Asymmetric Hydrogenation of Olefins using Chiral Crabtree-type Catalysts – Scope and Limitations

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1 Introduction

1.1 Motivation and Scope

Asymmetric hydrogenation of alkenes using transition metal catalysts continues to be a growing field and a fundamental tool for organic synthetic chemists. Enantioselective addition of two hydrogen atoms to carbon-carbon double bonds, in contrast to, for example carbonyl reductions, relies almost exclusively on transition metal based catalysts and the reaction frequently exhibits excellent chemo-, regio- and enantioselectivities. For alkenes carrying coordinating functional groups such as amides and carboxylic acids in close proximity to the double bond, Rh(I) and Ru(II) species bearing diphosphine ligands (P,P ligands) are the catalysts of choice for asymmetric hydrogenation.[1] Complementary, for non-functionalized olefins carrying no neighboring coordinating group, chiral mimics of Crabtree's catalyst, $[Ir(cod)(Py)(PCy_3)][PF_6]$, have been developed into versatile reagents that can reduce both di- tri- and tetrasubstituted alkenes with high enantioselectivity.[2] A broad range of interesting alkene substrates have properties that lie in between these two extremes of functionalized and non-functionalized alkenes. Compounds such as α,β-unsaturated esters, enols and vinyl phosphonates, can be reduced selectively with several, fundamentally different, catalytic systems although chiral analogues of Crabtree's catalyst has proven superior to other catalyst types in many cases. Figure 1 depicts how we will regard alkene substrates in this review and, of course, is only a rough classification useful for the discussion and understanding. A specific alkene may in some cases form a chelate to metal centers and in other cases not.

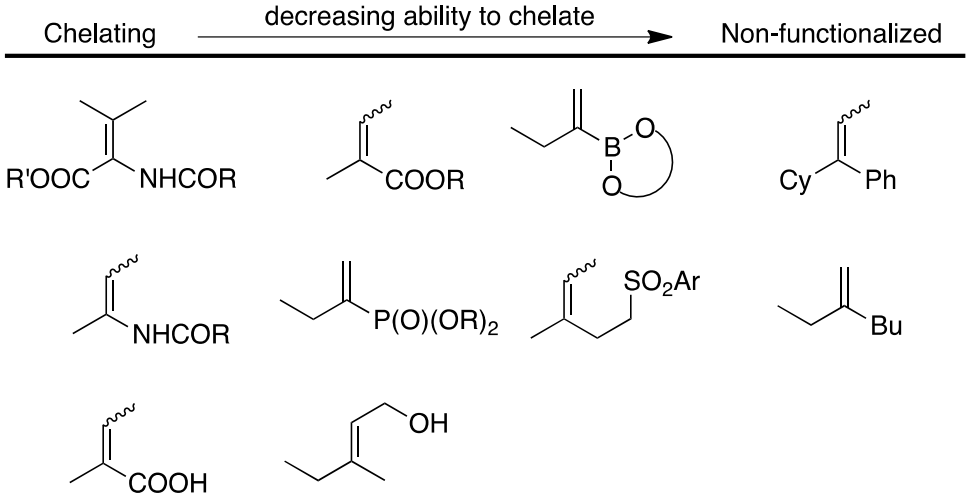


Figure 1 Alkene substrates for the asymmetric hydrogenation can be categorized as chelating (containing adjacent coordinating functional groups), intermediate, and non-functionalized (containing no heterofunctions).

In this comprehensive review, we want to summarize the developments of chiral analogues of Crabtree's catalyst for the asymmetric hydrogenation of alkenes with particular emphasis on the developments during the last five years. The field has seen substantial expansion, especially in applications of

and the substrate scope for this type of catalysts and most of the published surveys of the field do not cover the most recent advances.[2a,b,2d,e,3] Much of the recent developments concern the use of N,P-ligated iridium-catalysts for hydrogenation of weakly-functionalized alkenes, giving chiral products with great potential in chemical synthesis. Our aim is to give a clear overview of which, depending on the alkene type, catalysts are suitable for a certain application and to find areas in need of further studies.

In addition to reviewing the recent advances, we also want to clarify the scopes and limitations of N,P-ligated iridium system and, where relevant, compare it to other available catalytic systems.

The mechanistic understanding of the asymmetric hydrogenation using [Ir(cod)(N,P*)][BAr_F] (cod = 1,5-cyclooctadiene, BAr_F = *tetrakis*(3,5-bis(trifluoromethyl)phenyl)borate) complexes have been significantly expanded by several computational works and will also be considered along with the possibility to predict the stereochemical outcome.

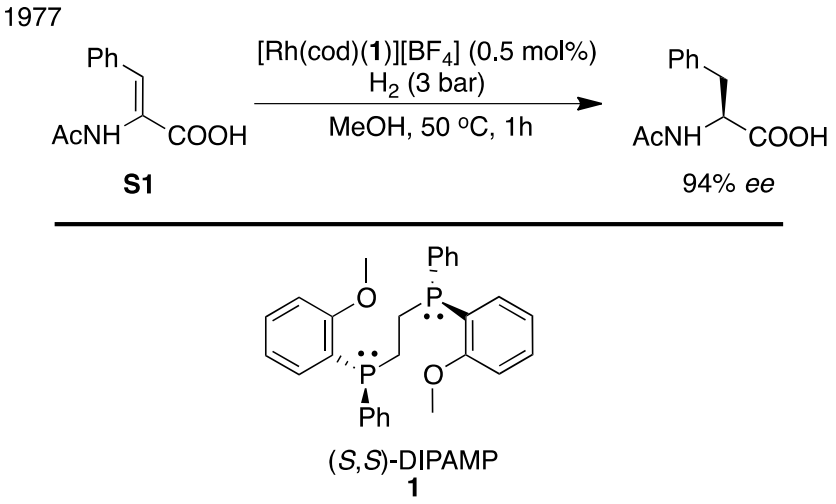
We will exclusively focus on enantioselective reduction of carbon-carbon double bond using hydrogen gas, thus excluding carbonyl and imine reduction and the asymmetric hydrogenation of heteroaromatic substrates, a topic that has been recently and comprehensively reviewed.[4]

1.2 A note on conversion and yield

Since metal-catalyzed asymmetric hydrogenation is a uniquely mild chemical transformation the amount of by-products formed in the reaction is usually very low or non-existent. It has therefore become practice in screening experiments to only report the alkene conversion (conversion = product / (starting material + product)) except in cases where the reactions are not proceeding cleanly. Since the conversion for a specific catalytic system can be altered by parameters such as pre-catalyst loading, reaction time and temperature, and since in most cases authors develop systems that generate complete or at least high conversion, we will not discuss the alkene conversion except when of special relevance. Instead, focus will be on the reaction conditions that describe the effectiveness of the catalytic system and the reader should assume that the reactions proceeds cleanly and in high conversion unless otherwise stated. Yields will be used when relevant, mainly in cases where asymmetric hydrogenation is used in longer syntheses sequences and when the reaction does not proceed cleanly.

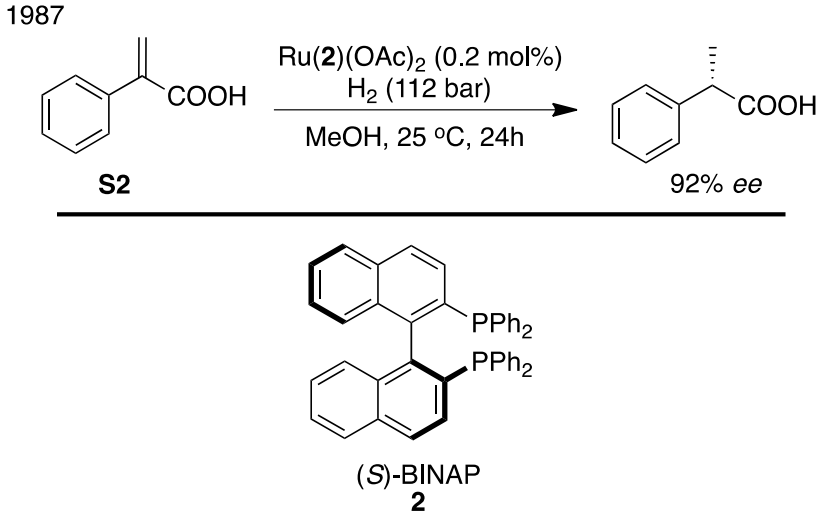
1.3 Early developments, reduction of functionalized alkenes

The birth of asymmetric hydrogenation is usually associated with the introduction of the first chiral bidentate ligand DIOP, (2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane), and its use in rhodium-catalyzed hydrogenation of dehydroaminoacids. Using tartrate-derived (–)-DIOP, Dang and Kagan successfully reduced several dehydroaminoacids in >50% enantioselectivity in the beginning of the 1970s.[5] In 1975, Knowles concluded that asymmetric hydrogenation finally approached nature's capability in terms of stereospecificity.[6] The results obtained upon hydrogenation of α-acetamidoacrylic acids such as **S1** using Rh-DIPAMP (Scheme 1), showed enantioselectivities above 90% ee for a range of derivatives.[7] The catalytic asymmetric synthesis of the anti-parkinson drug L-DOPA using this methodology became a commercial process.[8]



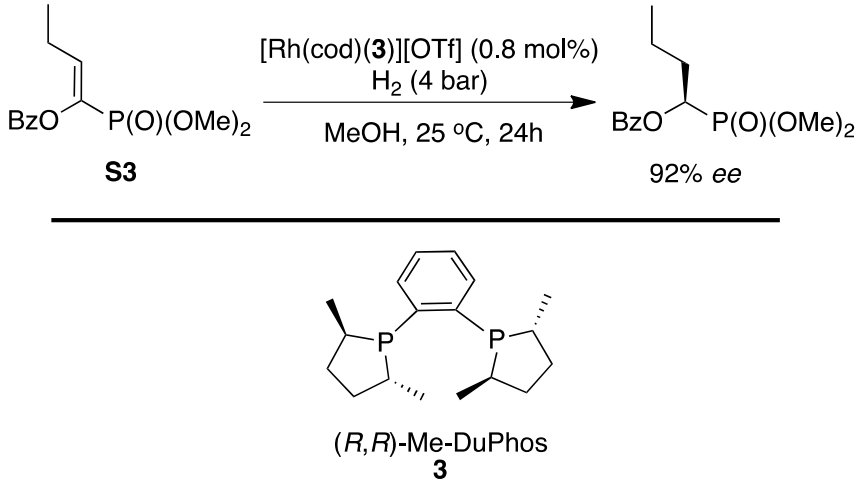
Scheme 1 Asymmetric hydrogenation of a dehydroamino acid using Rh-DIPAMP.

More than ten years later, Noyori and co-workers published the asymmetric hydrogenation of allylic and homoallylic alcohols using $Ru(BINAP)(OAc)_2$.[9] BINAP,[10] **2**, proved to be a uniquely versatile ligand and the same year the first asymmetric hydrogenation of α,β-unsaturated carboxylic acids was presented using the same catalytic system (Scheme 2).[11]



Scheme 2 The asymmetric hydrogenation of 2-phenyl-propenoic acid with the Ru-BINAP system developed by Noyori.

The DuPhos ligand **3**, developed by Burk and co-workers in 1990,[12] was unique in the sense that it was probably the first ligand that could be easily modified and tuned to fit a specific substrate class. Another class of alkenes, enol esters, could be reduced in very high enantioselectivities using DuPhos variants.[13] Other novel substrate classes that could be reduced using DuPhos systems were α-enolbenzoate- and α-acetamido phosphonates[14] (Scheme 3) and β-acylamino acrylates.[15]



Scheme 3 Rh-DuPhos asymmetric hydrogenation of an enolbenzophosphonate.

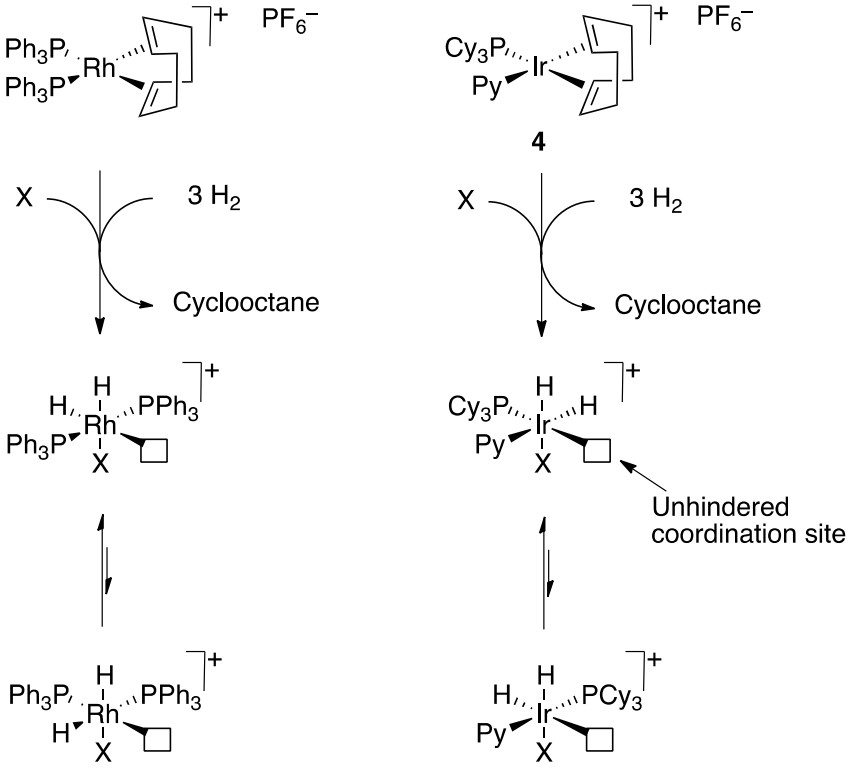
Thus, the asymmetric hydrogenation using Rh-P,P and Ru-P,P systems has developed significantly over the last 40 years and allowed the enantioselective synthesis of a range of chiral synthetic intermediates with different functionalities. The asymmetric hydrogenation of alkenes by complexes of the types $[Rh(diene)(P,P)]^+[X]^-$ and $Ru(P,P)(OOCR)_2$ both rely on coordination of additional functional groups to the metal in order to obtain high stereoselectivity.[16] Typically, the alkene coordination would be accompanied by that of an acetamide, acetate or alcohol to form a chelate, thus locking the alkene in position and limiting the set of coordination modes. Additionally, since these catalysts usually operate in alcoholic solvents that stabilize the metal complex towards decomposition and allow proton-transfer, non-chelating alkenes competes less favorably with the solvent for metal coordination sites and are reduced at a lower rate. Attempts to use the P,P-ligated systems for hydrogenation of weakly- or non-functionalized alkenes have frequently proved unsuccessful.[17]

1.4 The iridium-N,P catalytic hydrogenation system

During the 1970s, Crabtree and co-workers studied the properties of metal complexes of the type $[M(cod)L_2][X]$ (M = Rh or Ir, L = phosphine ligand, X = Cl, BF_4 or PF_6), previously reported by Schrock and Osborn, to form viable hydrogenation catalysts when subjected to H_2.[18] Ir-analogues were found to be less active than the rhodium counterparts in the hydrogenation reaction and, in coordinating solvents, the Ir-complexes formed the stable solvate complexes $[Ir(H)_2(S)_2L_2][PF_6]$ (S = solvent) upon exposure to H_2.[19] When Crabtree and co-workers exchanged the coordinating solvents with polar, non-coordinating solvents such as CH_2Cl_2, more active catalytic systems were obtained, especially in the iridium case.[20]

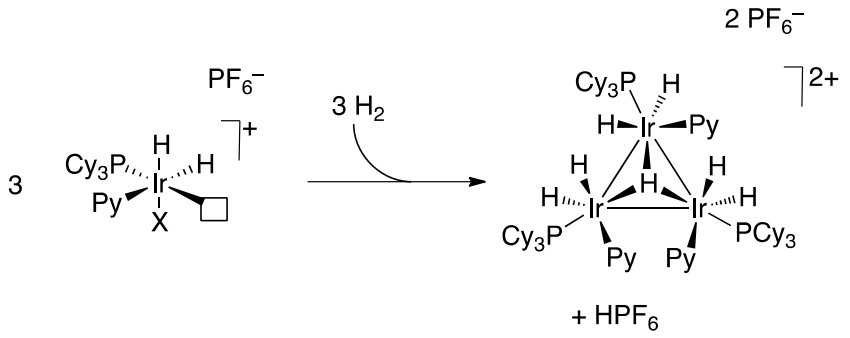
In a ligand-screening experiment, searching for Ir-catalysts with improved properties, the mixed ligand complex $[Ir(cod)(Py)PCy_3][PF_6]$ **4** (Py = pyridine, PCy_3 = tricyclohexylphosphine) was found form a catalyst which was both faster than the corresponding diphosphine-catalyst and able to reduce tri- and tetrasubstituted non-functionalized alkenes efficiently.[20a]

The higher activity of complex **4** compared to the diphosphine analogue was attributed partially to the small size of the pyridine ligand but also, a *cis* conformation of the pyridine and PCy_3 ligands could be observed in some cases.[21] It is thus possible that activation of **4** with dihydrogen forms cations $[Ir(H)_2(Py)PCy_3X]^+$ (X = solvent, alkene or H_2), where an unusually open alkene coordination site is produced (Scheme 4). This is in contrast to the corresponding diphosphine complexes, which upon activation with dihydrogen, arranges the two bulky phosphines in a *trans* fashion.[22]



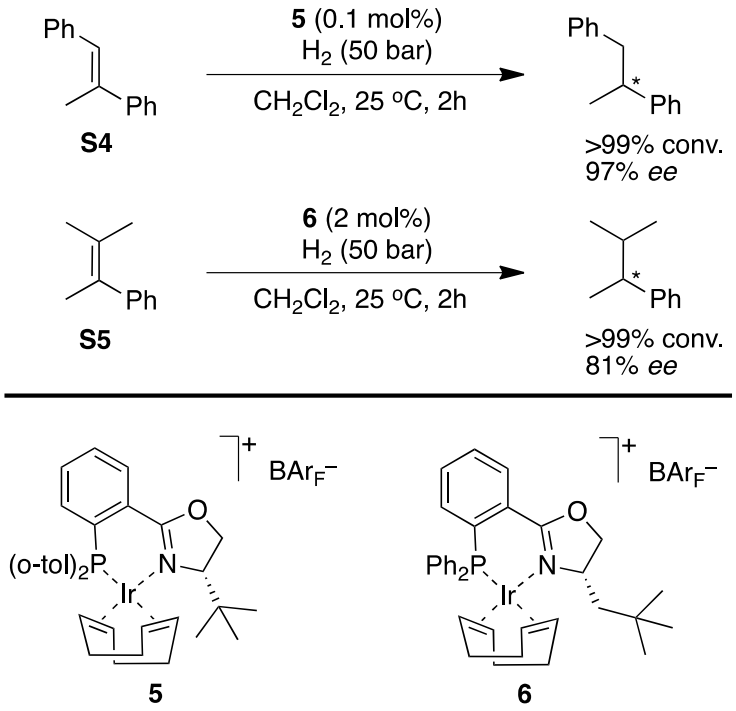
Scheme 4 Activation of **4** by H_2 generates an iridium-complex with an unhindered coordination site.

