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# Evolution in the metal-catalyzed asymmetric hydroformylation of 1,1'-disubstituted alkenes

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## Abstract

Despite remarkable progress over the past decade, asymmetric hydroformylation (AHF) is still an underdeveloped field compared to other enantioselective transformations involving alkenes and thus has not encountered a place at an industrial scale yet. The research in AHF has been mainly focused on monosubstituted and 1,2-disubstituted substrates and many excellent reviews about its progress have been published. Less attention has been paid to the AHF of 1,1'-disubstituted alkenes although in the last years significant advances were made in expanding substrate scope and catalyst design. This review focuses on the progress made in the AHF of 1,1'-disubstituted alkenes, from the most studied alkenes bearing coordinating groups to the most challenging unfunctionalized ones.

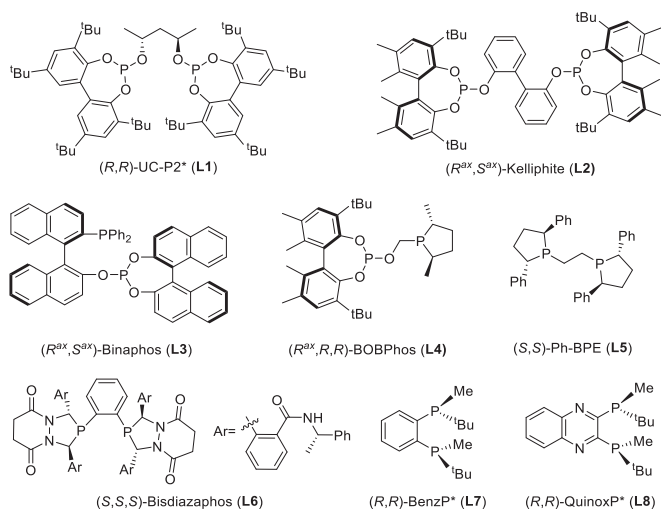
## 1. Introduction

Hydroformylation is an atom-economical way to form aldehydes from readily available feedstocks, namely syngas (a mixture of CO and H<sub>2</sub>) and olefins. The versatility of the obtained aldehydes makes this reaction interesting for organic synthesis, since they can be easily converted to other valuable building blocks, such as alcohols, amines, carboxylic acids or nitriles. Hence, oxo-alcohols, which is the name given to the resulting aldehyde products, have a wide range of industrial applications. For example, they can be used for the manufacturing of plasticizers, as chemical intermediates, and for solvent formulations, among others. The hydroformylation of alkenes is therefore one of the most industrially applied transformations catalyzed by homogeneous metal-catalysts (1). About 10 million tons of oxo-products are produced per year, and this amount is expected to rise nearby 5% during 2021–26 (1,2).

The asymmetric hydroformylation (AHF) reaction thus offers direct access to chiral aldehydes. However, despite the remarkable progress made over the past decade, AHF has not encountered yet a place at an industrial scale and is still underdeveloped compared to other asymmetric transformations involving alkenes (3) such as hydrogenations (4) or hydroborations (5). The current drawbacks for the practical application of AHF are: interesting catalytic performances were only reported for a reduced range of substrates, there are only a few validations of efficient catalysts immobilization/recyclability and flow processes, and the reaction mechanism is not well understood yet. There are many difficulties associated with this transformation. Besides the general chemoselectivity issues arising from direct competition between hydroformylation and hydrogenation or isomerization processes, the simultaneous control of regio- and enantioselectivity is often challenging. The fact that regioselectivity is difficult to control in some specific substrates explains its limited substrate scope. The most successful substrates for AHF are mono-substituted alkenes containing an electron withdrawing substituent that induces branched-selectivity by creating two olefinic carbons with different electronic properties. Thus, styrenes and vinyl acetates can be nowadays exclusively hydroformylated into the branched-product exclusively with enantioselectivities higher than 90% ee (3). Symmetrical alkenes like norbornene and stilbene derivatives are other substrates for which the regioselectivity is also easier to control (3). In contrast, the AHF of simple alkenes without electron withdrawing groups and 1,2-disubstituted olefins are still a challenge (3).

In the current state of the art, a specific ligand is needed for each type of substrate (Fig. 1).<sup>3d</sup> For example, while Binaphos (**L3**) works best for styrene, Ph-BPE (**L5**) is optimal for allyl cyanide and BOBphos (**L4**) is the ligand of choice for 1-alkyl alkenes. The only ligand with somewhat diverse applicability has been the Bisdiazaphos (**L6**) that works with styrene, vinyl acetate and challenging 1,2-disubstituted olefins.

Other challenging substrates are the 1,1'-disubstituted alkenes. According to the empirical Keuleman's rule (6,7), the main product formed in their AHF is the linear aldehyde, mainly due to increased steric bulk at the  $\alpha$ -position of the olefin. However, reaching high enantioselectivities in the AHF of 1,1'-disubstituted alkenes is tricky because the steric difference between the two substituents of the olefinic carbon makes it difficult to differentiate between each coordinative face of the olefin. This review focuses on the AHF of 1,1'-disubstituted olefins. Since the excellent review about the AHF of this challenging type of substrates was published in 2015 (3b), some remarkable advances were made in the field, mainly with unfunctionalized alkenes as substrates. Two recent short reviews on the efforts in the AHF were published (3d,e) with updated examples about 1,1'-disubstituted substrates, although they are only briefly discussed and miss the progress in ligand design and substrate scope that a review covering only 1,1'-disubstituted substrates could provide. We therefore report here an updated overview about the progress made in the field, from the most studied alkenes bearing coordinating

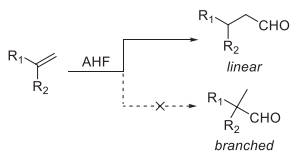


**Fig. 1** A selection of the most successful ligands used in the asymmetric hydroformylation.

groups to the most challenging unfunctionalized ones. The review is divided in five sections. After short [Section 2](#) about the regioselectivity issues of AHF of 1,1'-disubstituted substrates, [Sections 3 and 4](#) collect the examples reported about the AHF of 1,1'-disubstituted alkenes considering whether the substrates contain a coordinative group or not. In [Section 5](#), we discuss the key ligand parameters for high selectivities. Initial attempts were performed using mixed Pt/Sn, but more recently, only Rh-systems were utilized. The first ligands tested were chiral diphosphines but later, higher selectivities were achieved with diphospholanes, such as the Ph-BPE (**L5**), and P-stereogenic diphosphines, such as BenzP\* (**L7**) or QuinoxP\* (**L8**). More recently, it has been found that P-phosphoramidite ligands are interesting candidates for this reaction, providing unprecedented high enantioselectivities for some type of 1,1'-disubstituted olefins.

## 2. Regioselectivity on the asymmetric hydroformylation of 1,1'-disubstituted alkenes

In 1948, Keuleman stated that “addition of the formyl group to a tertiary carbon atom does not occur, so that no quaternary C atoms are formed” (6). According to this empirical rule, the steric bulk at the  $\alpha$ -position of the olefin favors the addition of the formyl group onto the less crowded terminal carbon, and therefore the AHF of 1,1'-disubstituted alkenes would only provide the linear product and avoid any regioselectivity issues ([Scheme 1](#)) (7). Most of the reported AHF reactions discussed in this review support this rule. However, examples of racemic hydroformylation of 1,1'-disubstituted alkenes giving exclusively the branched aldehyde have been documented (8) and in few cases, the stereo controlled quaternary center could be even obtained (see below in [Section 3.2](#)). Indeed, it has been observed that the branched aldehyde can be formed using certain substrates holding highly electron withdrawing substituents and hindered ligands. This finding is highly appealing because the branched product possesses a stereogenic tetrasubstituted center, which has increased the interest of finding catalysts and substrates that can preferentially produce  $\alpha$ -tetrasubstituted aldehydes.



**Scheme 1** Regioselectivity achieved in the asymmetric hydroformylation according to Keuleman's rule.

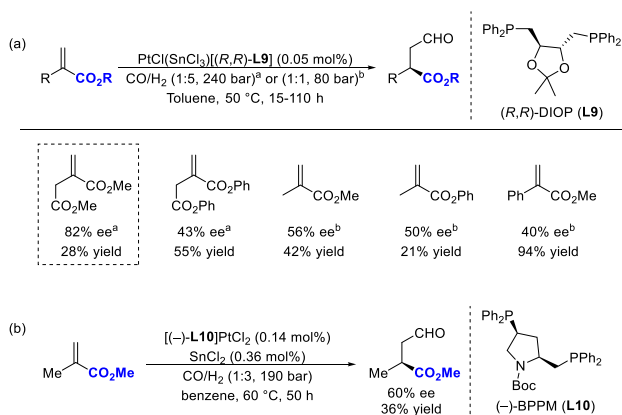
### 3. Asymmetric hydroformylation of 1,1'-disubstituted alkenes with coordinative groups

In this Section, we discuss the progress made in the AHF of 1,1'-disubstituted alkenes with coordinative groups according to the type of selectivity achieved (*n*-selectivity to the linear aldehyde; see Section 3.1 or *i*-selectivity to the branched aldehyde; see Section 3.2).

#### 3.1 *N*-selective asymmetric hydroformylation

*α*-Substituted acrylate and acrylamide derivatives.

