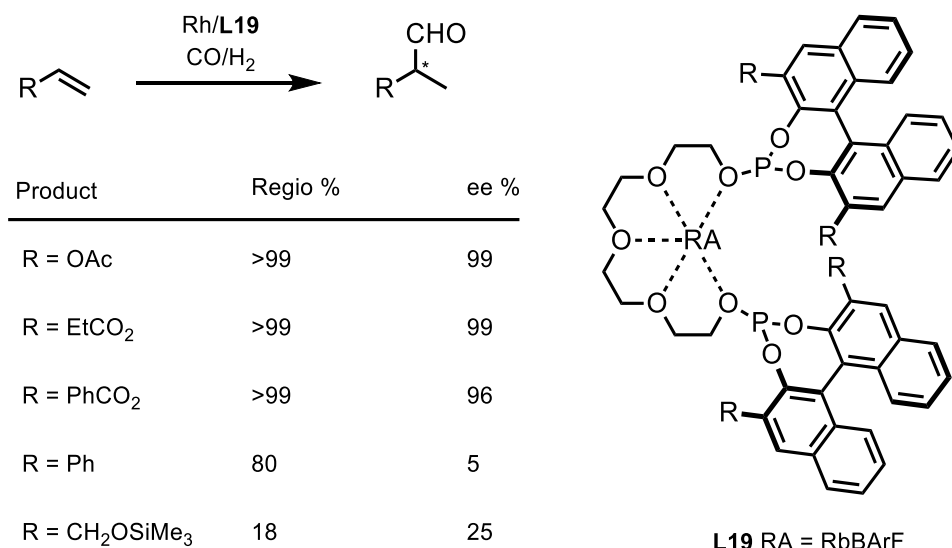
Moreover, the ligands **L7** and **L11**, for which a single  $[\text{RhH}(\text{CO})_2(\text{L})]$  species with eq-eq coordination was identified by HP-NMR technique, provided higher enantioselectivity (*ee* up to 93%) than the related **L8** and **L10** ligands (*ee* up to 64%), for which an equilibrium between eq-eq and eq-ax species was observed.<sup>38c, d, 39</sup>



**Scheme 7. Asymmetric hydroformylation of monosubstituted alkenes catalyzed by Rh/Kelliphite (**L18**) catalytic system.**

In contrast with the previously mentioned diphosphites, the Kelliphite ligand (**L18**) developed by Dow Chemical Company, and which contain an achiral backbone with a chiral bisphenol unit (Scheme 7) gave very good enantioselectivity in the reaction of vinyl acetate and allyl cyanide, but low *ee* in the case of styrene.<sup>40</sup>

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).<sup>41</sup> Using metal complexes bearing  $\alpha,\omega$ -bisphosphite-polyether ligands (**L19**), the enantiomeric excess was increased by up to 82 % in the AHF of vinyl benzoate (96 % *ee*).



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

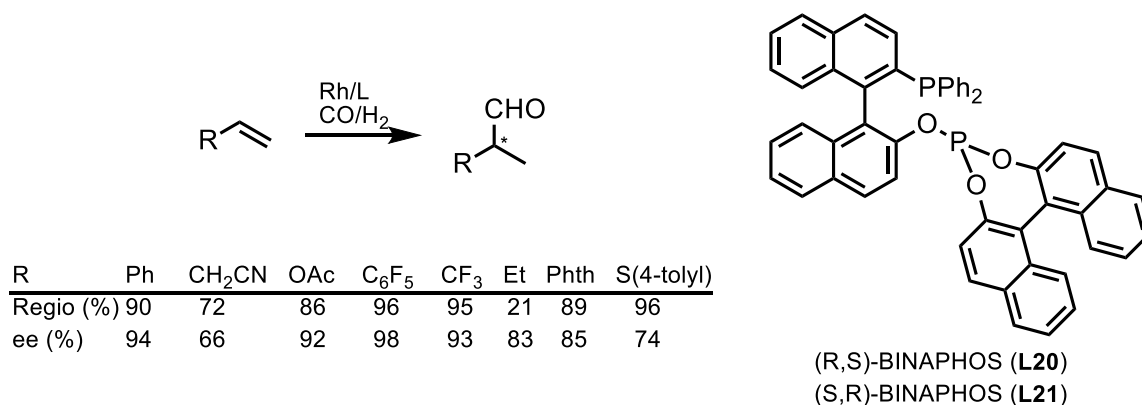
This methodology was also applied with chiral diphosphoramidite ligands on diaza crown ether backbone by Fan and co-workers.<sup>42</sup> Chirality was brought by the (*S*)-BINOL motif. When applied in AHF of styrene, a moderate conversion and 26% ee were measured. However, when the additive NaBArF was used, reactivity and enantioselectivity increased drastically, reaching full conversion and 70% ee with a reversal of product absolute configuration.

### 2.2.2. Phosphine-Phosphite ligands

Following the discovery of (*R,S*)-Binaphos (**L20**) and (*S,R*)-Binaphos (**L21**) ligands by Takaya and Nozaki in 1993, a significant advance was made in the Rh-catalyzed asymmetric hydroformylation reaction (Scheme 9).<sup>43</sup>

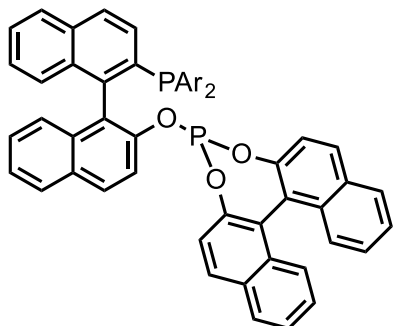
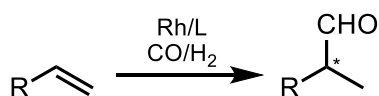
These ligands provided for the first time high enantioselectivity for several classes of monosubstituted alkenes such as vinyl arenes, 1-heteroatom-functionalized alkenes, and disubstituted 1,3-dienes (Scheme 9), and still remain a reference to date.<sup>44</sup> Importantly, (*R,S*)-Binaphos (**L20**) or the (*S,R*)-Binaphos (**L21**) ligands yielded the two enantiomers of the product with high enantioselectivity.<sup>45</sup> However, the (*R,R*)- and (*S,S*)-Binaphos diastereoisomers of **L20** and **L21** generated much lower enantioselectivity in this process, thus demonstrating the importance of the combination of opposite configurations at the phosphine and phosphite moieties.

Using the **L20** ligand, De Vries and co-workers reported in 2003 the first Rh-catalyzed AHF of allylcyanide<sup>46</sup>



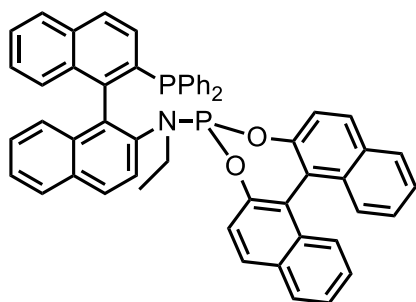
**Scheme 9. Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using (*R,S*)- and (*S,R*)-Binaphos (**L20** and **L21**).**

In contrast with the eq-eq coordination of the previously mentioned diphosphite ligands at the Rh center, the Binaphos ligand coordinates to Rh in an eq-ax mode as a single isomer in the resting state  $[\text{RhH}(\text{CO})_2(\text{L-L})]$  of the process.<sup>46</sup> DFT calculations indicated that the coordination of this ligand with the phosphite moiety in apical position is key 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.<sup>47</sup> They also showed that in the transition state determining the stereoselectivity, the main substrate-ligand interactions occur between the styrene and the phosphite moiety and that these interactions are repulsive in nature. The introduction of 3-methoxy substituents on the arylphosphine units giving the **L22** ligand (Scheme 10)<sup>44b,44c</sup> and the replacement of the phosphite group by a phosphoramidite function giving the Yanphos **L23** ligand resulted in the second generation of Binaphos type ligands (Scheme 10).<sup>48</sup> The Rh/**L22** catalytic system increased the regio- and enantioselectivity in the AHF of styrene, vinylfuranes, and thiophenes (Scheme 10). Recently, the use of (*S,R*)-Bn-Yanphos was reported in the asymmetric hydroformylation reaction of vinyl-heteroarenes such as pyrroles and provided excellent regio- and enantioselectivities (up to 96%).<sup>49</sup>



**L22** Ar = 3-MeOC<sub>6</sub>H<sub>4</sub>

| <b>L22</b>          | Regio(%) | ee(%) |
|---------------------|----------|-------|
| R= Ph               | 95       | 97    |
| R= 2-vinylfuran     |          | 79    |
| R= 3-vinylfuran     |          | 99    |
| R= 2-vinylthiophene |          | 93    |
| R= 3-vinylthiophene |          | 91    |



(*R,S*)-Yanphos (**L23**)

| <b>L23</b>  | Regio(%) | ee(%) |
|---|----------|-------|
| R= Ph   | 89       | 99    |
| R= CH <sub>2</sub> CN                                   | 80       | 96    |
| R= OAc  | 93       | 98    |
| R= CH <sub>2</sub> NHBOC                                | 66       | 94    |
| R= CH <sub>2</sub> NBz                                  | 78       | 95    |
| R= CH <sub>2</sub> NHPhthaloyl                          | 84       | 96    |
| R= CH <sub>2</sub> NHSO <sub>2</sub> ( <i>p</i> -MeOPh) | 71       | 96    |

**Scheme 10. Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using the L22 and L23 ligands.**

Higher enantioselectivity was achieved with Yanphos (**L23**) than that obtained with the Binaphos ligand without changing the regioselectivity in the reaction of styrene and vinyl acetate (ee up to 99 and 98%, respectively) (Scheme 10).<sup>50</sup>

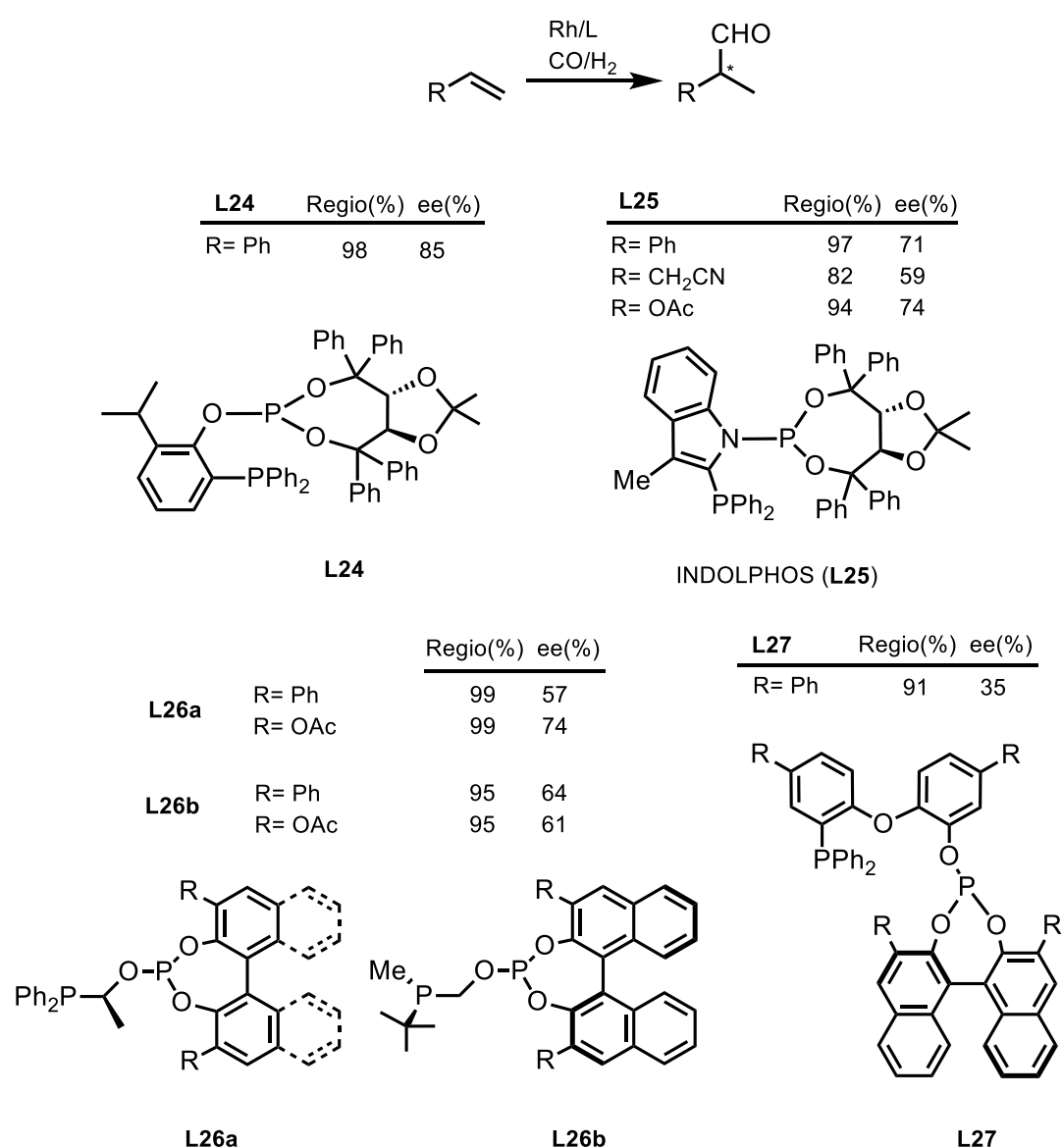
More recently, **L23** was used in the Rh-catalyzed asymmetric hydroformylation of *N*-allylamides, *N*-allylphthalamides and *N*-allylsulfonamides and afforded good regioselectivities (up to 84%) with excellent ee's (up to 96%) and a turnover number (TON) up to 9700.<sup>51</sup>

DFT calculations on a series of chiral Rh catalysts suggested an explanation for the high enantioinduction observed for Rh-CHIRAPHITE, -Binapine, -diazaphospholane, and Yanphos catalytic systems.<sup>52</sup> Concerning Binapine and Yanphos ligands, the main contribution to the selectivity was assigned to the naphthyl groups, while for CHIRAPHITE and



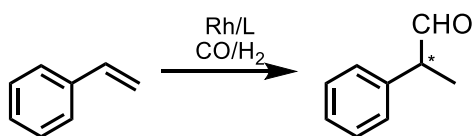
diazaphospholane ligands, the *tert*-butyl and chiral amine groups were highlighted as the key to enantioselective induction. Significantly, the effective placement of these groups to interact with the substrate is acquired through the coordination of phosphane moieties in the apical site of the complex.

Inspired by the excellent results reached with **L20** and **L21** Binaphos ligands, new phosphine-phosphite ligands presenting different backbones were synthesized 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.<sup>53</sup> However, some of these ligands helped to elucidate the correlation between the ee and the electronic withdrawing properties of the substituent on the alkene.<sup>54</sup>

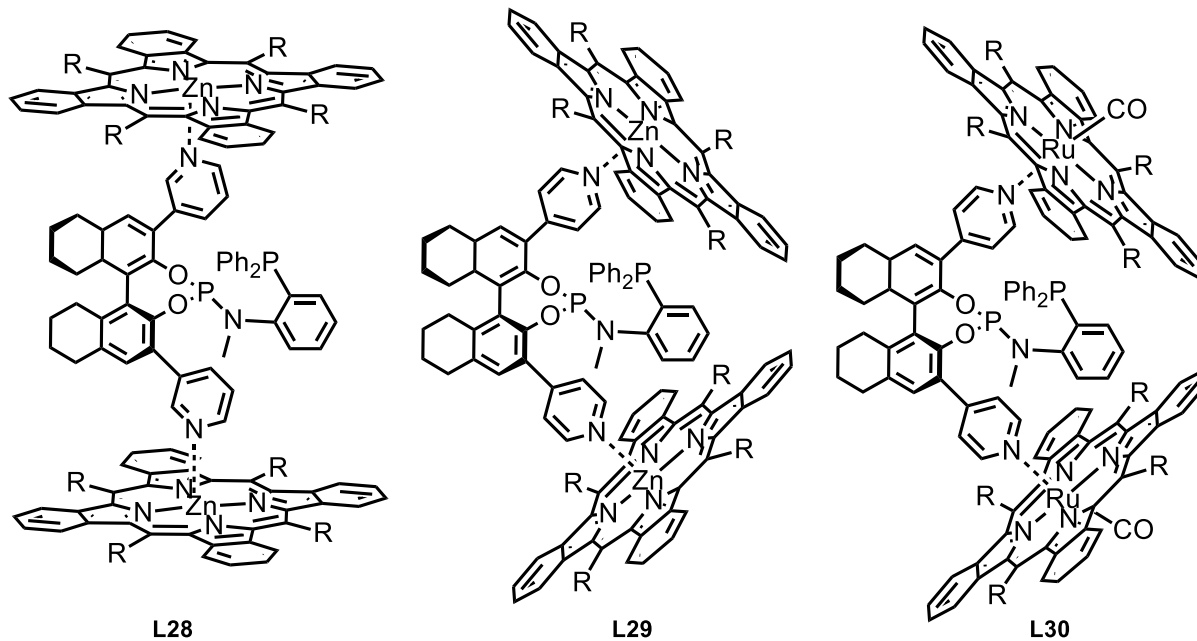


**Scheme 11.** Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using Taddol-based ligands (**L24** and **L25**) and phosphine-phosphite ligands (**L26**) and (**L27**).

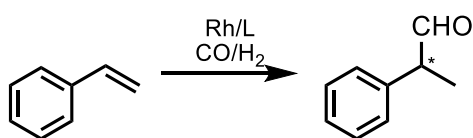
A series of phosphine-phosphite and phosphine-phosphoramidite ligands (**L24** and **L25**, Scheme 11) containing a Taddol-based backbone in the phosphite or phosphoramidite moiety, were applied in the Rh-catalyzed asymmetric hydroformylation of styrene, allyl cyanide and vinyl acetate and provided excellent regioselectivities (up to 98%) and good ee's (up to 85%).<sup>55</sup> The group of Vidal-Ferran reported the use of the small bite angle phosphine-phosphite ligands **L26a** and **L26b** in the hydroformylation of styrene and vinyl acetate, obtaining excellent regioselectivity but with moderate ee's (up to 74%).<sup>56</sup> Interestingly, the introduction of the P-stereogenic center in **L26b** ligand slightly increased the ee in the case of styrene but showed a lower enantioinduction for vinyl acetate. The use of the large bite angle ligand **L27** containing a diphenylether backbone only provided low ee's (up to 35%) in the Rh-catalyzed hydroformylation of styrene.<sup>57</sup> The application of phosphine-phosphite ligands built on an  $\alpha$ -cyclodextrin scaffold provided moderate regioselectivity (*ca.* 75%) and ee (50%) in the Rh-catalysed hydroformylation of styrene.<sup>58</sup> Reek and co-workers described a supramolecular approach for the Rh-catalyzed hydroformylation of styrene derivatives involving phosphine-phosphoramidite hydride ligands (**L28-L30**) (



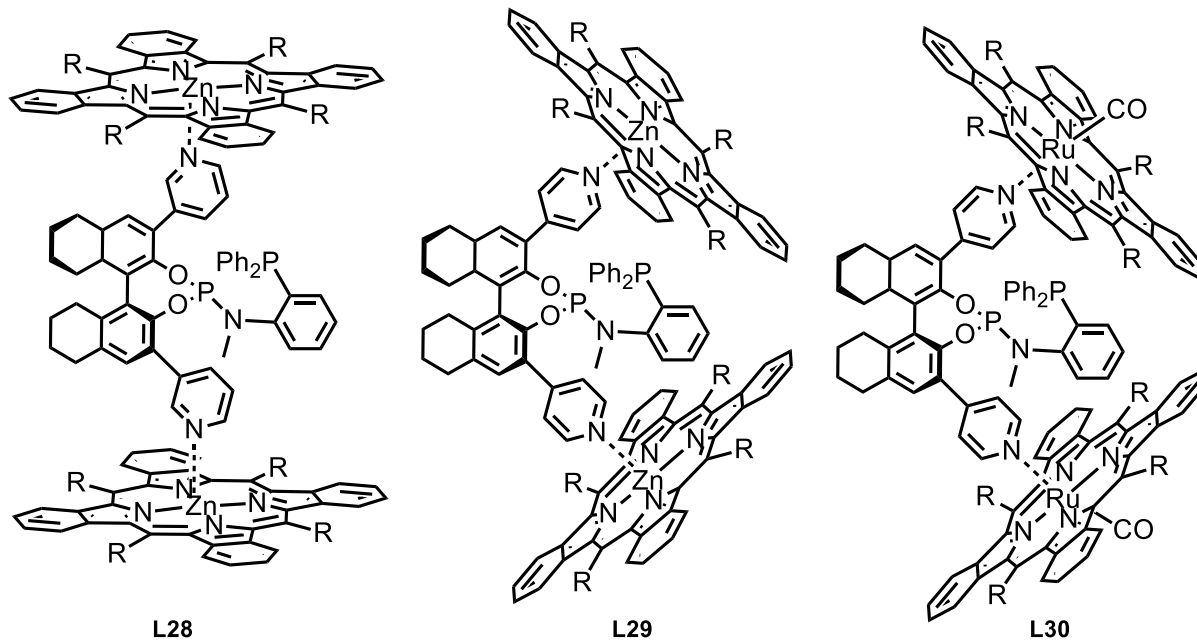
| L          | Regio (%) | ee (%) |
|------------|-----------|--------|
| <b>L28</b> | 94        | 52     |
| <b>L29</b> | 99        | 51     |
| <b>L30</b> | 92        | 59     |



Scheme 12).<sup>59</sup> With these ligands, the electronic and steric properties of the M(II) (M=Zn, Ru) templates had a significant effect on the outcome of the reaction. When styrene was employed, ee's up to 59% were obtained using **L30** ligand.