Compound **4**, usually called Crabtree's catalyst, also proved to be unusually air-stable both as a solid and in solution, but, in cases where the coordination of the alkene to the metal was poor, the active catalyst decomposes into inactive trinuclear iridium hydrides (Scheme 5),[23] thus requiring high loadings of pre-catalyst in order to produce high product yields.



Scheme 5 Decomposition of **4** under H_2 takes place when no alkene is coordinated to the metal.

In 1997, Pfaltz and co-workers prepared the first chiral mimic of Crabtree's catalyst, [Ir(cod)(N,P*)][PF_6], using a phosphinooxazoline (PHOX)[24] as a chiral N,P-chelating species.[25] The complex performed exceptionally in terms of enantioselectivity in the asymmetric hydrogenation of non-functionalized tri- and tetrasubstituted alkenes such as **S4** and **S5** (Scheme 6).[26] It did however, just like the achiral version, decompose during the reaction, and full conversion could not be obtained using less than 3 mol% catalyst.[27] Working from the conclusion drawn by Crabtree et al. that the catalyst deactivated due to poor alkene coordination, the extremely weakly coordinating counter-ion BAr_F^- was tested as a replacement for PF_6^-, forming complexes of the type [Ir(cod)(PHOX)][BAr_F] such as **5** and **6** (Scheme 6). Indeed, both BAr_F and other similar counter-ions, gave catalysts with higher turn-over frequency and stability, and consequently the catalyst loading could be decreased below 1 mol%, still being highly enantioselective (Scheme 6).[26,28] Additionally, the catalyst gained improved stability towards humidity and increased solubility in non-polar solvents.

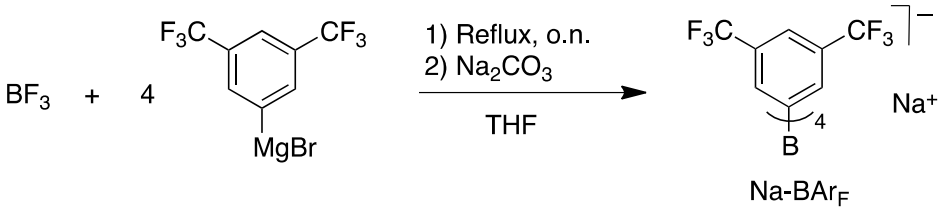


Scheme 6 The PHOX-ligands were first used in complexes of the type [Ir(cod)(PHOX)][BAr_F] such as **5** and **6** for the asymmetric hydrogenation of non-functionalized tri- and tetrasubstituted alkenes.

Due to the benefits of using BAr_F and its convenient preparation by quadruple alkylation of BF_3 with 3,5-ditrifluoromethyl-bromomagnesium-benzene[29] (Scheme 7), it has become the standard counter-ion to use with these catalytic systems.

Following the groundbreaking initial discoveries by Pfaltz, hundereds of chiral nitrogen-phosphorus, nitrogen-carbene and other ligands have been tested in the asymmetric hydrogenation as [Ir(cod)(N,X*)][BAr_F] complexes (X = phosphorus or heterocyclic carbene).[2e,3a,3d] Highly selective catalysts have

been prepared for a wide range of sterically and electronically different alkene substrates.[3c]

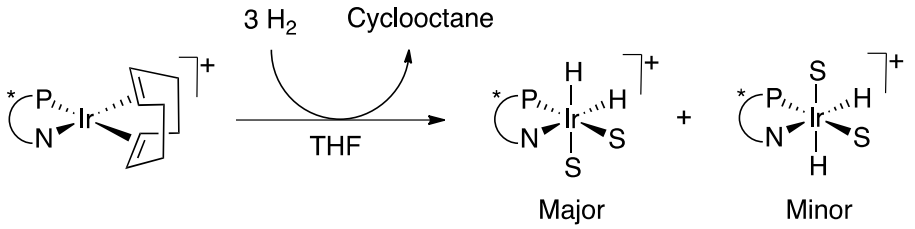


Scheme 7 Preparation of $NaBAr_F$.

1.5 Mechanistic aspects

This section aims to describe the fundamental mechanics of catalytic hydrogenation using $[Ir(cod)(N,P)][BAr_F]$ complexes. For a discussion about the implications of the mechanism on selectivity, see section 8.

As noted by Crabtree for cations of the type $[Ir(cod)LL']^+$, oxidative addition of H_2 and subsequent alkene coordination are feasible,[30] especially for Crabtree's catalyst itself.[21] The catalyst resting state was proposed to be $[IrH_2LL'(alkene)X]^+$ where X = solvent or alkene or H_2.[22b] Additionally, it was suggested that the rate-determining step in the catalytic cycle is the migratory insertion and that the high (+3) oxidation state of the complex is one reason for the exceptional stability of these catalysts towards oxidation.[22b] Despite thorough studies of the $[Ir(cod)LL'][PF_6]$ systems, mechanistic details proved to be hard to elucidate, mainly due to the high catalytic activity of the systems. Meuwly, Pfaltz and co-workers performed the first studies on the addition of dihydrogen to a chiral version, $[Ir(cod)(N,P)][BAr_F]$ carrying a PHOX bidentate ligand.[31] ^1H NMR revealed that in THF, at 0 °C and under an atmosphere of H_2, cyclooctadiene was quickly hydrogenated to form complexes of the type $[Ir(H)_2(N,P)(THF)_2]^+$. As shown in Scheme 8, hydrides arrange themselves *trans* to the oxazoline nitrogen and to one of the solvent molecules. In dichloromethane, a complex mixture of hydridic metal complexes was observed but DFT calculation indicated that similar structures were favorable.

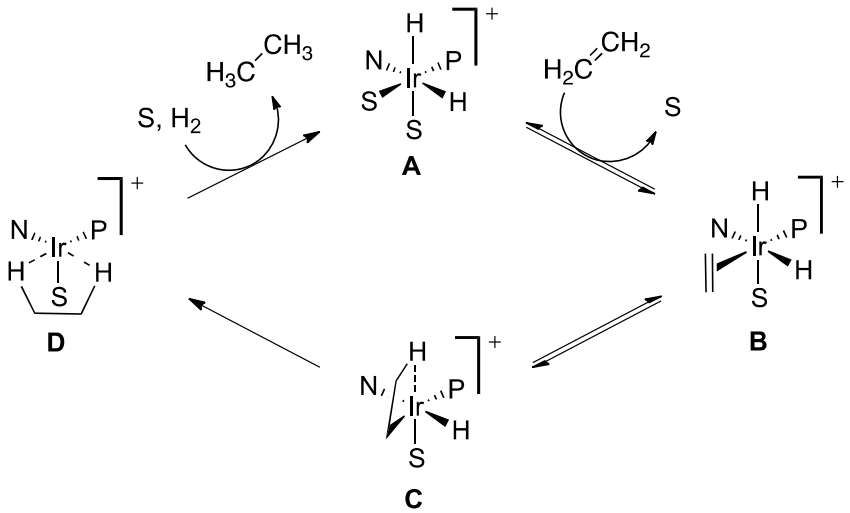


Scheme 8 Activation of $[Ir(cod)(N,P)][BAr_F]$ by H_2 in THF generates a pair of isomers of $[Ir(H)_2(N,P)(THF)_2][BAr_F]$. The BAr_F^- counter-ion has been omitted for clarity.

The most straightforward catalytic hydrogenation cycle starting from $[Ir(H)_2(N,P)S_2]^+$ would be substitution of an alkene to form $[Ir(H)_2(N,P)(alkene)X]^+$, where X = solvent or H_2, followed by migratory insertion and reductive elimination to release the product alkane. Such a reaction pathway, analogous to the case of alkene hydrogenation by $[Rh(diene)(P,P)]^+$,[32] was indicated by Dieteker and Chen.[33] They studied gas-

phase reactions of [Ir(cod)(PHOX)][BAr_F], H_2 and styrene using ESI-MS/MS and found that when isolating the hydrogenation product cation $[Ir(PHOX)(PhEt)]^+$ and colliding it with argon, $[Ir(PHOX)(styrene)]^+$ was the major species, thus showing that the reaction was reversible in the gas phase. Observation of cations with masses corresponding to $[Ir(H_2)(PHOX)(styrene)]^+$ and $[Ir(H_2)_2(PHOX)(styrene)]^+$ implied that oxidation states of iridium of both +3 and +5 were possible, but collisions of $[Ir(PHOX)(styrene)]^+$ with D_2 gave additional masses corresponding to d_1-$[Ir(PHOX)(styrene)]^+$ and d_2-$[Ir(PHOX)(styrene)]^+$. Since only mono- and di-deuterated complexes could be detected, a mechanism involving more than two hydrides (such as Ir(V)) was deemed unlikely and an Ir(I)/Ir(III) catalytic cycle was proposed.

A similar, dihydride catalytic cycle, was proposed by Buriak and co-workers for complexes of the type [Ir(cod)(IMes)(P(^{n}Bu)$_3$)][BAr_F], (IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene) i.e. achiral modifications of Crabtree's catalyst.[34] *Para*-hydrogen induced polarization (PHIP) ^{1}H NMR experiments indicated that a dihydride mechanism was operating but the authors concluded that other mechanisms could not be ruled out.[35] Roseblade and Pfaltz also considered a related mechanism,[36] starting from the oxidative addition product $[Ir(H)_2(N,P)S_2]^+$ (Complex **A**, Scheme 9). Complex **A** undergoes substitution by an alkene *trans* to the phosphorus, resulting in complex **B**. Alkene coordination to form **B** is usually feasible, the hydrogenation using [Ir(cod)(PHOX)][BAr_F] has proven to be close to zero order with respect to alkene for a trisubstituted alkene.[27] Hydride migration to the alkene then gives the σ-alkyl **C** which subsequently undergoes reductive elimination to form **D**. Oxidation by a new molecule of H_2 and solvent coordination then regenerates **A**.

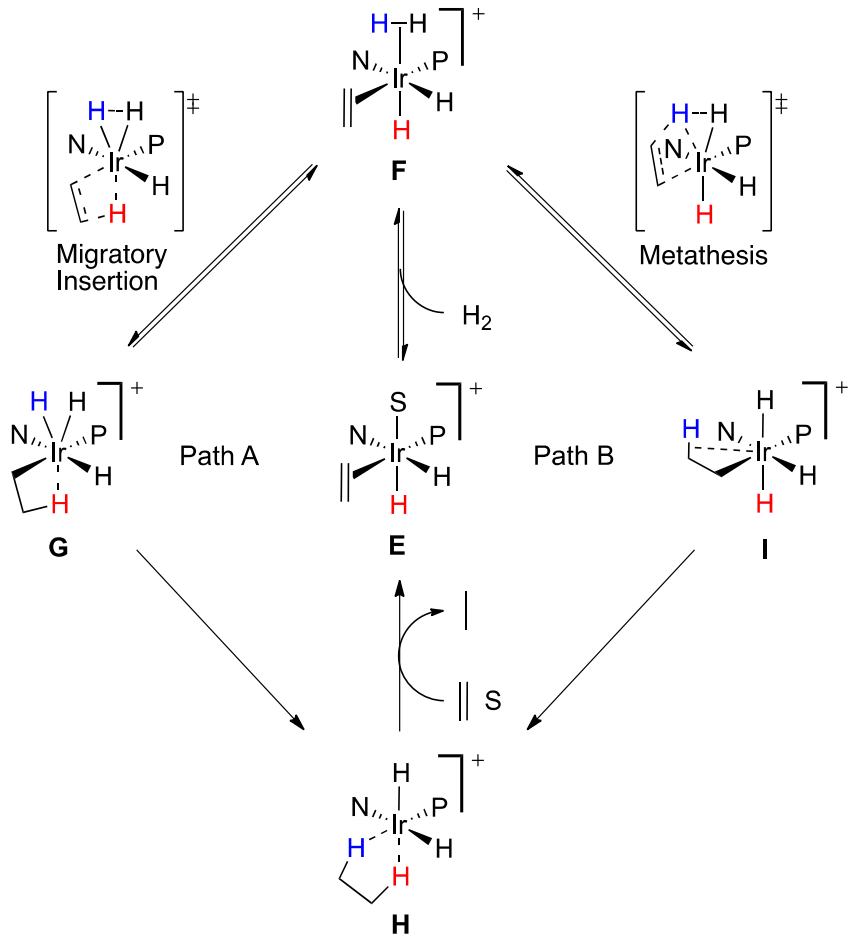


Scheme 9 Alkene hydrogenation by an Ir(I)/Ir(III) dihydride catalytic cycle. The BAr_F^- counter-ion has been omitted.

DFT studies starting from complexes of the type $[Ir(H)_2(N,P)(alkene)X]^+$ (X = solvent or H_2, alkene = ethene) (Complex **B**, Scheme 9) with a truncated N,P ligand (N,P = MeN=CH–CH=CH–PMe_2) prompted Brandt and co-workers to suggest an alternative mechanism.[37] Calculations on this system (S = CH_2Cl_2) indicated that both migratory insertion and reductive elimination had high energy-barriers. Exchanging the coordinated CH_2Cl_2 for a η^2-H_2 gave a

complex, $[Ir(H)_2(H_2)(N,P)(alkene)]^+$, (Complex **F**, Scheme 10). Starting from **F**, both migratory insertion and reductive elimination were much more feasible. Additionally, the migratory insertion takes place simultaneously with the oxidative addition of the coordinated dihydrogen molecule to form **G** (Scheme 10, Path A). The Ir(V) species **G** then quickly undergoes reductive elimination to form **H**, which by coordination of alkene and a solvent molecule reforms **E**, which was suggested as the catalyst resting state. The migratory insertion (step **F** $\rightarrow$ **G**), calculated as the only significant energy barrier was proposed to be the rate-determining step. However, kinetic studies showed that the reaction was first-order in hydrogen-pressure, a result that was later confirmed by Pfaltz and co-workers, for pressures up to 50 bar.[28] Since the substitution of CH_2Cl_2 by H_2 was calculated to be thermodynamically neutral, the authors reasoned that the reaction is probably endergonic and could be the rate-determining step. It is also possible however, that the reaction is limited by H_2 diffusion, at least in cases where the alkene hydrogenation is fast, as reported by Blackmond and co-workers.[38] In their study, mass-transfer (i.e. convection) was shown to be a more important parameter to control than the gas pressure over the solution as it had greater impact on the concentration of H_2 in solution.

Burgess and co-workers have studied the effect of hydrogen pressure in the asymmetric hydrogenation using $[Ir(cod)(N,C)][BAr_F]$ complexes (C = N-heterocyclic carbene). For some alkene substrates, no pressure-dependence could be observed, while for others, pressure had significant influence on both the reaction rate and enantioselectivity.[39]



Scheme 10 Hydrogenation of an alkene starting from a η^2-H_2 complex **F** and going through an Ir(III)/Ir(V) catalytic cycle. The reaction has been suggested to go through either a concerted migratory insertion-oxidative addition (Path A) or a hydrogen metathesis (Path B). The BAr_F counter-ion has been omitted for clarity.

Burgess, Hall and co-workers performed DFT calculations on the mechanism of the Ir-catalyzed asymmetric hydrogenation using their N,C-ligated system.[40] The lowest energy pathway they found (Scheme 10, Path B) was similar to the one proposed by Brandt et al. Starting also from complex **F**, the first hydrogen is transferred to the alkene from the coordinated dihydrogen molecule by metathesis. The Ir(V) σ-alkyl complex **I** thus formed then undergoes reductive elimination to yield **H**.

Calculations made in both gas- and solvent field on the full catalytic system and starting from complex cations of the type $[Ir(H)_2(N,P)(alkene)X]^+$ revealed that the lowest energy barriers were available when X = H_2 and that the system followed an Ir(III)/(V) pathway (Scheme 10).[41] It also indicated that the migratory insertion (Path A) was lower in energy than the metathesis (Path B) for this type of catalyst. The Ir(I)/(III) pathways calculated for X = CH_2Cl_2 and empty coordination site were more than 10 kcal/mol higher in energy. Analogous results were obtained by Hopmann and Bayer who studied a similar $[Ir(H)_2(N,P)(alkene)X]^+$ system.[42]

To conclude the mechanistic discussions, while much relevant experimental data is still lacking, several DFT studies indicates that the alkene

hydrogenation of non-functionalized alkenes by chiral mimics of Crabtree's catalyst proceeds by an Ir(III)/Ir(V) tetrahydride mechanism. It is likely, as noted by several authors, that the mechanism can be dependent on the substrate and the hydrogen concentration. For instance, chelating substrates can easily be envisioned to disfavor the formation of the Ir-dihydride-dihydrogen complex (**F**, Scheme 10) and instead form a dihydride complex with a chelating alkene (i.e. replacement of S by a coordinating functional group from the alkene in complexes **B** and **C**, Scheme 9).