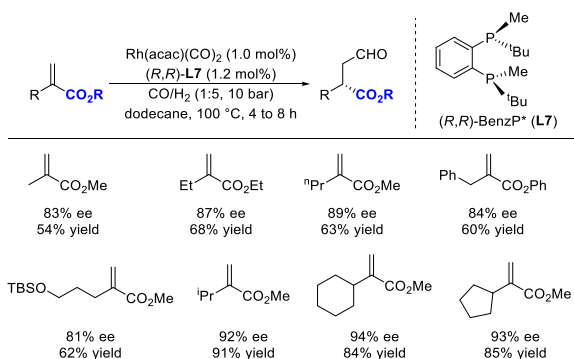
The first reported examples of the AHF of 1,1'-disubstituted olefins appeared in 1987 and were focused on 2-substituted acrylates (Scheme 2) (9,10). In both reports, a combined Pt/Sn catalytic system and a chiral diphosphine ligand were employed. Kollár and co-workers were able to obtain a promising enantioselectivity of 82% ee in the AHF of dimethyl itaconate with the PtCl(SnCl<sub>3</sub>)[(*R,R*)-DIOP] catalytic system (9). Unfortunately, when other unsaturated esters were tested, enantioselectivities were lower (ranging from 40% to 56% ee, Scheme 2A). While the system showed full regioselectivities for hydroformylation at the terminal methylene group, hydrogenation of the substrate could not be avoided, resulting in low yields in most cases (21–94% yield). It should be pointed out that (*R,R*)-DIOP (**L9**) was also tested in combination with [Rh(CO)<sub>2</sub>Cl<sub>2</sub>] in the AHF of dimethyl itaconate (11). In contrast to the PtCl<sub>2</sub>-SnCl<sub>2</sub> catalytic system, similar amount of the



**Scheme 2** First Pt/Sn-catalytic systems for the asymmetric hydroformylation of 1,1'-disubstituted acrylates.

linear and branched aldehydes were obtained (43% vs 40%). Furthermore, both products were yielded with very low enantioselectivities (8% and 1% ee for the linear and the branched, respectively). The same year, Stille tested a ((-)-BPPM)PtCl<sub>2</sub> chiral catalyst combined with SnCl<sub>2</sub> in the AHF of methacrylate, affording the corresponding linear aldehyde with 60% ee (Scheme 2B) (10). Again, a low yield was afforded but in this case it was due to a low branched/linear ratio. It should be noted that the same catalyst provided higher enantioselectivities (70–80% ee) in the AHF of monosubstituted vinylic substrates, such as styrenes, vinyl acetates or N-vinylphthalimide (10), reinforcing that in AHF for each type of substrate, a specific ligand must be developed.

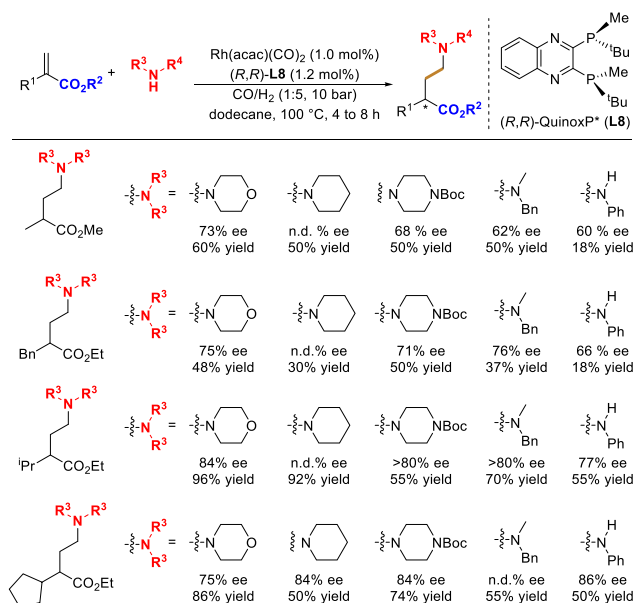
Besides the poor yields, the low substrate scope (being mostly limited to dimethyl itaconate and methacrylate) and modest enantioselectivities obtained, the systems of Kollár and Stille required high hydrogen pressure (80–240 bar) and a very long reaction time (typically 45–110 h). It was not until 2011 that Buchwald et al. reported the first AHF of various  $\alpha$ -alkyl acrylates performed under milder reaction conditions using a Rh-catalyst (Scheme 3) (12). Both the pressure and the reaction time could be significantly reduced to 10 bar and 4–8 h, respectively. However, the temperature had to be increased up to 100 °C. By screening a wide range of earlier ligands that were efficient for mono- and 1,2-disubstituted olefins (e.g., Binaphos, diazaphospholane, and Kelliphite, etc.), they found that the use of P-stereogenic diphosphine ligands was crucial to achieve the highest enantioselectivities. Concretely, (*R,R*)-BenzP\* (**L7**) and (*R,R*)-QuinoxP\* (**L8**) (Fig. 1) provided 82% and 75% ee in the AHF of ethyl 2-benzylacrylate. With (*R,R*)-BenzP\*, a selection of the desired chiral linear aldehydes were obtained with unprecedented



**Scheme 3** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -alkylacrylates with the P-chirogenic phosphine ligand (*R,R*)-BenzP\* (**L7**).

enantioselectivities (81–94% ee) (Scheme 3). In addition, the authors found the optimal CO/H<sub>2</sub> ratio of 1:5 to avoid side reactions and achieve good chemo- and regioselectivities. The highest yields and enantioselectivities were obtained for alkenes bearing secondary alkyl substituents, such as isopropyl, cyclohexyl, and cyclopentyl groups (84–91% yield and 92–94%). It was suggested that one of the reasons for the better yields achieved with these substrates is the presence of bulkier secondary alkyl groups that hampers the formation of the branched Rh-alkyl intermediate, resulting in a better regioselectivity toward the chiral linear aldehydes.

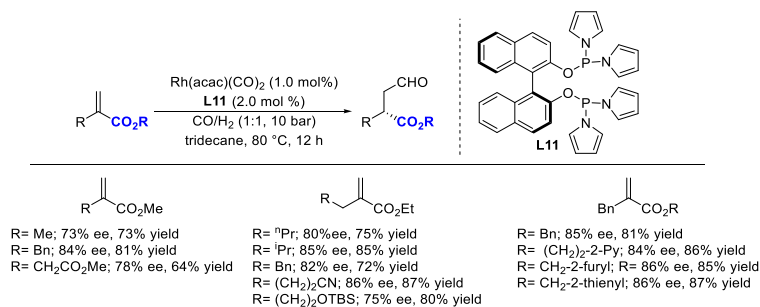
The success of (*R,R*)-BenzP\* (**L7**) and (*R,R*)-QuinoxP\* (**L8**) in the Rh-catalyzed AHF of acrylates (**12**), prompted Godard and co-workers to test them in the asymmetric intermolecular hydroaminomethylation (HAM) of  $\alpha$ -alkyl acrylates (**13**). In this case, (*R,R*)-QuinoxP\* (**L8**) 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 4). As for the Buchwald's system, the best results were achieved with substrates containing bulky secondary alkyl groups.



**Scheme 4** Rh-catalyzed asymmetric intermolecular hydroaminomethylation of  $\alpha$ -alkyl acrylates with (*R,R*)-QuinoxP\* (**L8**).



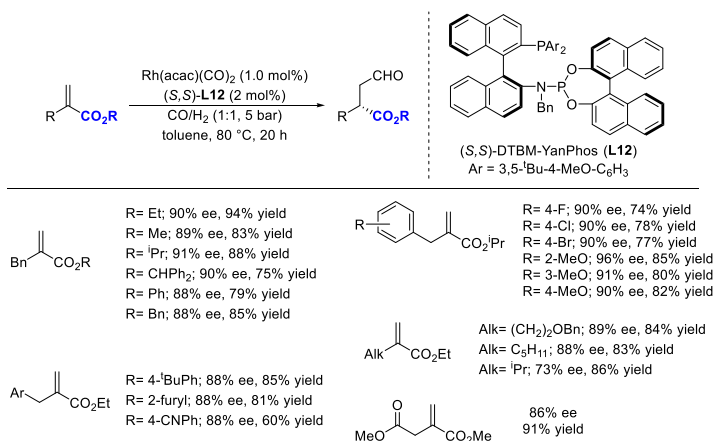
Much after the Buchwald achievement, in 2019, Chin et al. reported the application of pyrrolylphosphinite ligand **L11**, without a stereogenic P group, in the Rh-catalyzed AHF of  $\alpha$ -substituted acrylates (**14**). A range of chiral aldehydes were achieved in good-to-high enantioselectivities (73–86% ee) (Scheme 5). Although, the enantioselectivities were somewhat lower than those reported with the Rh-(*R,R*)-BenzP\* system, the system also operated at low pressure (10 bar) but at a lower temperature (80 °C), with high productivity (turnover number (TON) up to 8900), excellent regioselectivity, and good-to-high chemoselectivities, which resulted in good yields (up to 87%).



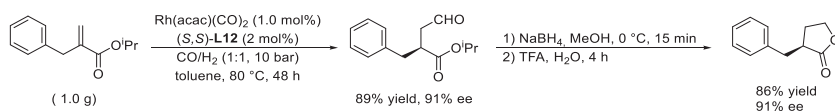
**Scheme 5** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -alkylacrylates with pyrrolylphosphinite ligand **L11**.

The most recent contribution in the AHF of  $\alpha$ -substituted acrylates has been made by Zhang and co-workers with a phosphine-phosphoroamide ligand from the (*S,S*)-YanPhos family (**15**). This ligand family was previously successfully applied on the AHF of 1,1'-disubstituted alkenes with weakly coordinative groups (**16**) and without coordinative groups (**17**) providing high activities and selectivities (see in Section 4). They initially studied the AHF of ethyl 2-benzylacrylate by testing two (*S,S*)-Yanphos ligands, with distinct substituents in the phosphine moiety (Ar = 3,5-<sup>t</sup>Bu-4-MeO-C<sub>6</sub>H<sub>3</sub> and 3,5-<sup>t</sup>Bu-C<sub>6</sub>H<sub>4</sub>, Scheme 6), and a range of representative ligands that were efficient for AHF and hydrogenation, such as (*S<sup>ax</sup>*,*R*)-Duanphos, XuPhos, (*S,S*)-Me-DuPhos and Walphos. They found that the (*S,S*)-DTBM-YanPhos ligand (**L12**) provided the best catalytic performance. Advantageously, they could even reduce the H<sub>2</sub> pressure down to only 5 bars, maintaining the temperature used in the previous example. With this ligand, a range of linear aldehydes with  $\beta$ -chirality (Scheme 6) could be obtained with high enantioselectivities (88–96% ee) and high yields (up to 94%). In contrast to (*R,R*)-BenzP\* (**L7**) and (*R,R*)-QuinoxP\* (**L8**), a slightly lower enantioselectivity was observed with a substrate bearing a bulkier isopropyl group

on the  $\alpha$ -position (73% ee). The authors also showed that the AHF of  $\alpha$ -methyl methacrylate could be performed at a Gram-scale and at a lower catalyst loading of 0.05 mol%, without compromising the yield nor enantioselectivity. The utility of the methodology was further demonstrated by the concise synthetic route to chiral  $\gamma$ -butyrolactone (Scheme 7).