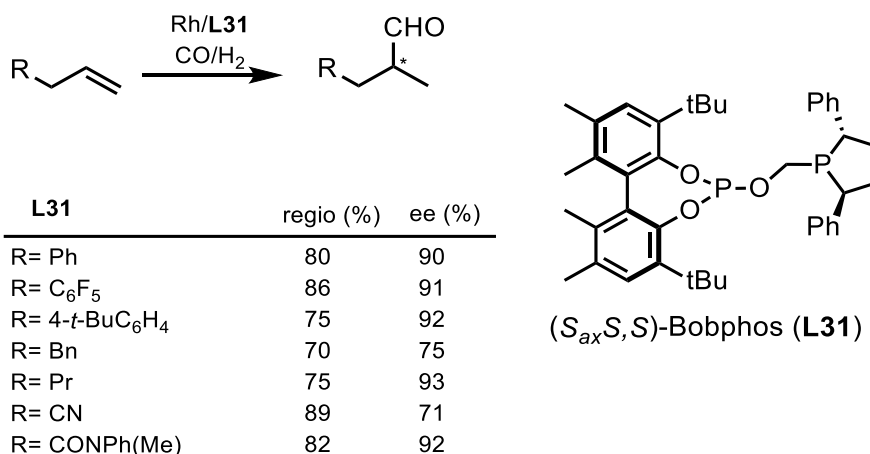


| L          | Regio (%) | ee (%) |
|------------|-----------|--------|
| <b>L28</b> | 94        | 52     |
| <b>L29</b> | 99        | 51     |
| <b>L30</b> | 92        | 59     |



**Scheme 12. Asymmetric hydroformylation of styrene using supramolecular phosphine-phosphoramidite ligands.**

The making of chiral aldehyde from simple terminal alkyl olefins of formula  $RCH_2CH=CH_2$  with high regio- and enantioselectivity has been a longstanding goal and a large set of ligands was tested in this reaction. Using these substrates, poor regioselectivity was usually obtained as the formation of linear aldehyde is preferred in most cases. In 2012, Clarke and co-workers reported the first efficient production of branched aldehydes from alkyl alkenes with high regioselectivity and ee's using the Bobphos phosphine-phosphite ligand (**L31**) (Scheme 13).<sup>60</sup>

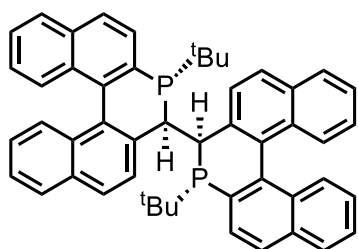
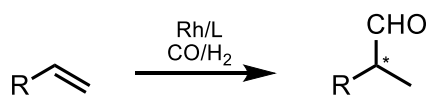


**Scheme 13. Rh-catalyzed asymmetric hydroformylation of terminal alkyl alkenes using the Bobphos ligand L31.**

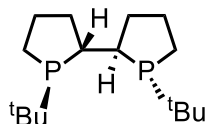
The same group later developed the highly selective hydroformylation of propene towards isobutanal using (*R*<sub>ax</sub>, *R, R*)-Bobphos and octafluorotoluene. They applied their system in AHF of allylbenzene derivatives and produced the *iso*-aldehyde in 86% selectivity and 92% ee.<sup>61</sup>

### 2.2.3. Bisphosphacyclic ligands

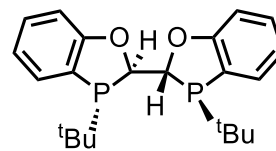
Several bisphospholane chiral ligands known as efficient ligands for asymmetric hydrogenation were evaluated in asymmetric hydroformylation (Scheme 14).<sup>62</sup>



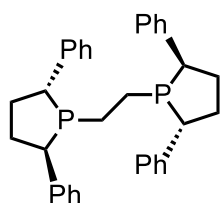
(*R,S*)-Binapine (**L32**)



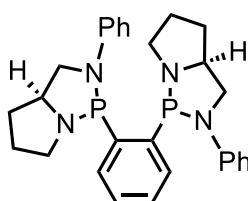
(*S,S,R,R*)-Tangphos (**L33**)



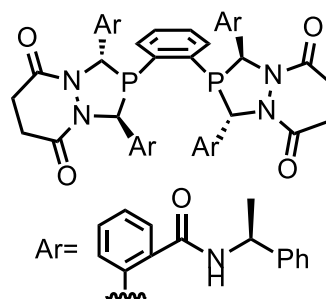
(*R*)-BIBOP (**L34**)



(*R,R*)-Ph-BPE (**L35a**)



Esphos (**L36**)



Bis-3,4-diazaphospholane (**L37a**)

| L               | R= Ph | R= CH <sub>2</sub> CN | R= OAc |
|-----------------|-------|-----------------------|--------|
| Regio (%) ee(%) |       |                       |        |
| <b>L32</b>      | 90 94 | 87 94                 | 97 87  |
| <b>L33</b>      | 93 90 | 88 93                 | 97 83  |
| <b>L34</b>      | 91 67 |                       | 96 82  |
| <b>L35a</b>     | 98 94 | 88 90                 | 99 82  |
| <b>L36</b>      |       |                       | 94 89  |
| <b>L37a</b>     | 97 82 | 83 87                 | 98 96  |

**Scheme 14. Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using the diphosphine ligands L32-L37a.**

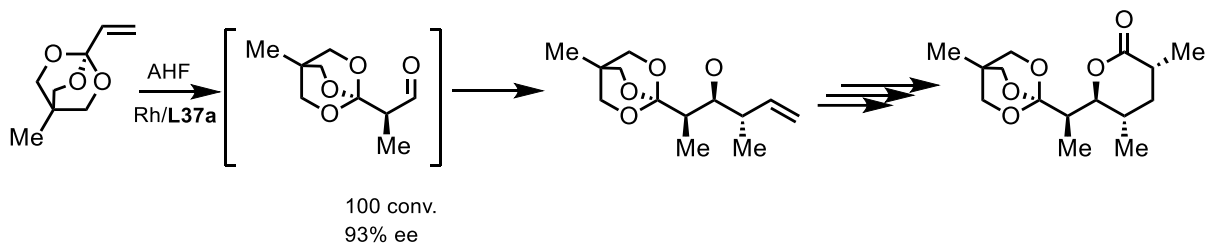
(*R, S*)-Binapine (**L32**) and (*S,S,R,R*)-Tangphos(**L33**) afforded excellent enantioselectivities in the AHF of styrene, allyl cyanide, and vinyl acetate (Scheme 14).<sup>40</sup> It is noteworthy that the enantioselectivities reached with these ligands are the highest ever reported for the allyl cyanide substrate. The ligand BIBOP **L34** also provided excellent results in the AHF of vinyl acetate and allylic substrates.<sup>63</sup> Moreover, ee's up to 91% were obtained in the AHF of ethyl 2-vinylbenzoate providing a route to enantioenriched 4-methyl-3,4-dihydroisocoumarin after NaBH<sub>4</sub> reduction and in situ lactonization.<sup>64</sup>

Moreover, novel and improved bisphospholane-type ligands were discovered and the (*R,R*)-Ph-BPE ligand (**L35a**) (Scheme 14) revealed an outstanding ligand for asymmetric hydroformylation affording excellent regio- and enantioselectivities in the AHF of styrene, allyl cyanide, and vinyl acetate.<sup>65</sup> The influence of spacers between the two phosphorus donor atoms was evaluated and the two carbon bridge of **L35a** provided the highest selectivity for these three substrates.<sup>66</sup> This ligand was also successfully used in the Rh-catalyzed AHF of vinylarenes with ee's up to 95% using formaldehyde as syngas precursor.<sup>67</sup> It also provided excellent results in the branched selective AHF of varied 1-alkenes, as well as 1-dodecene, with regioselectivity up to 93% and ee up to 96%.<sup>68</sup>

A series of bis-2,5-diazaphospholane ligands was also evaluated in this process and the Esphos ligand (**L36**) provided the best results in the hydroformylation of vinyl acetate (*ee* up to 89%) (Scheme 14).<sup>69</sup> The bis-3,4-diazaphospholane ligand **L37a** also offered excellent regio- and enantioselectivity (*ee* up to 96%) in this reaction (Scheme 14).<sup>70</sup> A detailed spectroscopic characterization of catalytic Rh intermediates bearing ligand **L37a** was described for the hydroformylation of octene, vinyl acetate, allyl cyanide and 1-phenyl-1,3-butadiene.<sup>71</sup> Interestingly, when the tetrahydropyridazine-3,6-dione backbone of **L37a** was reduced, the selectivity towards the branched aldehyde increased in the AHF of styrene, vinyl acetate and allyl cyanide.<sup>72</sup>

It is noteworthy that immobilization of **L37a** onto resins and silica supports provided excellent results for the Rh-catalyzed hydroformylation of styrene and vinyl acetate with excellent recyclability in batch and under flow conditions.<sup>73</sup> This catalytic system was also used for the continuous flow asymmetric hydroformylation of 2-vinyl-6-methoxynaphthalene during 8h using a reactor consisting of 20 vertical bubble pipe-in-series connected by small tubing jumpers.<sup>74</sup>

Two derivatives of the **L37a** ligand 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).



**Scheme 15. Synthesis of the Prelog-Djerassi Lactone via asymmetric hydroformylation/crotylation tandem sequence in the presence of derivatives of ligand L37a.**

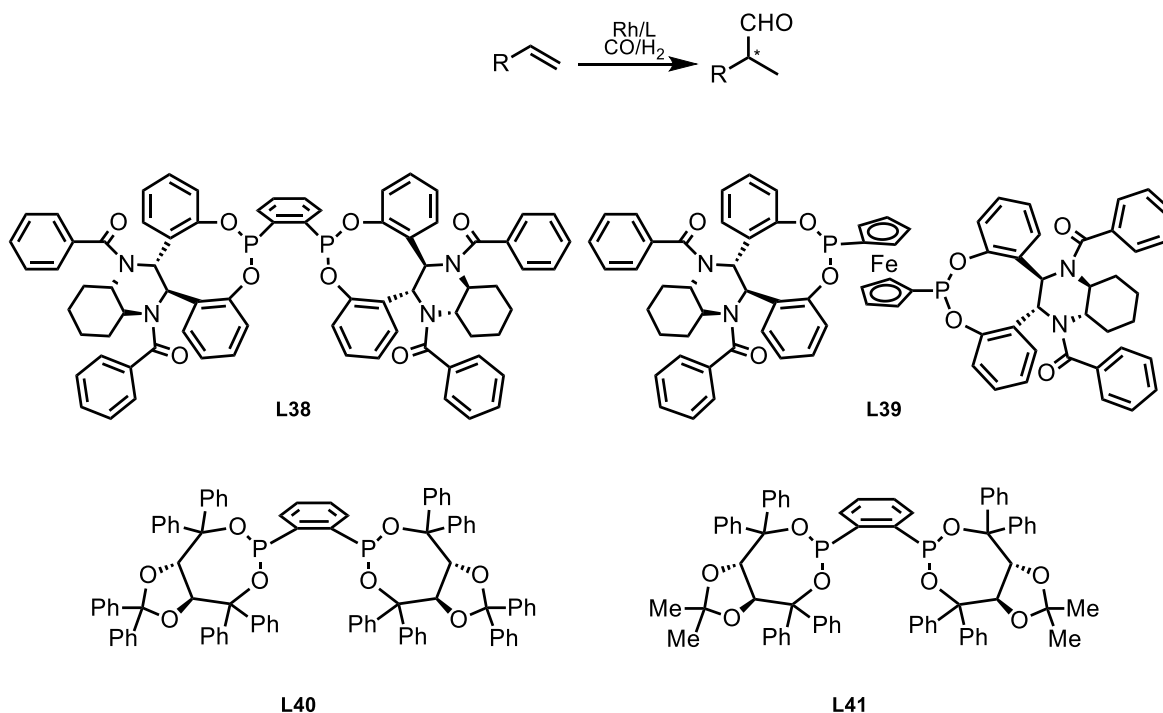
The sequential asymmetric hydroformylation/aerobic aldehyde oxidation providing an access to  $\alpha$ -chiral carboxylic acids without racemization was recently reported using the same ligand.<sup>75</sup>

#### 2.2.4. Bis-phosponite ligands

The bis-phosponite ligand **L38** showed moderate selectivities in the hydroformylation of styrene and allyl cyanide (Scheme 16) but provided hydroformylation of vinyl acetate in 91% ee.<sup>76</sup> The related **L39** diphosphinite ligand derived from ferrocene was also described by Ding and co-workers and gave good conversion but lower enantioselectivities in the hydroformylation of styrene and vinyl acetate (ee up to 55% and 83%, respectively).<sup>77</sup> A family



of TADDOL-derived bis-phosphonite ligands was reported, among which the ligands **L40** and **L41** provided excellent enantioselectivity in the AHF of styrene and derivatives.<sup>78</sup>



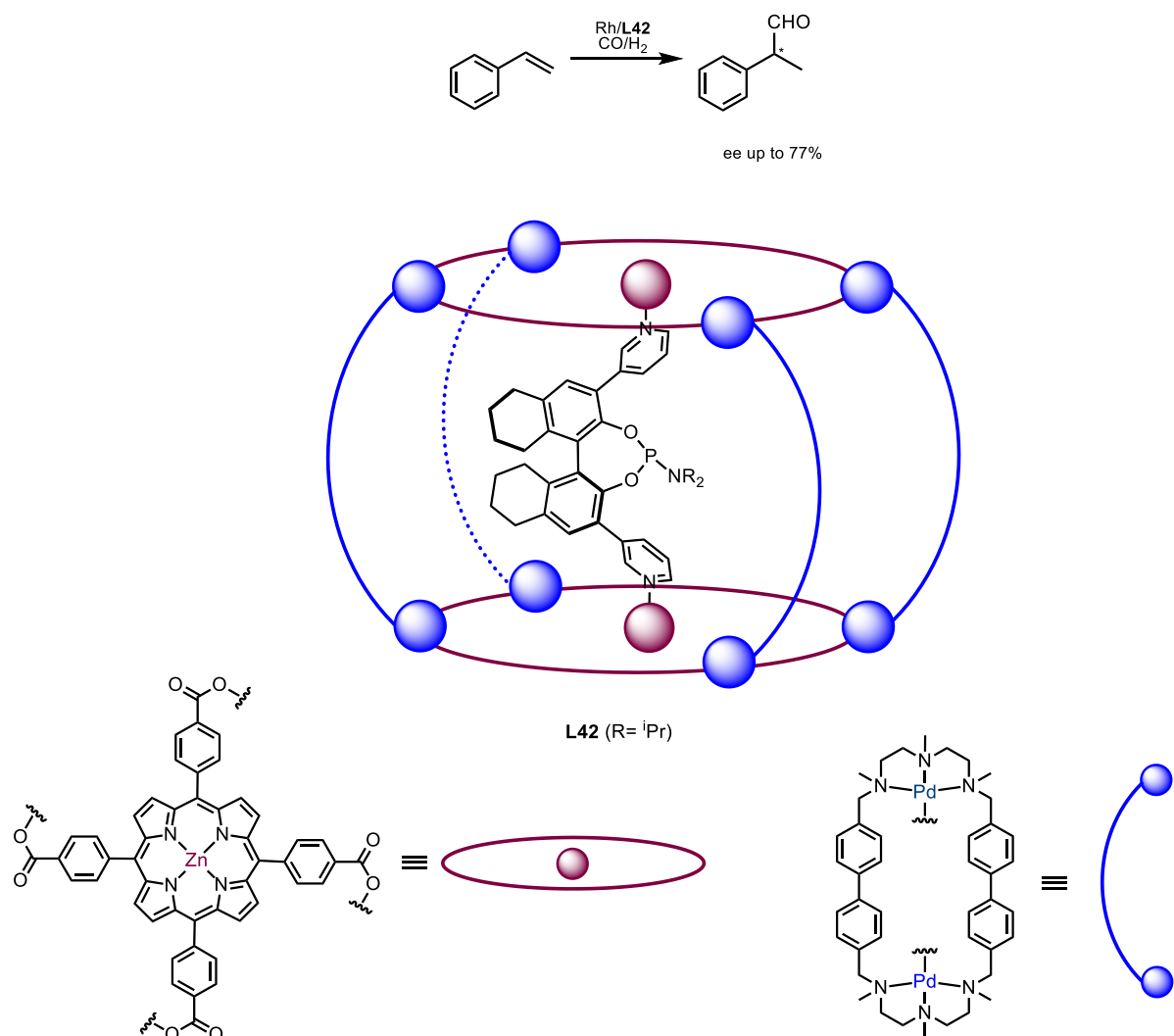
| L          | R= Ph     |       | R= CH <sub>2</sub> CN |       | R= OAc    |       |
|------------|-----------|-------|-----------------------|-------|-----------|-------|
|            | Regio (%) | ee(%) | Regio (%)             | ee(%) | Regio (%) | ee(%) |
| <b>L38</b> | 92        | 79    | 82                    | 79    | 98        | 91    |
| <b>L39</b> | 95        | 55    |                       |       | 94        | 83    |
| <b>L40</b> | 84        | 90    |                       |       |           |       |
| <b>L41</b> | 84        | 91    |                       |       |           |       |

**Scheme 16.** Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes with ligands **L38-L41**.

### 2.2.5. Monodentate Phosphorus based ligands

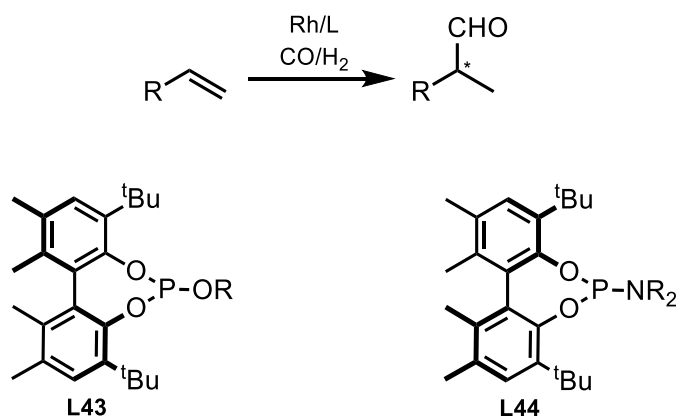
To date, the use of monodentate ligands in asymmetric hydroformylation with high enantioselectivities remains a challenge. In 2015, a Rh complex bearing a monodentate phosphoramidite ligand (**L42**) encapsulated in a self-assembled molecular cage (Scheme 17) provided the highest enantioselectivity (74%) in the asymmetric hydroformylation of styrenes using the monoligated catalyst.<sup>79</sup> The authors demonstrated that the presence of the cage

enhance the enantioinduction of the catalyst acting as a second coordination sphere.



**Scheme 17.** Rh-catalyzed asymmetric hydroformylation of styrene using Rh/monodentate phosphoramidite (**L42**) catalyst encapsulated in a self-assembled molecular cage.

The monophosphite ligand **L43** was tested in the Rh-catalyzed asymmetric hydroformylation of styrene and allyl cyanide and provided moderate enantioselectivities (Scheme 18). When vinyl acetate was the substrate, very poor *ee*'s were obtained (Scheme 18).<sup>44</sup> However, in 2004, Ojima and co-workers reported the use of the phosphoramidite ligand **L44** (Scheme 18), related to monophosphite **L43**, 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.<sup>80</sup>

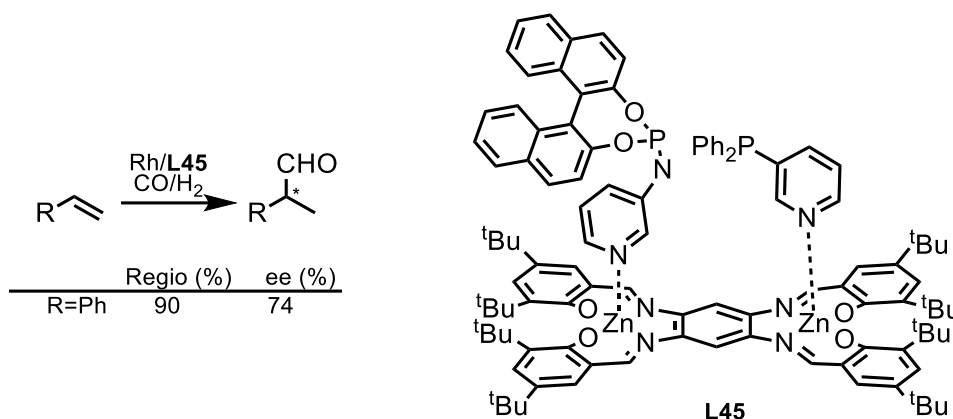


| L          | R= Ph     |       | R= CH <sub>2</sub> CN |       | R= OAc    |       |
|------------|-----------|-------|-----------------------|-------|-----------|-------|
|            | Regio (%) | ee(%) | Regio (%)             | ee(%) | Regio (%) | ee(%) |
| <b>L43</b> | 94        | 38    | 84                    | 43    | 93        | 8     |
| <b>L44</b> |           |       | 96                    | 80    |           |       |

**Scheme 18. Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using L43 and L44 ligands.**

Later, Dieguez and coworkers reported the testing of monodentate phosphoramidite and aminophosphine libraries in the asymmetric hydroformylation of styrene derivatives.<sup>81</sup> However, only *ee*'s up to 50% could be achieved.

In 2005, Breit described 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.<sup>82</sup> This method has 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 illustrated 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 19).<sup>83</sup> The templated **L45** heterobidentate ligand gave 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.