2 Aryl and alkyl substituted alkenes

2.1 Trisubstituted alkenes

Aryl/alkyl trisubstituted alkenes (Figure 2) have become the benchmark substrates for assessing the efficiency of new catalytic systems in the hydrogenation of minimally functionalized olefins. In general the asymmetric reduction of 1,2-diarylalkenes (such as *trans* α-methylstylbene **S4**) proceeds with higher enantioselectivities than monoarylated alkenes (i.e. *E*-2-(4-methoxyphenyl)-2-butene **S6**), for which only a limited number of catalysts provides high levels of enantioselectivity.[2d,e,3a,3c,d,36,43] On the other hand, the geometry of the double bond also affects the catalytic outcome. Thus, the hydrogenation of *E*-olefins affords higher enantioselectivities than that of *Z*-olefins. The lower enantioselectivities usually achieved in the hydrogenation of *Z*-isomers can be attributed to an *Z*/*E* isomerization process to form the more stable *E*-alkene, which usually leads to the formation of the opposite enantiomer of the hydrogenated product.[2d,e,3a,3c,d,36,43] Nevertheless, if isomerization can be suppressed the fact that the sense of enantioselectivity is controlled by the olefin geometry can be used to gain access to both enantiomers of the hydrogenated product with the same catalyst. However, this also represents a limitation because mixtures of *Z*/*E* isomers should be avoided to achieve high enantioselectivities. *Z*-2-(4-methoxyphenyl)-2-butene **S7** and dihydronaphthalenes (i.e. 7-methoxy-4-methyl-1,2-dihydronaphthalene **S8**) are frequently used to study the ligand scope in the hydrogenation of *Z*-alkenes. Dihydronaphthalenes have recently received much attention because the corresponding chiral tetraline motif can be found in numerous natural products.[44]

Trialkyl substituted alkenes have yet to be studied in depth. The reasons for the lack of reports are likely because of the difficulty to develop methods for ee-determination and the lack of an aryl group that could serve to direct the reaction via for instance a π-stacking interaction between the substrate and the chiral catalyst. Nevertheless, Pfaltz and coworkers have shown that Ir-N,P catalysts are able to hydrogenate this substrate class with high efficiency (ee's up to 95% in the hydrogenation of 1-methoxy-4-(3-methyl-pent-3-enyl)-benzene **S9**).[45]

More recently, the substrate scope has been extended to the use of 1,1-diaryl or 1,1,2-triaryl substituted substrates (i.e. 1-(1,2-diphenyl-vinyl)-3,5-dimethyl-benzene **S10**) and cyclic dienes (i.e. 1,5-dimethyl-cyclohexa-1,4-diene **S11**). The former substrate class provides an easy entry point to

diarylmethine chiral centers, which are present in several important drugs and natural products.[46]

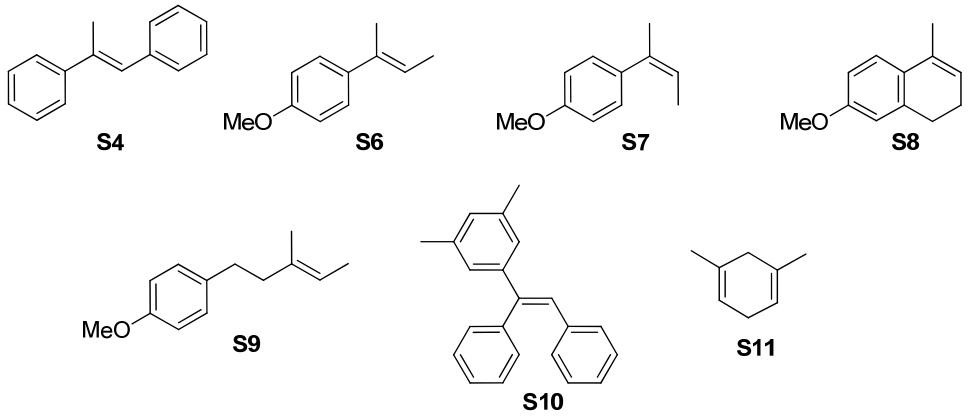
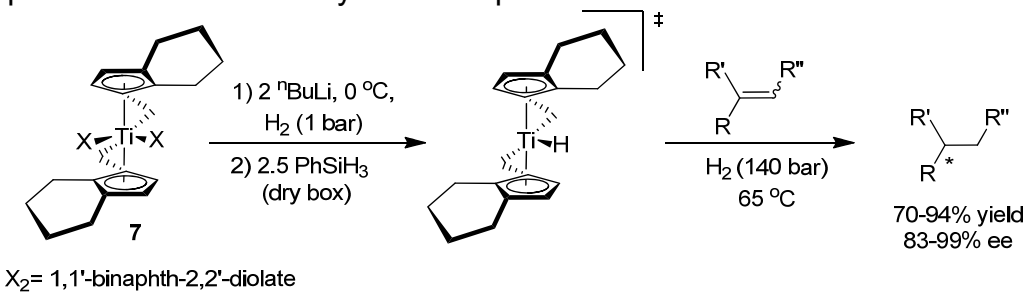


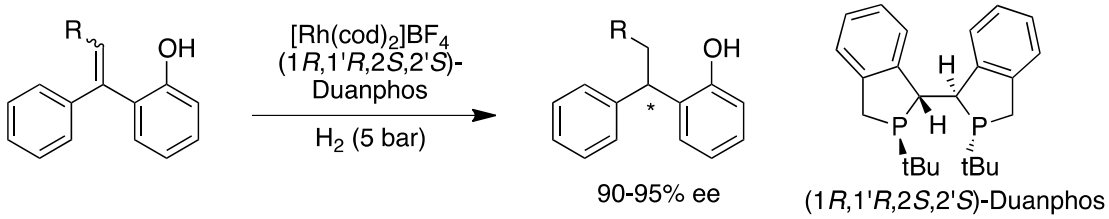
Figure 2 Representative aryl-alkyl, alkyl-alkyl and aryl-aryl trisubstituted alkenes.

The first successful application in the asymmetric reduction of minimally functionalized olefins was reported by Buchwald's group in 1993.[47] They reported the application of a chiral titanocene catalyst precursor **7** that provided high enantioselectivities (ee's ranging from 83% - >99%; Table 1, entry 1) in the hydrogenation of a limited range of *E*- and *Z*-trisubstituted olefins (Scheme 11). However, they required high pressure (140 bar of H_2), high temperature (65 ºC) and long reactions times (several days) to achieve full conversions. Moreover, the catalyst is highly unstable and for its preparation the use of a dry-box is required.



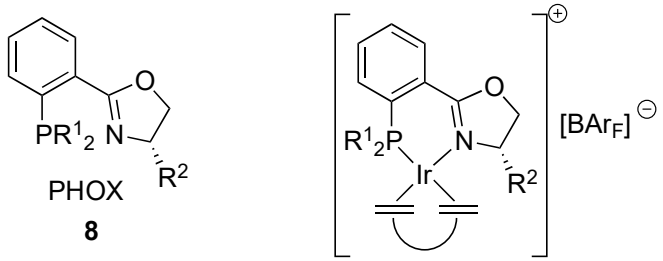
Scheme 11 Asymmetric hydrogenation of trisubstituted olefins using chiral titanocene complex **7**.

The application of Rh- and Ru-catalyst precursors modified with phosphorus ligands to the asymmetric reduction of minimally functionalized trisubstituted olefins has not been accomplished with good enantioselectivities.[48] Nevertheless, very recently Wang's group has reported the successful application of [Rh(cod)(1*R*,1'*R*,2*S*,2'*S*-Duanphos)]BF_4 in the asymmetric hydrogenation of trisubstituted olefins in various *E*/*Z*-mixtures (Scheme 12).[49] However, the presence of a directing hydroxyl group at the *ortho* position of a phenyl substituent of the substrate is required. The authors therefore found that coordination of the phenol to Rh plays a crucial role in the enantiodiscrimination process. Thus, for instance, the hydrogenation of methyl ether analogues led to lower activities and enantioselectivities (ee's < 20%).



Scheme 12 Asymmetric hydrogenation of trisubstituted olefins containing a directing hydroxyl group using Rh-Duanphos catalysts.

As already mentioned in the introduction, a breakthrough in the hydrogenation of minimally functionalized olefins came in 1997 when Pfaltz and coworkers used phosphine-oxazoline ligands PHOX **8**[26-27,50] (Figure 3; R^1= Ph, *o*-Tol and R^2= ^{i}Pr, ^{t}Bu, $CH_2{}^t$Bu) to design [Ir(cod)(PHOX)][BAr_F], a chiral analogue of Crabtree's catalyst.[30] These catalysts, in contrast to previous titanocene complex **7**, required lower pressures (50 bar of H_2), temperatures (rt) and reaction times (full conversions in 2 hours) and have been successfully used for the asymmetric hydrogenation of a limited range of alkenes (mainly trisubstituted *E*-1,2-diaryl olefins including those bearing a furyl and a thiophenyl heterocyclic substituents, ee's up to 98%; Table 1, entry 2).[26-27,43,45,51] These catalysts, however, afforded lower levels of enantioselectivity in the hydrogenation of more demanding *Z*-olefins (i.e. 42% ee in the hydrogenation of **S7**; Table 1, entry 2). The authors found that enantioselectivity is affected by the ligand parameters and the best enantioselectivities were obtained with the ligand that combines a *tert*-butyl on the oxazoline and a bis(*o*-tolyl)phosphanyl group (ligand **8a**, Table 1, entry 2).



a: R^1 = *o*-Tol R^2 = ^{t}Bu
b: R^1= Ph R^2= $CH_2{}^t$Bu
c: R^1= Mes R^2= ^{t}Bu
d: R^1= Ph R^2= ^{t}Bu

Figure 3 Phosphine-oxazoline PHOX ligands **8**.

Since then, the composition of the ligands has been extended by replacing the phosphine moiety with other phosphorus-donor group analogues (i.e. phosphinite, carbene and phosphite) and the oxazoline moiety with other N-donor groups (such as pyridine, thiazole and oxazole). The structure of the chiral ligand's backbone has also been modified. More recently, the use of iridium catalysts containing P,S and P,O heterodonor ligands have been presented. All these modifications have led to the discovery of new ligands that have considerably broadened the scope of Ir-catalyzed hydrogenation of minimally functionalized trisubstituted olefins and the enantioselective reduction of aryl/heteroayl-alkyl *E*- and *Z*-olefins, triarylsubstituted olefins and pure alkyl olefins can be efficiently achieved.

In the following sections, we compile the most representative catalytic data reported in the Ir-catalyzed hydrogenation of minimally functionalized trisubstituted olefins grouped according to the type of ligands. We also discuss their application to the synthesis of more complex molecules.

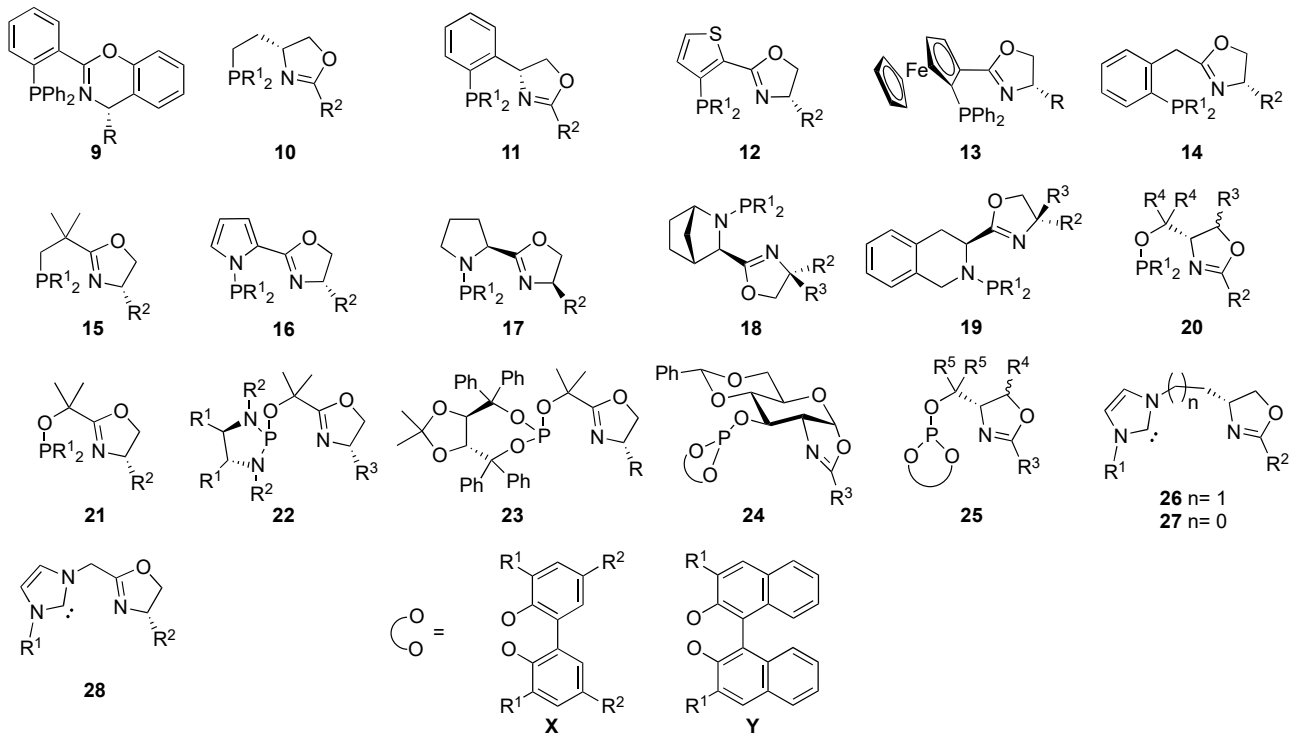
2.1.1 Phosphorus/carbene-oxazoline ligands

Inspired by the work of Pfaltz and coworkers using PHOX ligands, several other successful phosphorus/carbene-oxazoline compounds have been developed for the Ir-catalyzed asymmetric hydrogenation (Figure 4). Most of them are phosphine-oxazoline, N-phosphine-oxazoline and phosphinite-oxazoline ligands and to a lesser extent phosphite/phosphoroamidite-oxazoline and carbene-based ligands.

Phosphine-oxazoline ligands

In 2001, Kündig and coworkers reported a modification in the oxazoline moiety of the PHOX ligands, with the development of phosphine-benzoxazine analogues **9** (Figure 4, R = ^{t}Bu, ^{i}Pr).[52] As observed with the PHOX ligands, the presence of bulky *tert*-butyl groups at the oxazine ring lead to the highest enantioselectivities. However, these ligands provided somewhat lower enantioselectivities (ee's up to 90% for substrate **S4**) than the PHOX ligands **8**.

Burgess' group reported the synthesis of ligands **10** and applied them in the Ir-catalyzed hydrogenation of several trisubstituted aryl-alkyl alkenes (Figure 4, R^1 = Ph, *o*-Tol, R^2 = Me, ^{t}Bu, 1-adamantyl, CPh_3).[53] They found that enantioselectivities depend strongly on both the ligand parameters and the substrate type. Thus, while for *Z*-isomer **S7** the best enantioselectivities were obtained with a *tert*-butyl group at the oxazoline and a diphenylphosphanyl group (ligand **10a**; Table 1, entry 3), for stilbene derivatives the presence of a bis(*o*-tolyl)phosphanyl group is needed for ee's to be high (ligand **10b**; Table 1, entry 3). These ligands proved to be superior to the PHOX ligands in the hydrogenation of *Z*-alkenes (i.e. 75% ee for substrate **S7**; Table 1, entries 2 vs 3), while ee's for the hydrogenation of *E*-alkenes were lower (ee's up to 94% for *trans*-α-methylstilbene **S4**; Table 1, entries 2 vs 3). Later, Zhang and coworkers further modified ligands **10**, by introducing again the *ortho*-phenylene tether backbone motif of the PHOX ligands. [54] New ligands **11** (Figure 4, R^1= Ph, Cy, and R^2= ^{t}Bu, 1-Ad, $CHPh_2$, 3,5-$^{t}Bu_2$-Ph) proved to be excellent in the hydrogenation of *trans*-α-methylstilbene derivatives (ee's up to 99%). Again the presence of bulky substituents at both oxazoline and phosphine moieties (ligand **11a**) led to the highest enantioselectivities (Table 1, entry 4).



10a R^1 = Ph R^2 = ^{t}Bu
10b R^1 = *o*-Tol R^2 = ^{t}Bu

11a R^1 = Cy R^2 = ^{t}Bu

12a R^1 = Cy R^2 = ^{t}Bu

13a R = Me
13b R = ^{t}Bu

14a R^1 = Ph R^2 = ^{i}Pr

15a R^1 = Xyl R^2 = ^{t}Bu
15b R^1 = *o*-Tol R^2 = ^{t}Bu
15c R^1 = Cy R^2 = ^{i}Pr

16a R^1= *o*-Tol R^2= ^{t}Bu
16b R^1 = Cy R^2= ^{t}Bu
16c R^1= Ph R^2= ^{t}Bu

18a R^1 = Ph R^2 = Ph R^3 = Ph
18b R^1 = *o*-Tol R^2 = H R^3 = ^{i}Pr
18c R^1 = *o*-Tol R^2 = Ph R^3 = Ph
18d R^1 = Ph R^2 = H R^3 = ^{t}Bu

20a R^1 = Ph R^2 = Ph R^3 = (*S*)-Me R^4 = Bn
20b R^1 = Ph R^2 = 3,5-Me_2-Ph R^3 = (*S*)-Me R^4 = Bn
20c R^1 = Ph R^2 = Ph R^3 = (*R*)-Me R^4 = Bn
20d R^1 = *o*-Tol R^2 = ^{t}Bu R^3 = H R^4 = Me

21a R^1 = *o*-Tol R^2 = ^{t}Bu

24a Phosphite = **X** R^1 = $SiMe_3$ R^2 = H R^3 = Ph
24b Phosphite = **X** R^1 = ^{t}Bu R^2 = ^{t}Bu R^3 = Ph

25a Phosphite = **X** R^1 = ^{t}Bu R^2 = ^{t}Bu R^3 = Ph R^4 = H R^5 = Me
25b Phosphite = (*S*)-**Y** R^1 = ^{t}Bu R^3 = Ph R^4 = H R^5 = Ph
25c Phosphite = **X** R^1 = ^{t}Bu R^2 = ^{t}Bu R^3 = 2,6-Me_2-Ph R^4 = H R^5 = Me
25d Phosphite = **X** R^1 = ^{t}Bu R^2 = ^{t}Bu R^3 = 4-CF_3-Ph R^4 = H R^5 = Me

26a R^1 = 2,6-^{i}Pr$_2$-Ph R^2 = 1-Ad

Figure 4 Phosphorus/carbene-oxazoline ligand families developed for the Ir-catalyzed asymmetric hydrogenation of aryl/alkyl trisubstituted olefins.There is a mistake in the description of ligand 25b; R1 should be H rather than tBu.

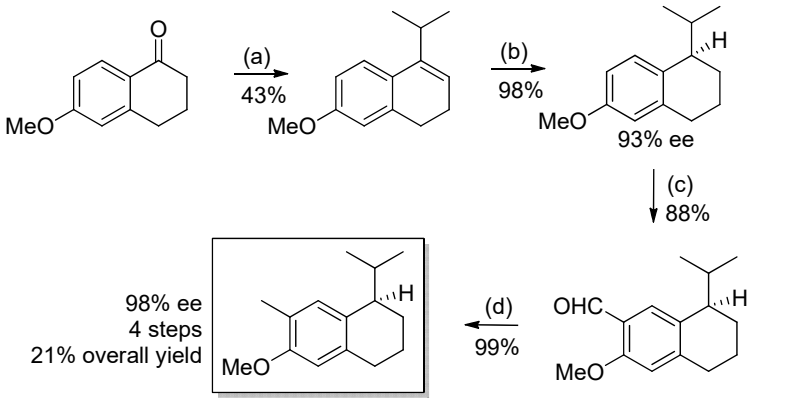
In 2003, Cozzi and coworkers reported the application of ligands **12** (Figure 4, R^1 = Ph, *o*-Tol, Cy, R^2 = ^{i}Pr, ^{t}Bu), in which the phenyl ring of the PHOX has been replaced by thiophene, in the hydrogenation of *trans*-α-methylstilbene (ee's up to 99%).[55] As for ligands **11**, the best enantioselectivity was obtained with the ligand that contains a *tert*-butyl group at the oxazoline and a biscyclohexylphosphanyl group (ligand **12a**; Table 1, entry 5).