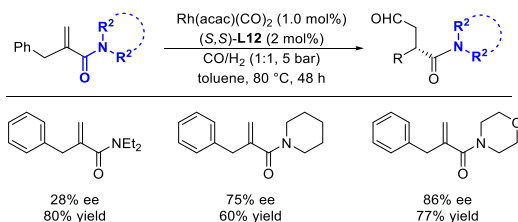


**Scheme 6** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -substituted acrylates with  $(S,S)$ -DTBM-YanPhos (**L12**).



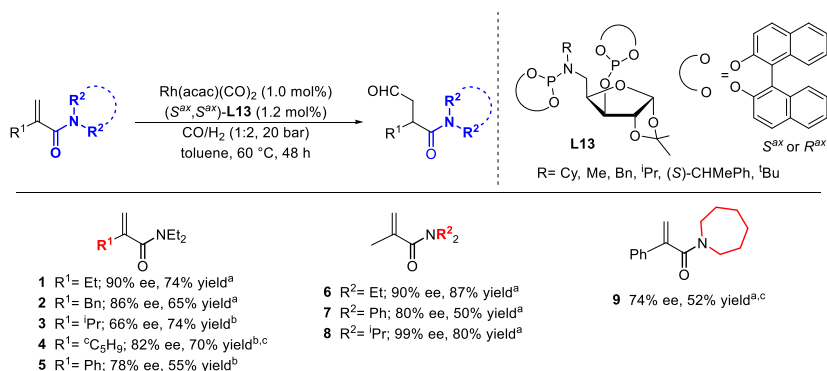
**Scheme 7** Synthesis of chiral  $\gamma$ -butyrolactone at a 1.0 g scale with  $(S,S)$ -DTBM-YanPhos (**L12**).

Despite the similarity of  $\alpha$ -substituted acrylamides with  $\alpha$ -acrylates, the AHF of the former was not explored until very recently. Indeed, only a few examples were reported in the asymmetric hydroformylation of non-substituted acrylamides with moderate yields and enantioselectivities (18). The only two existing publications reporting the AHF of  $\alpha$ -substituted acrylamides appeared in 2020 (15,19). In one of them, only three substrates were studied. In particular, three 2-benzylacrylamides, with different amide substituents were tested with the Rh/ $(S,S)$ -DTBM-YanPhos (**L12**) complex (Scheme 8) (15). While acrylamides with cyclic amide substituents provided good levels of enantioselectivity (up to 86% ee), the presence of a diethyl group resulted in a poor enantioselectivity (28% ee). It is interesting to note that a longer reaction time was required compared to the AHF of acrylates with the same catalyst (48 h vs 20 h, Schemes 6 vs 8, respectively).



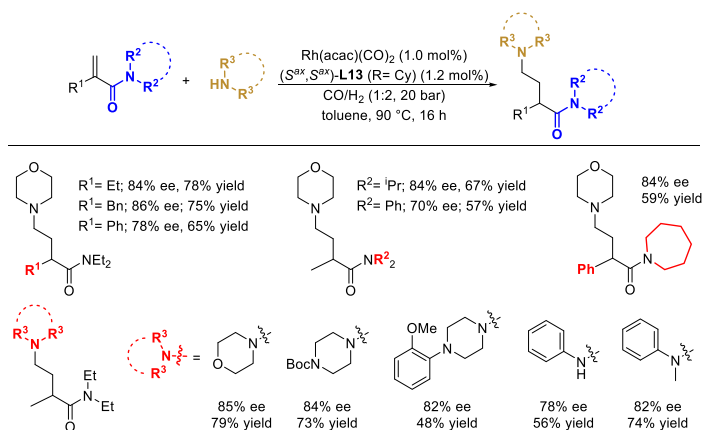
**Scheme 8** Asymmetric hydroformylation of acrylamides catalyzed by the Rh/(*S,S*)-DTBM-YanPhos (**L12**) complex.

The second study about the AHF of  $\alpha$ -substituted acrylamides employed 1,3-phosphite-phosphoramidite ligands based on a sugar backbone derived from D-xylose (**L13**, **Scheme 9**). Their modularity was key to achieve the best catalytic performance, being ligands with a bulky N-group and an ( $S^{ax}$ ,  $S^{ax}$ )-biaryl moiety the ones that provided the best results ( $R = \text{Cy}$  and  $R = (S)\text{-CHMePh}$ ) (**Scheme 9**). With the optimal ligands, it was possible to hydroformylate for the first time a broad range of acrylamides with different substituents at the  $\alpha$ -position and on the amide group with high-to- excellent enantioselectivities (74–99% ee) and good-to-high yields (50–87%) (19). Furthermore, hydroformylation reactions could be performed at 60 °C. For most of the substrates the best results were achieved with Rh/( $S^{ax}$ ,  $S^{ax}$ )-**L13** ( $R = \text{Cy}$ ) catalytic system. For more sterically hindered alkenes (**3–5**) ligand with a (*S*)- $\sigma$ -methylbenzyl amine substituent provided the best results. The results for substrates **5** and **9** are relevant since important biologically active molecules include a phenyl substituent in  $\alpha$ -position and the catalysts reported to date (12, 13, 15) were only efficient for  $\alpha$ -alkyl substituted substrates.

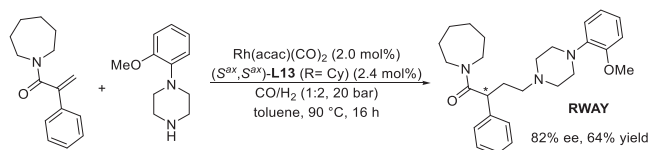


**Scheme 9** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -substituted acrylamides with sugar-based phosphite-phosphoramidite ligands **L7**. <sup>a</sup>Ligand ( $S^{ax}$ ,  $S^{ax}$ )-**L13** ( $R = \text{Cy}$ ) was used. <sup>b</sup>Ligand ( $S^{ax}$ ,  $S^{ax}$ )-**L13** ( $R = (S)\text{-CHMePh}$ ) was used. <sup>c</sup>Temperature = 90 °C for 16 h.

Moreover, Rh/( $S^{ax},S^{ax}$ )-**L13** (R = Cy) successfully promoted the one-pot asymmetric HAM of different  $\alpha$ -substituted acrylamides and amines to directly yield chiral  $\gamma$ -aminobutyric acid (GABA) derivatives, with also high yields and enantioselectivities (Scheme 10). The practicality of the reaction was shown by synthesizing the brain imaging molecule RWAY in one single step with high enantioselectivity (Scheme 11).



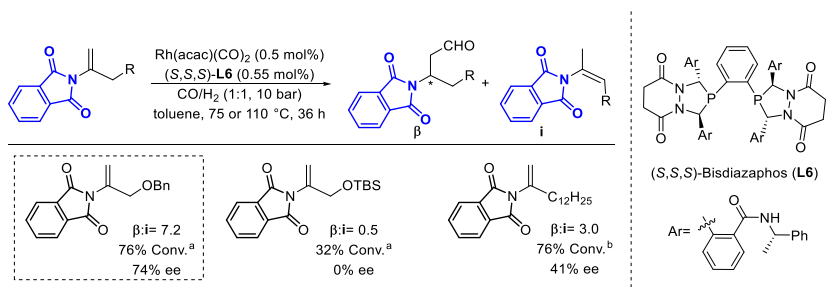
**Scheme 10** Rh-catalyzed asymmetric hydroaminomethylation of  $\alpha$ -substituted acrylamides with ligand ( $S^{ax},S^{ax}$ )-**L13** (R = Cy).



**Scheme 11** Synthesis of RWAY via HAM Reaction catalyzed by Rh/( $S^{ax},S^{ax}$ )-**L13** (R = Cy).

### 3.1.1 Other functionalized 1,1'-disubstituted alkenes

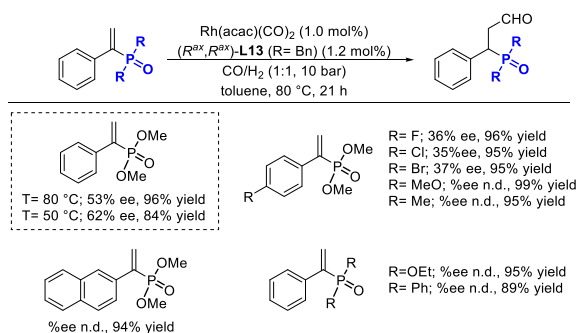
Besides  $\alpha$ -substituted acrylates and acrylamides, a few substrates containing a coordinative group other than an ester or an amide at the olefinic carbon have been studied. In 2010, Landis and co-workers explored the AHF of 1,1'-disubstituted ene-phthalimides with a Rh-complex of ( $S,S,S$ )-Bisdiazaphos (**L6**) (Scheme 12) (20). The reaction was selective toward the  $\beta$ -aldehyde although variable amounts of the isomerized internal alkene were also observed. Promising results were achieved for the allyl benzyl ether derived ene-phthalimide, which provided a chemoselectivity up to



**Scheme 12** Rh-catalyzed asymmetric hydroformylation of 1,1'-disubstituted ene-phthalimides with the (*S,S,S*)-Bisdiazaphos ligand (**L6**). <sup>a</sup>75 °C. <sup>b</sup>110 °C.

7:1 ( $\beta$ -aldehyde/internal alkene) and an enantioselectivity of 74% ee. Unfortunately, poorer chemo- and enantioselectivities were observed when other derivatives were used. Nevertheless, this reaction constitutes a straightforward way to prepare chiral  $\beta^3$ -aminoaldehydes.