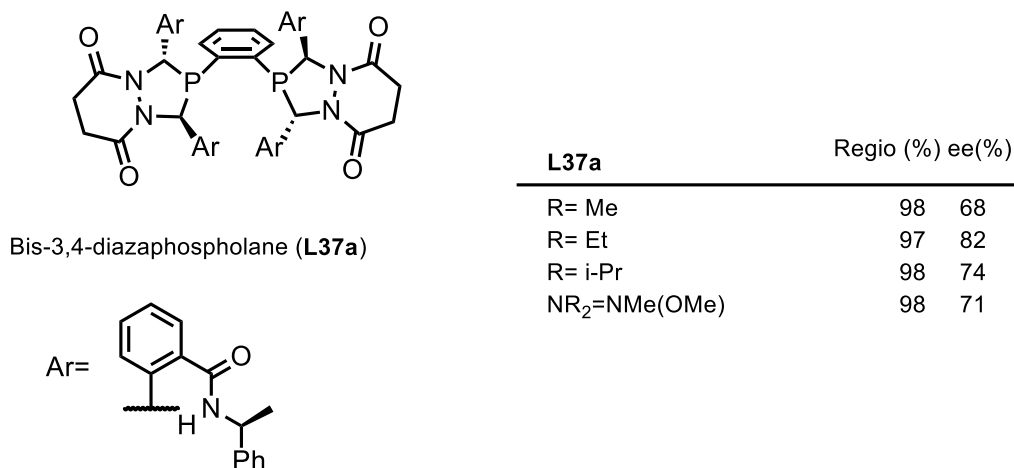
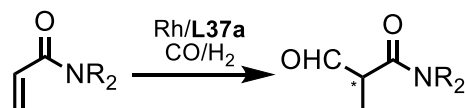


**Scheme 19.** Rh-catalyzed asymmetric hydroformylation of styrene using the templated ligand L45.

Recently, Reek and co-workers proposed another approach involving porphyrin as a chiral capsule incorporating a non-chiral Rh catalyst inside. Each of the 4-phenyl groups of the porphyrin are carrying a chiral group while the rhodium is attached to tris-pyrid-3-ylphosphine. Pyridine moieties bind to a Zn porphyrin to create a chiral capsule. This technique provided AHF of vinyl acetate with 33% ee.<sup>84</sup>

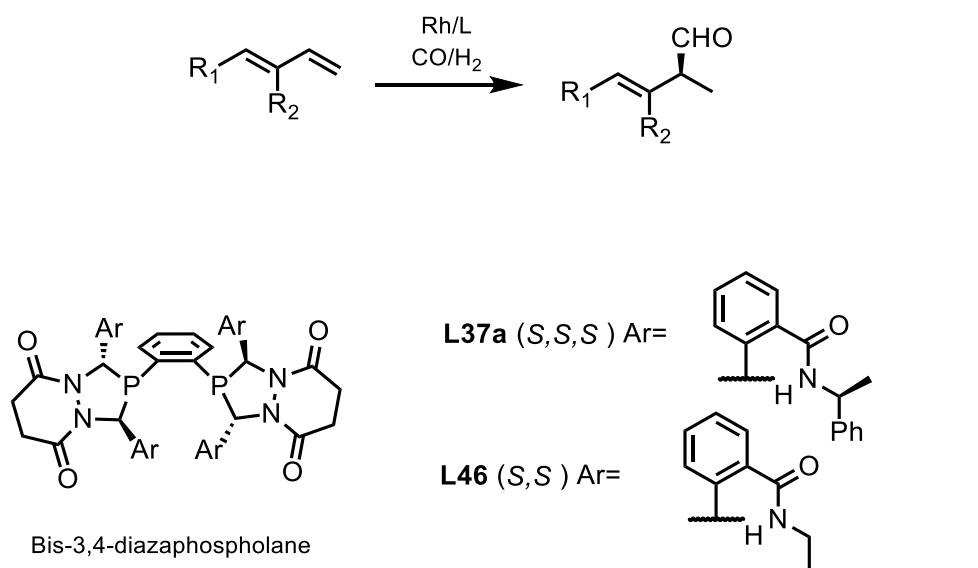
### 2.3. Other monosubstituted alkene substrates

In this section, recent reports on the Rh-catalyzed asymmetric hydroformylation of “uncommon” monosubstituted alkene substrates using chiral phosphorus ligands are presented. The asymmetric hydroformylation of dialkylacrylamides initially provided rather low enantioinductions (20-50% ee’s).<sup>85</sup> However, Clarke and co-workers showed that the use of the bis-diazaphospholane ligand (**L37a**) could provide total regioselectivity and ee’s up to 82% in the Rh-catalyzed asymmetric hydroformylation of *N,N*-dialkylacrylamides (Scheme 20).<sup>86</sup>



**Scheme 20. Rh-catalyzed asymmetric hydroformylation of N,N-dialkylacrylamides.**

In the rhodium-catalyzed hydroformylation of 1,3-dienes, *N*-vinyl carboxamides, allyl carbamates and allyl ethers, the use of the *bis*-3,4-diazaphospholane type ligands have also been reported with excellent regio- and enantioselectivities by Landis et al.<sup>87</sup> (Scheme 21).

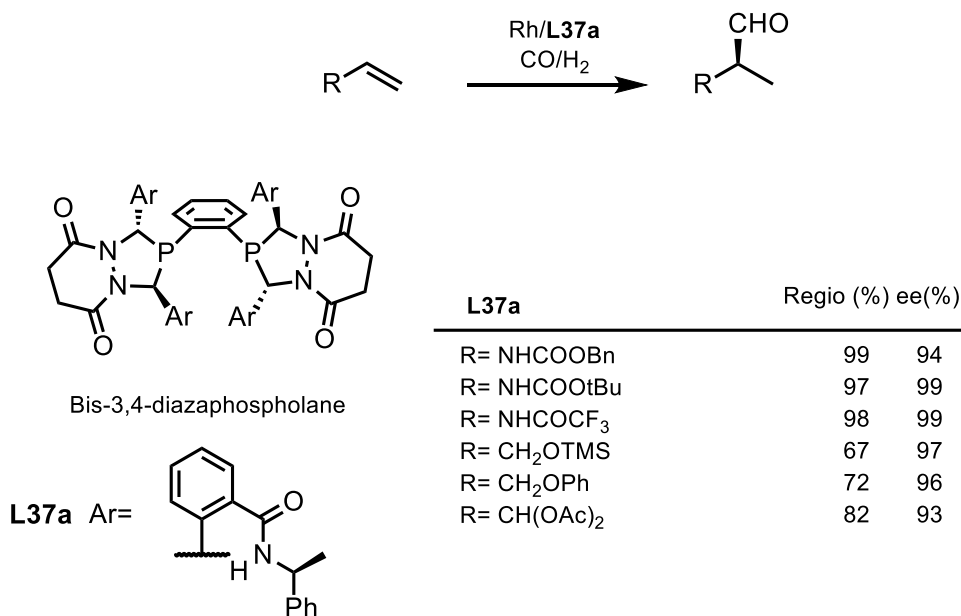


| <b>L37a</b>        | Regio (%) ee(%) |    |
|--------------------|-----------------|----|
| R1= Ph, R2= H      | 99              | 91 |
| R1= 2-furan, R2= H | 99              | 97 |
| R1= MeO, R2= H     | 99              | 94 |

| <b>L46</b>          | Regio (%) ee(%) |    |
|---------------------|-----------------|----|
| R1= Ph, R2= Me      | 88              | 93 |
| R1= 2-furan, R2= Me | 98              | 93 |

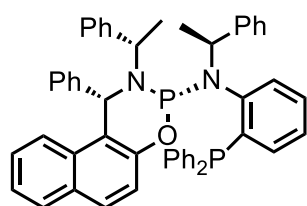
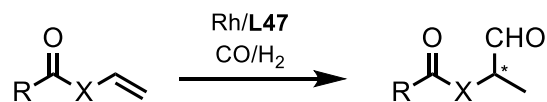
**Scheme 21. Rh-catalyzed asymmetric hydroformylation of 1,3-dienes with ligands L37a and L46.**

The **L37a** ligand was also successfully employed in the Rh-catalyzed asymmetric hydroformylation of other alkene substrates containing amine and ether substituents, with ee's up to 99% and 97% respectively (Scheme 22).<sup>87b</sup>

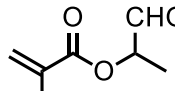
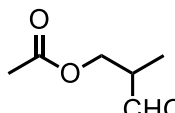


**Scheme 22. Rh-catalyzed asymmetric hydroformylation of monosubstituted enamides and other allylic substrates with the ligand L37a.**

Leitner and co-workers reported the use of bidentate phosphine, P-chiral phosphoramidate ligands for highly regio- and enantioselective hydroformylation of vinyl esters.<sup>88</sup> The BettiPhos ligand (**L47**) was particularly efficient and afforded total regioselectivity and ee's up to 97% for a number of these substrates (Scheme 23).



BettiPhos (**L47**)

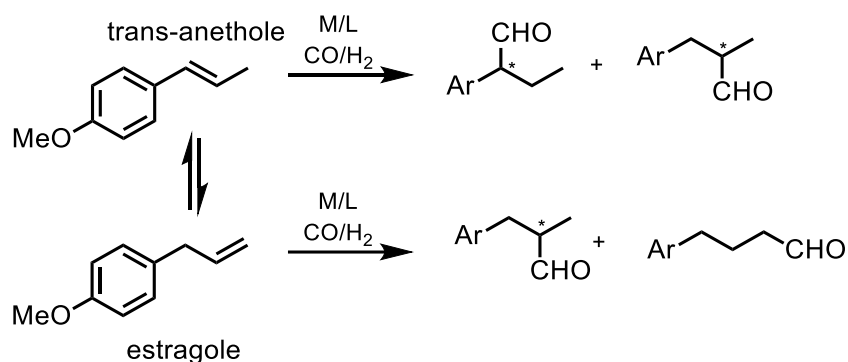
| Product   | Regio % | ee % |
|---|---------|------|
| R = Et; X = O   | >99     | 94   |
| R = tBu; X = O  | >99     | 95   |
| R = Ph; X = O   | >99     | 94   |
| R = 4-MeOC <sub>6</sub> H <sub>4</sub> ; X = O                                      | >99     | 91   |
| R = 4-FC <sub>6</sub> H <sub>4</sub> ; X = O  | >99     | 92   |
| R = naphthyl; X = O   | 98      | 88   |
| R = CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> ; X = O                        | >99     | 95   |
|   | >99     | 96   |
|  | -       | 5    |
| R = CH <sub>3</sub> ; X = NH  | 96      | 82   |
| R = CH <sub>3</sub> ; X = NCH <sub>3</sub>  | 86      | 83   |

Scheme 23. Rh-catalyzed asymmetric hydroformylation of vinyl esters using the **L47** BettiPhos ligand.

#### 2.4. Rh-catalyzed asymmetric hydroformylation of 1,2-disubstituted alkenes

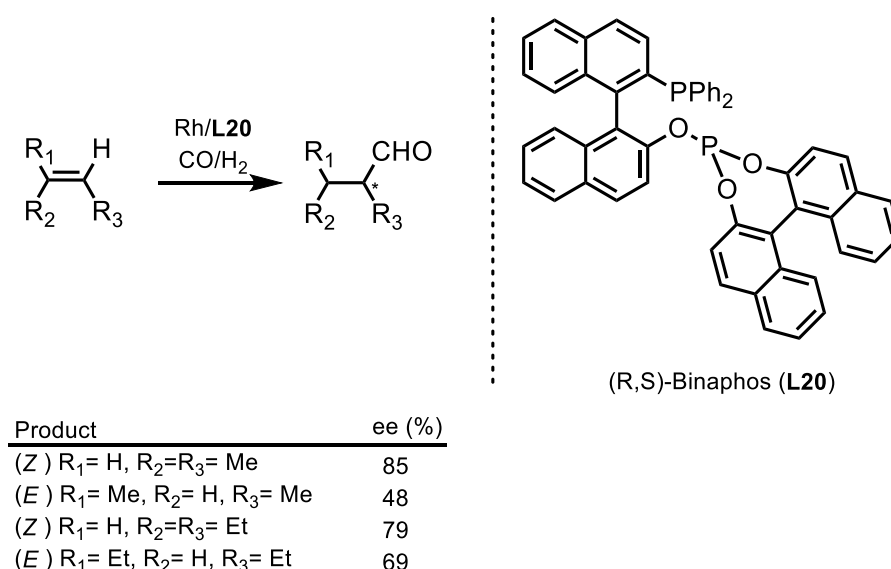
The Rh-catalyzed asymmetric hydroformylation of disubstituted alkenes has received much less interest than their monosubstituted counterparts. To our knowledge, only a few examples of Rh-catalyzed asymmetric hydroformylation of 1,2-disubstituted have been reported so far (Scheme 2).<sup>25a,89</sup>

The 1,3-diphosphite ligand **L6** was used in the reaction of *trans*-anethole and estragole (Scheme 24) but moderate to low enantioselectivities were achieved (*ee* up to 15%).<sup>90</sup> Nozaki and co-workers reported the asymmetric Rh-catalyzed hydroformylation of *trans*-anethole into 2-phenylbutanal using the Binaphos ligand **L20** with excellent regioselectivity (98%) and a remarkable 80% *ee*.<sup>91</sup>



**Scheme 24.** Isomerization processes and asymmetric hydroformylation of *trans*-anethole and estragole.

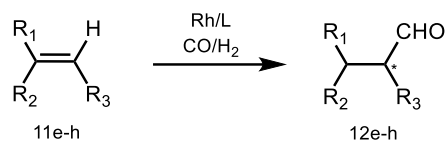
The same ligand also provided high *ee* values in the Rh-catalyzed asymmetric hydroformylation of 1,2-alkyl-disubstituted alkenes (Scheme 25).<sup>91</sup> Interestingly, the *E*-isomers yielded lower enantioselectivity than their *Z*-counterparts.



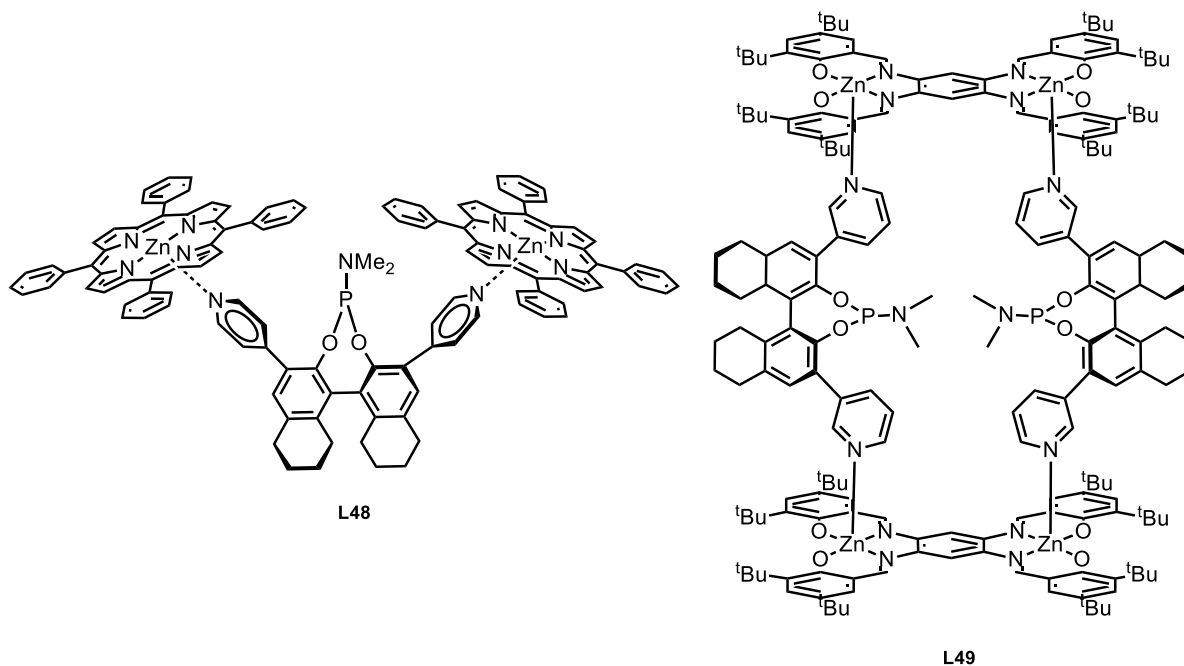
**Scheme 25.** Rh-catalyzed asymmetric hydroformylation of di-substituted alkenes.

More recently, Reek and co-workers applied a supramolecular approach in the asymmetric Rh-catalyzed hydroformylation of internal alkenes (Scheme 26).<sup>92</sup> When a monodentate phosphoramidite template ligand (**L48**), containing two pyridine functions in the bis(naphthol) skeleton that are bounded to zinc (II) porphyrins, moderate conversions (up to 56%) and *ee*'s (up to 45%) were achieved in the Rh-catalyzed asymmetric hydroformylation of *trans*-2-octene. However, when the ligand **L49** (Scheme 26) containing two phosphoramidite moieties was tested, remarkable enantioselectivities were obtained.<sup>93</sup>



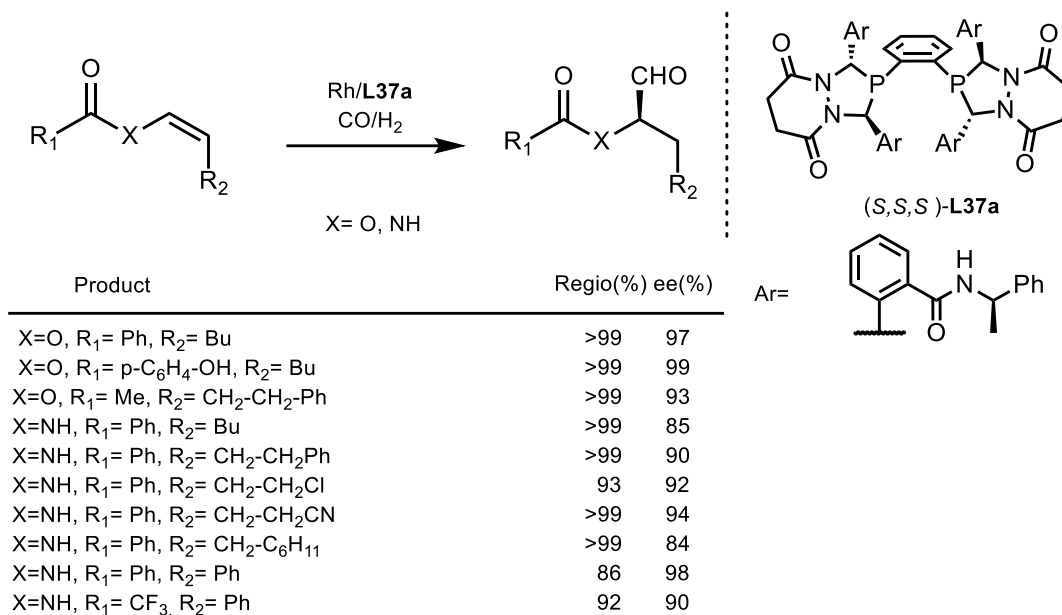


| Product   | L          | ee (%) |
|---|------------|--------|
| R <sub>1</sub> = Me, R <sub>2</sub> =H, R <sub>3</sub> = Pent | <b>L48</b> | 45     |
|   | <b>L49</b> | 72     |
| R <sub>1</sub> = Me, R <sub>2</sub> =H, R <sub>3</sub> = hex  | <b>L49</b> | 62     |
| R <sub>1</sub> = H, R <sub>2</sub> =Me, R <sub>3</sub> = Pent | <b>L49</b> | 80     |
| R <sub>1</sub> = H, R <sub>2</sub> =Me, R <sub>3</sub> = Bu   | <b>L49</b> | 82     |



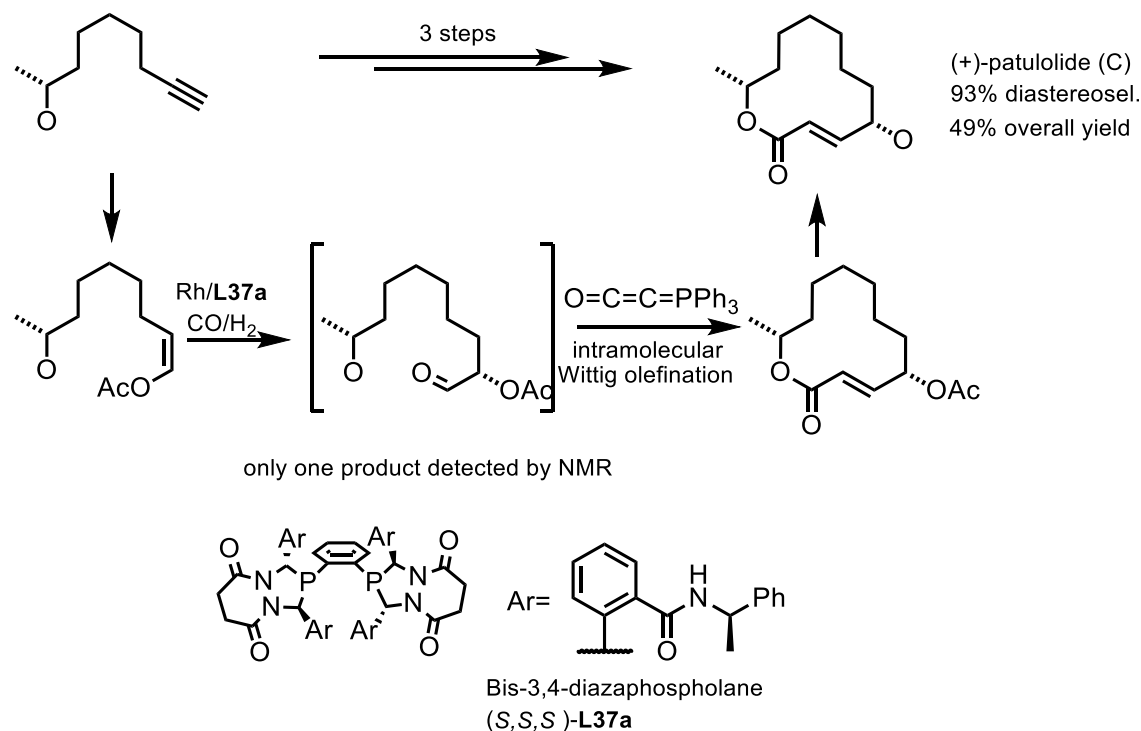
**Scheme 26. Rh-catalyzed asymmetric hydroformylation of internal alkenes with the ligands L48 and L49.**

Landis and co-workers demonstrated that the diazaphospholane ligand **L37a** could provide high enantioselectivity in the hydroformylation of *Z*-enamides and enol esters, providing excellent enantioselectivities for a broad range of these substrates (Scheme 27).<sup>94</sup>



**Scheme 27.** Rh-catalyzed asymmetric hydroformylation of *Z*-enamides and enol esters with the (*S,S,S*)-bis diazaphospholane ligand (**L37a**) reported by Landis and co-workers.