Li and coworkers modified the PHOX ligands by introducing a ferrocenyl group instead of the phenyl ring (ligands **13**; Figure 4, R= Me, ^{i}Pr, ^{t}Bu, Ph, Bn).[56] Interestingly, the best enantioselectivities were obtained with

the ligand that contains a small methyl substituent at the oxazoline moiety. These ligands proved to be superior to the PHOX ligands in the hydrogenation of the 4-methyl-1,2-dihydronaphthalene **S8** (89% ee) in which the alkene has *Z*-configuration, while ee's for the hydrogenation of *E*-alkenes were lower (ee's up to 89% for *trans*-α-methylstilbene **S4**).

In 2008, based on the PHOX ligands, Hou and coworkers developed new phosphine-oxazoline ligands **14** in which the flat *ortho*-phenylene tether is replaced by benzylic type group (Figure 4; R^1 = Ph, *o*-Tol, *p*-Tol, R^2 = Me, ^{i}Pr, ^{t}Bu).[57] These ligands were successfully applied in the Ir-catalyzed asymmetric hydrogenation of a range of *E*- and *Z*-stilbene derivatives (ee's up to 97% and 90%, respectively; Table 1, entry 6). The best enantioselectivities were achieved with the ligand that contains an isopropyl oxazoline substituent and a diphenylphosphanyl group (ligand **14a**; Table 1, entry 6).

Pfaltz and coworkers have further modified PHOX ligands by replacing the *ortho*-phenylene tether by a branched alkyl chain. Ligands **15** (Figure 4, R^1= Ph, *o*-Tol, Xyl, R^2= ^{i}Pr, ^{t}Bu, Bn) provided higher enantioselectivities in the hydrogenation of trisubstituted *E*- and *Z*-aryl/alkyl alkenes than the PHOX ligands (ee's up to 98% for *E*-isomers and 96% for *Z*-isomers).[44] Enantioselectivities were again best using ligand **15a** with bulky substituents at both oxazoline and phosphine moieties (Table 1, entry 7). The potential utility of these new ligands was demonstrated in the synthesis of (*R*)-7-demethyl-2-methoxycalamenene, an antitumor natural product (Scheme 13).



(a) ^{i}PrMgCl (1.3 eq), $ZnCl_2$ (0.1 eq), THF, then *p*-TsOH (cat.), I_2 (cat), toluene, 110 ºC, 16 h; (b) catalyst Ir-**15a** (0.5 mol%) H_2 (5 bar), CH_2Cl_2, 4 h; (c) *N*-methylformanilide, $POCl_3$, CH_2Cl_2, 40 ºC, 48 h (d) Pd/C (10%), H_2 (100 bar), 24 h.

Scheme 13 Total synthesis of (*R*)-7-demethyl-2-methoxycalamenene.

N-Phosphine-oxazoline ligands

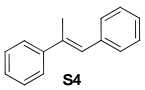
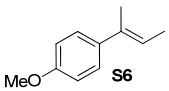
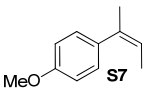
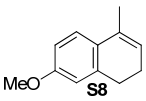
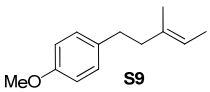
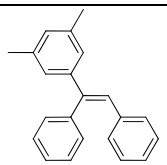
In 2001, the Pfaltz's group modified the PHOX ligands by introducing a pyrrole group.[58] These new ligands **16** proved to be highly efficient in the hydrogenation of trisubstituted alkenes (Figure 4, R^1= Ph, *o*-Tol, Cy; R^2 = ^{i}Pr, ^{t}Bu). Enantiomeric excesses surpassed those previously obtained with the PHOX ligands (i.e. ee's up to 99% for *E*-stilbenes and up to 92% for 4-methyl-1,2-dihydronaphthalenes; Table 1, entry 8). The best enantioselectivities were obtained with ligands that contain a *tert*-butyl group in the oxazoline moiety

and either *ortho*-tolyl or cyclohexenyl P-substituents (ligands **16a** and **16b**, respectively).

Later, Gilbertson and coworkers developed the proline derived N-phosphine-oxazoline ligands **17** (Figure 4, R^1 = Ph, *o*-Tol, R^2 = ^{i}Pr, ^{t}Bu) that provided lower enantioselectivities than previous pyrrole-based ligands **16** (ee's up to 94% for *E*-stilbenes and up to 64% for 4-methyl-1,2-dihydronaphthalenes).[59] Again, the highest enantioselectivities were achieved using a bulky *tert*-butyl oxazoline moiety.

Andersson's group developed ligands **18** and **19** for the Ir-catalyzed hydrogenation of alkenes (Figure 4, **18**; R^1 = Ph, *o*-Tol, Cy, R^2 = H, ^{t}Bu, Ph, R^3 = H, Ph and **19**; R^1 = Ph, R^2 = H, ^{i}Pr, Ph, R^3 = H, ^{i}Pr, Ph).[60] Ligands **18**, containing a chiral rigid bicyclic backbone, provided much higher enantioselectivities than ligands **19**, with a more flexible backbone. The authors found that ligand **18a** with phenyl substituents at R^1, R^2 and R^3 positions provided the best enantioselectivities (ee's up to 99% for *E*-isomers and 95% for 4-methyl-1,2-dihydronaphthalene **S8**; Table 1, entry 9).[60a] It should be pointed out that Ir-**18a** catalyst also provided enantioselectivities up to 80% in the hydrogenation of triarylsubstituted olefins (Table 1, entry 9).[61] Additionally, the catalysts afforded for the first time high enantioselectivities in the hydrogenation of enol phosphinates,[62] vinyl silanes,[63] fluorinated olefins[64] and vinyl boronates[65] (*vide infra*).

Table 1 Enantioselectivities achieved using selected ligands in the asymmetric hydrogenation of the most representative, weakly functionalized, trisubstituted olefins.

Entry	[M]/L	 S4	 S6	 S7	 S8	 S9	 S10
1	Ti (**7**)	>99	95	-	93	-	-
2	Ir-**8a**	97	61	42	-	87	-
3	Ir-**10a**	88 (94)[a]	80	75	-	-	-
4	Ir-**11a**	99	-	-	-	-	-
5	Ir-**12a**	99	-	-	-	-	-
6	Ir-**14a**	97	-	-	-	-	-
7	Ir-**15a**	98	90	96	96	-	-
8	Ir-**16a**	99	56 (75)[b]	59 (70)[b]	92	-	-
9	Ir-**18a**	98	99	-	95	-	80[c]
10	Ir-**20a**	99	99	89	71	-	-
11	Ir-**20b**	99	92	92	74	-	-
12	Ir-**20c**	97	98	88	85	-	-
13	Ir-**24a**	>99	99	78	-	-	-
14	Ir-**24b**	99	97	95	98	-	>99
15	Ir-**25a**	99	>99	92	96	-	-
16	Ir-**26a**	98	96	79	-	-	-
17	Ir-**29a**	96	-	-	-	-	-
18	Ir-**32a**	97	87	90	-	-	-

19	Ir-**33a**	>99	>99	98	92 (99)[d]	95	-
20	Ir-**39**	95	-	-	-	-	-
21	Ir-**41a**	94	81 (90)[e]	88	91	-	-
22	Ir-**42a**	93 (98)[f]	94	-	-	-	>99[c]
23	Ir-**43a**	>99	96	-	94	-	94[c]
24	Ir-**46a**	98	99	90	99	-	-
25	Ir-**59a**	99	99	94	86	-	99
26	Ir-**62a**	98	-	-	-	-	-
27	Ir-**62b**	99	-	-	-	-	-

[a] Using ligand **10b**. [b] Using ligand **16b**. [c] With substrate 1-(1,2-diphenyl-vinyl)-4-methyl-benzene. [d] Using ligand bearing bulky 2,4,6-tri-Me-Ph as R^2-substituent. [e] Using ligand **41b**. [f] Using ligand **42b**.

Phosphinite-oxazoline ligands

Two families of phosphinite-oxazoline ligands have been developed for this process. Phosphinite-oxazolines **20** (Figure 4, R^1 = Ph, *o*-Tol, Cy, R^2 = ^{t}Bu, Ph, ferrocenyl, 2-Naph; R^3 = H, Me, 3,5-Me_2-Ph and R^4 = Me, ^{i}Pr, ^{i}Bu, Bn), reported by Pfaltz's group soon after the development of the PHOX ligands **8**, constitute one of the most effective ligands for this transformation.[66] The results show that the presence of a second stereocenter in the oxazoline moiety (R^3= Me) has an effect on enantioselectivity.[66b] Enantioselectivities up to 99% for a range of *E*-isomers and up to 92% for *Z*-isomers were achieved. In general, the best enantioselectivities were achieved with ligands containing a methyl substituent at R^3, a benzyl substituent at R^4 and a phenyl at R^1. However, the correct substituent at the oxazoline and the configuration of the R^3 substituent depends on the substrate to be reduced. Thus, for *E*-trisubstitued olefins ee's are best with ligands **20a** (Figure 4; Table 1, entry 10) and **20b** (Table 1, entry 11), while for *Z*-olefins **S7** and **S8** the highest enantioselectivities were achieved using ligands **20b** and **20c**, respectively (Table 1, entries 11-12). These ligands not only provided excellent enantioselectivities in the hydrogenation of a broad range of both *E*- and *Z*-trisubstituted olefins but also in the reduction of α,β-unsaturated esters[66] and a limited range of more challenging terminal olefins (*vide infra*).[67] It should be pointed out that Börner's group has demonstrated that these catalysts can be used in propylene carbonate as an environmental friendly solvent.[68] This allowed the Ir-catalysts to be reused while maintaining the excellent enantioselectivities.

The second family of phosphinite-oxazoline ligands **21** (Figure 4, R^1 = Ph, *o*-Tol, R^2 = ^{i}Pr, ^{t}Bu) is based on previously phosphinite-oxazoline ligands **20** in which the alkyl chain is bonded to carbon 2 instead of carbon 4 of the oxazoline moiety, which shifts the chirality from the alkyl chain to the oxazoline substituent.[69] The scope of these ligands is narrower in comparison to the phosphinite-oxazoline ligands **20**, however, they are complementary. Ligands **21** provided high enantioselectivities for allylic alcohols (ee's up to 97%) and alkenes bearing heteroaromatic substituents (ee's up to 99%), for which the privileged ligands **20** provided moderate enantioselectivities (*vide infra*).

Phosphoroamidite/phosphite-oxazoline ligands

Despite the advantage of phosphite/phosphoroamidite ligands in asymmetric catalysis,[70] only a few phosphite/phosphoroamidite-oxazoline ligand-types have been applied in Ir-catalyzed asymmetric hydrogenation. The first reports were based on the use of chiral 1,2-bis-sulfonylamines and TADDOL to synthesize chiral phosphoroamidite-oxazolines **22** and phosphite-oxazolines **23**, respectively (Figure 4, **22**; R^1 = Ph, *p*-Tol, Cy, 3,5-Xyl-$(CH_2)_4$, R^2 = SO_2-R, 3-OMe-Ph, 4-OMe-Ph, 4-^{t}Bu-Ph, 4-Ph-Ph, 2-Naph, R^3 = ^{t}Bu, Ph and **23**; R= Ph, ^{t}Bu).[71] However, their substrate range limitation was higher and enantioselectivities and activities lower than their related phosphinite/phosphine-oxazoline ligands (i.e. **15**, **20** and **21**). They also required higher catalyst loadings (4 mol %) and higher pressures (100 bar) to achieve full conversions.

In 2008, it was reported the first successful application of phosphite-oxazoline ligands for this process. Pyranoside phosphite-oxazoline ligands **24** (Figure 4, R^3= Me, ^{t}Bu, ^{i}Pr, Ph and Bn), derived from D-glucosamine, provided excellent enantioselectivities in the hydrogenation of a wide range of *E*- and *Z*- trisubstituted olefins, including 4-methyl-1,2-dihydronaphthalenes and triarylsubstituted alkenes (Table 1, entries 13 and 14).[72] The best enantioselectivities were obtained with ligands that contain a phenyl oxazoline substituent and either an *ortho* disubstituted trimethylsilyl biphenyl phosphite moiety (for *E*-isomers, ee's up to 99%; ligand **24a**, entry 13) or a tetra *tert*-butyl biphenyl phosphite moiety (for *Z*-isomers and triarylsubstituted alkenes, ee's up to 98% and >99%, respectively; ligand **24b**, entry 14). The effectiveness of this ligand family extends to the use of more challenging 1,1-disubstituted olefins and also to the use of olefins containing a neighboring polar group (*vide infra*). DFT calculations on this system agree with an Ir(III/V) catalytic cycle with migratory insertion of a hydride as selectivity-determining step (*vide supra*).

Soon after, biaryl phosphite-oxazoline ligands **25** (Figure 4, R^3= Ph, 4-Me-Ph, 4-CF_3-Ph; R^4= H, Me and R^5= H, Me), which are based on previous phosphinite-oxazoline ligands **20**, were successfully applied in the hydrogenation of a range of *E*- and *Z*-trisubstituted olefins.[73] The results indicated that introducing a biaryl-phosphite moiety in the ligand design was highly advantageous in terms of catalytic activity and substrate versatility. Therefore they provided higher enantioselectivities and activities for a wider range of range of alkenes, including *E*- and *Z*-trisubstitued olefins (ee's up to >99% for *E*-isomers and up to 96% for *Z*-isomers; Table 1, entry 15), 1,1-disubstituted alkenes and alkenes containing a neighboring polar group (*vide infra*). The highest enantioselectivities for trisubstituted olefins were achieved with ligand **25a** (Figure 4), which contains bulky *tert*-butyl groups at the R^1 and R^2 positions of the biaryl phosphite moiety, a phenyl group at the oxazoline (R^3), a hydrogen at R^4 and methyl substituents at the R^5 positions (entry 15).

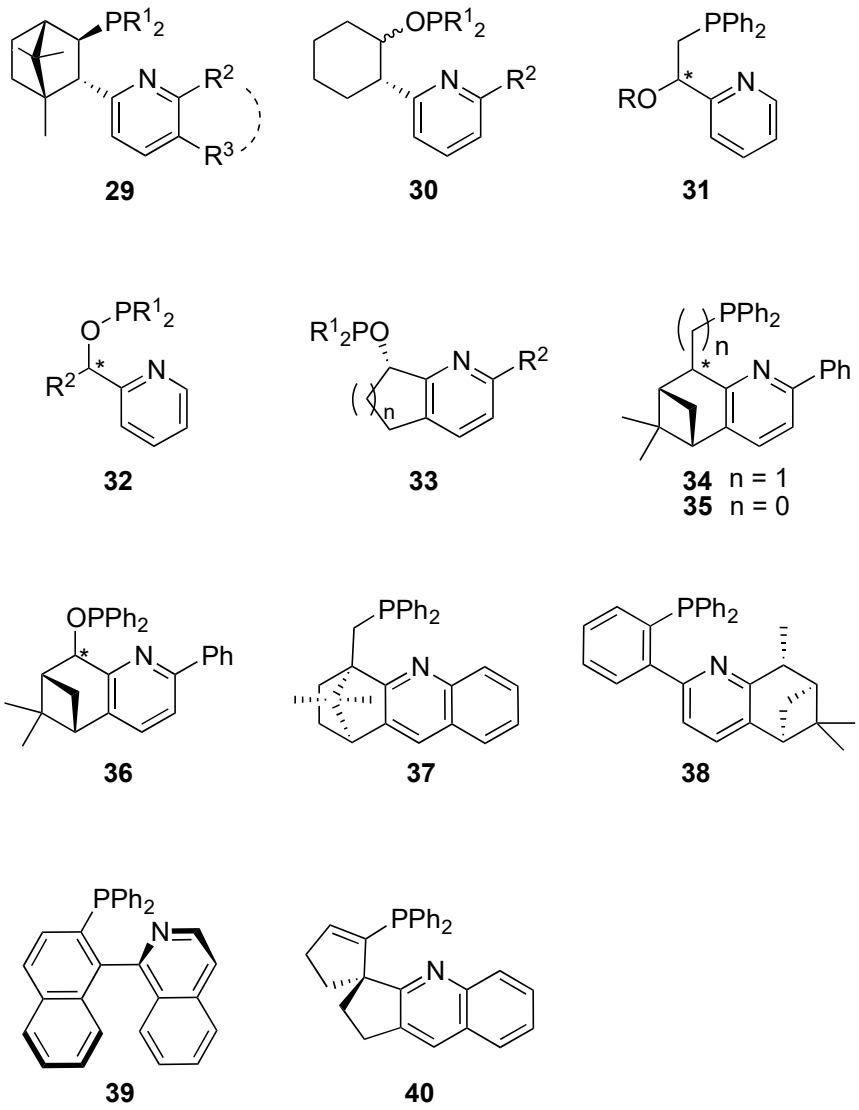
Carbene-oxazoline ligands

In 2003, Burgess and coworkers replaced the phosphine group in ligands **10** by a carbene moiety with the development of ligands **26** (Figure 4, R^1= ^{t}Bu, $CHPh_2$, Cy, 1-Ad, 2,4,6-Me_3-Ph, 2,6-$^i Pr_2$-Ph and R^2= 1-Ad, ^{t}Bu, Bn, Ph).[39]

These ligands were successfully applied in the reduction of a range of *E*-trisubstituted (ee's up to 98%; Table 1, entry 16) and *Z*-trisubstituted olefins (ee's up to 79%; Table 1, entry 16). This ligand library has also provided excellent enantioselectivities with substrates containing neighboring polar groups, which has been used in the synthesis of valuable chiral intermediates (*vide infra*). The results, which are comparable to those obtained with ligands **10**, indicated that the presence of a sterically hindered 1-adamanthyl group in the oxazoline and an *ortho*-disubstituted aryl group in the carbene moiety is necessary to achieve the highest levels of enantioselectivity (ligand **26a**, entry 16). In certain cases the carbene group also allowed a decrease in hydrogen pressure to 1 bar (i.e. in the reduction of *Z*-2-(4-methoxyphenyl)-2-butene **S7**). These excellent results prompted the development of other carbene-based ligands (ligands **27** and **28**).[74] Ligands **27** (Figure 4; R^1= ^{i}Pr and R^2= ^{t}Bu) and **28** (Figure 4; R^1= Me, ^{i}Pr, ^{t}Bu, 2,4,6-Me_3-Ph, Neopentyl and R^2= ^{t}Bu, Ph, 1-Ad, 2,6-Me_2-Ph), which are developed by replacing the P-moiety in privileged ligands **20** and **8** respectively, afforded lower levels of enantioselectivity.