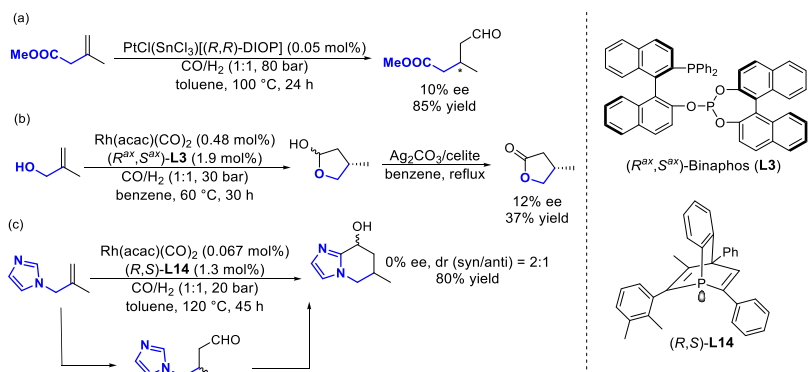
Börner et al. were the first to explore the AHF of  $\alpha$ -phosphorylated vinyl arenes as an alternative route toward 3-aryl-3-phosphorylated propanals (**21**). An extensive ligand screening (e.g., (*S,S*)-DIOP (**L9**), (*R,R*)-QuinoxP\* (**L7**), (*S,S*)-BenzP\* (**L8**), (*R,R,S*)-Bisdiazaphos (**L6**), (*R,R*)-Kelliphite (**L2**)) revealed sugar-based ligands **L13** (Scheme 9) as the best candidates for this transformation. In particular, **L13** (R = Bn) containing an (*R*<sup>dx</sup>)-binaphthyl group on the phosphite and phosphoramidite moieties provided the highest yields and enantioselectivities. The  $\beta$ -chiral aldehydes were obtained as the major products and only small amounts of hydrogenated products were observed, so high yields were in general achieved (up to 99%) (Scheme 13). Unfortunately, the enantioselectivity was only moderate and not determined



**Scheme 13** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -phosphorylated vinyl arenes with ligand (*R*<sup>dx</sup>, *R*<sup>dx</sup>)-**L13** (R = Bn).

for all the substrates tested due to issues in finding a suitable method for their separation. The maximum enantioselectivity obtained was 53% ee, which could be raised up to 62% by decreasing the temperature to 50 °C, at the expense of the yield (96% vs 84%).

Another group of functionalized 1,1'-terminal alkenes are substituted allylic compounds. The first substituted allylic substrate tested was 3-methylbut-3-enoate with the Pt/Sn/(*R,R*)-DIOP system developed by Kollár and co-workers (9). The chiral linear aldehyde was afforded in 85% yield, however, a poor enantioselectivity was obtained (10% ee) (Scheme 14A). Note that among all 1,1'-substituted alkenes tested with Kollár's system (see Scheme 2A), the substituted allylic substrate shown in Scheme 14A is the substrate that gave the lowest ee value.



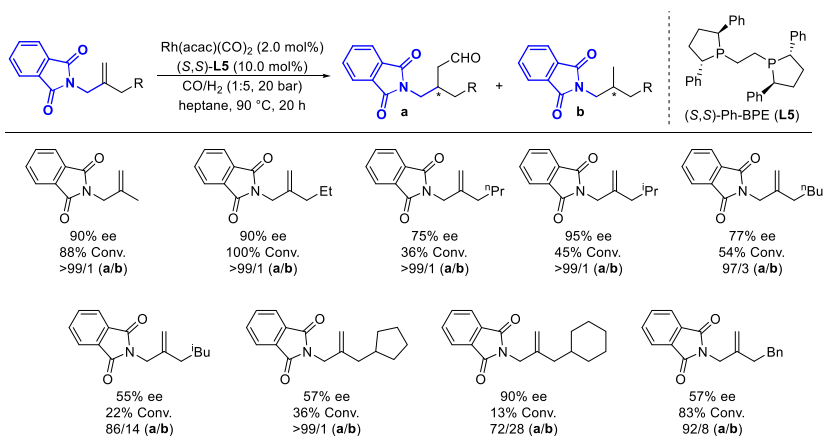
**Scheme 14** First attempts on the asymmetric hydroformylation of allylic substrates.

Other allylic substrates were then tested but also with low success (22,23). For instance, Nozaki explored the AHF of an isobutyl alcohol with (*R,S*)-Binaphos (**L3**). The reaction gave exclusively the corresponding lactol formed by intramolecular nucleophilic attack of the hydroxy group to the aldehyde moiety. This product was sequentially subjected to oxidation with  $\text{Ag}_2\text{CO}_3$  on Celite to afford the desired-butylrolactone (Scheme 14B) (22). In this case, not only the enantioselectivity was low (12% ee), but also a disappointing yield was recorded (37%). Although it was expected that the presence of the hydroxyl group would be beneficial for the stereoinduction due to coordination to Rh, the results obtained with **L3** suggest that maybe this coordination is too weak.

Müller also explored the hydroformylation of N-( $\beta$ -methylallyl)imidazole (23). The authors found that  $\sigma$ -donor ligands were necessary to achieve

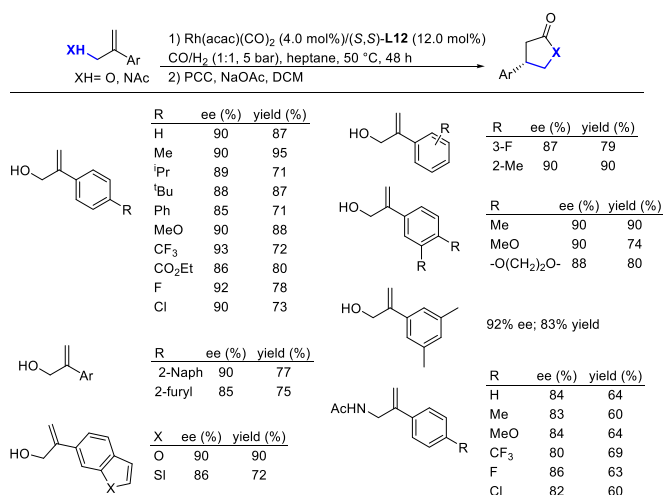
full conversions, since  $\pi$ -acceptor ligands failed to provide the desired product, most likely due to the coordination of the imidazole group of the substrate to the metal center in view of the poor  $\sigma$ -donating character of the ligands. Thus, the more  $\sigma$ -donating phosphabarrelene ligand (*R,R*)-**L14** (Scheme 14C) provided the hydroformylated product in almost full conversion at 80 °C. Increasing the temperature up to 120 °C promoted the intramolecular cyclization of formed linear aldehyde to give 8-hydroxy-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (Scheme 14C). However, the corresponding product was obtained as a racemate and with a low diastereoselectivity of 2:1 (syn/anti).

Better results were later achieved in the AHF of allyl phthalimides. The use of a Rh/(*S,S*)-Ph-BPE (**L5**) catalyst allowed the synthesis of a series of  $\beta^3$ -aminoaldehydes with enantioselectivities up to 95% ee (Scheme 15) (24). However, the system was sensitive to the length of the substrate's alkyl chain, and such levels of asymmetric induction were only observed with substrates bearing a methyl, ethyl, isopropyl or a cyclohexyl group (Scheme 15). In contrast, moderate enantioselectivities were attained when other substrates were tested (55–77% ee). Similarly, the conversion and the chemoselectivity toward the hydroformylation reaction vs hydrogenation was only high in a few cases. Nevertheless, the authors showed the utility of this transformation to obtain chiral  $\beta^3$ -amino acids and alcohols through oxidation or reduction of the N-phthalimide-protected aldehydes. As an example, 3-(aminomethyl)-4-methylpentanoic acid and 3-(aminomethyl)-4-methylpentan-1-ol were prepared without affecting the stereochemistry.



**Scheme 15** Asymmetric hydroformylation of allyl phthalimides catalyzed by Rh/(*S,S*)-Ph-BPE (**L5**).

In contrast with the low enantioselectivity reported by Nozaki in the AHF of an allylic alcohol (Scheme 14B), Zhang's group recently published the successful AHF of allylic alcohols with the Rh/(*S,S*)-DTBM-YanPhos (**L12**, Scheme 6) system (16). They were able to hydroformylate a broad range of allylic alcohols with enantioselectivities ranging from 85% to 93% ee, independently of the nature of the aryl substituent. The afforded chiral linear aldehydes were subsequently oxidized to the corresponding lactones. It should be pointed out that only aryl-substituted alkenes were tested, which makes difficult to compare the performance of Rh/**L12** with the system used in the previously commented Nozaki's report (Scheme 14B) (22). The AHF of allylic amines revealed more challenging since the corresponding lactams were furnished in lower yields and enantioselectivities (up to 69% yield and 80–86% ee) (Scheme 16). Moreover, the scope of allylic amines was narrow in comparison with the AHF of allylic alcohols.



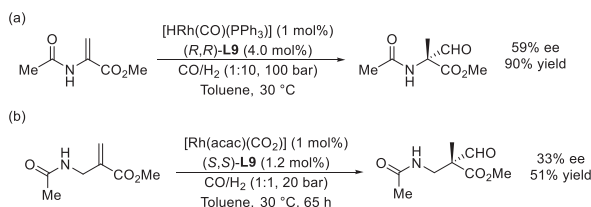
**Scheme 16** Rh-catalyzed asymmetric hydroformylation of allylic alcohols and amines with (*S,S*)-DTBM-YanPhos (**L12**).

### 3.2 *i*-Selective asymmetric hydroformylation

As previously commented, according to Keulemans' rule, the formation of the linear aldehyde is favored over the branched (see Section 2) (6,7). Nevertheless, in some cases, an unusual regioselectivity was observed and the chiral branched aldehyde was obtained as the major product. Three early examples of *i*-selectivity on the AHF of 1,1'-substituted alkenes were

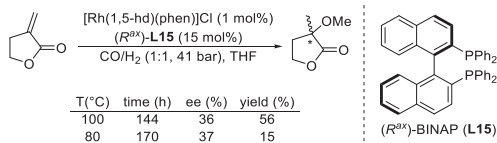


reported in 1995 (25,26). In all of them, the recorded enantioselectivity was insufficient (10–59% ee), but they showed the possibility of preparing chiral aldehydes with a quaternary stereocenter. The most successful example used  $\text{HRh}(\text{CO})(\text{PPh}_3)_3$  in the presence of a (*R,R*)-DIOP (**L9**) in the AHF of methyl *N*-acetamidoacrylate (25). The chiral formyl derivative with a quaternary stereogenic carbon was obtained in 90% yield and with 59% ee (Scheme 17). Although the reaction could be performed at a low temperature (30 °C), a high pressure of 100 bar ( $\text{CO}/\text{H}_2$  (1:1)) was needed. The authors speculated that polydentate binding of methyl *N*-acetamidoacrylate to rhodium is the responsible for the regio- and stereo-selectivity observed. More recently, Börner also observed the formation of the branched aldehyde when testing the structurally similar methyl 2-(acetamidomethyl)-acrylate, also using a Rh/DIOP catalyst (Scheme 17B) (21).