Using the same **L37a** ligand, Burke and Risi reported the total synthesis of (+)-patulolide **C**,<sup>95,96</sup> in including a Rh-catalyzed hydroformylation/ intramolecular Wittig olefination route affording a very short, high-yielding synthesis of this compound, that usually required over 14 steps. (Scheme 28).<sup>97</sup>

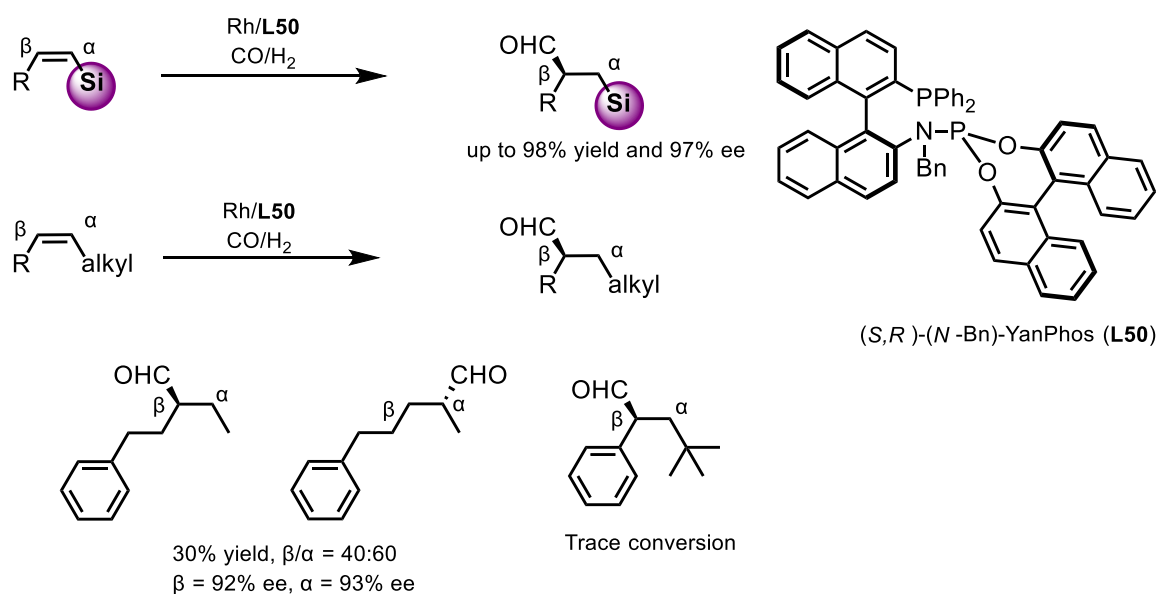


**Scheme 28.** Rh-catalyzed asymmetric hydroformylation/macrocyclization cascade using ligand **L37a** for the synthesis of (+)-patulolide **C**.

The same authors later employed this ligand in the synthesis of other biologically relevant molecules using asymmetric hydroformylation as the key step.<sup>98,99</sup>

Clarke and co-workers developed the asymmetric transfer hydroformylation (ATHF) of unsymmetric *cis*-stilbenes using a dual catalyst system including [RhCl(COD)]<sub>2</sub> and (*S,S*)-Ph-BPE (**L35b**) for the formation of CO and H<sub>2</sub> from paraformaldehyde and [Rh(acac)(CO)<sub>2</sub>] and (*S<sub>ax</sub>*, *S,S*)-Bobphos as active catalyst for AHF. They obtained up to 98% ee with moderate regioselectivity of 65:35.<sup>100</sup>

Zhang and co-workers reported the AHF of 1,2-disubstituted alkenylsilanes with high regioselectivity and high enantioselectivity using (*S,R*)-(*N*-Bn)-Yanphos.<sup>101</sup> In this reaction, the silicon group was critical for the regiocontrol and activation of the substrate. (Scheme 29).

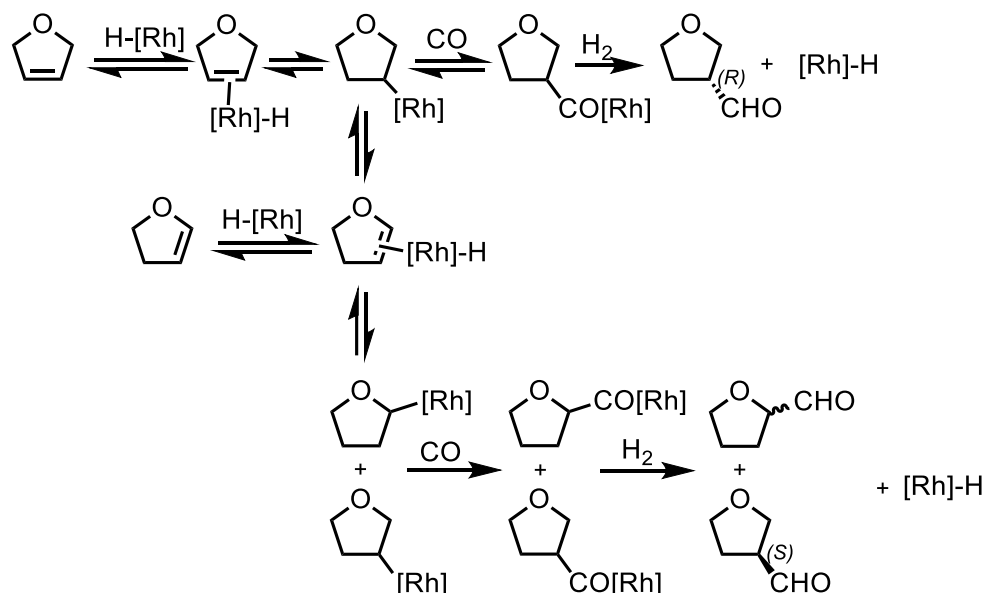


**Scheme 29.** AHF of *Z*-alkenylsilanes using Rh/L50

### 2.4.1. Monocyclic 1,2-Disubstituted alkenes

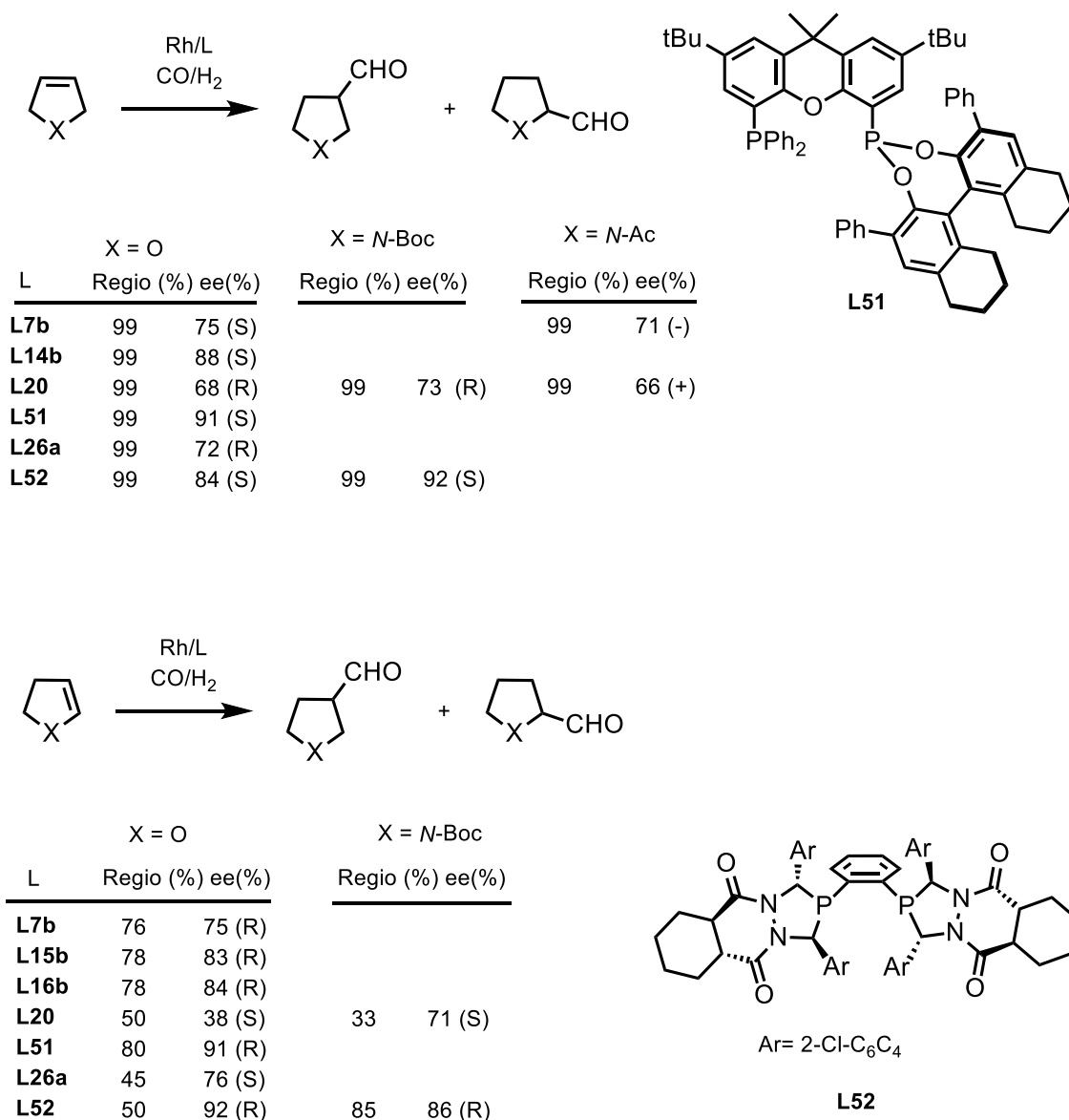
Among monocyclic 1,2-disubstituted alkene substrates, dihydrofurans and dihydropyrroles have been the most studied. With these 5-membered ring heterocycles, the simultaneous control of the chemo-, regio- and enantioselectivity is made difficult by the presence of a heteroatom in the ring that favors in some cases an isomerization process. Previous studies using achiral ligands demonstrated that the reaction conditions highly affected the chemo- and regioselectivity of this reaction.<sup>102</sup> Indeed, allyl ethers were observed to rapidly isomerize into their vinyl analog under hydroformylation conditions (Scheme 30). This isomerization has a direct influence on both the regioselectivity of the reaction and the enantioselectivity since the

opposite enantiomers of tetrahydrofuran-3-carbaldehyde are formed from the 2,5-dihydrofuran and 2,3-dihydrofuran isomers of the substrate.<sup>103</sup> The isomerization must therefore be inhibited to obtain high selectivities.



**Scheme 30.** Isomerization processes observed during the Rh-asymmetric hydroformylation of five-membered heterocyclic alkenes.

Nozaki and co-workers reported the first successful results in the Rh-catalyzed asymmetric hydroformylation of 2,5-dihydrofuran using the Binaphos ligand **L20**, obtaining total regioselectivity to (*R*)-tetrahydrofuran-3-carbaldehyde with 68% *ee* (Scheme 31).<sup>91,104</sup> However, when the 2,3-dihydrofuran was tested using the same catalyst, low regioselectivity was observed and the *ee* obtained for tetrahydrofuran-3-carbaldehyde dropped to 38% with *S* configuration. This catalytic system was thus suitable to avoid isomerization of 2,5-dihydrofuran into 2,3-dihydrofuran but not selective for the hydroformylation of 2,3-dihydrofuran. In the same study, the *N*-protected 2,5-dihydropyrrole and 2,3-dihydropyrrole analogs were also tried as substrates using the same catalytic system (Scheme 31) and similar results were obtained.



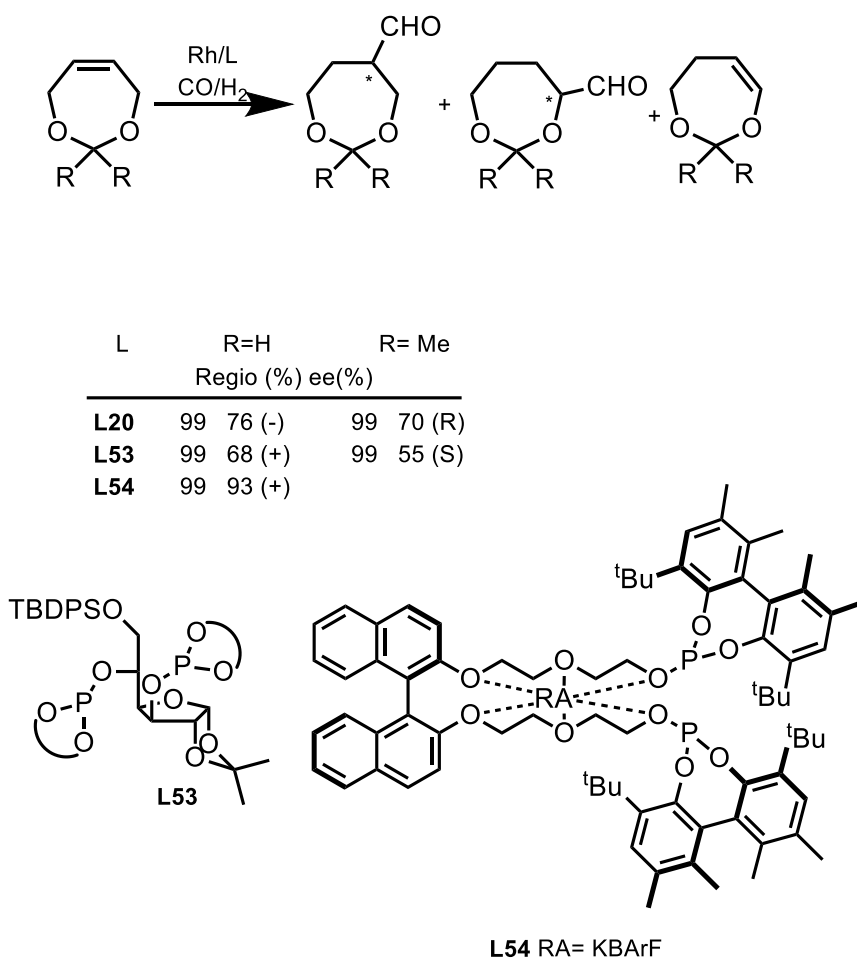
**Scheme 31. Rh-catalyzed asymmetric hydroformylation of five-membered heterocyclic alkenes.**

The previously mentioned 1,3-diphosphites **L7-L16** (Scheme 6) derived from carbohydrates were later successfully applied in the Rh-catalyzed hydroformylation of these substrates.<sup>105, 39b</sup> In the case of the 2,5-dihydrofuran, the highest enantioselectivity in the tetrahydrofuran-3-carbaldehyde was obtained using ligand **L14b** (88% *S*). Using this ligand, no isomerization was observed under hydroformylation conditions. Interestingly, the degree of isomerization increased when bulky substituents are introduced at C5 such as in ligands **L15b-L16b**. When the 2,3-dihydrofuran substrate was used, 80% regioselectivity for tetrahydrofuran-3-carbaldehyde was achieved with *ee*'s up to 84% (*R*) using ligands **L15b-L16b**. When the *N*-Ac-pyrroline was tested with the Rh/**L7b** system, results to similar those previously reported using ligand **L20** were obtained (71 and 66%, respectively) (Scheme 9).

Reek and co-workers described the synthesis and application of the ligand **L51**, containing a skeleton related to the Xantphos ligand, in the Rh-catalyzed asymmetric hydroformylation of the 2,5-dihydrofuran and 2,3-dihydrofuran (Scheme 31). This system provided regioselectivities of 99 and 80%, respectively, and very high enantioselectivities (up to 91%).<sup>106</sup>

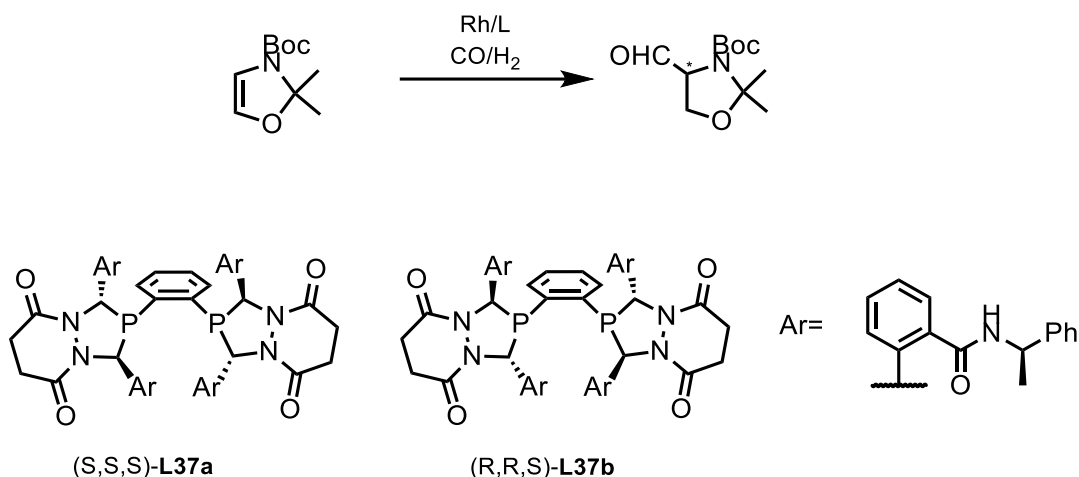
Recently, Zhang and co-workers reported the Rh-asymmetric hydroformylation of five-membered heterocyclic alkenes using a derivative of the diazaphospholane ligand **L52** (Scheme 31).<sup>107</sup> This system provided excellent regio- and enantioselectivities (up to 92%) for several of these substrates. The use of the small bite angle phosphine phosphite ligand **L26a** (Scheme 11) was also described in this reaction.<sup>56a</sup> When 2,5-dihydrofuran was the substrate, total regioselectivity was reached with *ee*'s up to 72%, while moderate regioselectivity and *ee*'s up to 76% were obtained when 2,3-dihydrofuran was used.

More recently, the same authors reported the use of conformationally transformable  $\alpha,\omega$ -bisphosphite ligands combined with an alkali metal BArF salt as a regulation agent (RA) and they obtained enantioselectivities up to 82% with **L54** in the AHF of the 2,5-dihydrofuran.<sup>41<sup>b</sup></sup> The Rh-catalyzed asymmetric hydroformylation of 4,7-dihydro-1,3-dioxepine was described using the Binaphos ligand **L20** and 1,3-diphosphite ligands derived from carbohydrates **L53** (Scheme 32).<sup>91-105<sup>b</sup></sup> Using the ligand **L20**, total regioselectivity to 1,3-dioxepane-5-carbaldehyde was achieved, together with *ee*'s up to 76%. Among the carbohydrate-derived ligands tested, ligand **L53** provided the best results (Scheme 32), affording total regioselectivity to 1,3-dioxepane-5-carbaldehyde and up to 68% *ee*, thus indicating that no isomerization of the dioxepine had occurred. More recently, Vidal-Ferran and co-workers reported the highest *ee* in the asymmetric hydroformylation of the dioxepine using a Rh complex bearing the diphosphite **L54** (Scheme 32).<sup>41<sup>b</sup></sup>



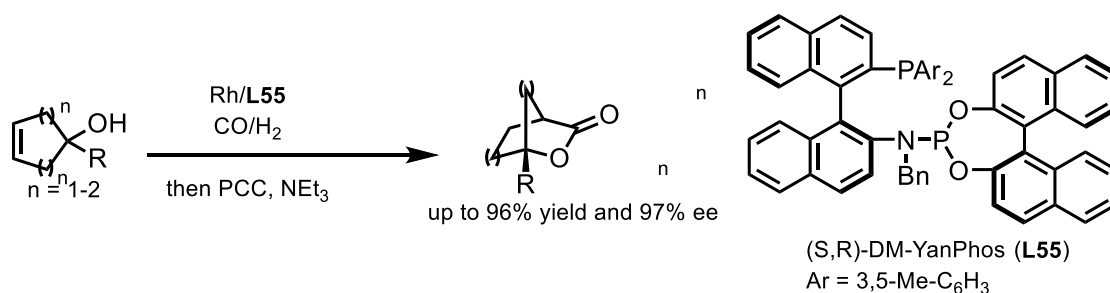
**Scheme 32. Rh-catalyzed asymmetric hydroformylation of 4,7-dihydro-1,3-dioxepine.**

Asymmetric hydroformylation of cyclic disubstituted olefins was employed to provide useful chiral molecules like Garner's aldehyde, a popular building block.<sup>108,109</sup> Both enantiomers of this molecule were prepared using catalytic systems bearing the diastereoisomeric bis-diazaphospholane ligands **L37a** and **L37b** (Scheme 33).<sup>110</sup> The *S* enantiomer can be produced in 97% ee in the presence of (*S,S,S*)-**L37a** while the *R* product is formed with a slightly lower ee (94%), using the ligand (*R,R,S*)-**L37b**.