2.1.2 Phosphorus-pyridine ligands

The intention to mimic the coordination sphere of Crabtree's catalyst motivated Knochel's group to prepare a new kind of N,P-ligand that incorporates a pyridine moiety as a N-donor. In this context they developed phosphine-pyridine ligands **29** (Figure 5; R^1= Ph, Cy; R^2= H, Ph; R^3= H; R^2-R^3= CH-CH=CH-CH), synthesized from readily available D-(+)-camphor, for the hydrogenation of trisubstituted olefins obtaining moderate-to-high enantioselectivities in the reduction of *E*-stilbenes (ee's up to 96%; Table 1, entry 17).[75] The results indicated that the best enantioselectivities were achieved with the ligand that contains a diphenylphosphanyl group and a quinoline moiety (ligand **29a**, entry 17).



29a R^1 = Ph R^2-R^3 = CH=CH-CH=CH

32a R^1 = ^{t}Bu R^2 = ^{t}Bu
32b R^1 = *o*-Tol R^2 = ^{t}Bu

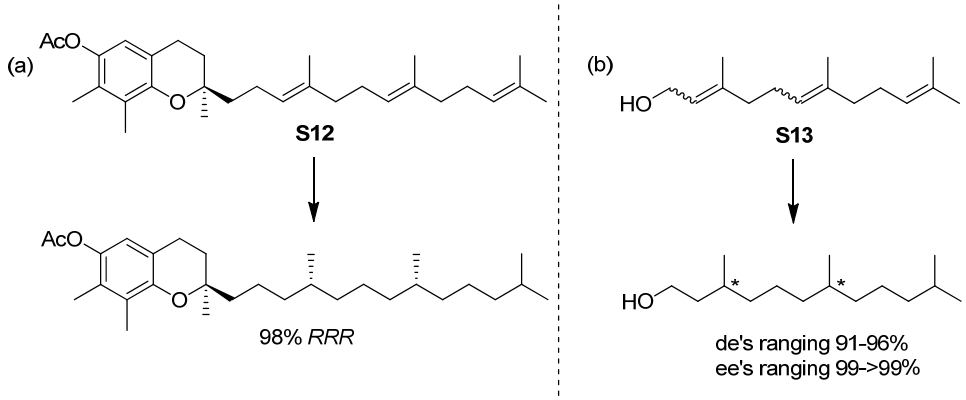
33a n = 1 R^1 = *o*-Tol R^2= Ph
33b n = 1 R^1 = ^{t}Bu R^2= Ph

Figure 5 Phosphorus-pyridine ligands developed for the Ir-catalyzed asymmetric hydrogenation of trisubstituted olefins.We think that a better alternative should be to drawn the ligands in 3 raws instead of 4. 1st raw: ligands 29-32; 2nd raw: ligands 33-37; 3rd raw: ligands 38-40.

Zhou and co-workers prepared phosphinite-pyridine ligands **30** (Figure 5, R^1= Ph, *o*-Tol; R^2= H, Me, ^{i}Pr), related to **29**, in which the camphor moiety is replaced by a cyclohexanol group.[76] This modification led to lower enantioselectivities in the reduction of *E*-stilbenes (ee's up to 93%), indicating the importance of the bulky camphor component for high enantioselectivity.

Pfaltz group has been very active in the development of phosphorus-pyridine ligands where they first prepared phosphine-pyridine ligands **31** (Figure 5).[77] These ligands contain several silyl ether substituents (R= Si(^{t}Bu)Me$_2$, Si(^{i}Pr)$_3$, Si(^{t}Bu)Ph$_2$) at the alkyl chain bridge with the aim to increase the rigidity and to provide a similar steric environment as the one in PHOX ligands **8**. Despite this, the catalytic performance was inferior to the previously commented PHOX ligands. In the same report the phosphinite version of **31** (ligands **32**; Figure 5, R^1= Ph, *o*-Tol, Cy, ^{t}Bu and R^2= Me, ^{t}Bu, Ph, CPh$_3$) were also tested.[77] The presence of a phosphinite moiety had a positive effect in terms of catalytic performance; i.e. the enantiomeric excess in the Ir-hydrogenation of *trans*-α-methylstilbene **S4** increased from 88% to 97%. The best enantioselectivities were obtained with ligand **32a** that contains *tert*-butyl substituents at both the phosphinite (R^1) and the alkyl backbone (R^2) moieties (Table 1, entry 18). Later, Moberg's group prepared a series of phosphinite-pyridine ligands related to **32**, but where a (–)-menthol moiety was introduced at the R^2 position. However these ligands were less enantioselective (ee's up to 80% in the reduction of *trans*-α-methylstilbene **S4**).[78]

Soon after, Pfaltz group developed a second generation of phosphinite-pyridine ligands **33** (Figure 5; R^1= Ph, *o*-Tol, Cy, ^{t}Bu ; R^2= H, Ph, Me; R^3= H, Me), with the aim to increase the rigidity in the alkyl bridge moiety.[79] This ligand family gave excellent enantioselectivities for a wide range of olefins (ee's up to >99%; Table 1, entry 19) including purely alkyl trisubstituted ones.[79a-c] In general, the enantioselectivity was highest with a phenyl substituent at R^2 position and bulky substituents at the phosphinite moiety (ligand **33a** and ligand **33b**). To obtain excellent enantiocontrol in the reduction of 7-methoxy-4-methyl-1,2-dihydronaphthalene, the introduction of large aryl substituents (i.e. 2,4,6-tri-Me-Ph) at R^2 are necessary (Table 1, entry 19).[79b] The utility of the catalytic system was demonstrated in the hydrogenation of γ-tocotrienyl acetate to obtain γ-tocopherol, a principal component of vitamin E,[80] resulting in enantioselectivity >98% for the *RRR* enantiomer (Scheme 14a).[45] Another synthetic application of Ir-**33a** can be found in the diastereo- and enantioselective hydrogenation of farnesol stereoisomers (Scheme 14b). By changing the double bond's geometry the same catalysts give access to the four stereoisomers of the product in high selectivity (diastereo- and enantioselectivity).[2d] See chapter 5 for a detailed discussion on the asymmetric hydrogenation of allylic alcohols.



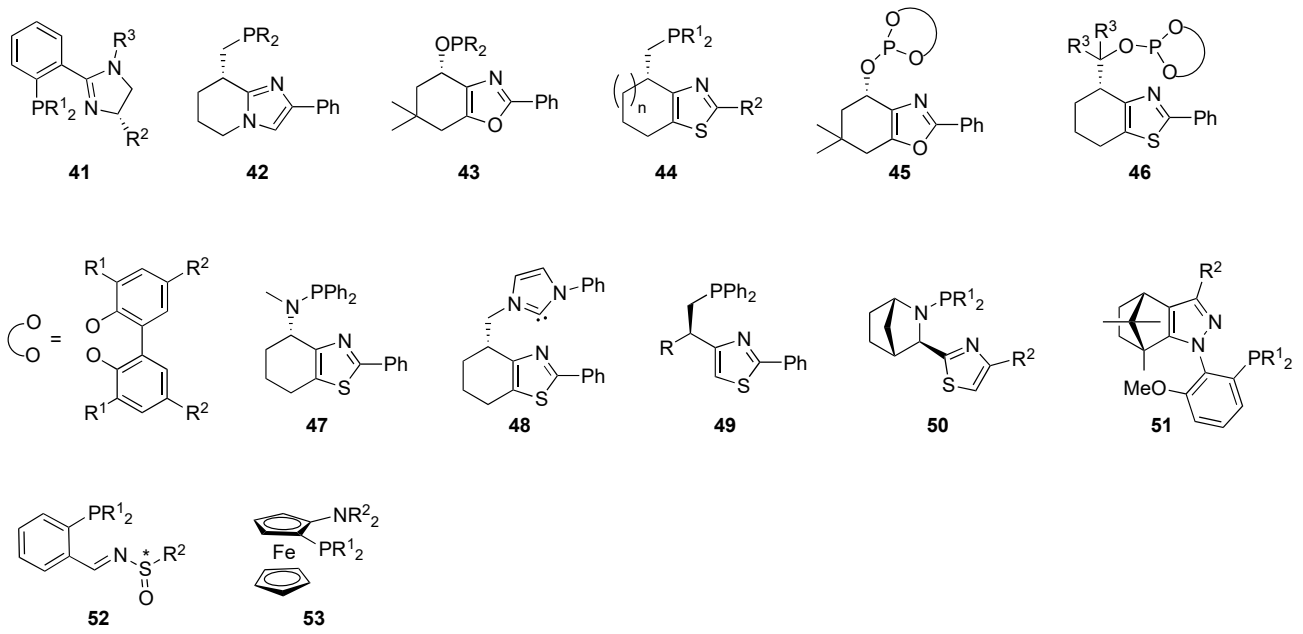
Scheme 14 Hydrogenation of: (a) γ-tocotrienyl acetate **S12** and (b) farnesol isomers **S13** using Ir-**33** catalysts.

Andersson's group synthesized the phosphine- and phosphinite-pyridine ligands **34** and **36** (Figure 5) with the aim to increase the rigidity of ligands **31** and **32** by introducing an enantiomerically pure bicyclic moiety.[81] These ligands, derived from readily available α-pinene, showed high enantioselectivities (ee's up to 97%) but poor activities. Li's group developed a modification of ligand **34** by attaching the phosphine group directly to the pinene moiety forming a five-membered chelate ring (ligand **35**, Figure 5).[82] Ligand **35** turned out to be more appropriate in the reduction of enolphosphonates (ee's up to 90%, *vide infra*) rather than aryl/alkyl trisubstituted olefins (ee' up to 37%). Very recently, Chelucci and coworkers increased the range of phosphine-pyridine ligands derived from α-pinene with the synthesis of compounds **37** and **38** (Figure 5).[83] However, these ligands provided lower enantioselectivities than ligand **34** (ee's up to 94% in the reduction of *trans*-α-methylstilbene **S4**).

In 2007, Li's group applied the phosphine-quinoline ligand **39** (Figure 5), with axial chirality, in the Ir-hydrogenation of minimally functionalized trisubstituted olefins obtaining promising results (ee's up to 95% for both *E*- and *Z*-isomers; Table 1, entry 20).[84] The same concept of axial chirality was followed by Ding's group with the preparation of the spiro phosphine-quinoline ligand **40** (Figure 5).[85] This ligand showed low enantioselectivities in the Ir-hydrogenation of *trans*-α-methylstilbene **S4** (ee's up to 48% ee).

2.1.3 Phosphorus/carbene-other nitrogen donor ligands

Although most of the ligands developed for the Ir-hydrogenation of minimally functionalized olefins contain either an oxazoline or a pyridine, other nitrogen donor groups have been successfully used in this process. The first application of this type of ligand in Ir-hydrogenation was reported by Pfaltz's group with phosphine-imidazoline ligands **41** (Figure 6, R^1 = Ph, *o*-Tol; R^2 = ^{i}Pr, ^{t}Bu; R^3 = ^{i}Pr, ^{t}Bu, Cy, Ph, Bn, *p*-Tol).[86] One advantage of the imidazoline moiety over the oxazoline is the possibility to introduce a new substituent R^3 at the nitrogen that could serve as a linker to attach the ligand to a solid support. Enantioselectivities up to 94% were achieved in a range of standard *E*- and *Z*-aryl/alkyl trisubstituted olefins (Table 1, entry 21). In several cases, higher enantiomeric excesses were obtained than with analogous phosphine-oxazoline PHOX ligands (i.e. enantioselectivities for *Z*-2-(4-methoxyphenyl)-2-butene **S7** increased from 42% to 88% ee). The best enantioselectivities were achieved with ligands containing bulky substituents at both R^1 and R^2 positions, while the substituent at R^3 has to be optimized for each particular substrate (i.e. ligands **41a** and **41b**, Table 1, entry 21). Very recently, Pfaltz and coworkers prepared zwitterionic iridium complexes by introducing an anionic moiety at R^3 position of the imidazole group.[51] However, the presence of the anionic derivatization has a negative influence on the asymmetric induction of the iridium complex.



41a R^1 = *o*-Tol R^2 = ^{t}Bu R^3 = Ph
41b R^1 = *o*-Tol R^2 = ^{t}Bu R^3 = Bn

42a R = Ph
42b R = *o*-Tol

43a R = *o*-Tol

44a n = 1 R^1 = Ph R^2 = Ph

45a R^1 = ^{t}Bu R^2 = ^{t}Bu

46a R^1 = ^{t}Bu R^2 = ^{t}Bu R^3 = H
46b R^1 = ^{t}Bu R^2 = ^{t}Bu R^3 = Me

49a R = Me

50a R^1 = Ph R^2 = Ph
50b R^1 = *o*-Tol R^2 = Ph

52a R^1 = *o*-Tol R^2 = ^{t}Bu

53a R^1 = *o*-Tol R^2 = ^{t}Bu

Figure 6 Phosphorus/carbene-other nitrogen donor ligands applied in the Ir-catalyzed asymmetric hydrogenation of aryl/alkyl trisubstituted olefins. We think that a better alternative should be to take advantatge of the 3 raws of the ligands to make the ligands a little bigger. So we porpose that 1st raw contain ligands 41-45; 2nd raw: ligands 46-4; 3rd raw: 50-53. In that way yhe font size should can be bigger.

Andersson's group developed phosphine-imidazole ligands **42** (Figure 6; R = Ph, *o*-Tol, 3,5-diMe-Ph) for the Ir-catalyzed hydrogenation of unfunctionalized olefins obtaining high enantioselectivities for *E*-aryl/alkyl trisubstituted olefins (ee's up to 98%; Table 1, entry 22)[61,87] and cyclic dienes (ee's up to >99% for the *trans* isomer),[88] but only moderate in the reduction of *Z*-olefins (ee's up to 72%).[87] In general, enantioselectivities were best for ligand **42a**, containing a bisphenylphosphanyl group (Table 1, entry 22). However, the highest enantioselectivity in the reduction of *trans*-α-methylstylbene **S4** was achieved with ligand **42b** containing a bis(*o*-tolyl)phosphanyl group (Table 1, entry 22).
The same group developed related phosphinite-oxazole ligands **43** (Figure 6; R = Ph, *o*-Tol, 3,5-diMe-Ph)[89] and phosphine-thiazole ligands **44** (Figure 6, R^1 = Ph, *o*-Tol; R^2 = H, Ph).[90] Both families of ligands have become privileged ligands for the hydrogenation of minimally functionalized olefins, including those containing a neighboring polar group (*vide infra*). These new ligands provided excellent enantioselectivities in the hydrogenation of both *E*- and *Z*-

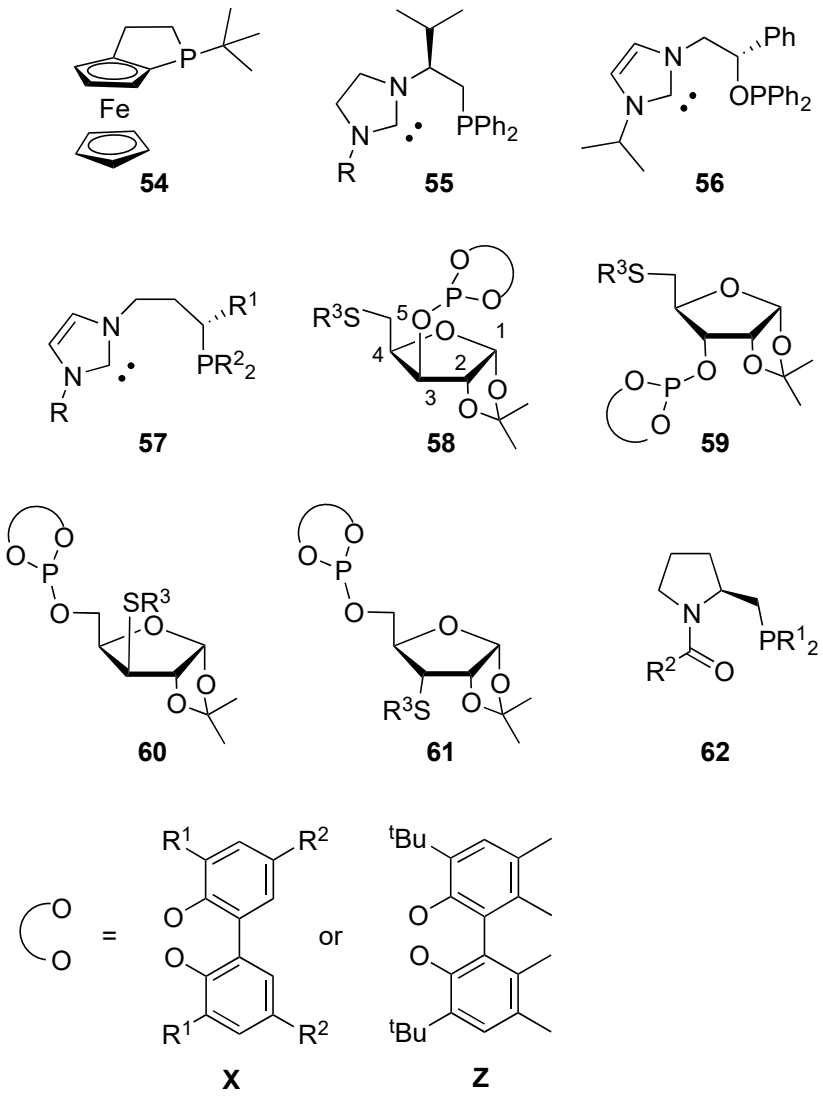
aryl/alkyl trisubstituted olefins (ee's up to >99% for *E*-substrates and up to 94% for *Z*-substrates; Table 1, entry 23).[89-90] Ligands **44** has also proved to be optimal for the hydrogenation of cyclic alkenes,[91] dienes (ee's up to 97% for the *trans* product in the hydrogenation of **S11**)[88] and 1,1-diaryl trisubstitued olefins (ee's up to >99%).[61] Interestingly, while oxazole ligands gave the highest enantioselectivities with bulky *ortho*-tolyl substituents at the phosphinite group (ligand **43a**), thiazole ligands performed best with a diphenylphosphanyl group (ligand **44a**). The authors found that the results could be rationalized by using a simple quadrant model (See section 8 for a detailed discussion).