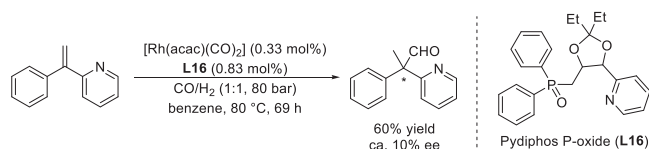
**Scheme 17** *i*-Selective asymmetric hydroformylation of (A) methyl *N*-acetamidoacrylate and (B) methyl 2-(acetamidomethyl)-acrylate with a Rh/(*R,R*)-DIOP (**L9**) catalyst.

Another of the three studies reported in 1995, consisted in the AHF of  $\alpha$ -methylene- $\gamma$ -butyrolactone with  $[\text{Rh}(1,5\text{-hexadienyl})(\text{phen})]\text{Cl}$  and (*R*)-BINAP (**L15**) as the chiral ligand (Scheme 18) (26). The corresponding aldehyde lactone with a quaternary chiral center was afforded with an enantioselectivity of only 36% ee that could be increased to 37% ee by decreasing the temperature to 80 °C, but the yield was compromised (15%) (Scheme 18). It should be pointed out that branched lactone was the only product obtained, and any traces of the hydrogenation or isomerization by-products were observed.



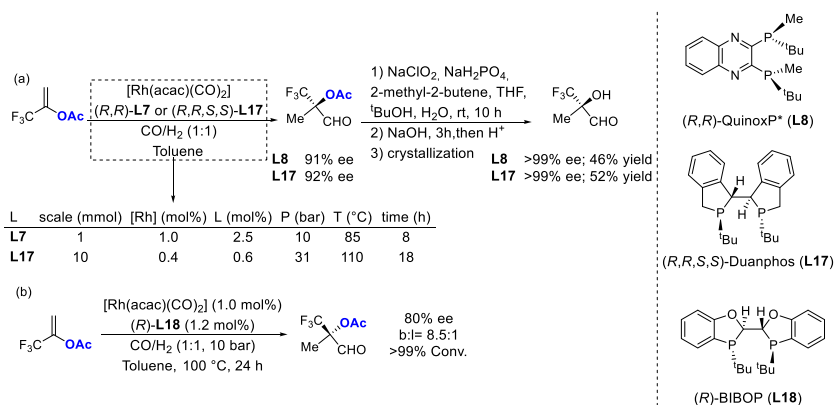
**Scheme 18** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -methylene- $\gamma$ -butyrolactone with (*R*)-BINAP (**L15**).

The last of the three early works showing *i*-selectivity was found in the AHF of the 1-phenyl-1-(2-pyridyl)ethene (**Scheme 16**) (25). In this case, the maximum enantioselectivity achieved was ca. 10% ee with a Pydiphos P-oxide ligand (**L16**) (**Scheme 19**) (25). The AHF of this type of substrates is very challenging because of the little steric difference between both aryl substituents that makes difficult the discrimination between the two prochiral faces. Although low enantioselectivity was achieved, the observed asymmetric induction was postulated to be due to the presence of the *ortho*-pyridyl ring, which could act as a directing group.



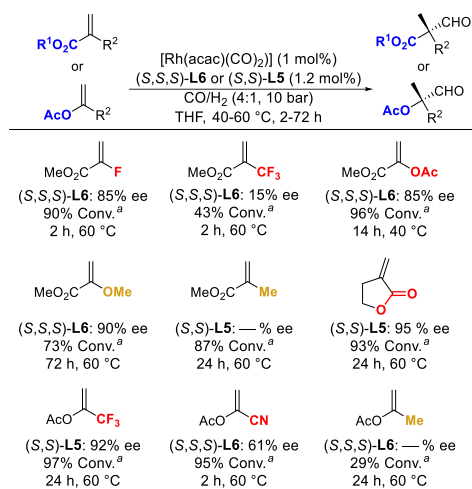
**Scheme 19** Rh-catalyzed asymmetric hydroformylation of 1-phenyl-1-(2-pyridyl)ethene with Pydiphos P-oxide ligand (**L16**).

The first successful example providing the branched aldehyde as the major product appears much later, in 2013, with the Buchwald's AHF of 3,3,3-trifluoroprop-1-en-2-yl acetate (27). As in their work about the AHF of  $\alpha$ -alkylacrylates, it was found that P-stereogenic ligands provided the best enantioselectivities. Thus, with the (*R,R*)-QuinoxP\* (**L8**) and (*R,R,S,S*)-Duanphos (**L17**) ligands, the chiral branched aldehyde was obtained with an enantioselectivity as high as 91% and 92% ee, respectively (**Scheme 20A**). To understand the origin of this unusual regioselectivity, the authors performed the AHF of 2-propenyl acetate under identical reaction conditions. The reaction yielded the chiral linear aldehyde as the major product, suggesting that the presence of the strongly electron-withdrawing trifluoromethyl group favors the branched intermediate. Importantly, the unexpected regioselectivity observed in the AHF of 3,3,3-trifluoroprop-1-en-2-yl acetate allowed the one-pot preparation of the 2-trifluoromethylactic acid (TFMLA) in excellent enantioselectivity, an important building block bearing a quaternary stereocenter found on many active pharmaceutical compounds (**Scheme 20A**). Later, Zhang's group reported the AHF of the same substrate, using another P-stereogenic diphosphine ligand, the (*R*)-BIBOP **L18** (28), however with a lower enantioselectivity (80% ee) than those obtained with QuinoxP\* or DuanPhos (**Scheme 20B**).



**Scheme 20** Reported examples for the Rh-catalyzed asymmetric hydroformylation of 3,3,3-trifluoroprop-1-en-2-yl acetate.

The last example was reported by Landis, Schomaker and co-workers in 2018 (29). By using (*S,S,S*)-BisDiazaphos (**L6**) or (*S,S*)-Ph-BPE (**L5**) ligands they could expand the scope of 1,1'-disubstituted alkenes that can be hydroformylated with high branched selectivity under rather mild conditions (10 bar, 60 °C and 2–72 h). In particular, high *i*-selectivities were achieved with some acrylates and enol ester 1,1'-disubstituted alkenes, which contain electron-withdrawing groups, such as an acetate, a fluorine and a trifluoromethyl (Scheme 21). Interestingly, some acrylates lacking electron



**Scheme 21** Selected results for the Rh-catalyzed asymmetric hydroformylation of acrylates and enol ester 1,1'-disubstituted alkenes with (*S,S,S*)-BisDiazaphos (**L6**) or (*S,S*)-Ph-BPE (**L5**). <sup>a</sup>Conversion toward the branched aldehyde.

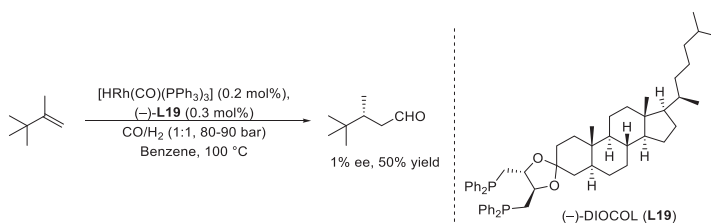
withdrawing groups also provided high *i*-selectivities (e.g., with a OMe or Me). The AHF of some substrates proceeded with high enantioselectivities (up to 95% ee) and with a ratio > 50:1 in favor of the branched product. However, in some cases, the chemoselectivity was low due to the formation of hydrogenation products. Similarly, the enantioselectivity was also dependent on the substrate substituents (Scheme 21).

## 4. Asymmetric hydroformylation of 1,1'-disubstituted alkenes with non-coordinative groups

As described in the first part, some progress was recently made in the AHF of 1,1'-disubstituted alkenes containing functional groups that might coordinate to the metal center, contributing to achieve the desired high levels of asymmetric induction. Reaching the same value of enantioselectivity is even more difficult when using 1,1'-disubstituted alkenes without a coordinating group. It's only very recently that high enantioselectivities were achieved with certain unfunctionalized substrates.

### 4.1.1 1,1'-Dialkyl alkenes

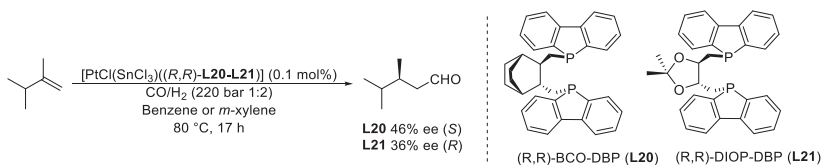
The first work on the AHF of purely unfunctionalized 1,1'-dialkyl substituted alkenes was carried out by Gladiali and Botteghi in 1983. Using a Rh catalyst with the DIOP cholesterol derivative ligand (**L19**), they reported the hydroformylation of 2,3,3-trimethyl-butene giving only the linear aldehyde but as a racemate (1% ee, Scheme 22) (30).



**Scheme 22** First attempt of Rh-catalyzed asymmetric hydroformylation of an unfunctionalized 1,1'-dialkyl substituted alkene with (–)-DIOPOL (**L19**).