**Scheme 33.** Synthesis of Garner's aldehyde through Rh-catalyzed asymmetric hydroformylation of the cyclic disubstituted olefin N-Boc-2,2-dimethyl-2,3-dihydrooxazole.

Very recently, Zhang and co-workers developed the AHF of cyclopent-3-en-1-ols, yielding after oxidation the bridged [2,2,1] bicyclic lactones in high yields and excellent enantiomeric excess.<sup>111</sup> Commercially available (*S,S*)-Ph-BPE (**L35b**) afforded good conversion and enantioselectivity but Yanphos derivative gave higher syn-selectivity, allowing the cyclization (Scheme 34).

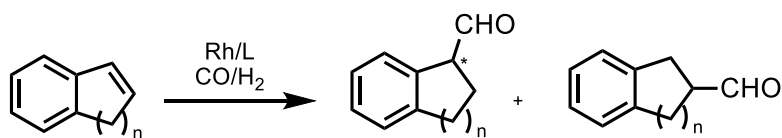


**Scheme 34.** Access to bridged [2,2,1] bicyclic lactones with a quaternary stereocenter via stereospecific hydroformylation.

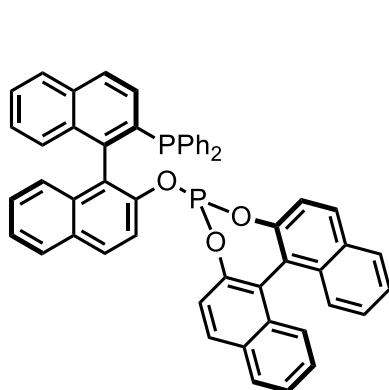
## 2.4.2. Bicyclic 1,2-Disubstituted alkenes

The Rh-catalyzed asymmetric hydroformylation of indene and 1,2-dihydronaphthalene substrates was reported by Nozaki and co-workers using the ligands **L20** and **L56** (Scheme 35). Outstanding results were obtained with 1,2-dihydronaphthalene, for which 1,2,3,4-tetrahydronaphthalene-1-carbaldehyde was produced with practically total regioselectivity and excellent ee (Scheme 35). The 2,3-dihydro-1H-indene-1-carbaldehyde can be converted in a single step into the corresponding amine which exhibits hypotensive activity while the product 1,2,3,4-tetrahydronaphthalene-1-carbaldehyde is a synthetic intermediate to produce a vasoconstrictor tetrahydrozoline.<sup>112</sup>

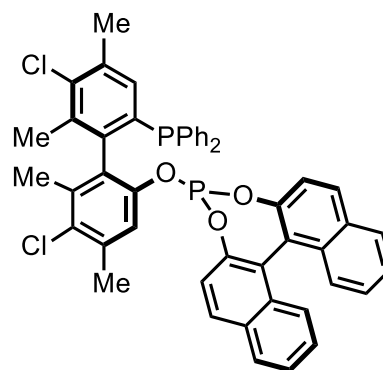




| Product | L          | Regio (%) | ee(%) |
|---------|------------|-----------|-------|
| n=1     | <b>L56</b> | 92        | 88    |
|         | <b>L20</b> | 92        | 83    |
| n=2     | <b>L56</b> | 96        | 97    |
|         | <b>L20</b> | 96        | 96    |



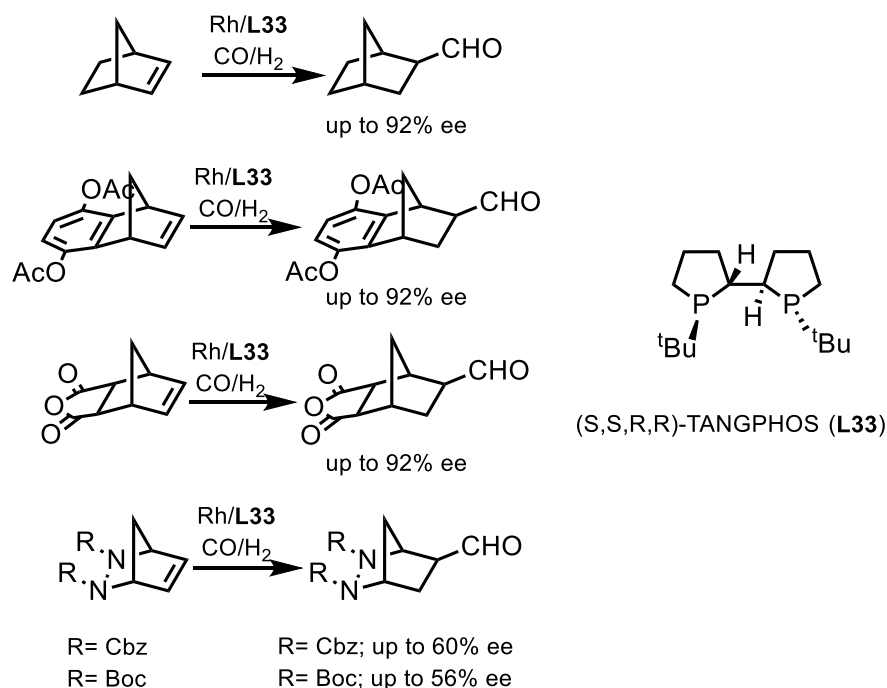
(R,S)-Binaphos (**L20**)



(S,R)-Biphemphos (**L56**)

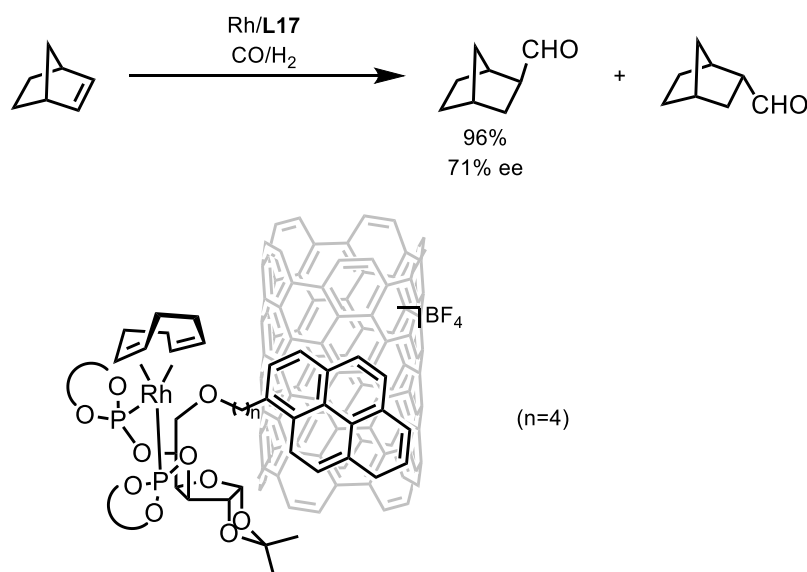
**Scheme 35. Rh-catalyzed asymmetric hydroformylation of bicyclic alkenes using the ligands (R,S)-Binaphos (**L20**) and Biphemphos (**L56**).**

Another bicyclic alkene substrate of interest for carbonylation reactions is norbornene and its derivatives. The first reports on the Rh- asymmetric hydroformylation of norbornene gave low enantiomeric induction with *ee*'s below 25%.<sup>113</sup> In 2005, Bunel and co-workers reported the first highly enantioselective Rh-catalyzed hydroformylation of norbornene using the Tangphos ligand **L33** forming the *exo* aldehyde with *ee*'s up to 92%.<sup>114</sup> Using the same ligand, they obtained similar enantioselectivities in the hydroformylation of several norbornene derivatives (Scheme 36).



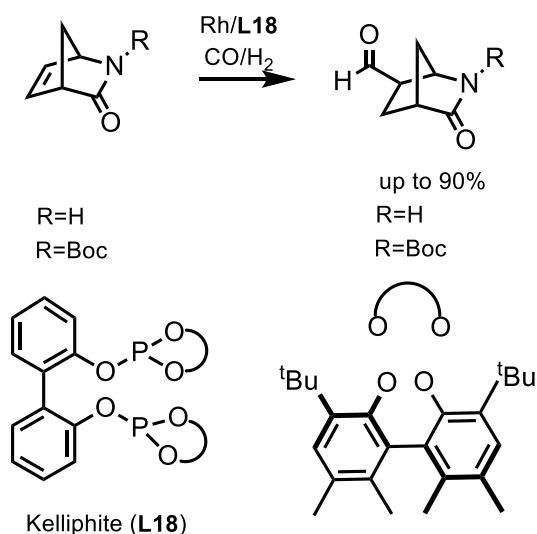
**Scheme 36. Rh-catalyzed asymmetric hydroformylation of norbornene derivatives using the diphospholane ligand L33.**

Godard and coworkers worked on AHF of norbornene with sugar-based diphosphate ligand **L17**, exhibiting outstanding activity and forming the exo aldehyde with 96% selectivity and 71% ee.<sup>115</sup> Moreover, immobilization of pyrene-tagged complexes based on **L17** onto carbon nanotubes via  $\pi$ - $\pi$  stacking interaction allowed its utilization under flow conditions to reach 73% ee (Scheme 37).



**Scheme 37. AHF of norbornene using sugar-based bis-phosphite ligands.**

In 2010, the Kelliphite ligand (**L18**) was employed in the Rh-catalyzed asymmetric hydroformylation of bicyclic lactam azabicyclo-[2.2.1]hept-5-en-3-ones. Complete *exo*-selectivity and excellent regioselectivities (up to 90%, Scheme 38) were obtained.<sup>116</sup>



**Scheme 38.** Rh-catalysed asymmetric hydroformylation of bicyclic lactam azabicyclo-[2.2.1]hept-5-en-3-ones using the Kelliphite ligand **L18**.

## 2.5. Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

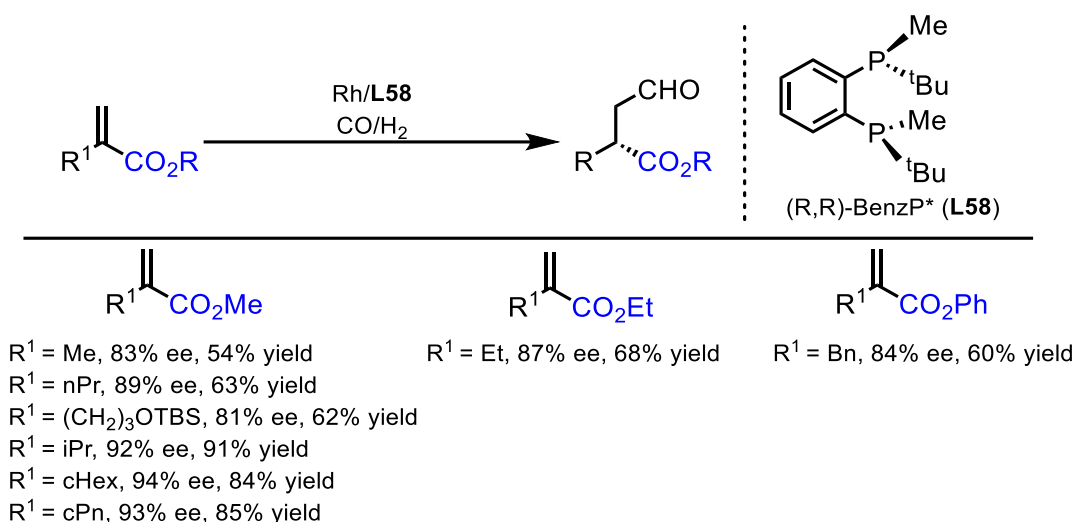
A recent review focuses on the AHF of 1,1'-terminal disubstituted olefins.<sup>117</sup>

### 2.5.1. Asymmetric hydroformylation of terminal 1,1'-disubstituted alkenes with coordinative groups

#### 2.5.1.1. *n*-Selective asymmetric hydroformylation

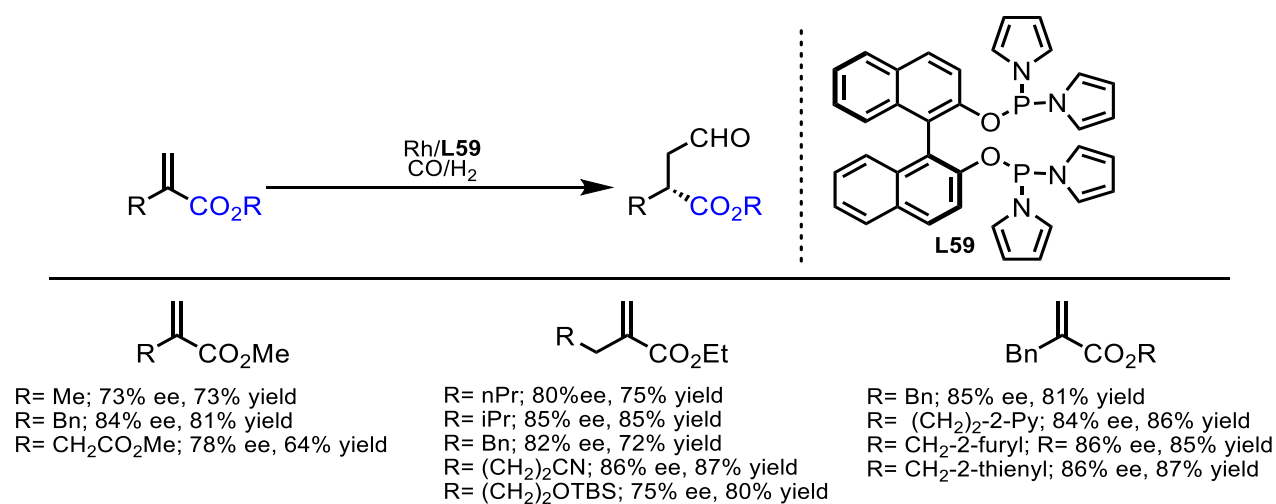
In 2011 Buchwald et al. reported the first AHF of various  $\alpha$ -alkyl acrylates using a Rh-catalyst (Scheme 39).<sup>118</sup> Short reaction times and 10 bar of pressure were necessary for the transformation of the substrates, although the temperature was 100 °C. The authors described that the P-stereogenic diphosphine (*R,R*)-BenzP\* (**L58**) ligand provided 82% ee in the AHF of ethyl 2-benzylacrylate. Unprecedented enantioselectivities (81-94% ee) were obtained towards a selection of chiral linear aldehydes (Scheme 39). Moreover, the authors found the optimal CO/H<sub>2</sub> ratio of 1:5 to achieve good chemo- and regioselectivities and avoid side reactions.

Alkenes bearing secondary alkyl substituents, such as isopropyl, cyclohexyl, and cyclopentyl groups gave the highest yields and enantioselectivities (84-91% yield and 92-94% ee). The higher yields could be explained by the presence of bulkier secondary alkyl groups that avoid the formation of the branched Rh-alkyl intermediate, leading to a better regioselectivity towards the chiral linear aldehydes.



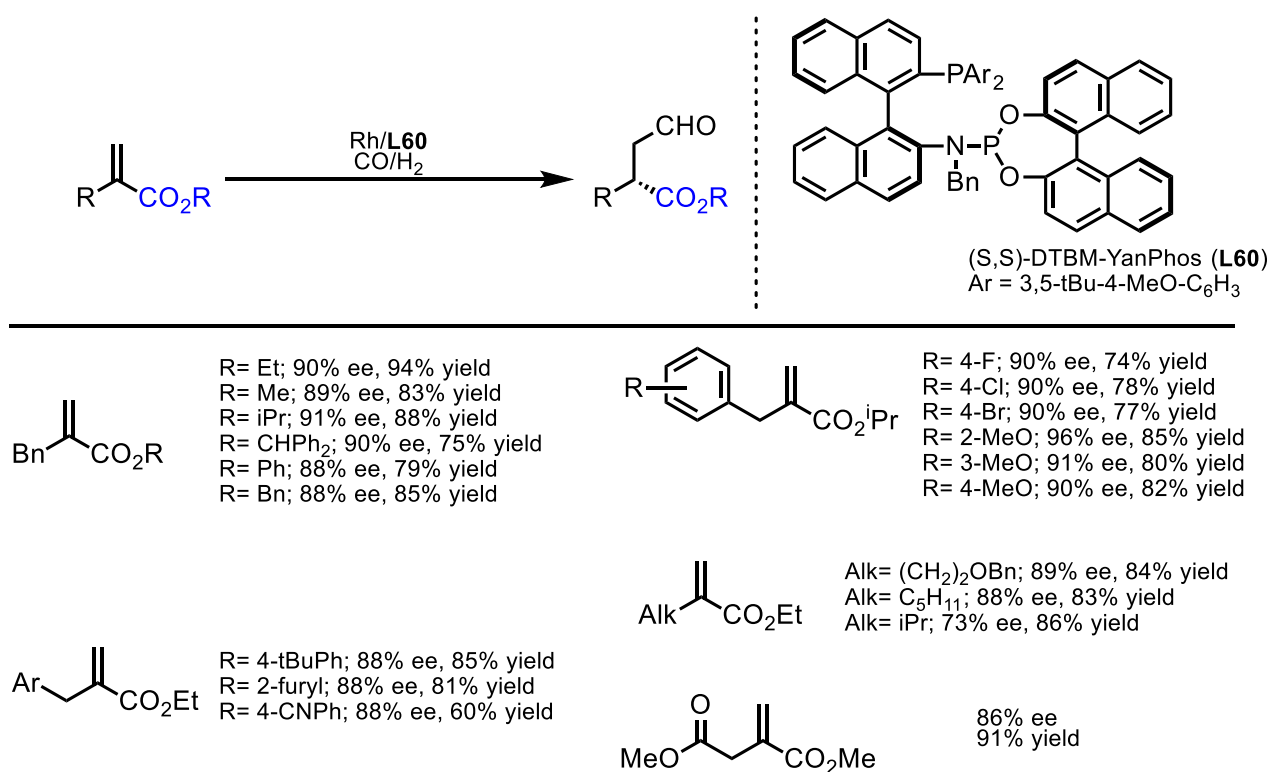
**Scheme 39.** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -alkylacrylates with the (*R,R*)-BenzP\* P-chirogenic phosphine ligand (**L58**).

The reaction of  $\alpha$ -substituted acrylates was also achieved by Chin et al. in 2019 using the pyrrolylphosphinite ligand **L11**. A range of chiral aldehydes were obtained in good-to-high enantioselectivities (73%-86% ee) (Scheme 40) and good yields (up to 87%).<sup>119</sup>



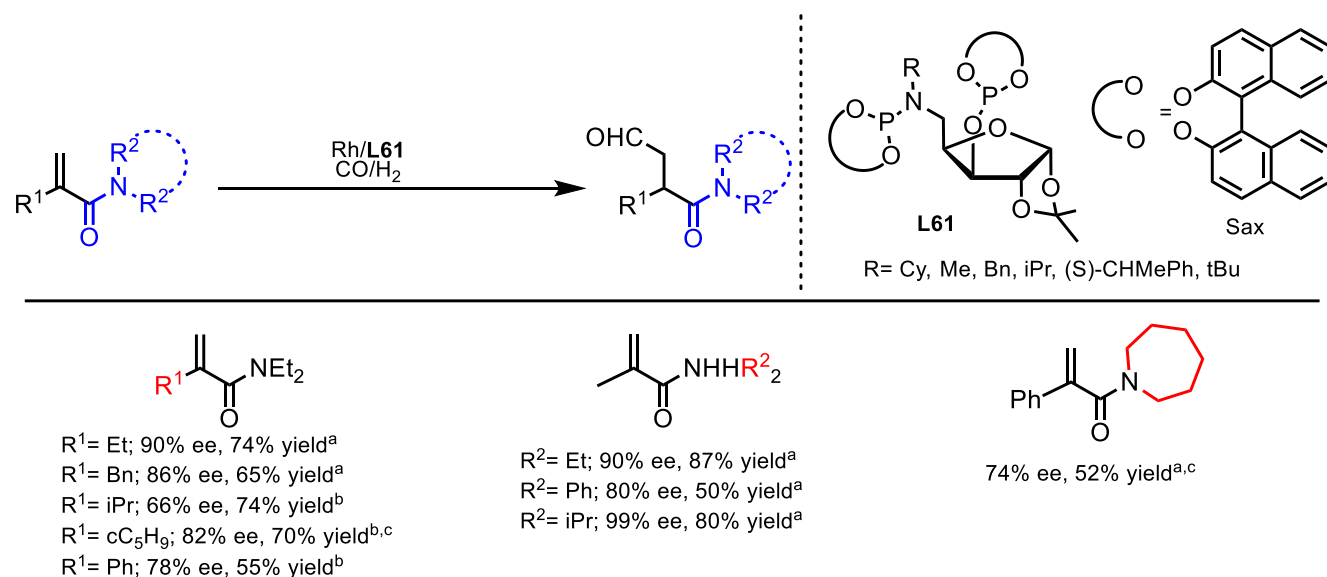
**Scheme 40.** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -alkylacrylates with pyrrolylphosphinite ligand **L59**.