Later, several modifications of these ligands were developed, including the replacement of the phosphine/phosphinite moieties by N-phosphine, carbene and phosphite groups as well as modification in the ligand backbone. In this respect, biaryl phosphite containing ligands **45** and **46** (Figure 6, R^3= Me or H), related to the successful ligands **43** and **44**, have also provided excellent enantioselectivities for both *E*- and *Z*-trisubstituted olefins (Table 1, entry 24).[92] It should be pointed out that the introduction of a biaryl phosphite moiety increases the substrate scope (i.e. ee's increased up to 99% in the reduction of 4-methyl-1,2-dihydronaphthalene). In general phosphite-thiazole ligands **46** provided higher enantioselectivities than related phosphite-oxazole ligands **45**. For ligands **46** the best enantioselectivities were achieved using ligand **46a** (Figure 6), containing bulky *tert*-butyl groups at the *ortho* and *para* positions of the biphenyl phosphite moiety and hydrogens at the R^3 positions. Related N-phosphine-thiazole ligand **47** has been successfully applied in the hydrogenation of 1,1-diarylsubstitued olefins, providing comparable excellent enantioselectivities (ee's up to >99%) to that of phosphine-thiazole ligands **44**.[61] On the other hand, the replacement of the phosphine group in ligands **44** by a carbene moiety (Figure 6, ligand **48**) led to lower enantioselectivities (ee's up to 90%).[93] Ligands **49**, in which the rigid cyclic backbone in ligands **44** were eliminated, were less successful (Figure 6, R= Me, Bn, allyl).[94] Recently, Andersson's group wanted to increase the rigidity in the ligand backbone by introducing a bicyclic moiety with the synthesis of N-phosphine-thiazole ligands **50** (Figure 6, R^1 = Ph, *o*-Tol; R^2 = Me, ^{t}Bu, Ph).[95] Similar enantioselectivities were achieved in the reduction of *E*-trisubstituted olefins (ee's up to 97%). However, enantioselectivities for *Z*-olefins decreased to 83% ee.

Other ligands in this class, **51**,[96] **52**,[97] and **53**[98] (Figure 6) have also been tested in the hydrogenation of *trans*-methylstilbene and other alkenes, but did not provide very high ee's.

2.1.4 Other ligands

The Ir-catalyzed hydrogenation of minimally functionalized olefins has been dominated by the use of bidentated N,P-ligands. In 2009 Pfaltz's group reported a new concept for the development of a chiral version of Crabtree's catalyst in which the chirality is only introduced by using a chiral ferrocene monodentated ligand **54** (Figure 7).[99] The use of [Ir(cod)(**54**)(Py)][BAr_F] catalyst precursor proved to be active in the hydrogenation of several trisubstituted olefins, but enantioselectivities were poor (ee's up to 12%).



59a Phosphite = **X** R^1 = ^{t}Bu R^2 = ^{t}Bu R^3 = 2,6-Me_2-Ph
59b Phosphite = (*R*)-**Z** R^3 = 2,6-Me_2-Ph
62a R^1 = ^{t}Bu R^2 = CPh_3
62b R^1 = Cy R^2 = 1-AdNH

Figure 7 Other ligands applied in the asymmetric Ir-catalyzed hydrogenation of trisubstituted olefins. We think that a better alternative should be that the ligands can be placed in two line rather than 3; 1st raw: ligands 54-57; 2nd raw: 58-62. Moreover in ligand 58, the sulfur seems not connected to the bond.

Most of the research in the design of new chiral ligands for this process has been centered in developing chiral mimics of the Crabtree's catalysts. Therefore, the possibility of changing the nature of the N-donor atom in these heterodonor ligands has been much less contemplated. In 2006, Pfaltz's group reported the application of phosphine/phosphinite carbene ligands **55** and **56** (Figure 7; R= Me, ^{i}Pr, Mes) in the Ir-catalyzed hydrogenation of both *E*- and *Z*-aryl/alkyl trisubstituted olefins with low activities and enantioselectivities (ee's up to 63%).[100] Later phosphine-carbene ligands **57** (Figure 7; R^1= Me, Et, ^{i}Pr; R^2= 2,4,6-Me_3-Ph, 2,6-$^i Pr_2$-Ph) that formed a larger

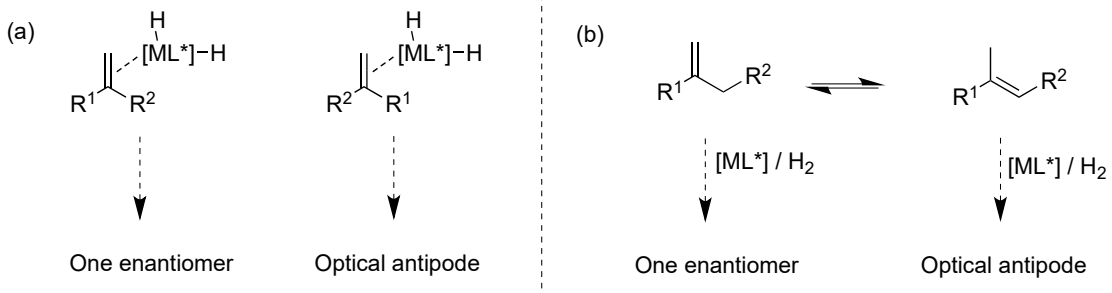
chelate ring-size upon coordination to Ir provided higher activities, but enantioselectivities were still moderate.[101]

A breakthrough in the development of chiral non-N-containing ligands for this transformation came with the recent work of Diéguez's group who developed a highly modular phosphite-thioether ligand library (ligands **58**-**61**; Figure 7, R^3= Me, ^{i}Pr, ^{t}Bu, Ph, 2,6-Me_2-Ph), which provides excellent activities and enantioselectivities for a wide range of *E*- and *Z*- trisubstituted olefins, including the more challenging 4-methyl-1,2-dihydronaphthalenes and 1,1-diaryl trisubstituted olefins (ee's up to 99%; Table 1, entry 25). These ligands consists of four main ligand backbones produced by systematically varying the position of the thioether group at either C-3 or C-5 of the furanoside backbone and the configuration of C-3. The introduction of a thioether moiety in the ligand design may be beneficial because: (i) the S atoms become a stereogenic center when coordinated to metal, which moves the chirality closer to the metal, and (ii) the thioether group is more stable than the oxazoline moiety. The best results were obtained with ribofuranoside ligands **59** containing a bulky 2,6-Me_2-Ph thioether group attached to C-5 position and either a tetra *tert*-butyl biphenyl phosphite moiety (ligand **59a**, Figure 7) or an enantiopure (*R)*-5,5',6,6'-tetramethyl-3,3'-di-tert-butyl-1,1'-biphenyl-2,2'-diol (ligand **59b**) attached to C-3 of the furanoside backbone.[102]

Soon after, Pfaltz's group reported the use of proline-based P,O ligands **62** (Figure 7, R^1= Ph, ^{t}Bu, Cy, *o*-Tol and R^2= ^{t}Bu, 1-Ad, CPh_3, 1Ad-NH, MesNH, CPh_3NH).[103] Either phosphines bearing a bulky amide (ligand **62a**; Table 1, entry 26) or urea groups (ligand **62b**; Table 1, entry 27) at the pyrrolidine N-atom formed efficient Ir-catalysts for the asymmetric hydrogenation of several minimally functionalized olefins (ee's up to 99% in the hydrogenation of *trans* α-methylstilbene **S4**).

2.2 1,1-Disubstituted alkenes

Disubstituted terminal alkenes are a challenging substrate class when compared to the more widely investigated trisubstituted olefins. This is mainly due to two reasons. The first one is that in the absence of a third substituent on the double bond, the catalyst has to distinguish solely between the two alkyl- or aryl-substituents R^1 and R^2 for enantiodiscrimination (Scheme 15a). This is a much more demanding task compared to distinguishing between a hydrogen and an akyl- or aryl-group as in the case of trisubstituted alkenes. The second reason is that the terminal double bond can isomerize to form the more stable internal alkene, which usually leads to the predominant formation of the other enantiomer of the hydrogenated product (Scheme 15b). Efficient catalytic systems for the asymmetric reduction of 1,1-disubstituted aryl-alkyl alkenes have been elusive until very recently. Next, we discuss the progress made in the asymmetric hydrogenation of minimally functionalized terminal olefins. We discuss the latest development in design, from the initial discovery of lanthanide catalytic precursors, through the use of transition metal-diphosphine/iminophosphorane precursors, to the successful Ir-N,P catalytic systems.



Scheme 15 Proposed reasons for the low enantioselectivities associated with the hydrogenation of terminal olefins.

The early approaches to tackle the asymmetric hydrogenation of disubstituted alkenes involved the use of chiral biscyclopentadienyl Sm-complexes[104] or the use of Ru-diphosphine catalysts.[105] In the first case, enantioselectivities up to 96% in the reduction of 2-phenyl-but-1-ene **S14** (Table 2, entry 1) were achieved using [Sm(**63**)(CH(TMS)$_2$)] catalyst precursor (Figure 8). However, the interest of using this type of complexes diminished due to the low temperatures (–78 °C) required to achieve the highest levels of enantioselectivity and the low modularity of the catalytic system.[104] In the second case enantioselectivities up to 89% were reported in the hydrogenation of a range of 2-phenyl-2-but-1-enes (Table 2, entries 2, 8, 10 and 22) using [RuCl$_2$(**64**)]$_n$·DMF (Figure 8).[17c] It should be pointed out that the use of other diphosphine ligands (i.e. Et-Duphos or BINAP) were not effective.[17c]

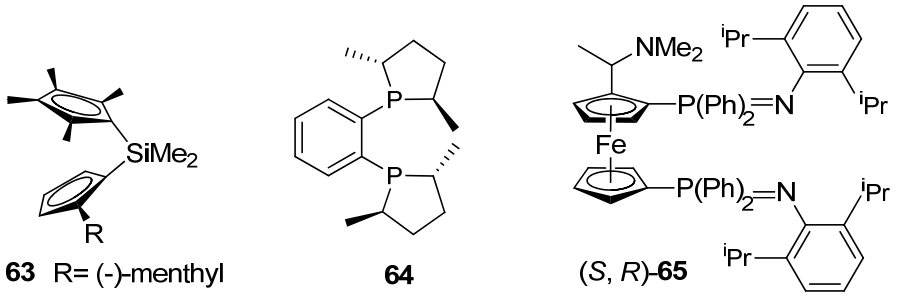
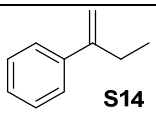
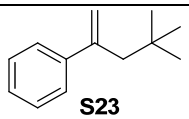
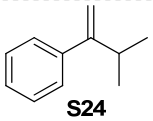
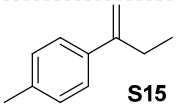
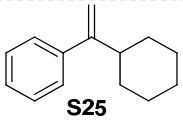
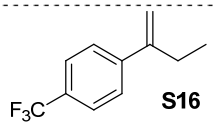
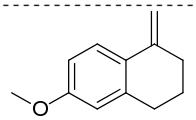
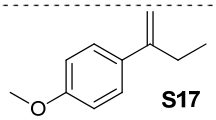
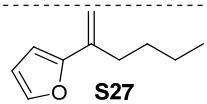
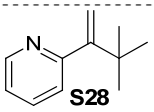
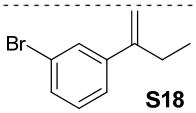
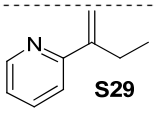
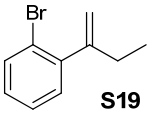
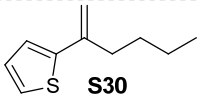
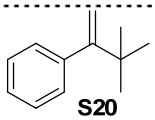
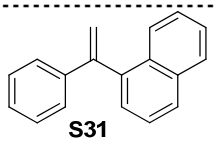
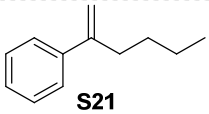
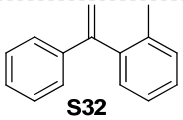
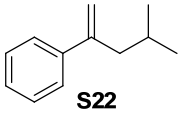
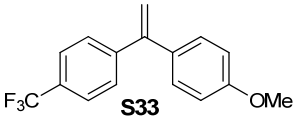


Figure 8 Ligands **63**-**65** applied in the asymmetric hydrogenation of 1,1-disubstituted aryl/alkyl olefins.

An important breakthrough in this area of research was made by Pfaltz et al. They successfully applied the protocols that use Ir-N,P catalytic systems for the hydrogenation of minimally functionalized trisubstituted olefins to terminal olefins.[2b,2d,e,3c,d] A complete screening of Ir-complexes containing highly modular phosphine-oxazoline ligands **8** (Figure 3) and phosphinite-oxazoline ligands **20** (Figure 4) in the reduction of a range of 2-phenyl-2-but-1-enes indicated that the ligand parameters have an important effect on enantioselectivity.[66-67] The enantioselectivities (ee's up to 94%, Table 2, entries 9, 11, 15, 23, 41 and 42) were best with the Ir-catalytic system containing the basic cyclohexyl phosphinite-oxazoline derived from threonine **20a** (Figure 4). These results surpass the enantioselectivities obtained using Ru-**64** catalytic system (i.e. Table 2, entries 9 and 11 *vs* 8 and 10, respectively). Interestingly, the selectivity is highly pressure dependent in the Ir-catalyzed reduction of these terminal alkenes. Hydrogenation at

atmospheric pressure of H_2 gave significantly higher ee's than at higher pressures (ee increases from 58% to 94% when pressure is decreased from 50 bar to 1 bar).[66b]

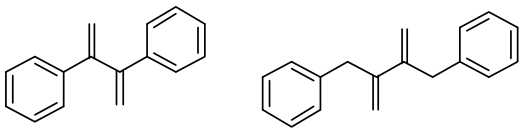
Table 2 Enantioselectivities achieved using selected ligands in the asymmetric hydrogenation of 1,1'-disubstituted aryl-alkyl alkenes

Entry	Substrate	[M]/L	% ee	Ref	Entry	Substrate	[M]/L	% ee	Ref.
1	 **S14**	Sm(**63**)	96	106	33	 **S23**	Ir-**24a**	93	74b
2		Ru-**64**	86	17c	34		Ir-**25b**	90	75b
3		Ir-**43a**	41	91					
4		Ir-**50a**	2	97	35	 **S24**	Ir-**50a**	44	97
5		Ir-**24a**	99	74b	36		Ir-**24a**	83	74b
6		Ir-**25b**	99	75b	37		Ir-**25b**	97	75b
7		Ir-**46a**	94	93					
8	 **S15**	Ru-**64**	87	17c	38	 **S25**	Ir-**24a**	84	74b
9		Ir-**20a**	91	69	39		Ir-**25b**	97	75b
					40		Ir-**46a**	94	93
10	 **S16**	Ru-**64**	81	17c	41	 **S26**	Ir-**20a**	46	69
11		Ir-**20a**	88	69	42		Ir-**20a**	82[a]	70a
12		Ir-**24a**	99	74b	43		Rh-**65**	94	110
13		Ir-**25b**	96	75b	44		Ir-**25b**	25	75b
14		Ir-**46a**	94	93	45		Ir-**25b**	87[a]	75b
15	 **S17**	Ir-**20a**	94	69	46	 **S27**	Ir-**25b**	99	75b
16		Ir-**26a**	89	39					
17		Ir-**43a**	97	91					
18		Rh-**65**	97	110	47	 **S28**	Ir-**24a**	99	74b
19		Ir-**24a**	98	74b	48		Ir-**25b**	>99	75b
20		Ir-**25b**	>99	75b	49		Ir-**46a**	96	93
21		Ir-**46a**	97	93	50		Ir-**59a**	99	104
22	 **S18**	Ru-**64**	86	17c	51	 **S29**	Ir-**24a**	99	74b
					52		Ir-**25b**	99	75b
					53		Ir-**46a**	99	93
					54		Ir-**59a**	60	104
23	 **S19**	Ir-**20a**	94	69	55	 **S30**	Ir-**24a**	90	74b
					56		Ir-**25b**	96	75b
					57		Ir-**46a**	90	93
24	 **S20**	Ir-**50a**	86	97	58	 **S31**	Ir-**24a**	70	74b
25		Ir-**24a**	97	74b	59		Ir-**25c**	>99	75b
26		Ir-**25b**	>99	75b	60		Ir-**59a**	43	104
27		Ir-**59a**	98	104					
28	 **S21**	Ir-**24a**	90	74b	61	 **S32**	Ir-**24a**	68	74b
29		Ir-**25b**	94	75b	62		Ir-**25c**	99	75b
30		Ir-**59a**	62	104					
31	 **S22**	Ir-**24a**	93	74b	63	 **S33**	Ir-**24a**	65	74b
32		Ir-**25b**	93	75b	64		Ir-**25d**	65	75b

[a] Using PC as solvent

Later, Börner's group disclosed that Ir-**20a** catalyst is efficient using propylene carbonate (PC) as an environmentally friendly alternative solvent to dichloromethane.[68a] Although reaction rates are lower in PC than in dichloromethane, its use has the advantage that isomerization of the terminal

double bond to the more stable internal alkene is also slower in PC than in dichloromethane. For example, the isomerization of 4-methylene-1,2,3,4-tetrahydronaphthalene **S26** to 4-methyl-1,2-dihydronaphthalene is around three times slower in PC than in dichloromethane. The suppression of the isomerization has a positive effect on enantioselectivity. Thus, enantioselectivities increased from 46% to 82% in the reduction of **S26** by using PC (Table 2, entries 41 *vs* 42). Another advantage of using PC as solvent is that it allows catalysts to be repeatedly recycled by a simple two phase extraction with an apolar solvent (typically hexane). Catalyst Ir-**20a** was used up to five times with no significant losses in enantioselectivity, although the reaction time increased.[68a] This is probably due to the iridium catalyst partially passing into the hexane phase and/or the formation of inactive triiridium hydride clusters.[23b,30] Soon after, Burgess and co-workers replaced the P-donor moiety with a carbene group by using Ir complexes containing N-heterocyclic carbene-oxazoline ligands **26** (Figure 4).[39] These catalyst precursors were applied to the reduction of 2-(4-methoxyphenyl)-1-butene **S17** (Table 2, entry 16). Enantioselectivities up to 89%, comparable to those obtained using Ru-**64** catalytic system, were obtained using Ir-precursor containing ligand **26a** (Figure 4). Interestingly, Burgess' group went one step further and successfully applied Ir-**26a** catalytic system in the asymmetric reduction of unfunctionalized 1,1-disubstituted dienes with enantioselectivities up to 87% and good diastereoselectivities (Figure 9).[106]



ent:*meso* % ee
1.0: 2.9 87

ent:*meso* % ee
1.0: 2.9 24

Figure 9 Asymmetric hydrogenation of 1,1-disubstituted dienes using Ir-**26a** catalyst.