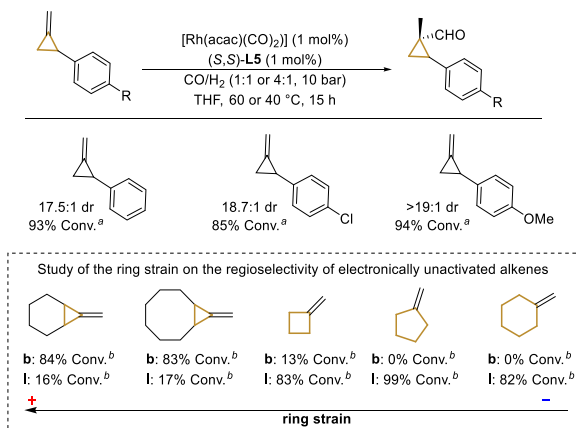
A few years later, Consiglio and co-workers developed the AHF of 2,3-dimethyl-1-butene with a  $\text{PtCl}_2\text{-SnCl}_2$  catalyst and phosphindole chiral ligands. They reached 46% ee toward the (*S*)-product using (*R,R*)-BCO-DBP (**L20**) and 36% ee for the opposite enantiomer with the (*R,R*)-DIOP-DBP one (**L21**). In both cases a complete control of the regioselectivity

was observed (Scheme 23) (31). Despite that the enantioselectivity was improved with respect to the Rh/DIOCOL system, enantioselectivities remained low. Furthermore, harsh reaction conditions of pressure and temperature were required.



**Scheme 23** Pt/Sn-catalyzed asymmetric hydroformylation of 1,1'-dialkyl substituted alkenes with (*R,R*)-BCO-DBP (**L20**) and (*R,R*)-DIOP-DBP (**L21**).

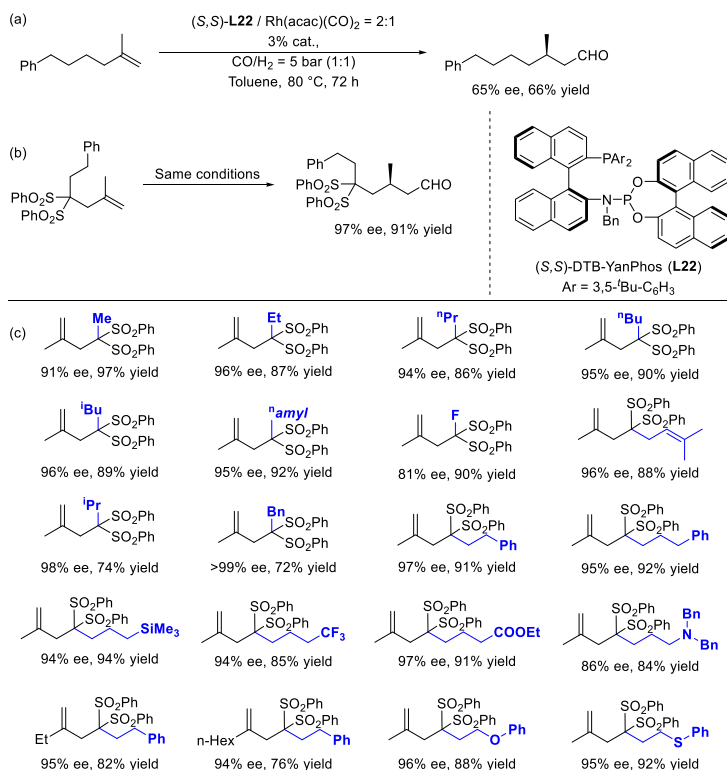
During the investigation of Landis and Schomaker on the *i*-selective AHF of electron deficient acrylates and acetates, they also explored unfunctionalized cycloalkanes as substrates. With (*S,S*)-Ph-BPE (**L5**) it was possible to induce the formation of the branched aldehyde when constrained aryl-substituted cyclopropenes were tested (Scheme 24). The desired chiral branched products were obtained in more than 83% yield and with high diastereoselectivities (up to >19:1 dr). It is interesting to note that the non-asymmetric hydroformylation of electronically unactivated alkenes 7-methylenebicyclo-[4.1.0]heptane and 8-methylenebicyclo-[5.1.0]octane also proceeded with high regioselectivities toward the *i*-aldehyde, in spite



**Scheme 24** Rh-catalyzed asymmetric hydroformylation of aryl-substituted cyclopropenes with (*S,S*)-Ph-BPE (**L5**). <sup>a</sup>Conversion toward the branched aldehyde. <sup>b</sup>The product obtained is not chiral.

of not containing any aryl group that could be considered as an electronically activating group. In contrast, the linear product was yielded from electronically unactivated cycloalkanes with ring sizes greater than three, which are therefore less strained rings (Scheme 24). This suggests that ring strain plays an important role in influencing the regioselectivity in the HF of 1,1'-disubstituted alkenes.

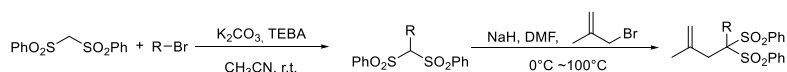
Very recently, Zhang's group developed an improved AHF of those very challenging substrates via the introduction of a steric disulfonyl auxiliary, using a Rh/(*S,S*)-DTB-YanPhos (**L22**) complex as catalyst. The authors proved that the incorporation of the disulfonyl moiety increases the yield of the reaction and drastically enhances the enantioselectivity (Scheme 25A vs B). In addition, a pressure of only 5 bar could be used. This methodology was applied over 20 substrates providing up to 97% yield and >99% ee (Scheme 25C).



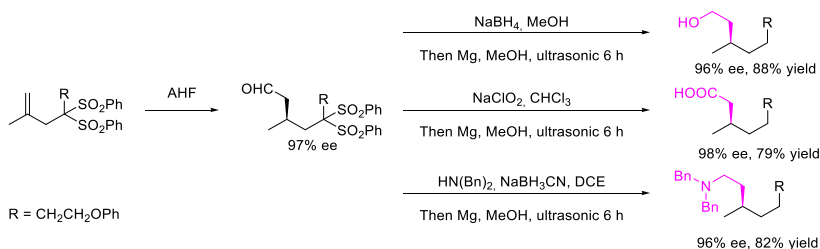
**Scheme 25** Efficient Rh-catalyzed asymmetric hydroformylation of 1,1'-dialkylsubstituted alkenes via steric auxiliary help with (*S,S*)-DTB-YanPhos (**L22**).

Furthermore, the sulfonyl groups can be easily introduced and removed to convert the chiral aldehyde into chiral building blocks with 22–25% overall yield starting from 1,3-benzodithiole tetraoxide, which enhances the synthetic applicability of this transformation (32) (Scheme 26). Moreover, the authors showed that the aldehyde group on the chiral products could be readily transformed into other valuable functionalities in a sequential manner followed by the removal of the disulfonyl groups.

(a) Synthesis of the substrate containing a disulfonyl auxiliary.



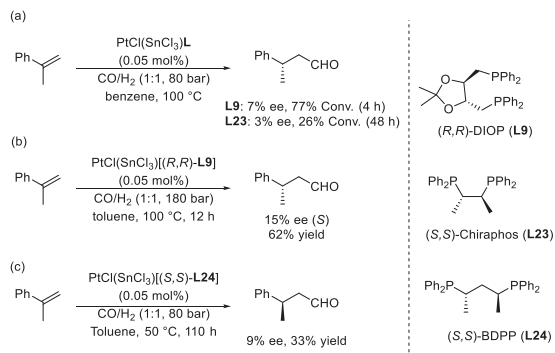
(b) Reaction of the aldehyde and removing of the auxiliary.



**Scheme 26** Synthesis of the substrates containing a disulfonyl auxiliary followed by sequential transformation of the aldehyde.

#### 4.1.2 1-Aryl-1-alkyl alkenes

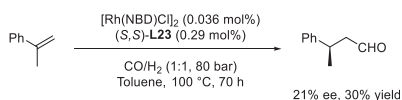
1-Aryl-1-alkyl substituted alkenes have been more studied than the 1,1'-dialkyl substituted ones, especially  $\alpha$ -methylstyrene. Early studies were performed by Consiglio's and Kollár's group using mixed Pt/Sn-catalysts for the AHF of methyl styrene (33–35). Consiglio first tested (*S,S*)-Chiraphos (**L23**) and (*R,R*)-DIOP (**L1**), obtaining a maximum of 7% ee with the (*S,S*)-DIOP ligand (**L9**) (Scheme 27A) (33). Later, the same authors reported the use of (*R,R*)-DIOP (**L9**) ligand in the AHF of several *para*-substituted styrene derivatives. In this case, the reaction was performed at a higher pressure (180 bar, 1:1 CO/H<sub>2</sub>) (34). With this conditions the AHF of methyl styrene proceeded with a slightly better enantioselectivity (15% ee, Scheme 27B). Kollár's group published the AHF of methylstyrene with the (*S,S*)-BDPP ligand (**L24**) that gave the opposite enantiomer than the obtained with Consiglio's Chiraphos system but under milder conditions, albeit with an even poorer ee value of 9% (Scheme 27C) (35). Moreover a lower yield was obtained due to the low reactivity at 50 °C, since only



**Scheme 27** Pt/Sn-catalyzed asymmetric hydroformylation of  $\alpha$ -methylstyrene.

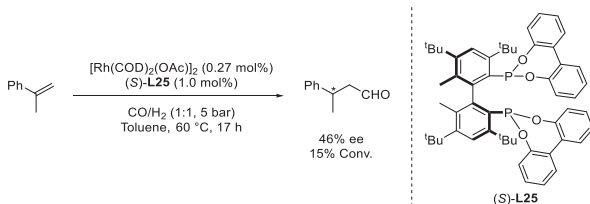
a conversion of 35% was achieved after 110 h. An increase of the temperature resulted in the complete loss of enantioselectivity (ca. 2% ee at 100 °C).

The first Rh-catalyzed AHF of  $\alpha$ -methylstyrene was reported by Consiglio's group with the  $[\text{Rh}(\text{NBD})\text{Cl}]_2/(\text{S},\text{S})$ -Chiraphos (**L23**) catalyst (Scheme 28) (33). Compared with the Pt/Sn systems, a higher ee of 21% ee was reached. This low value was the maximum level of enantioselectivity achieved at that time.