Zhang and co-workers made the most recent contribution to the AHF of  $\alpha$ -substituted acrylates with a phosphine-phosphoroamidite ligand from the (*S,S*)-Yanphos family.<sup>120</sup> This ligand family was previously successfully applied on the AHF of 1,1'-disubstituted alkenes with weakly coordinative groups<sup>121</sup> and without coordinative groups<sup>122</sup> providing high activities and selectivities. They found that the (*S,S*)-DTBM-Yanphos ligand (**L60**) provided the best catalytic performance for AHF of ethyl 2-benzylacrylate. With this ligand, a range of chiral linear aldehydes (Scheme 41) could be obtained with high enantioselectivities (88-96% ee) and high yields (up to 94%). A gram-scale AHF of  $\alpha$ -methyl methacrylate could be performed without compromising the yield and enantioselectivity while using a lower catalyst loading of 0.05 mol%.



**Scheme 41.** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -substituted acrylates with (*S,S*)-DTBM-Yanphos (**L60**).

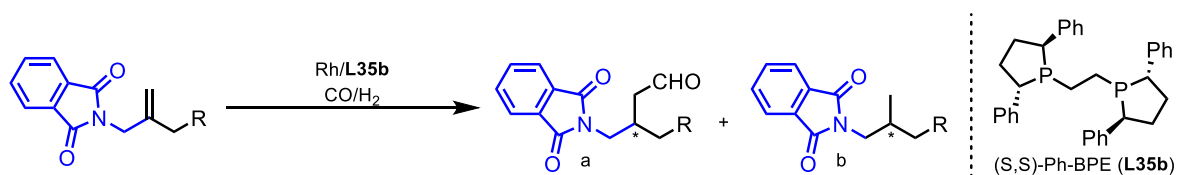
Only two existing publications reporting the AHF of  $\alpha$ -substituted acrylamides appeared in 2020.<sup>120,123</sup> Godard et al. reported the first use of 1,3-phosphite-phosphoramidite ligands based on a sugar backbone derived from D-xylose in AHF of  $\alpha$ -substituted acrylamides (**L13**, Scheme 42). The best catalytic performance was obtained with ligands bearing a bulky group on nitrogen atom (R= Cy and R= (*S*)-CHMePh) and a (*S*<sup>ax</sup>,*S*<sup>ax</sup>)-biaryl moiety (Scheme 42). A broad range of acrylamides, with different substituents in  $\alpha$ -position and at the amide group, were hydroformylated with high-to-excellent enantioselectivities (74-99% ee) and good-to-high yields (50-87%).<sup>123</sup> Furthermore, the reactions could be performed at only 60 °C. The catalytic system Rh/(*S*<sup>ax</sup>,*S*<sup>ax</sup>)-**L61** (R= Cy) was the most active for most of the substrates. When more sterically hindered alkenes (R<sub>2</sub> = NEt<sub>2</sub>, R<sub>1</sub> = iPr, cC<sub>5</sub>H<sub>9</sub>, Ph) ligand were used, the (*S*)- $\sigma$ -methylbenzyl amine substituent provided the best results. Importantly, this catalytic system could efficiently transform substrates bearing a phenyl substituent in  $\alpha$ -position (R<sub>1</sub> = Ph, R<sub>2</sub> = NEt<sub>2</sub>, azepane), which is present in several biologically active molecules whereas the catalysts previously reported<sup>141,120,118</sup> were only efficient for  $\alpha$ -alkyl substituted substrates.



**Scheme 42.** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -substituted acrylamides with sugar-based phosphite-phosphoramidite ligands **L61**. <sup>a</sup>Ligand (*S*<sup>ax</sup>,*S*<sup>ax</sup>)-**L61** (R= Cy) was used. <sup>b</sup>Ligand (*S*<sup>ax</sup>,*S*<sup>ax</sup>)-**L61** (R= (*S*)-CHMePh) was used. <sup>c</sup>Temperature= 90 °C for 16 h.

The use of a Rh/(*S,S*)-Ph-BPE (**L35b**) catalyst allowed the synthesis of a series of  $\beta^3$ -aminoaldehydes via AHF of allyl phthalimides with enantioselectivities up to 95% ee (Scheme 15).<sup>124</sup> The system was sensitive to the length of the substrate's alkyl chain. Indeed, high enantioselectivities and chemoselectivities were only achieved with some substrates (Scheme

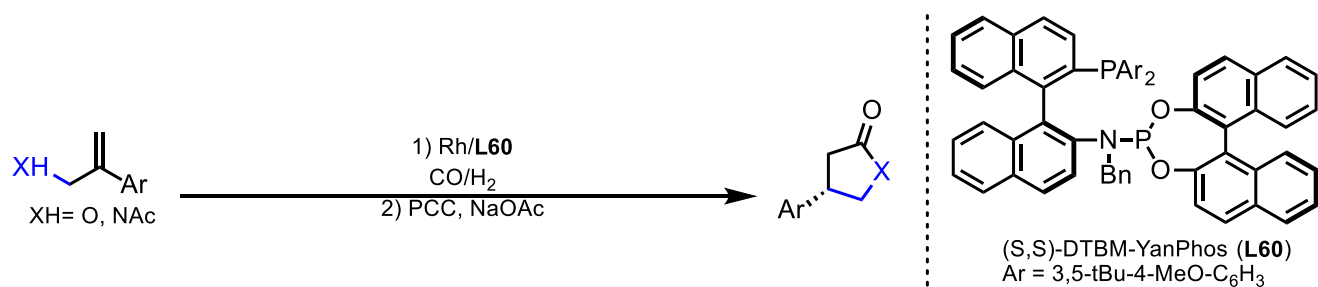
43). They showed the utility of this reaction to obtain chiral  $\beta^3$ -amino acids and alcohols through oxidation or reduction of the N-phthalimide-protected aldehydes.



|          | %ee | % conv. | a/b   |
|----------|-----|---------|-------|
| R = H    | 90  | 88      | >99/1 |
| R = Et   | 90  | 100     | >99/1 |
| R = nPr  | 75  | 36      | >99/1 |
| R = iPr  | 95  | 45      | >99/1 |
| R = nBu  | 77  | 54      | 97/3  |
| R = iBu  | 55  | 22      | 86/14 |
| R = cPn  | 57  | 36      | >99/1 |
| R = cHex | 90  | 13      | 72/28 |
| R = Bn   | 57  | 83      | 92/8  |

**Scheme 43.** Asymmetric hydroformylation of allyl phthalimides catalyzed by Rh/(*S,S*)-Ph-BPE (**L35b**).

Zhang's group reported the successfully AHF of allylic alcohols with the Rh/(*S,S*)-DTBM-Yanphos catalytic system (**L60**, Scheme 44).<sup>121</sup> A broad range of allylic alcohols were transformed with enantioselectivities ranging from 85 to 93% ee, independently on the nature of the aryl moiety. The afforded chiral linear aldehydes were then oxidized to the corresponding lactones. The AHF of allylic amines turned to be more difficult since the corresponding lactams were obtained in lower yields and enantioselectivities (up to 69% yield and 80-86% ee, Scheme 44).



| R                  | ee (%) | yield (%) |
|--------------------|--------|-----------|
| H                  | 90     | 87        |
| Me                 | 90     | 95        |
| iPr                | 89     | 71        |
| tBu                | 88     | 87        |
| Ph                 | 85     | 71        |
| MeO                | 90     | 88        |
| CF <sub>3</sub>    | 93     | 72        |
| CO <sub>2</sub> Et | 86     | 80        |
| F                  | 92     | 78        |
| Cl                 | 90     | 73        |

| R    | ee (%) | yield (%) |
|------|--------|-----------|
| 3-F  | 87     | 79        |
| 2-Me | 90     | 90        |

| R                                    | ee (%) | yield (%) |
|--------------------------------------|--------|-----------|
| Me                                   | 90     | 90        |
| MeO                                  | 90     | 74        |
| -O(CH <sub>2</sub> ) <sub>2</sub> O- | 88     | 80        |

92% ee; 83% yield

| R               | ee (%) | yield (%) |
|-----------------|--------|-----------|
| H               | 84     | 64        |
| Me              | 83     | 60        |
| MeO             | 84     | 64        |
| CF <sub>3</sub> | 80     | 69        |
| F               | 86     | 63        |
| Cl              | 82     | 60        |

| R       | ee (%) | yield (%) |
|---------|--------|-----------|
| 2-Naph  | 90     | 77        |
| 2-furyl | 85     | 75        |

| X  | ee (%) | yield (%) |
|----|--------|-----------|
| O  | 90     | 90        |
| Si | 86     | 72        |

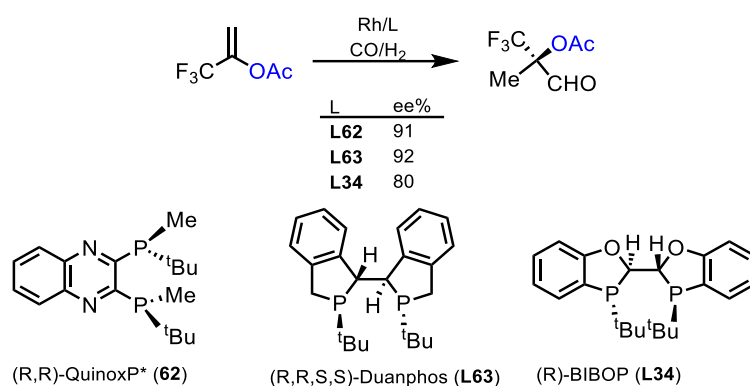
**Scheme 44.** Rh-catalyzed asymmetric hydroformylation of allylic alcohols and amines with (*S,S*)-DTBM-Yanphos (**L60**).

### 2.5.1.2. *i*-Selective asymmetric hydroformylation

The first efficient catalyst providing the branched aldehyde as the major product was reported by Buchwald et al. on the AHF of 3,3,3-trifluoroprop-1-en-2-yl acetate.<sup>125</sup> With the (*R,R*)-QuinoxP\* (**L62**) and (*R,R,S,S*)-Duanphos (**L63**) ligands, the chiral branched aldehyde was obtained with an enantioselectivity as high as 91% and 92% ee, respectively (Scheme 45). The origin of this unusual regioselectivity was suggested to come from the presence of the strongly electron-withdrawing trifluoromethyl group that favors the branched intermediate. Importantly, the unexpected regioselectivity observed in the AHF of 3,3,3-trifluoroprop-1-en-2-yl acetate permitted the one-pot preparation of the 2-trifluoromethylactic acid (TFMLA), an important building block bearing a quaternary stereocenter found on numerous active pharmaceutical compounds, with outstanding enantioselectivity (Scheme 45). Later, Zhang's

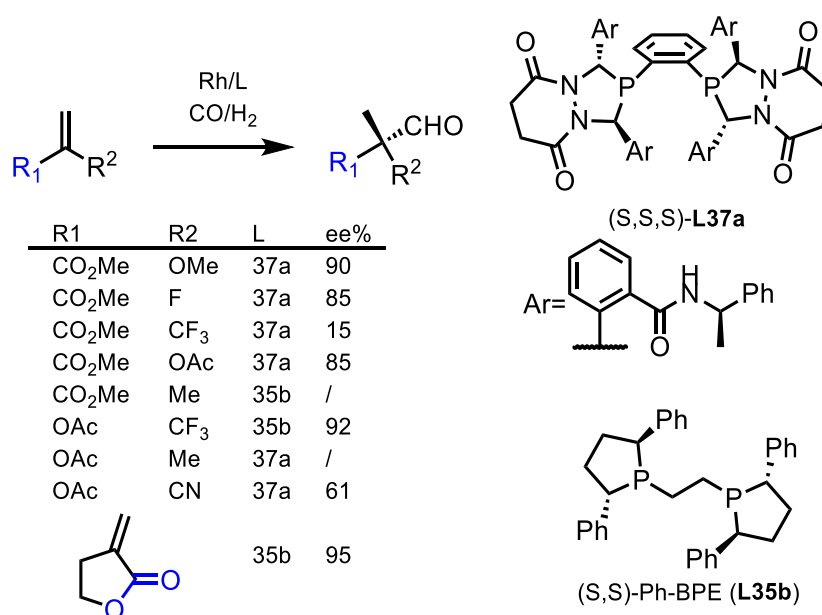


group reported the AHF of the same substrate, using another P-stereogenic diphosphine ligand, the (*R*)-BIBOP **L34**,<sup>126</sup> however, a lower enantioselectivity (80% ee) was reached than those obtained with QuinoxP\* or DuanPhos (Scheme 45).



**Scheme 45.** Reported examples for the Rh-catalyzed asymmetric hydroformylation of 3,3,3-trifluoroprop-1-en-2-yl acetate.

In 2018, Landis et al. reported another branched selectivity on a broader scope of substrates using (*S,S,S*)-BisDiazaphos (**L37a**) or (*S,S*)-Ph-BPE (**L35b**) ligands under mild conditions (10 bar, 60 °C and 2-72 h).<sup>127</sup> In particular, high *i*-selectivities were reached with 1,1'-disubstituted alkenes containing electron-withdrawing groups, such as a fluorine, a trifluoromethyl or an acetate (Scheme 46). Interestingly, some acrylates without electron withdrawing groups also provided high *i*-selectivities (e.g. with Me or OMe).



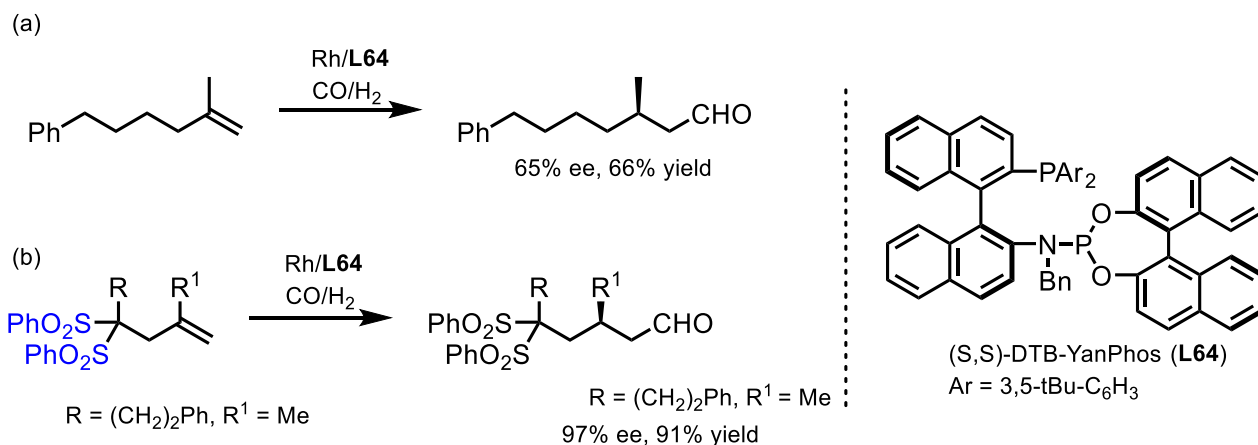
**Scheme 46.** Selected results for the Rh-catalyzed asymmetric hydroformylation of acrylates and acetates 1,1'-disubstituted alkenes with (*S,S,S*)-BisDiazaphos (**L37a**) or (*S,S*)-Ph-BPE (**L35b**).

### **2.5.2. Asymmetric hydroformylation of 1,1'-disubstituted alkenes with non-coordinating groups**

In recent years, progress was made in the AHF of 1,1'-disubstituted alkenes containing functional groups that might coordinate to the metal center, with high levels of asymmetric induction. High enantioselectivity is even more challenging using unfunctionalized 1,1'-disubstituted alkenes and only very recently, the first examples of catalysts providing high selectivity for these substrates were reported.

#### **2.5.2.1. 1,1'-dialkyl alkenes**

Zhang et al. developed an improved AHF of 1,1'-dialkyl substrates via the introduction of a steric disulfonyl auxiliary, using the Rh/(*S,S*)-DTB-Yanphos (**L64**) catalytic system. The incorporation of the disulfonyl moiety increased the yield of the reaction and considerably enhanced the enantioselectivity (Scheme 47 (a) vs (b)). This methodology has been applied over 20 substrates giving up to 97% yield and >99% ee.



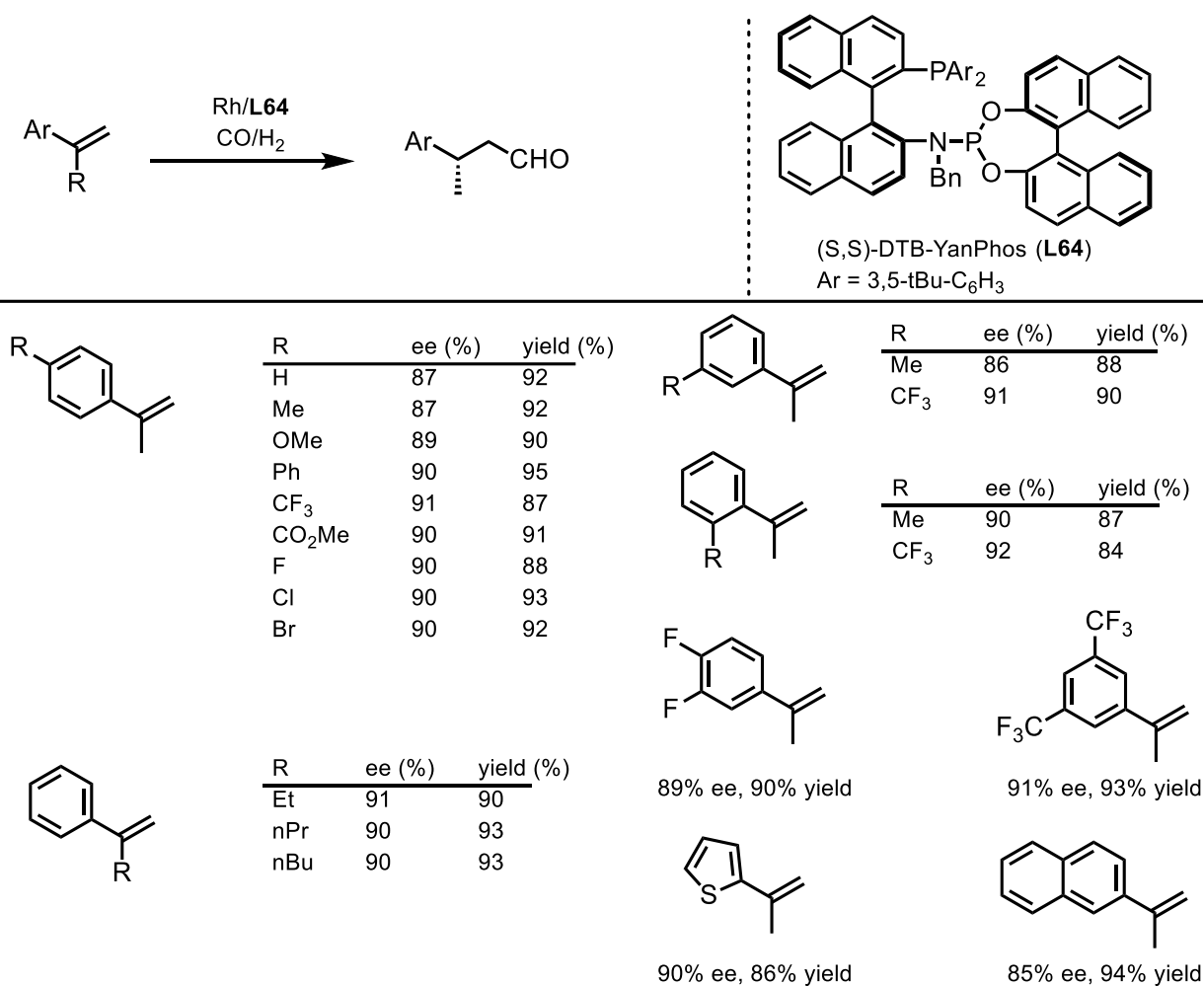
|                        | R  | %ee | % yield |
|------------------------|--|-----|---------|
|                        | Me   | 90  | 88      |
|                        | Et   | 90  | 100     |
|                        | nPr  | 75  | 36      |
|                        | nBu  | 95  | 45      |
|                        | iBu  | 77  | 54      |
|                        | n-amyl   | 55  | 22      |
|                        | F  | 57  | 36      |
|                        | iPr  | 90  | 13      |
| R <sup>1</sup> = Me    | Bn   | 57  | 83      |
|                        | (CH <sub>2</sub> ) <sub>2</sub> Ph                 | 97  | 91      |
|                        | (CH <sub>2</sub> ) <sub>3</sub> Ph                 | 95  | 92      |
|                        | (CH <sub>2</sub> ) <sub>3</sub> SiMe <sub>3</sub>  | 94  | 94      |
|                        | (CH <sub>2</sub> ) <sub>3</sub> CF <sub>3</sub>    | 94  | 85      |
|                        | (CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Et | 97  | 91      |
|                        | (CH <sub>2</sub> ) <sub>3</sub> NBn <sub>2</sub>   | 86  | 84      |
|                        | (CH <sub>2</sub> ) <sub>2</sub> OPh                | 96  | 88      |
|                        | (CH <sub>2</sub> ) <sub>2</sub> SPh                | 95  | 92      |
|                        |  |     |         |
| R <sup>1</sup> = Et    | R = (CH <sub>2</sub> ) <sub>2</sub> Ph             | 95  | 82      |
| R <sup>1</sup> = n-Hex | R = (CH <sub>2</sub> ) <sub>2</sub> Ph             | 94  | 76      |

**Scheme 47.** Efficient Rh-catalyzed asymmetric hydroformylation of 1,1'-dialkylsubstituted alkenes via steric auxiliary help with (*S,S*)-DTB-Yanphos (**L64**).