Subsequently, Andersson and coworkers applied Ir-catalytic system containing phosphinite-oxazole **43a** (Figure 6) to hydrogenate 2-(4-methoxyphenyl)-1-butene **S17** with enantioselectivities up to 97% (Table 2, entry 17).[89] However, enantioselectivities were only moderate for other terminal 2-arylbut-1-enes (i.e. Table 2, entry 3).[107] The same group reported the application of a series of *N*-phosphine-thiazole ligands **50** (Figure 6) in the hydrogenation of some terminal aryl-alkyl olefins with moderate success (Table 2, entries 4, 24 and 35).[95] The best enantioselectivity (up to 86%) was obtained in the reduction of **S20** (Table 2, entry 24) using ligand bearing phenyl substituents at both thiazole and N-phosphine moieties (ligand **50a**; Figure 6).

In 2006, the group of Kim reported the successful application of (iminophosphoranyl)ferrocene ligands **65** (Figure 8) in the Rh-catalyzed hydrogenation of **S13** (ee's up to 97%, Table 2, entry 18) and **S26** (ee's up to 94%, Table 1, entry 43).[108] Despite this success, no other systems or substrates have been applied and the potential of this type of catalyst system needs to be verified.

Despite all these important contributions, the asymmetric hydrogenation of terminal alkenes using Ir-N,P catalyst systems still suffered

from a limited substrate scope. In 2008, Andersson, Diéguez and their respective groups discovered that the presence of biaryl-phosphite moieties in ligand design is highly advantageous for the Ir-catalyzed reduction of minimally functionalized olefins.[72-73] In this context three families of phosphite-nitrogen ligands have been successfully applied in the reduction of a broad range of disubstituted alkenes (ligands **24**, **25** in Figure 4 and ligands **46** in Figure 6). The use of biaryl phosphite moieties in the ligand design is a common feature of these ligand libraries. The high availability of biaryl alcohols and the robustness towards oxidizing agents of the phosphite moiety are the key factors for the high modularity and stability of the phosphite-nitrogen ligands. The first family was the previously mentioned phosphite-oxazoline ligands **24** derived from D-glucosamine (Figure 4).[72a] By carefully selecting the ligand parameters (substituents at the oxazoline moiety and substituents/configuration at the biaryl phosphite moiety) enantioselectivities ranging from 83 to 99% were obtained using ligand **24a** (Figure 4).[72b] The results with several 1,1-disubstituted aryl/heteroaryl-alkyl substrates indicated that enantioselectivity is affected by the nature of the substrate alkyl chain (ee's ranging from 83% to 99%, Table 2, entries 5, 12, 19, 25, 28, 31, 33, 36, 38, 47, 51 and 55). One possible explanation for this can be found in the competition between direct hydrogenation versus isomerization for the different substrates. This is supported by the fact that the hydrogenation of substrate **S20** bearing a *tert*-butyl group, for which isomerization cannot occur, provides high levels of enantioselectivity (ee's up to 97%; Table 2, entry 25), while the lowest enantioselectivity of the series (ee's up to 84%; Table 2, entries 36 and 38) is found for substrates **S24** and **S25**, which form the most stable isomerized tetrasubstituted olefins.

The second family, related to ligands **20**, showed to be superior to the previous glucosamine-based phosphite-oxazoline ligands.[73] In this respect, [Ir(cod)(**25**)][BAr_F] (Figure 4) appeared as a privileged catalytic system for the hydrogenation of several type of aryl-alkyl, heteroaryl-alkyl and aryl-aryl 1,1-disubstituted olefins, including those bearing a neighboring polar group (*vide infra*).[73b] However, all the examples required the presence of an aromatic substituent conjugated to the alkene and there are no reported examples of purely alkyl-substituted terminal olefins. In contrast to trisubstituted olefins, enantioselectivities were best with ligand containing an *S*-binaphthyl phosphite moiety and phenyl substituents at the alkyl backbone chain (ligand **25b**; Figure 4). In this respect several *para*-substituted 2-phenylbut-2-enes and several α-alkylstyrenes bearing increasingly sterically demanding alkyl substituents were hydrogenated with excellent enantioselectivities (90-99% ee) (Table 2, entries 6, 13, 20, 26, 29, 32, 34, 37 and 39). Ir-**25b** catalytic system was also used in combination with PC as solvent. As observed by Börner and coworkers using Ir-**20a**, enantioselectivity in the reduction of **S26** was improved (Table 2, entries 44 *vs* 45) and catalysts were used up to five times with no significant losses in enantioselectivity. A range of heteroaryl-alkyl substrates containing a furyl, pyridyl and thiophenyl groups could be hydrogenated highly efficiently at 1 bar of hydrogen using the Ir-**25b** catalytic system (ee's ranging 96->99%, Table 2, entries 46, 48, 52 and 56). By suitable tuning of the ligand components, the Ir-**25c** (Figure 4) and Ir-**25d** (Figure 4) catalysts were also very efficient in the hydrogenation of 1,1-diaryl substrates, which provides a facile alternative for the preparation of

diarylalkanes present in several drugs and research materials (Table 2, entries 59, 62 and 64).

The third family was designed in order to study whether the biaryl phosphite moiety is still as effective when combined with *N*-donor groups other than oxazolines. Two types of *N*-donor group were studied, oxazole (Figure 6, ligands **45**) and thiazole (Figure 6, ligands **46**).[92] The results indicated that the phosphite-thiazole ligand **46a** (Figure 6) provides similar levels of enantioselectivity than those obtained with glucosamine-based Ir-**24a** catalytic system (Table 2, entries 7, 14, 21, 40, 49, 53 and 57).

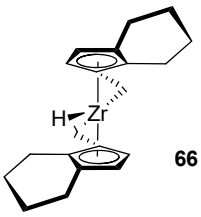
The previously mentioned phosphite-thioether ligands **58**-**61** (Figure 7) were screened in the hydrogenation of several aryl/alkyl disubstituted substrates, including those containing a heteroaryl group. Again, furanoside ligand **59a** provided the highest enantioselectivities (ee's up to 99%; Table 2, entries 27, 30, 50, and 60).[102a,b] For this substrate class the enantioselectivity is dependent on the alkyl substituent and this can, at least in part, be attributed to the presence of an isomerization process under hydrogenation conditions. Enantioselectivities were therefore best in the asymmetric reduction of aryl and heteroaryl/*tert*-butyl substrates **S20** and **S28**. Conveniently, both enantiomers of the hydrogenation product can be obtained in high enantioselectivity, simply by changing the configuration of the biaryl phosphite moiety.

While chiral versions of Crabtree's catalyst have proven very useful for the asymmetric hydrogenation of unfunctionalized 1,1-disubstituted alkenes as, a complementary reactivity can be found in the previously described Rh-Duanphos catalytic system (Scheme 12). Here the hydrogenation of 1,1-diaryl substrates bearing a directing hydroxyl group at the *ortho* position of one of the aryl groups gives ee's up to >99% while the corresponding alkenes devoid of the hydroxyl moiety gives essentially racemic mixtures.[49]

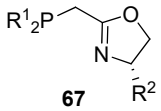
2.3 Tetrasubstituted aryl/alkyl alkenes

Despite all advances achieved in the last five years in the hydrogenation of minimally functionalized olefins, with the development of new ligand libraries that allowed a considerably increased range of substrates that can be hydrogenated, the enantioselective reduction of tetrasubstituted olefins remain a challenge and the range of substrates that can be efficiently hydrogenated is still narrow.

Buchwald's group reported the first successful example on the asymmetric hydrogenation of tetrasubstituted alkenes. In this study, a chiral zirconocene complex **66** (Figure 10), which is the Zr analogue of previously mentioned titanocene complex **7** was used.[109] The hydride-zirconocene catalyst afforded high enantioselectivities (ee's over 90%) for a range of tetrasubstituted acyclic olefins and dihydronaphthalenes (Table 3, entries 1, 12, 15, 19 and 21). However, as observed for the titanium analogue **7**, the potential utility is hampered by the high catalysts loadings, long reaction times and high pressures required.



66



67

Figure 10 Zirconocene complex **66** and phosphine-oxazoline ligands **67** applied in the asymmetric hydrogenation of tetrasubstituted olefins.

Ir-PHOX catalytic systems (Figure 3) were also applied in the hydrogenation of tetrasubstituted olefin 1-(1,2-dimethyl-propenyl)-4-methoxy-benzene **S5**, providing promising results (ee's up to 81% and full conversion after 2 hours) at a lower catalyst loadings and pressures than that required using Zr-**66** (Table 3, entry 2).[26-27,50] Nevertheless the ligand requirements to achieve high enantioselectivities for tetrasubstituted olefins are different from those for the reduction of trisubstituted ones. Enantioselectivities are best using the less bulky ligand **8b** that contains a $CH_2{}^tBu$ group on the oxazoline and a bisphenylphosphanyl group (Figure 3). The Ir-PHOX ligands has been successfully applied in the hydrogenation of tricyclic ring olefins **S34** (Table 3, entry 10).[110] These results opened up the asymmetric reduction of this substrate class to the use of other Ir-N,P catalysts and some of the ligands used in the reduction of trisubstituted olefins, have also been tested. In this context, the previously mentioned phosphine-benzoxazine ligands **9** (Figure 4) provided low conversions (up to 63%) and enantioselectivities (up to 31%) in the hydrogenation of 1-(1,2-dimethyl-propenyl)-4-methoxy-benzene **S5** (Table 3, entry 3) and 1-isopropylidene-6-methoxy-1,2,3,4-tetrahydro-naphthalene.[52]

The proline based N-phosphine-oxazoline ligands **17** (Figure 4), which provided higher enantioselectivities in the hydrogenation of trisubstituted olefins than PHOX ligands, have been tested in the hydrogenation of tetrasubstituted substrate **S5**.[59] However for this substrate low activities and enantioselectivities were obtained (ee's up to 16%; Table 3, entry 4).

The use of phosphinite-ligands **20** (Figure 4) provided similar high levels of enantioselectivity compared with PHOX-based catalytic system in the hydrogenation of tetrasubstituted olefins (ee's up to 82%; Table 3, entry 5).[110] As observed in the hydrogenation of disubstituted olefins and in contrast to the hydrogenation of trisubstituted olefins, the ligand that provided the highest enantioselectivity with tetrasubstituted olefin **S5** contains cyclohexyl substitutents at the phosphinite moiety (ligand **20a**; Figure 4). The same authors also evaluated the phosphinite-oxazoline ligands **21** (Figure 4). As for trisubstituted aryl/alkyl olefins they provided low levels of enantioselectivity in the reduction of standard tetrasubstituted substrate **S5** (ee's up to 14%; Table 3, entry 6).[110] However, the same ligand **21a** (Figure 4) provided excellent enantioselectivities (ee's up to 95%) for a limited range of tetrasubstituted dihydronaphthalenes (Table 3, entries 13 and 17).

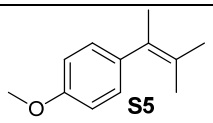
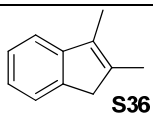
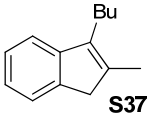
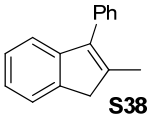
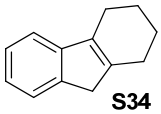
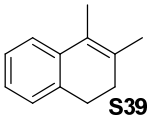
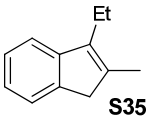
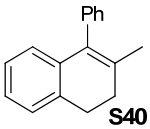
The group of Pfaltz screened the phosphinite-pyridine ligands **32** and **33** (Figure 5) for the Ir-catalyzed asymmetric hydrogenation of tetrasubstituted alkenes and found that Ir-**32** afforded higher enantioselecivities than Ir-**33** (Table 3, entries 7 vs 8).[77,79a] Comparable enantioselectivities (ee's up to

81%) to that of PHOX ligands were achieved using the phosphinite-pyridine ligand **32a** (Figure 5) in the reduction of substrate **S5**.

Andersson's group also evaluated phosphinite-oxazole ligands **43** (Figure 6) in the hydrogenation of standard substrate **S5**. Nevertheless, enantioselectivities and activities were low (ee's up to 15%).[89]

An important discovery was the use of simple and readily available phosphine-oxazoline ligands **67** (Figure 10; R^1= Ph, Cy, ^{t}Bu, *o*-Tol and R^2= Ph, ^{i}Pr, ^{t}Bu, $CH_2{}^t$Bu, Bn), which form five membered chelate rings.[110] This ligand family not only provided excellent enantioselectivities for the hydrogenation of the standard tetrasubstituted substrate **S5**, but also provided high enantioselectivities for a broad range of tetrasubstituted dihydronaphthalenes, including tricyclic ring olefins (Table 3, entries 9, 11, 14, 16, 18, 20, 22 and 23). Although, in general, it has been observed that small changes at both the substituents of the ligands and the substituents of the substrate led to large effects on catalytic performance, the authors found that ligand **67a** (Figure 10, R^1= Ph and R^2= ^{i}Pr), containing an isopropyl oxazoline substituent and a bisphenylphosphanyl group, provided the highest enantioselectivities for a broad range of tetrasubstituted dihydronaphthalenes.

Table 3 Enantioselectivities achieved using selected ligands in the asymmetric hydrogenation of tetrasubstituted alkenes.

Entry	Substrate	[M]/L	% ee	Ref	Entry	Substrate	[M]/L	% ee	Ref.
1	 **S5**	Zr (**66**)	96[a]	111	15	 **S36**	Zr (**66**)	93	111
2		Ir-**8b**	81	26	16		Ir-**67a**	94	112
3		Ir-**9**	31	53					
4		Ir-**17**	16	61	17	 **S37**	Ir-**21a**	95	112
5		Ir-**20a**	82	112	18		Ir-**67a**	94	112
6		Ir-**21a**	14	112					
7		Ir-**32a**	81	79	19	 **S38**	Zr (**66**)	78	111
8		Ir-**33a**	64	81a	20		Ir-**67a**	96	112
9		Ir-**67a**	97	112					
10	 **S34**	Ir-**8b**	94	112	21	 **S39**	Zr (**66**)	92	111
11		Ir-**67a**	96	112	22		Ir-**67a**	73	112
12	 **S35**	Zr (**60**)	52	111	23	 **S40**	Ir-**67a**	91	112
13		Ir-**21a**	94	112					
14		Ir-**67a**	93	112					

[a] Using *p*-fluoro derivative instead of OMe in **S5**.

3 Enols

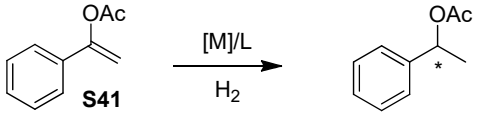
Traditionally, the asymmetric hydrogenation of enols has been subject of interest as alternative method to the asymmetric hydrogenation of ketones for the preparation of chiral alcohols. However, the hydrogenation of enol derivatives can give chiral products other than alcohols that are more difficult to access from ketone reduction like chiral cyclic ethers and phosphines.

Moreover the great diversity of protecting groups that can be introduced in the enol substrate can be used after hydrogenation as an alcohol protective group that can be deprotected at any later point in the synthesis of a more complex molecule.

3.1 Enol esters and enol carbamates

Enol esters are the most widely used enol type substrate in asymmetric hydrogenation.[111] The asymmetric hydrogenation of this substrate class readily gives access to chiral alcohols after hydrolysis of the ester group. The hydrogenation of this substrate class is dominated by Rh- and Ru-catalysts modified with chiral phosphorus ligands mainly because of the coordinative ability of the ester group to the metal center (enol esters are structurally and electronically similar to enamides) (Table 4).[111-112] There are very few examples of Crabtree's analogues Ir-chiral catalysts applied to this substrate class. For instance, the hydrogenation of 1-phenylvinyl acetate **S41** using phosphine-thiazoline ligands **44** (Figure 6) was ineffective (no conversion; Table 4, entry 5) but the use of Ir-**18** catalysts (Figure 4) afforded exclusively the desired acetate but in racemic form (Table 4, entry 3).[62b] On the other hand phosphinite-oxazole ligands **43** (Figure 6) led to the formation of decomposition product ethyl benzene as a major product (Table 4, entry 4).