**Scheme 28** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -methylstyrene with  $(\text{S},\text{S})$ -Chiraphos (**L23**).

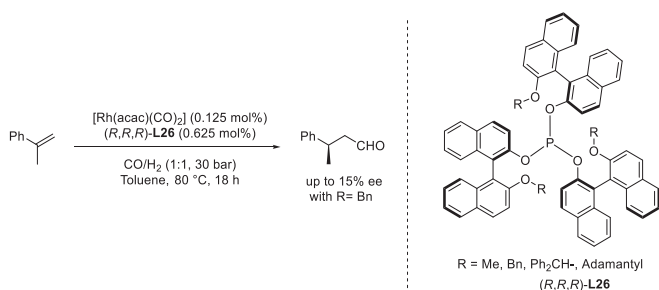
In 2004, the Rh-catalyzed AHF of  $\alpha$ -methylstyrene using the diphosphonite ligand **L25** was patented by the State University of New York and Mitsubishi Chemical Corporation (36). They reported 46% ee but a very low conversion of 15%, which is not surprising considering the low pressure and temperature used (Scheme 29).



**Scheme 29** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -methylstyrene with  $(\text{S})\text{-L25}$  as chiral ligand.

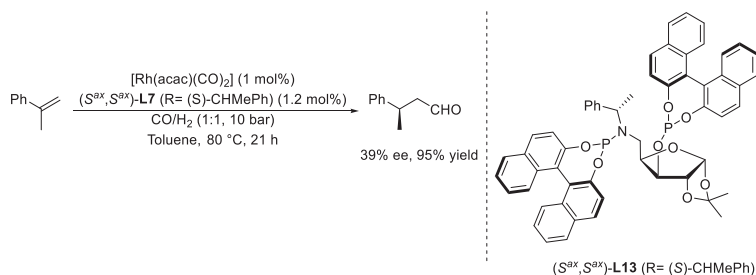


Bayón and Pereira applied bulky chiral monoposphite ligands (*R,R,R*)-**L26** with large cone angle (240–270°) in the AHF of 1,1'-methylstyrene, but unfortunately they obtained an even more disappointing enantioselectivity than the achieved at this point with Rh-catalysts (15% ee, [Scheme 30](#)) ([37](#)).



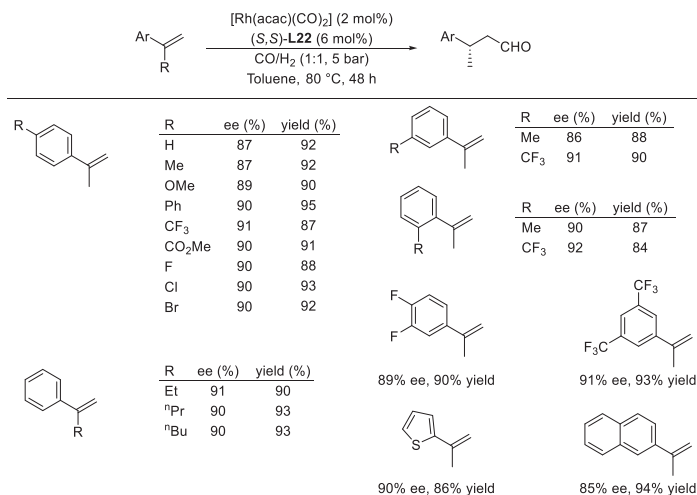
**Scheme 30** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -methylstyrene with chiral monoposphite (*R,R,R*)-**L26**.

Börner et al. tested the family of sugar based phosphite-phosphoramidites ligands **L13** ([Scheme 9](#)) in the AHF of  $\alpha$ -methylstyrene and reached a moderate enantioselectivity (39% ee) with high yield (95%) ([Scheme 31](#)) ([21](#)). They observed that the substituent at the N-moiety of the ligand has a crucial effect on the enantioselectivity. Indeed, they observed that sterically demanding substituents such as Cy or <sup>t</sup>Bu had a negative effect on the enantioselectivity, which contrasts with the results observed in the AHF of acrylamides (see [Scheme 9](#)). Interestingly the best ligand contained a (*S*)- $\sigma$ -methylbenzyl moiety at the N-atom and (*S*)-configuration of the biaryl moieties (see [Section 5](#)).



**Scheme 31** Rh-catalyzed asymmetric hydroformylation with the furanoside-based phosphite-phosphoramidite ligand (*S*<sup>ax</sup>, *S*<sup>ax</sup>)-**L13** (R = (*S*)-CHMePh).

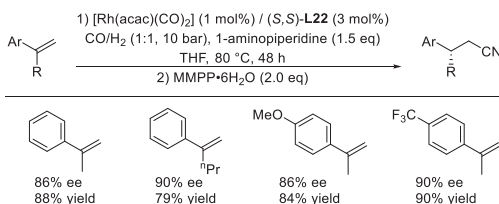
In 2018, Zhang group reported the best results so far in the AHF of 1,1'-methylstyrene using Rh(acac)(CO)<sub>2</sub> as precatalyst and a YanPhos-type ligand. They observed that lowering the pressure from 20 to 5 bar increases the conversion, thus affording very mild conditions for this reaction. The authors tested a series of YanPhos ligands and reported that the key parameter to achieve high conversion and enantioselectivity is the use of 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, a conversion of 5% with 37% ee was obtained, which is very low compared to the results achieved in the preliminary results (65% and 82% ee). After optimization of the ligand and reaction conditions, the AHF of  $\alpha$ -methylstyrene was achieved with 87% ee with (*S,S*)-DTB-YanPhos (**L22**, Scheme 25). With this ligand, a range of 1,1'-alkylstyrene derivatives could be hydroformylated with unprecedented enantioselectivities (up to 92% ee, Scheme 32). In addition, the AHF of  $\alpha$ -methylstyrene was successfully performed at a Gram scale using only 0.05 mol% of the Rh-precursor and 0.15 mol% ligand for 90 h at 80 °C, to provide the desired chiral product in 92% yield and with 87% ee (17).



**Scheme 32** Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -methylstyrene with (*S,S*)-DTB-YanPhos (**L22**).

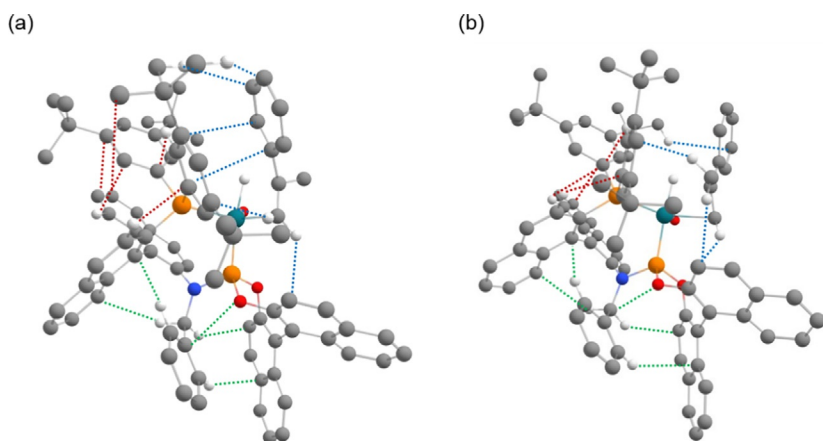
More recently, the use of (*S,S*)-DTB-YanPhos ligand (**L22**, Scheme 25) was also reported in the efficient Rh-catalyzed asymmetric cyanide-free hydrocyanation of some 1-aryl-1-alkyl alkenes (38). The transformation consists in the asymmetric hydroformylation/condensation/aza-Cope elimination sequence. The reaction of  $\alpha$ -methyl styrene yielded the corresponding

chiral nitrile with 86% ee and 88% yield. The high enantioselectivity was maintained for substrates with a longer alkyl chain and with electron withdrawing and donating groups in *para*-position of the benzyl ring (ee's up to 90%) (Scheme 33).



**Scheme 33** Rh-catalyzed asymmetric cyanide-free hydrocyanation of 1-aryl-1-alkyl alkenes via tandem hydroformylation/condensation/aza-Cope elimination.

Dangat and Sunoj have recently performed a comprehensive DFT study on the asymmetric hydroformylation of  $\alpha$ -methylstyrene catalyzed by the Rh/(S,S)-DTB-YanPhos (**L22**) system, with the aim to unravel the origin of the attained high regio- and enantioselectivities (39). These calculations pointed out that non-covalent interactions (NCI) between the N-benzyl group and the other aromatic moieties in the ligand backbone are crucial for reaching good enantioselectivities (Fig. 2). Those interactions, in particular CH $\cdots$  $\pi$  and  $\pi\cdots\pi$ , seem to stabilize the most preferred conformers, giving an

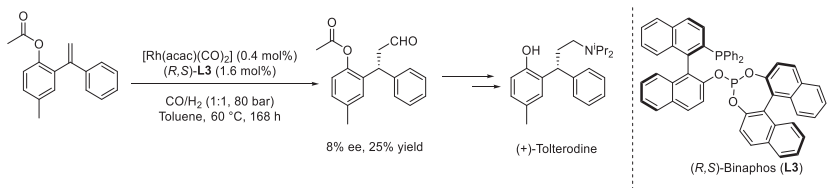


**Fig. 2** Transition state geometries for the migratory insertion with coordination of the substrate through the *si*- (A) and *re*-faces (B). The figure shows the found NCIs. Ligand-ligand interactions are shown in red, substrate-ligand in blue and Bn group-ligand in green. Hydrogen atoms, wherever possible, are omitted to ensure better clarity.

appropriate shape to the chiral cavity to accommodate the incoming substrate. Moreover, NCIs between the chiral ligand and the substrate are also important since they favor a *si*-face binding, which leads to the (*S*)-linear product obtained experimentally. Fig. 2 shows the transition state geometries for the migratory insertion with coordination of the substrate through the *si*- and *re*-faces (Fig. 2A and B, respectively). The number of NCIs between the catalyst and the substrate (shown in blue dotted lines) is higher in the *si*-transition state (Fig. 2A), resulting in a higher stabilization, which is reflected by its lower relative free energy compared to that of the *re*-transition state.