### 2.5.2.2. 1-Aryl-1-alkyl alkenes

Zhang et al. published in 2018 the best result reported so far for the AHF of  $\alpha$ -methylstyrene using a Yanphos-type ligand. The authors tested a series of Yanphos ligands and described that the key to reach high conversion and enantioselectivity is to use an (*S,S*)-configured-binol group on the phosphite moiety together with a hindered aryl group on the phosphine. Indeed, when using (*S,R*)-ligands, conversion and enantioselectivity were drastically reduced. After optimization of the ligand structure and reaction conditions, the AHF of  $\alpha$ -methylstyrene was achieved with 87% ee with (*S,S*)-DTB-Yanphos (**L64**). In addition, the reaction could be

performed at a gram scale with only 0.05 mol% of Rh. With this ligand, a range of 1-aryl-1-alkyl disubstituted alkenes could be hydroformylated with excellent enantioselectivities (up to 92% ee, Scheme 48).<sup>122</sup>



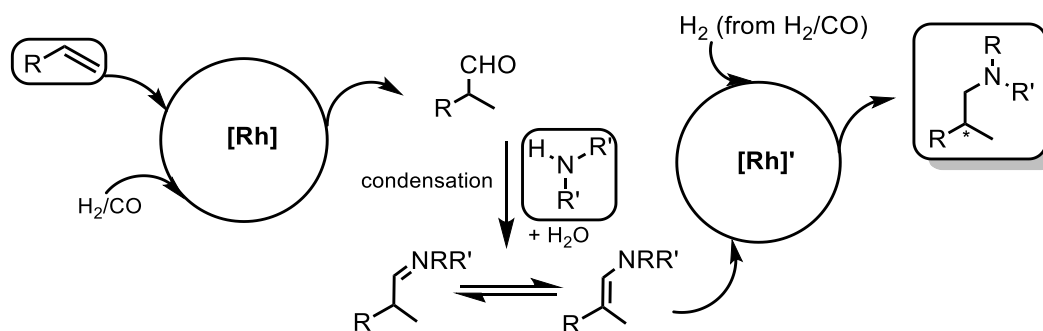
**Scheme 48.** Rh-catalyzed asymmetric hydroformylation of 1-aryl-1-alkyl disubstituted alkenes with (S,S)-DTB-Yanphos (**L64**)

### 3. Asymmetric hydroaminomethylation of alkenes

#### 3.1. Introduction

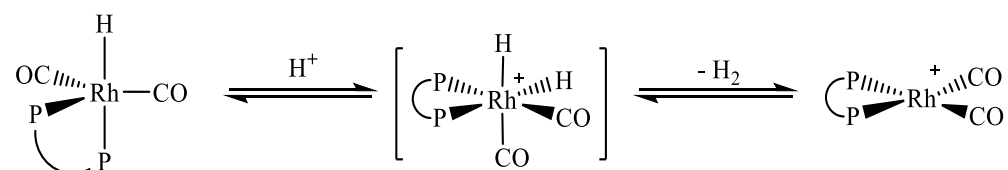
Chiral amine moieties are present in around 40% of pharmaceutical products. The introduction of these chiral units is therefore of high importance and usually performed in multistep processes<sup>128-129</sup>. As enantiomerically pure amines are required in large quantities in the pharmaceutical and agrochemical industry, the development of efficient methodologies for their preparation is of great significance and highly desirable. In the context of green chemistry, research on organometallic catalysis is still progressing to build the best tool to access and produce optically pure chiral amines. However, significant efforts to reach the appropriate coordination sphere around the transition metal center are still necessary to achieve full selectivity.

The goal of this section is to focus on the recent advances in enantioselective rhodium-catalyzed hydroaminomethylation reaction (HAM) for the synthesis of chiral amines. HAM is a tandem reaction involving in the first step the hydroformylation of an alkene. The achiral version of this reaction has been significantly investigated and some reviews have recently appeared<sup>130, 131, 132</sup>. The rhodium-catalyzed HAM represents an attractive atom economy reaction providing amines from alkenes in a one-pot way. This tandem reaction is composed of three successive steps. Aldehydes produced by the hydroformylation step react with primary or secondary amines present in the medium to afford the corresponding imines or enamines. Most of the time isomerization between imine and enamine occurs and hydrogenation of these two intermediates in the second catalytic cycle results in the formation of the desired amines (Scheme 49).



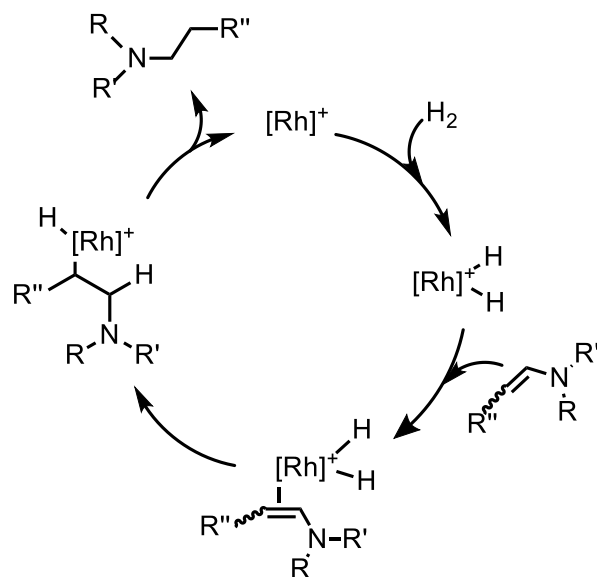
Scheme 49. Hydroaminomethylation reaction of olefins

It is necessary to carefully control the design of the catalytic system to obtain not only high chemoselectivity but also regioselectivity depending on the branched or linear expected final amine. The hydrogenation reaction represents the rate-determining step in HAM. In recent investigations on the mechanism, it has been demonstrated that an equilibrium between the neutral  $[\text{Rh}(\text{H})(\text{CO})_2\text{L}_2]$  and the cationic  $[\text{Rh}(\text{CO})(\text{X})\text{L}_2]^+$  species exists to perform the two catalytic cycles<sup>133</sup>. Probably, the neutral rhodium-hydride species catalyzes the hydroformylation reaction whereas the cationic species performs the hydrogenation reaction. In order to increase both catalytic activity and amine selectivity, an appropriate rhodium system able to generate in situ the two catalytic active species is necessary, instead of using simultaneously a cationic and a neutral rhodium precursors (Scheme 55).



**Scheme 50. Equilibrium between the two neutral and cationic rhodium species (from ref. 122)**

As the first catalytic cycle of hydroformylation is related in the first part of the chapter, only the second catalytic cycle concerning hydrogenation is proposed (Scheme 56). It is devoted to the imine/enamine hydrogenation, showing the main catalytic steps. Classically, the cationic active species, represented as  $[\text{Rh}]^+$ , reacts with dihydrogen by an oxidative addition reaction to give a dihydride which coordinates the imine/enamine. The hydride transfer and the reductive elimination steps provide the final amine, restoring the  $[\text{Rh}]^+$  active species.



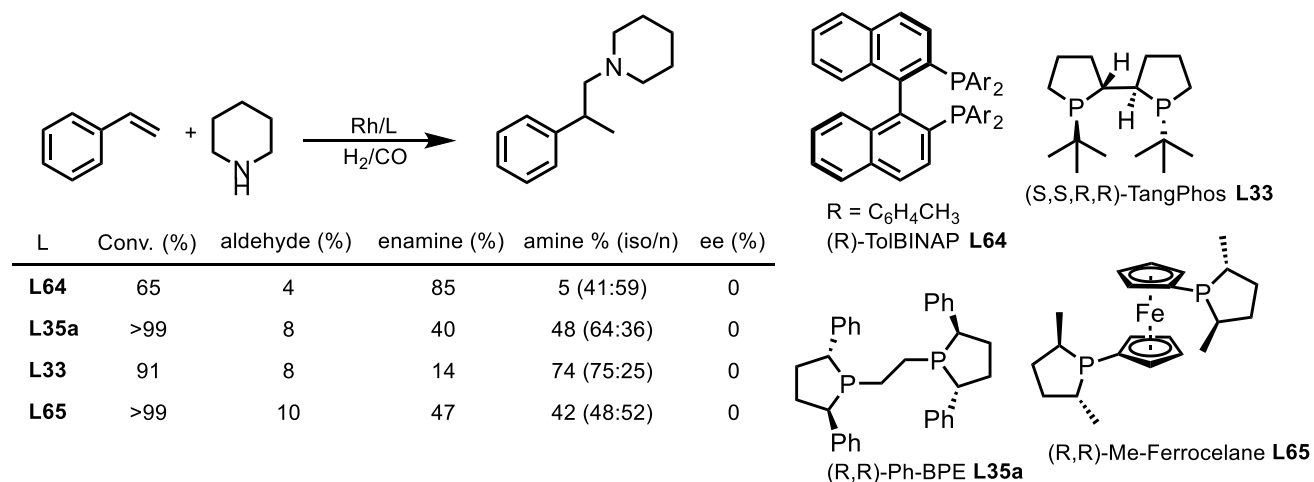
**Scheme 51. Hydrogenation catalytic cycle of an enamine**

This tandem reaction is generally carried out at temperatures between 90-130°C and 30-60 bar of CO:H<sub>2</sub> pressure to obtain amines in good yields. These operating conditions are somewhat more severe than those for the hydroformylation reaction consistent with a rate-determining step for the hydrogenation reaction of imines/enamines. The CO/H<sub>2</sub> composition generally varies from 1:1 to 1:5 depending on the experimental procedures.

Although the asymmetric HAM constitutes an interesting strategy to obtain chiral amines, scarce results were reported to date. They are described in the following section.

### 3.2. Asymmetric HAM of monosubstituted alkenes

A thorough study was performed by Kalck and co-workers on the asymmetric hydroaminomethylation of styrene with piperidine, using a variety of chiral diphosphine ligands which had been previously reported as very efficient in both asymmetric hydroformylation and hydrogenation reactions (Scheme 52)<sup>134</sup>. The study also included <sup>1</sup>H and <sup>31</sup>P NMR investigations as well as DFT calculations.



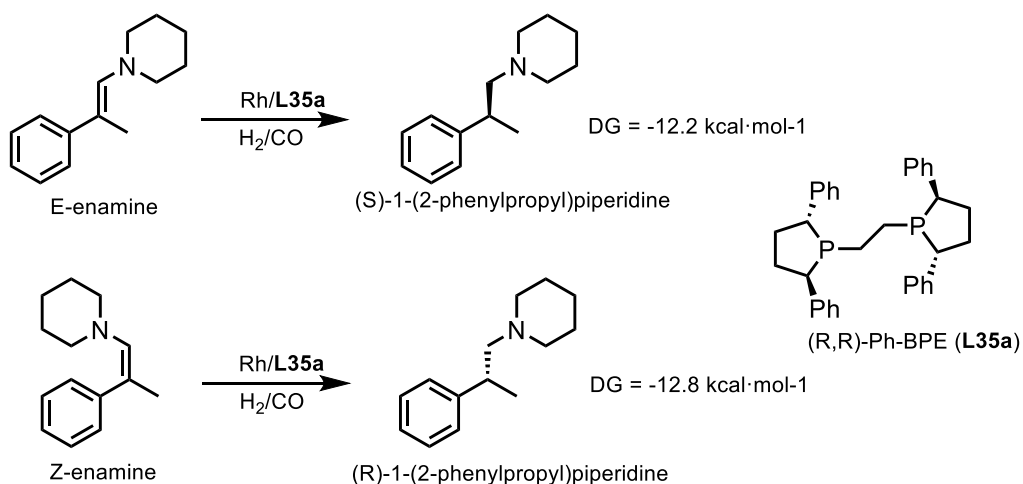
**Scheme 52. Rh-catalyzed hydroaminomethylation of styrene using chiral diphosphine ligands.**

It was observed that the hydroformylation and the condensation proceeded rapidly, while the hydrogenation step was slower and therefore rate determining. In this reaction, the enantioselectivity should be induced in the hydrogenation step, since the chiral information obtained in the hydroformylation is lost after condensation of the amine with the chiral aldehyde to form the corresponding enamine.

High to full conversions were obtained, and good chemo- and regioselectivity towards the branched intermediates were also attained, even if only diphospholane ligand **L33** provided the amine with high selectivity (Scheme 56). However, in all the cases, no enantiomeric excess was obtained.

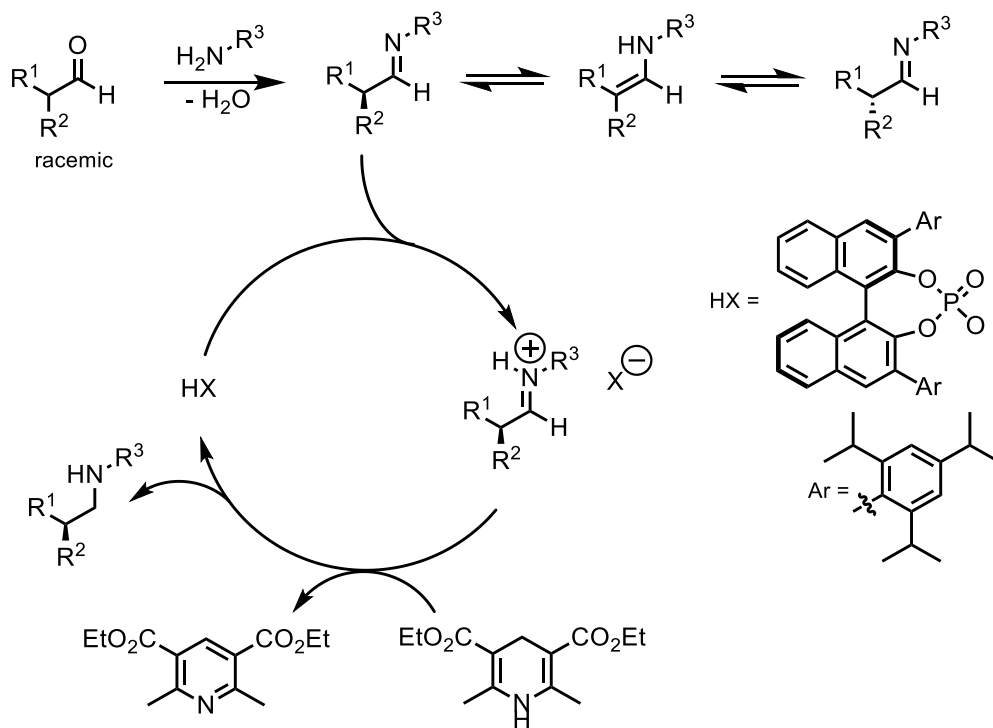
As detected by NMR spectroscopy, upon condensation of the amine, both (*E*)- and (*Z*)-enamines are produced. This is a crucial fact as the asymmetric hydrogenation of these enamines will lead to the opposite enantiomers, namely the (*S*) or (*R*)-products, respectively. DFT calculations established that the hydrogenation of both enamines is very close in energy (Scheme 57), thus supporting why no enantiomeric excess could be obtained.





**Scheme 53. Energy values for the hydrogenation of E- and Z-enamines**

Several groups attempted to overcome this issue using alternative approaches. List and co-workers reported the catalytic asymmetric amination of aldehydes via dynamic kinetic resolution<sup>135</sup>. Such strategy takes advantage of the imine-enamine equilibrium, through the use of a chiral phosphoric acid that promotes the formation of the iminium corresponding to an enantiomer reduced later with a Hantzsch ester (HEH) to give the desired chiral amine (Scheme 54).

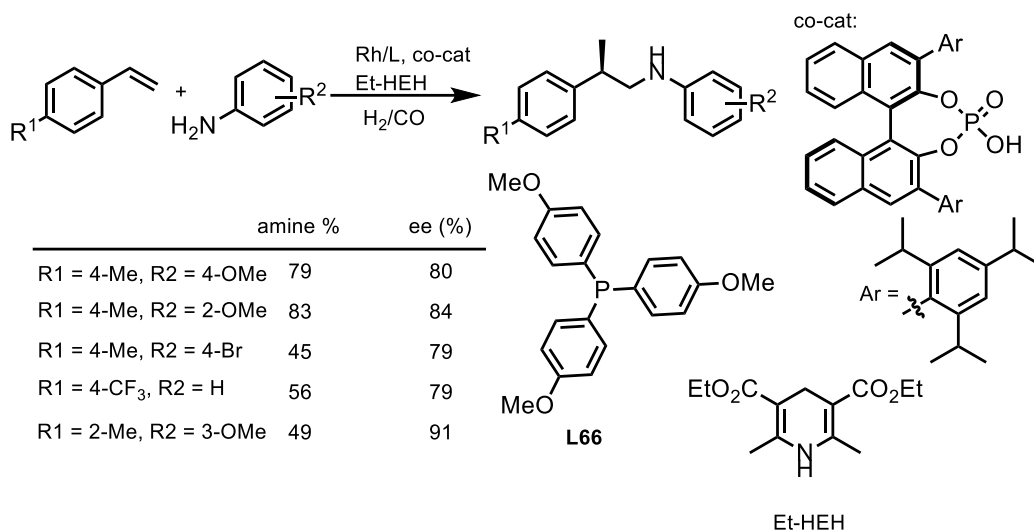


**Scheme 54. Dynamic kinetic reductive amination of aldehydes developed by List et al<sup>135</sup>.**

Xiao and co-workers adapted this methodology to the rhodium-catalyzed HAM to convert styrene and its derivatives into  $\beta$ -chiral amines with significant enantioselectivity combining metal- and organocatalysts<sup>136</sup>. Indeed, the reaction was operated with the  $[\text{Rh}(\text{acac})(\text{CO})_2]/\text{Lx}=\text{P}(\text{p-MeOC}_6\text{H}_4)_3$  catalytic system under 11 bar  $\text{CO}/\text{H}_2$  pressure, in the presence of the Hantzsch ester (1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate), as hydride source, and the chiral TRIP phosphoric acid (3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate) for the asymmetric induction during the hydrogenation of the imine intermediate. The reaction proceeded slowly during 3 days with good to excellent isolated yields and enantioselectivities ranging from 79 to 91%.

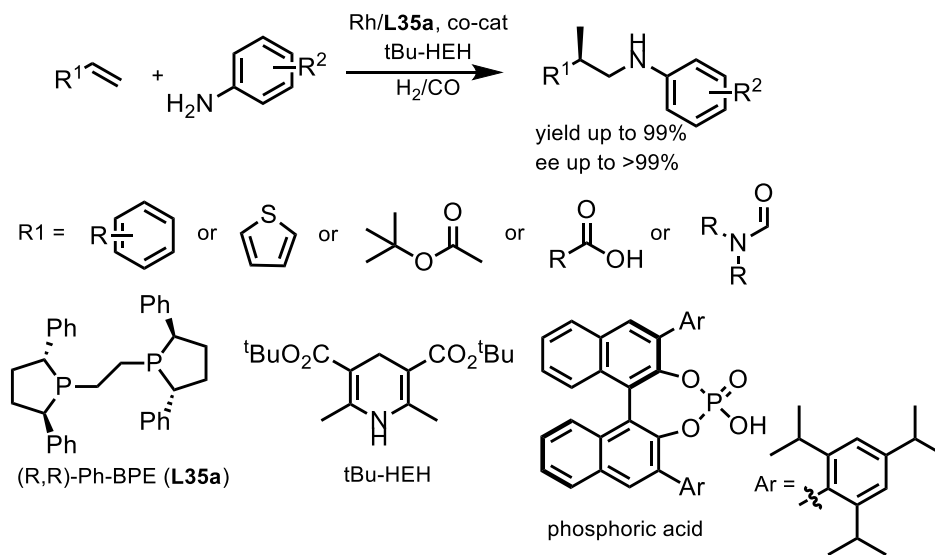
Styrene derivatives were first converted into the corresponding branched aldehyde via rhodium-catalyzed hydroformylation using the ligand **L66**. Subsequently, the condensation took place in the presence of aniline and derivatives to give the corresponding imines, which were reduced via the same strategy depicted in Scheme 54 to produce the final amines in moderate to good yields and moderate to excellent enantioselectivities (Scheme 55). This system required stoichiometric

amounts of Et-HEH, the use of a chiral phosphoric acid in catalytic amounts, long reaction times (up to 72h). Moreover, the system is limited to aniline derivatives.



**Scheme 55. Rh- and organocatalyzed asymmetric hydroaminomethylation of styrene and aniline derivatives.**

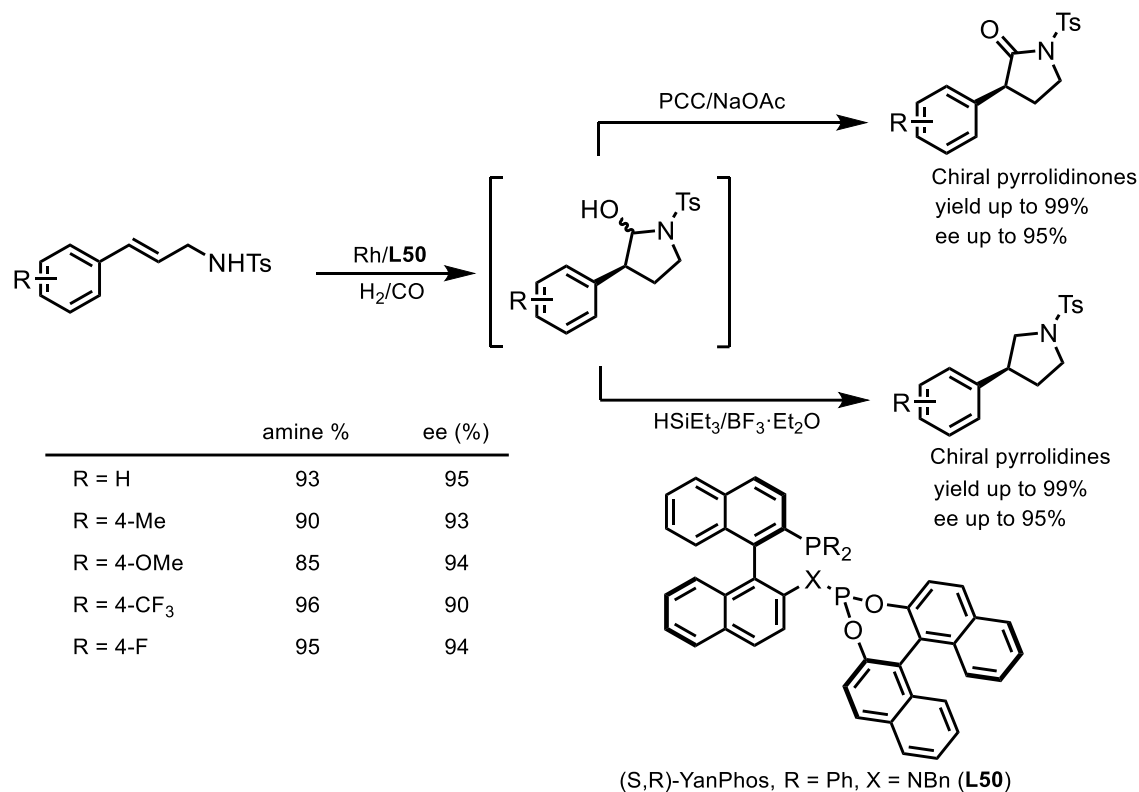
Han et al. improved the system involving another bulky phosphoric acid, (*R,R*)-Ph-BPE (**L35a**) ligand in the hydroformylation, and *t*Bu-HEH as the reducing agent (Scheme 56)<sup>137</sup>. These variations allowed reducing the total pressure to 1 bar, in lower temperatures, while providing chiral amines in higher yields (up to >99%) and enantioselectivities (up to >99.5:0.5 er). Moreover, the scope of styrene derivatives was expanded to other aromatic cycles such as thiophene, naphthalene and non-aromatic alkenes such as acrylamides and acrylates. However, the reaction requires long reaction times (up to 72 h) and additional stoichiometric reagents.



**Scheme 56.** Asymmetric HAM of various alkenes with anilines catalyzed by rhodium and organo-catalysts.

### 3.3. Asymmetric HAM of 1,2-disubstituted alkenes

Zhang et. al. adopted a different strategy to transform trans-1,2-disubstituted olefins. They reported an intramolecular HAM reaction following an interrupted approach, called interrupted hydroaminomethylation (Scheme 57)<sup>138</sup>. In order to circumvent the problem of the equilibrium between imines and enamines (Scheme 53), the formation of these species was interrupted by the use of external oxidants or reducing agents. The following strategy for conducting the reaction was applied: first, the Rh-catalysed asymmetric hydroformylation of 3-substituted allylamines was carried out with a catalytic system involving the (*S,R*)-Yanphos ligand (**L50**). Then, intramolecular condensation yielded a stable hemiacetal that was subsequently either oxidized by pyridinium chlorochromate (PCC), to obtain chiral pyrrolidinones, or reduced using triethylsilane and boron trifluoride diethyl etherate to access chiral pyrrolidines.



**Scheme 57. Interrupted asymmetric hydroaminomethylation of styrene derivatives using Rh/(S,R)-Yanphos catalytic system.**

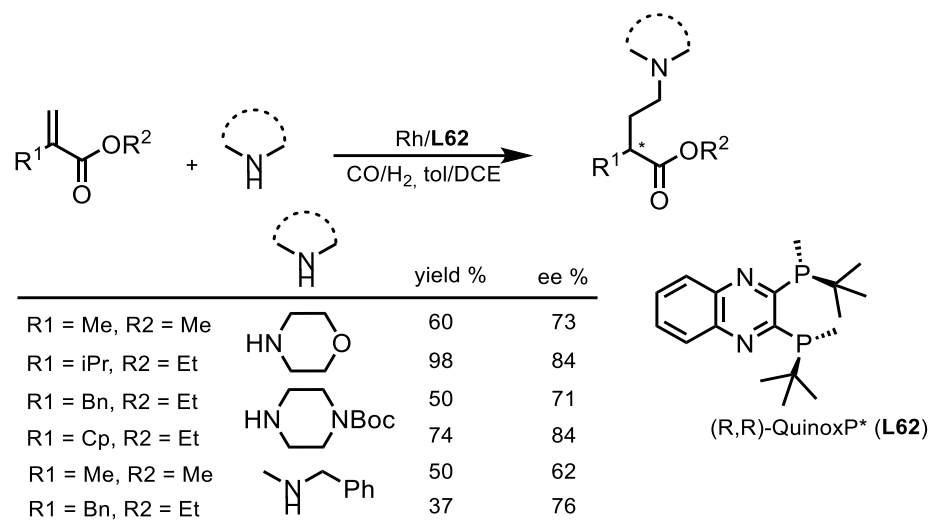
Both products were afforded in excellent yields and enantioselectivities up to 99% and 95%, respectively. The enantioselectivity was induced during the hydroformylation step in contrast to the classical approach where the enantioselectivity is induced in the hydrogenation step.

Interestingly, the system was also tolerant to naphthyl- and heteroaryl groups such as thiophene and furan. The corresponding products were obtained in high yields and excellent ee. However, the system suffered from drawbacks such as the requirement of additional reagents in stoichiometric amount, the restriction to tosyl group in the amine moiety and long reaction times (up to 70 h). Despite these disadvantages, the authors claimed that this reaction represents a new pathway for the synthesis of Vernakalant<sup>139</sup> and Enablex<sup>140</sup> drugs.

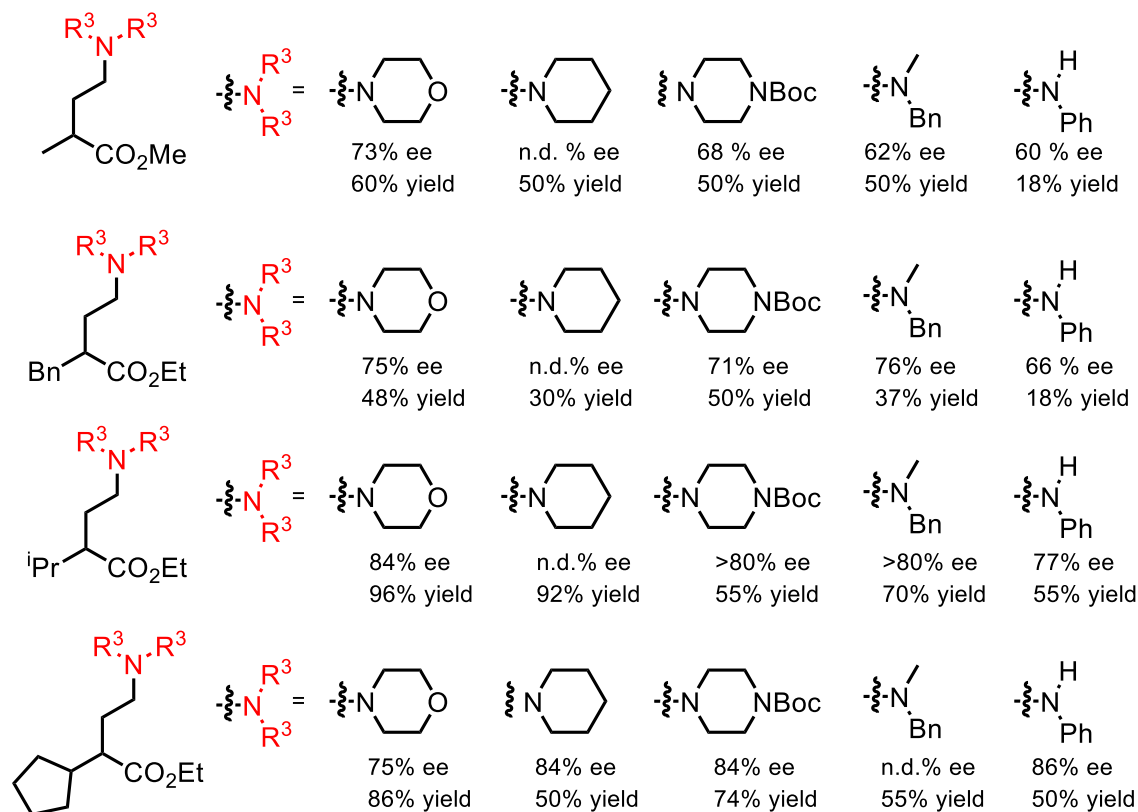
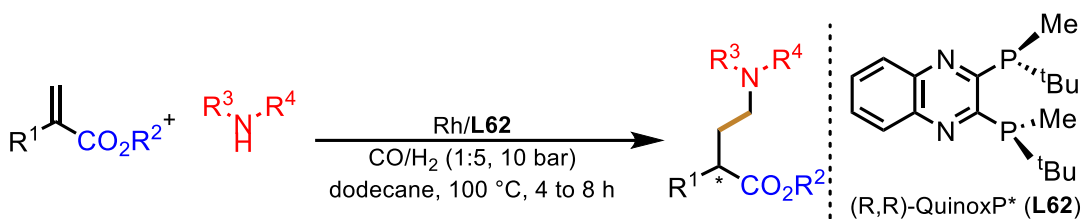
### 3.4. Asymmetric HAM of 1,1'-disubstituted alkenes

The first successful example of rhodium-catalyzed asymmetric hydroaminomethylation of  $\alpha$ -alkyl acrylates using one single catalyst was recently reported by Godard and co-workers (Scheme 58)<sup>141</sup>. The authors had previously published very interesting results on the regioselectivity of the reaction of  $\alpha$ -substituted acrylates to access  $\beta^{2,2}$ -amino esters<sup>142</sup>. In this case, the products were not chiral, but provided  $\beta^{2,2}$ -amino acid derivatives containing a quaternary carbon center which are scaffolds present in various medicinal drugs<sup>143</sup>

In this study, the authors focused on the  $[\text{Rh}(\text{COD})_2]\text{BF}_4/(\text{R,R})\text{-QuinoxP}^*$  catalytic system to access chiral  $\gamma$ -aminobutyric esters in poor to high yields (up to 98%) and high enantioselectivities (up to 86%). A variety of acrylates were used and it was revealed that the steric hindrance in  $\alpha$ -position was crucial to achieve high enantioselectivities. These final products are derivatives of  $\gamma$ -amino acids, which act as major inhibitory transmitters in the mammalian central nervous system<sup>144</sup>. Indeed, drugs containing  $\gamma$ -amino acids are currently commercialized as pharmaceutical agents<sup>145</sup>. The success of  $(\text{R,R})\text{-BenzP}^*$  (**L58**) and  $(\text{R,R})\text{-QuinoxP}^*$  (**L62**) in the Rh-catalyzed AHF of acrylates prompted the authors to test them in the asymmetric intermolecular HAM. In this case,  $(\text{R,R})\text{-QuinoxP}^*$  (**L62**) showed the best catalytic performance. For the first time, a single catalyst allowed the efficient and straightforward synthesis of chiral  $\gamma$ -aminobutyric esters from readily available acrylates. Different acrylates and amines were subjected to the HAM reaction releasing a range of synthetically valuable chiral  $\gamma$ -aminobutyric esters with ee's up to 86% (Scheme 64). As the Buchwald's system, the best results were achieved with substrates containing bulky secondary alkyl groups.



**Scheme 58. Rh-catalyzed asymmetric hydroaminomethylation of  $\alpha$ -alkyl acrylates.**

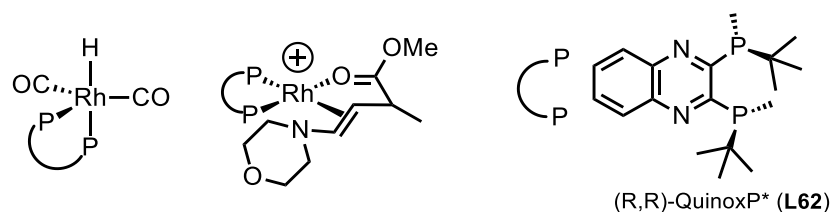


**Scheme 59. Rh-catalyzed asymmetric intermolecular hydroaminomethylation of  $\alpha$ -alkyl acrylates with (R,R)-QuinoxP\* (L62).**

In this amine synthesis strategy, the previously pointed out isomerization issue in the hydrogenation step was avoided since the chiral position generated during the hydroformylation was not affected in the subsequent condensation and hydrogenation steps. The challenges in this approach relied on the use of the appropriate ligand to induce high chirality in the hydroformylation step in finding the correct combination of reaction conditions. Mechanistic studies were conducted by HP-NMR experiments under catalytic conditions. The results revealed that the co-existence of a neutral rhodium hydride involved the hydroformylation, and a cationic species involved in the hydrogenation is crucial (Scheme 60), in agreement with the results described previously<sup>133</sup>. It was also evidenced that a mixture of toluene/DCE was necessary to achieve the coexistence of both



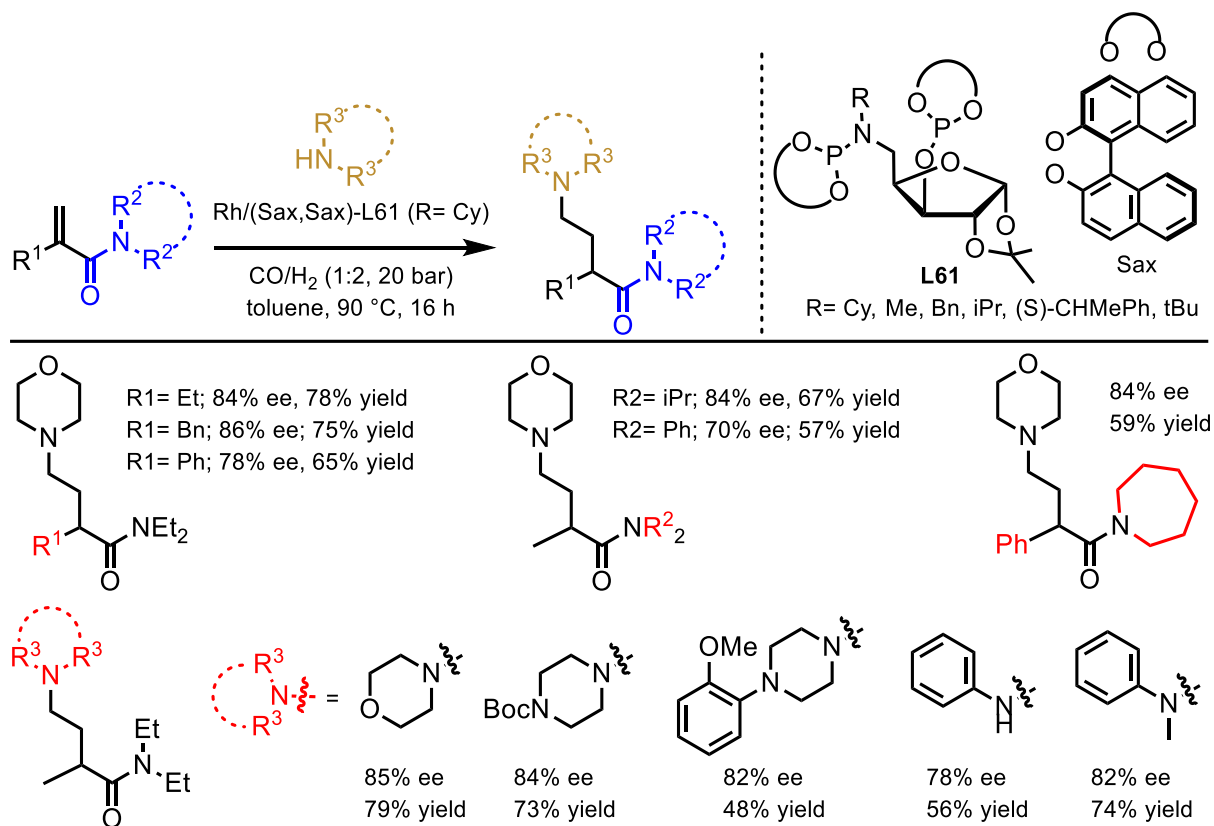
species. No extra reducing agents or co-catalyst were needed, highlighting the efficiency of the reaction.



**Scheme 60. Neutral and cationic rhodium species detected in the Rh-catalyzed asymmetric hydroaminomethylation of  $\alpha$ -alkyl acrylates.**

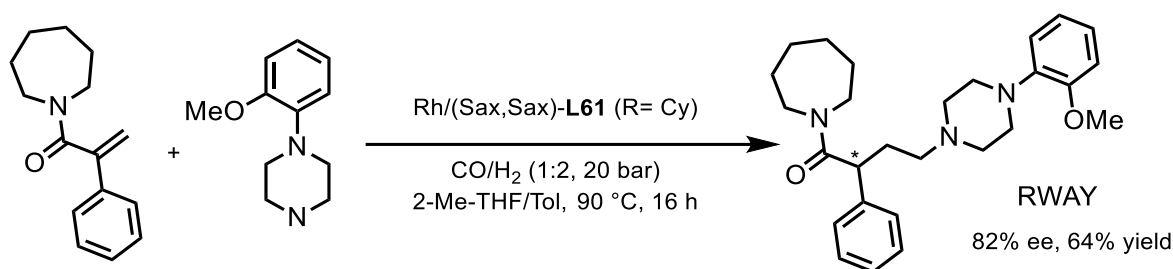
This new direct atom-efficient pathway was used by the same group for the synthesis of amide GABA derivatives from  $\alpha$ -substituted acrylamides.<sup>123</sup> Indeed, these molecules are of great interest as this backbone is present in CCR2 antagonists for chronic inflammatory processes such as atherosclerosis, multiple sclerosis, and rheumatoid arthritis<sup>146</sup> and CCR5 antagonists for HIV drug<sup>147</sup>, or brain imaging<sup>148</sup>.

Following their results on the asymmetric hydroformylation of  $\alpha$ -acrylamides (Cf part 1.4), Godard and his group studied the asymmetric HAM of different  $\alpha$ -substituted acrylamides and a series of amines with the  $[\text{Rh}(\text{acac})(\text{CO})_2]/(S_{ax}, S_{ax})\text{-L61}$  (R= Cy) catalytic system. The latter turned out to be active to directly yield chiral  $\gamma$ -aminobutyric acid (GABA) derivatives, with good to high yields (59-70%) and high enantioselectivities (70-86%) (Scheme 61).



**Scheme 61.** Rh-catalyzed asymmetric hydroaminomethylation of  $\alpha$ -substituted acrylamides with various amines

The synthetic potential of this method was demonstrated by the single-step synthesis of the brain imaging molecule RWAY which contains both amine and amide groups (Scheme 62). The compound was obtained in 64% isolated yield and 82% ee by slightly varying the previously optimized conditions by using the mixture 2-Me-THF/toluene instead of DCE/toluene.



**Scheme 62.** Synthesis of RWAY via HAM reaction catalyzed by Rh/(S<sup>ax</sup>,S<sup>ax</sup>)-L61 (R= Cy).

## 4. 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.

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.

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 centre. For years, ligands containing phosphite moieties such as diphosphites and phosphine-phosphites were considered as the most successful ligands to achieve high enantioselectivities. For instance, diphosphite ligands are highly effective in the asymmetric Rh-catalyzed hydroformylation of several alkene substrates and the phosphite-phosphine Binaphos or its derivatives like Yanphos have been very successful ligands in terms of selectivity and scope. Recently, however, diphosphines in which the P atoms are incorporated in a ring have also shown to induce high levels of enantioselectivity in this process. Furthermore, diazaphospholane ligands are currently the most efficient ligands 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.

Recently, a Rh catalyst was reported to convert alkenes to aldehydes without the need of gases through transfer hydroformylation.<sup>100-149</sup> In this promising process, the catalyst transfers the equivalent of H<sub>2</sub> 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.

Since aldehydes are not usually isolated as final products because the real products of interest are generally derived products, tandem processes with hydroformylation as the initial step constitute an interesting strategy. As chiral amines constitute important building blocks in the pharmaceutical and agrochemical industry, the hydroaminomethylation reaction appears as a powerful tool to obtain these products from readily available reagents. The combination of CO/H<sub>2</sub> (syngas), alkene and amine, and a rhodium catalyst enables the rapid assembly of complex amine products with perfect atom economy and little environmental impact. The first successful direct Rh-catalyzed intermolecular asymmetric hydroaminomethylation of acrylates for the efficient synthesis of chiral  $\gamma$ -aminobutyric esters was reported. A wide variety of chiral  $\gamma$ -aminobutyric esters has been obtained in poor to excellent yields, reaching high enantioselectivities. In contrast with previous reports, neither an external reducing agent nor a co-catalyst was required. The reaction was successfully extended to the transformation of  $\alpha$ -substituted acrylamides using chiral phosphite-phosphoramidite ligands with high yields and high to excellent enantioselectivities. The system could tolerate different substituents at the acrylamide and various secondary amines and aniline could be applied.

The potential of asymmetric HAM proves its utility for the production of chiral amines, to attain pharmaceutical and agrochemical active products, such as vitamins, hormones, alkaloids, and neurotransmitters.

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