### 4.1.3 1,1'-Diaryl olefins

So far, the AHF of 1,1'-diaryl olefins haven't receive much interest, which is reflected by the fact that only two papers describe its use as substrates (25, 40). One study was already discussed above (see Section 3.2, Scheme 19), considering the *ortho*-pyridyl group of the substrate as an anchoring group to the metal center (25). Another example was reported in 2002 by Botteghi and coworkers, who studied the asymmetric synthesis of the anti-muscarinic Tolterodine compound using as a key step the AHF of 1-[(2-hydroxy-5-methyl)-1-phenylethene]. Unfortunately, only 8% ee was obtained using (*R,S*)-Binaphos (L3) as the chiral ligand (Scheme 34). Moreover, high pressure and very long reaction time were needed. Moreover, high amounts of the hydrogenated product were obtained (27%) (40).



**Scheme 34** Rh-catalyzed asymmetric hydroformylation of a diarylethene derivative with (*R,S*)-Binaphos (L3).

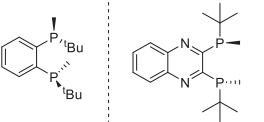
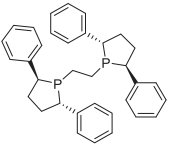
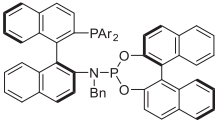
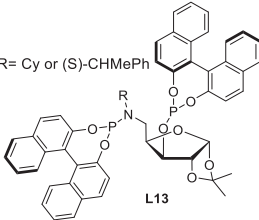
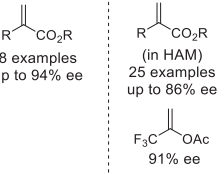
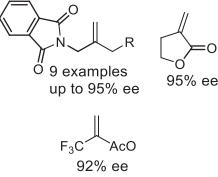
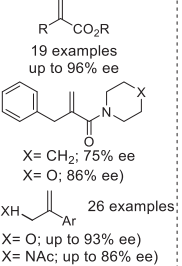
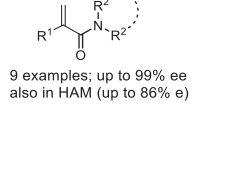
## 5. Rationalization of the catalyst efficiency

Achieving high chemo-, regio- and enantioselectivities on the AHF of 1,1'-disubstituted alkenes is not a trivial task. To deal with all those constraints, the selection of the catalyst is a must. Rhodium, despite its high cost, is more efficient in hydroformylation than platinum. Concerning ligands,

it was observed that small structural changes from one type of 1,1'-disubstituted olefin to another require significant changes in ligand structure and reaction conditions. In addition, earlier ligands that were efficient for mono- and 1,2-disubstituted olefins such as Binaphos and Kelliphite did not work well for 1,1'-disubstituted olefins. Therefore, an approach based on fine-tuning modular ligands can be advantageous to improve the outcome in the hydroformylation of 1,1'-disubstituted olefins. Organophosphorus compounds maintain a privileged position in the AHF of 1,1'-disubstituted olefins with bidentate ligands providing the best selectivities. Only a few monodentate ligands were developed for this process, although with little success. Table 1 shows the most outstanding ligands for the AHF of 1,1'-disubstituted olefins, providing access to the desired chiral aldehydes with high yields and ee's for a set of substrates.

Rh catalytic systems containing P-stereogenic diphosphines, namely BenzP\* (**L7**) and QuinoxP\* (**L8**) were the first in providing high catalytic performance. Both can hydroformylate  $\alpha$ -substituted acrylates with high yields and enantioselectivities, and in the case of QuinoxP\*, a tandem reaction involving the AHF of acrylates and the subsequent amine condensation and Rh-catalyzed hydrogenation steps (the direct HAM) was also reported. Furthermore, QuinoxP\* was also used in the *i*-selective AHF of 3,3,3-trifluoroprop-1-en-2-yl acetate, allowing the synthesis of an aldehyde with a quaternary stereocenter. Later, the diphospholane Ph-BPE (**L5**) was used in the AHF of allyl phthalimides and provided also high *i*-selectivities with electron deficient 3,3,3-trifluoroprop-1-en-2-yl acetate and  $\alpha$ -methylenebutyrolactone. An important breakthrough came with the use of the phosphine-phosphoramidite YanPhos ligands. Rh complexes bearing this ligand family provided for the first time the AHF of different type of substrates with high yields and enantioselectivities. Hence, using either **L12** or **L22** (which differ in the substituents on the phosphine group, Table 1), the efficient asymmetric hydroformylation of  $\alpha$ -substituted acrylates, allylic alcohols and amines, and even challenging unfunctionalized substrates as  $\alpha$ -alkylstyrene derivatives and dialkyl-1,1'-alkenes, was demonstrated although the last group of substrates requires the introduction of a disulfonyl auxiliary. Moreover, they are also efficient in tandem reactions involving AHF. Finally, a last group of sugar-based phosphite-phosphoramidite ligands (**L13**) has also recently shown their potential, unlocking the AHF  $\alpha$ -acrylamides. Furthermore, Rh/**L13** catalytic system also promoted the intermolecular asymmetric hydroaminomethylation (HAM) of a wide range of  $\alpha$ -acrylamides.

**Table 1** Selection of the most successful ligands developed for the AHF of 1,1'-disubstituted alkenes until now.

Ligand	 <p>(<i>R,R</i>)-BenzP* (L7)     (<i>R,R</i>)-QuinoxP* (L8)</p>		 <p>(<i>S,S</i>)-Ph-BPE (L5)</p>	 <p>(<i>S,S</i>)-DTBM-YanPhos (L12); (<i>S,S</i>)-DTB-YanPhos (L22)          Ar = 3,5-<i>t</i>Bu-4-MeO-C<sub>6</sub>H<sub>3</sub> ;     Ar = 3,5-<i>t</i>Bu-C<sub>6</sub>H<sub>3</sub></p>		 <p>R = Cy or (S)-CHMePh          L13</p>
Ligand type	P stereogenic diphosphine		Phospholane	Phosphine phosphoramidite		Phosphite phosphoramidite
Substrate	 <p>R-CH=CH-CO<sub>2</sub>R          8 examples          up to 94% ee</p> <p>R-CH=CH-CO<sub>2</sub>R          (in HAM)          25 examples          up to 86% ee</p> <p>F<sub>3</sub>C-CH=CH-OAc          91% ee</p>		 <p>9 examples          up to 95% ee</p> <p>95% ee</p> <p>F<sub>3</sub>C-CH=CH-OAc          92% ee</p>	 <p>R-CH=CH-CO<sub>2</sub>R          19 examples          up to 96% ee</p> <p>X = CH<sub>2</sub>; 75% ee          X = O; 86% ee)</p> <p>XH-CH=CH-Ar    26 examples;          X = O; up to 93% ee)          X = NAc; up to 86% ee)</p> <p>20 examples          up to &gt;99% ee</p> <p>Ar-CH=CH-Alk          20 examples; up to 92% ee</p>		 <p>9 examples; up to 99% ee          also in HAM (up to 86% ee)</p>

All the ligands collected on [Table 1](#) have the common feature of having a bulky environment around the phosphorus center. Indeed, the poor results achieved with 1,1'-disubstituted olefins can be mainly attributed to the difficulty in differentiating the two pro-chiral faces, and the bulkiness of the coordinative groups probably help in this task. On the other hand, looking at the two newest groups of successful ligands, both contain an N-substituted phosphoramidite group (Yanphos ligands **L12/L22** and sugar-based ligands **L13**). Another common characteristic found in the P-phosphoramidite ligands is that both contain a chiral binaphthyl moiety on the phosphoramidite group. Moreover, in both ligand families, the optimal configuration of this biaryl moiety is the (*S*). The substituent on the phosphoramidite moiety plays also an important role on the enantioselectivity. In the case of sugar-based ligands **L13** it was found that the best enantioselectivities were achieved with bulky groups, such as cyclohexyl or (*S*)-CHMePh. In contrast, Yanphos ligands work better with a less bulky benzyl group.

## 6. Conclusions and outlook

Due to the difficulty in differentiating the prochiral faces of the alkene, the AHF of 1,1'-disubstituted alkenes is much less developed than the reaction with monosubstituted or 1,2-disubstituted substrates. In this respect, it was not until 2011 that the first catalyst that provided useful enantioselectivities was developed; this was the Rh/BenzP\* catalyst for the AHF of  $\alpha$ -substituted acrylates (>80% ee). Since then, new advances have been made and nowadays some Rh-catalysts can hydroformylate 1,1'-disubstituted alkenes with high enantioselectivities, although the substrate scope is still limited. The most important advances were made for  $\alpha$ -substituted acrylates and to a lesser extent for  $\alpha$ -acrylamides, allylic alcohols and unfunctionalized substrates as  $\alpha$ -alkylstyrene derivatives and dialkyl-1,1'-alkenes. Interests are also shifting to obtain exclusively the less favorable branched aldehyde giving access to the highly appealing  $\alpha$ -tetrasubstituted aldehydes. It was shown that the formation of these products is favored for certain substrates holding electron withdrawing substituents using sterically hindered ligands, but high enantioselectivities has only been described for a few substrates and not always with satisfactory catalytic performance.

A survey of the literature also shows that only a few chiral ligands provide effective rates and selectivities. The first successful ligands were P-stereogenic diphosphines and chiral diphospholanes until the phosphine-phosphoramidite YanPhos ligands appeared and allowed for the first time the AHF of different

substrate types. Lately, sugar-based phosphite-phosphoramidite ligands also demonstrated their potential, unlocking the AHF of  $\alpha$ -acrylamides.

To ensure the industrial applicability of a chemical process it becomes crucial to achieve catalytic systems that operate under mild reaction conditions. Gratifyingly, despite the very high CO/H<sub>2</sub> pressures required in the first attempts (typically 80–190 bar), nowadays it is possible to operate at a pressure as low as 5–20 bar. However, the reaction temperature required is still high, only few systems work at 60 °C and in most of the cases temperatures of 80 °C or higher are needed. This is a drawback not only for the sustainability of the reaction, but also because it complicates even more to reach high levels of asymmetric induction.

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