Table 4 Selected results for the asymmetric hydrogenation of model enol ester 1-phenylvinyl acetate **S41**



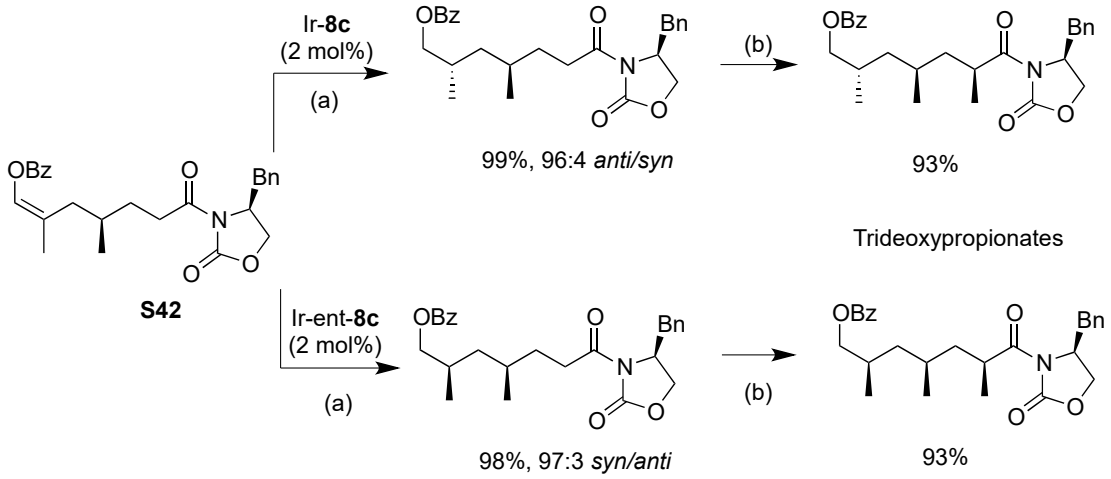
S41

Entry	[M]/L	% Conv	% ee	Ref.
1	Rh-ZhangPhos	100	97	114b
2	Rh-Cy-SMS-Phos	100	97	114a
3	Ir-**18**	100	0	64b
4	Ir-**43**	100[a]	-	64b
5	Ir-**44**	0	-	64b

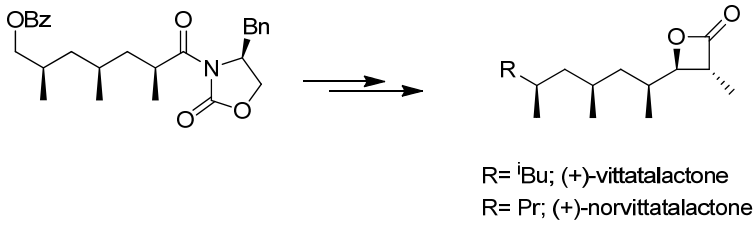
[a] Ethyl benzene was the major product

Very recently, Schneider and coworkers have successfully applied Ir-phosphine/phosphinite-oxazoline catalysts in the diastereoselective hydrogenation of enol benzoate **S42** (Scheme 16, step (a)).[113] It should be pointed out that various chiral Rh-catalysts failed to hydrogenate this substrate. After screening several Ir-N,P systems the authors found that the best results were obtained with the Ir-PHOX catalytic systems (Figure 3) affording significant diastereoselectivities. They also found that the steric bulk within the P-aryl group exerted a decisive effect both on activity and selectivity. The best activities and selectivities were achieved using ligand **8c** containing bulky mesityl groups at the phosphine moiety (Figure 3).[113] Enol benzoate **S42** was hydrogenated to the *anti* product in 99% yield and 96:4 dr, whereas the epimeric *syn* product was achieved in 98% yield and 97:3 dr using the enantiometic **8c** ligand (Scheme 16, step (a)). The hydrogenated products were used to prepare biologically relevant trideoxypropionate building blocks in optically pure form by a simple auxiliary-controlled enolate

methylation (Scheme 16, step (b)). Trideoxypropionate has further been applied in the total synthesis of the pheromones (+) vittatalactone and (+)-norvittatalactone of the striped cucumber beetle *Acalymma vittatum* (Scheme 17).[113-114]

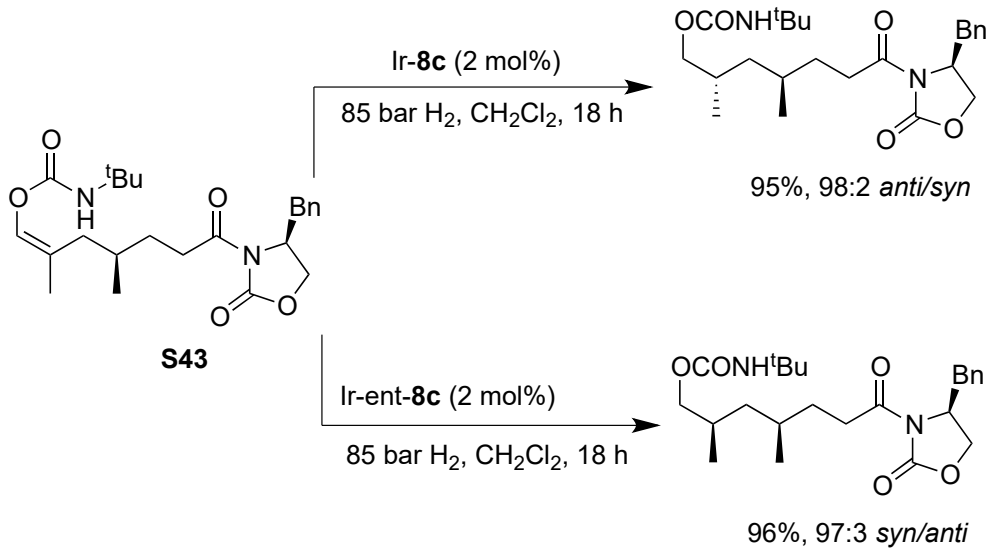


Scheme 16 Hydrogenation of **S42**-α-methylation sequence toward trideoxypropionates. Reaction conditions: (a) CH_2Cl_2, 85 bar H_2, 18 h, rt. (b) NaHMDS, MeI, THF, -78 °C



Scheme 17 Application of trideoxypropionate in the total synthesis of pheromones from the striped cucumber beetle *Acalymma vittatum*

Enol carbamates have recently appeared as an alternative to enol esters mainly because the coordinating ability to the metal of the carbamate acyl group more resembles the corresponding enamide than the acyl group of an enol ester, which has a slightly weaker coordinating ability.[115] For this substrate class the use of Rh-phosphoroamidite catalysts have afforded excellent levels of enantioselectivities (ee's up to 98%).[115-116] However, Ir-PHOX catalysts (Figure 3) have been shown to be highly efficient in the diastereoselective hydrogenation of the enol carbamate **S43**, analogue to enol ester **S42**, for which several Rh/P catalysts failed.[113] As previously observed with enol ester **S42**, the use of the bulky PHOX ligand **8c** (Figure 3) and its enantiomer (ent-**8c**) afforded both diastereoisomers in high yields and diastereomeric ratios (Scheme 18).[113]

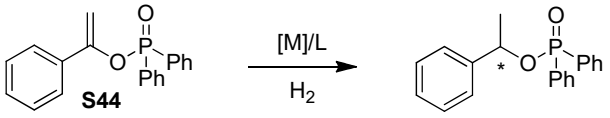


Scheme 18 Diastereoselective hydrogenation of enol carbamate **S43** using Ir-PHOX catalysts

3.2 Enol phosphinates and enol phosphonates

Although the phosphinate and the phosphonate group are coordinative groups, there is only one report on the use of Rh-catalysts for the hydrogenation of enol phosphinates/phosphonates. Moderate enantioselectivities were achieved in the hydrogenation of enol phosphinates using a cationic Rh-catalyst modified with (*R*)-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethanol ligand ((*R*)-(*S*)-BPPFOH) (ee's up to 78%; Table 5, entry 1).[117] The presence of triethylamine was necessary for high activities, which underlines the highly acid-sensitive nature of these substrates. Enol phosphinates and in some cases also enol phosphonates can, however, be reduced effectively using chiral analogues of Crabtree's catalysts. A screening of the ligands developed in Andersson's group disclosed that N-phosphine-oxazoline ligand **18b** (Figure 4) is effective for the hydrogenation of terminal enol phosphinates (Table 5, entries 2 vs 3 and 4).[62b] Excellent enantioselectivities were achieved for a wide range of aryl and alkyl enol phosphinates (Figure 11). Moreover, the authors took advantage of Berens work[118] to demonstrate that this methodology can also be used to prepare chiral phosphines by replacing the phosphityl group with diphenylphosphine. In the same study the authors found that the Ir-**18b** catalyst can be used in the hydrogenation of enol phosphonates albeit with lower enantioselectivities (i.e. ee's dropped from 95% to 65% by replacing the phosphinate group by a phosphonate moiety). It should be noted that for the more acid-sensitive substrates (i.e. substrate **S47**, Figure 11) the use of small amounts of poly(4-vinylpyridine) resin were necessary to avoid substrate hydrogenolysis.[62b]

Table 5 Selected results for the asymmetric hydrogenation of model enol phosphinate 1-phenylvinyl diphenylphosphinate **S44**

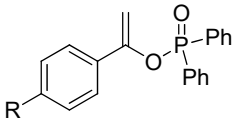


S44

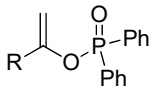
Entry	[M]/L	% Conv	% ee	Ref.
1	Rh-(*R*)-(*S*)-BPPFOH	100	78	119
2	Ir-**18b**	100	95	64b
3	Ir-**44**	0	-	64b
4	Ir-**43**	47	63%	64b
5	Ir-**45a**	100	82%	93

The same authors found that Ir-**18b** catalyst was able to efficiently reduce trisubstituted aryl-alkyl and ester-functionalized enol phosphinates.[62a] Excellent enantioselectivities (up to >99%) and full conversion were observed for a range of substrates, including purely alkyl trisubstituted enol phosphinates (Figure 11). This latter finding is of great importance because the hydrogenation products, after deprotection, gives access to chiral alkyl alcohols that are difficult to obtain in high enantioselectivity from ketone hydrogenations.

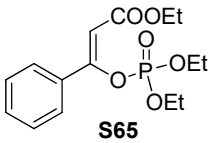
Later, the groups of Andersson and Diéguez have demonstrated that replacing the phosphinite moiety in ligands **43** by a biaryl phosphite group (ligand **45a**; Figure 6) has a positive effect on enantioselectivity (Table 5, entry 4 vs 5).[92] High enantioselectivities (up to 92%) were obtained in the hydrogenation of several di- and trisubstituted enol phosphinates. However, the enantioselectivities achieved do not surpass the values achieved with Ir-**18b** catalytic system.



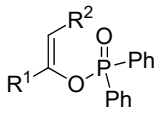
	R	%ee
S45	Me	96
S46	^{t}Bu	94
S47	OMe	98
S48	CF_3	99
S49	Br	>99



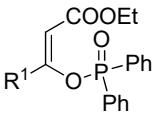
	R	%ee
S50	Cy	92
S51	^{t}Bu	>99
S52	^{i}Pr	92



S65
99 % ee



	R^1	R^2	%ee
S53	Ph	Me	96
S54	Ph	Et	92
S55	Ph	^{i}Pr	90
S56	^{t}Bu	Et	90
S57	^{i}Pr	Me	91



	R^1	%ee
S58	Ph	>99
S59	4-Me-Ph	>99
S60	4-CF_3-Ph	99
S61	Me	>99
S62	Et	99
S63	^{i}Pr	>99
S64	^{t}Bu	93

Figure 11 Representative enol phosphinates (**S45**-**S64**) and enol phosphonate (**S65**) efficiently reduced using Ir-**18b** catalytic system

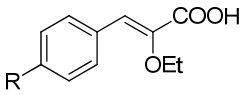
3.3 Enol ethers

In this section, in addition to simple enols, α-alkyloxy and α-alkyloxy α,β-unsaturated carbonyls will be discussed along with a few examples of enol ethers that also are allylic alcohols.

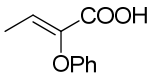
Asymmetric hydrogenation of enol ethers directly provides chiral ethers, which is advantageous to access building blocks used to prepare bioactive compounds such as Eriprotabid, Tesaglitazar and Aleglitazar[119] of

interest for agrochemical and pharmaceutical industries.[120] On the other hand, enol ethers are sensitive to acid and since homogeneous hydrogenations tend to form protons, the addition of base is required.

Among the variety of enol ethers, α-aryloxy and α-alkoxy α,β-unsaturated carboxylic acids have been the most popular for asymmetric hydrogenation, mainly because the resulting optically active α-oxy-functionalized carboxylic acids are important building blocks.[120-121] A feature of this α-aryloxy and α-alkoxy α,β-unsaturated carboxylic acids is that the carboxylate coordinates to the metal center, thus favoring the potential use of classical Rh- and Ru-diphosphine catalysts. In this context, a range of 3-methyl-2-aryloxyacrylic acids and 3-aryl-2-ethoxyacrylic acids have been successfully hydrogenated in excellent enantioselectivities using both Rh- and Ru-catalysts in the presence of base (Figure 12).[122] However, none of the Rh- and Ru-catalysts have been reported to give high enantioselectivity in the asymmetric hydrogenation of both α-aryloxy and α-alkoxy α,β-unsaturated carboxylic acids.



S66 R= OBn; Rh-Valphos; 92% ee
S67 R= CN; Rh-**68**; 98% ee

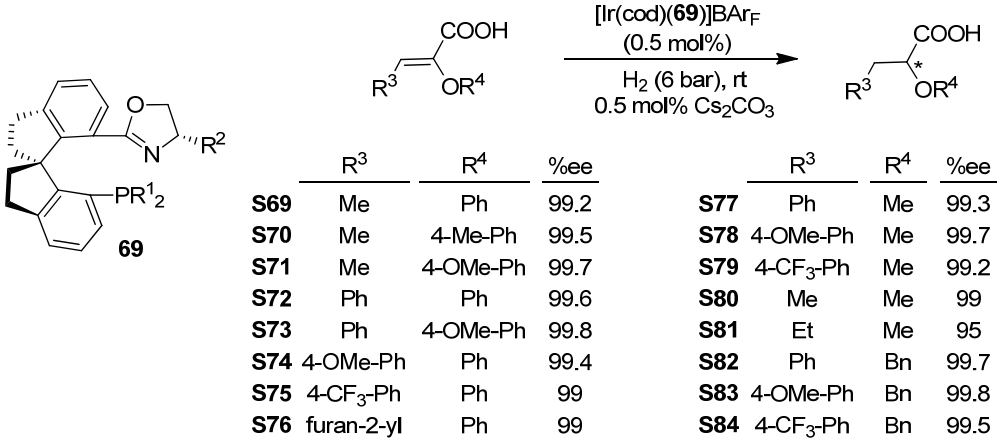


S68

Ru-SFDP; 94% ee
Ru-TMBTP; 99% ee

Figure 12 Representative enantioselectivities in the hydrogenation of 3-methyl-2-aryloxyacrylic acids and 3-aryl-2-ethoxyacrylic acids achieved using Rh- and Ru-catalytic systems. **68** = [(R_C,R_C), (S_{Fc},S_{Fc}), (S_P,S_P)]-1,1'-Bis[2-(1-N,N-Dimethylaminoethyl)-1-ferrocenyl]phenyl phosphino ferrocene.

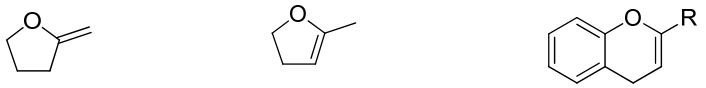
Zhou and coworkers have recently shown that chiral Crabtree's analogues are extremely effective in the hydrogenation of both α-aryloxy and α-alkoxy α,β-unsaturated carboxylic acids.[123] In this context, the authors found that using chiral spiro phosphino-oxazoline ligands **69** (Figure 13, R^1= Ph, 3,5-Me_2-Ph, 3,5-$^tBu_2$-Ph and R^2= Bn, Ph, Me and H), the hydrogenation proceeded smoothly to produce various α-aryloxy and α-alkoxy-substituted carboxylic acids with excellent enantioselectivities (ee's up to >99%) and reactivities (TON up to 10 000) under mild conditions (Figure 13). The results indicated that for aryloxy enol ethers **S69**-**S76** enantioselectivitites were best using ligand **69a**, containing bulky aryl phosphine substituents and a benzyl moiety in the oxazoline (Figure 13, R^1=3,5-$^tBu_2$-Ph and R^2= Bn), while for alkoxy enol ethers **S77**-**S84** enantioselectivities were best with ligand **69b** with a methyl oxazoline substituent (Figure 13, R^1=3,5-$^tBu_2$-Ph and R^2= Me). It should be noted that the hydrogenation of α-benzyloxy-substituted α,β-unsaturated acids provided an efficient alternative for the synthesis of chiral α-hydroxy acids after an easy deprotection. A mechanism involving a catalytic cycle between Ir^I and Ir^{III} was proposed on the basis of the coordination model of the unsaturated acids with the iridium metal center. The rationale for the catalytic cycle, with an olefin dihydride complex as the key intermediate, was supported by the deuterium-labeling studies.



	R^3	R^4	%ee		R^3	R^4	%ee
S69	Me	Ph	99.2	**S77**	Ph	Me	99.3
S70	Me	4-Me-Ph	99.5	**S78**	4-OMe-Ph	Me	99.7
S71	Me	4-OMe-Ph	99.7	**S79**	4-CF_3-Ph	Me	99.2
S72	Ph	Ph	99.6	**S80**	Me	Me	99
S73	Ph	4-OMe-Ph	99.8	**S81**	Et	Me	95
S74	4-OMe-Ph	Ph	99.4	**S82**	Ph	Bn	99.7
S75	4-CF_3-Ph	Ph	99	**S83**	4-OMe-Ph	Bn	99.8
S76	furan-2-yl	Ph	99	**S84**	4-CF_3-Ph	Bn	99.5

Figure 13 Representative enantioselectivities achieved in the hydrogenation of α-aryloxy substituted carboxylic acids (**S69**-**S76**) and α-alkoxy substituted carboxylic acids (**S77**-**S84**) using Ir-**69** catalytic system.

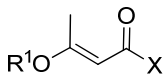
Another important class of enol ethers is the non-coordinating alkylated ones (that is to say those without the carboxylic group). For this substrate class, very few Rh- and Ru-catalysts have been applied and moderate enantioselectivities were observed. The Ru-BINAP catalytic system afforded enantioselectivities ranging from 64% to 91% for a small range of cyclic alkyl enol ethers (Figure 14).[124] Due to the lack of a coordinating group, Crabtree's analogues should be very appropriate for this substrate class and the first report on the use of Ir/N,P catalysts for this purpose was done by Pflatz and coworkers.[2d] They disclosed that Ir-**20a** catalyst (Figure 4) was able to hydrogenate 2-phenyl-1,4-benzopyran **S88** with complete conversion and 98% ee (Figure 14).



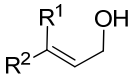
S85; Ru-BINAP 91% ee **S86**; Ru-BINAP 87% ee **S87** R= Me; Ru-BINAP 64% ee
S88 R= Me; Ir-**20d** 98% ee

Figure 14 Representative enantioselectivities for the hydrogenation of cyclic alkyl enol ethers using Ru-BINAP and Ir-**20** catalysts.

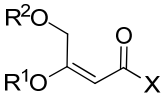
Burgess and coworkers disclosed an important finding in the hydrogenation of alkyl enol ethers. They showed that complexes of the type [Ir(cod)(N,P*)][BAr_F] generates protons under hydrogenation conditions and tend to decompose the substrates before they can be hydrogenated.[125] Iridium precursor with carbene-oxazoline ligand **26a** (Figure 4) is less prone to generate protons (i.e. less acidic) than similar N,P-ligated complexes and gave the chiral product without significant acid-mediated decomposition (Figure 15, ee's up to 98%).[126]



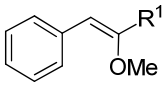
	R^1	X	%ee
S89	Me	OEt	78
S90	Et	OEt	66
S91	Me	NMe(OMe)	90
S92	Me	O^{t}Bu	88



	R^1	R^2	%ee
S93	Me	OMe	96
S94	Me	OEt	98
S95	Bu	OMe	93
S96	OMe	^{i}Pr	91



	R^1	R^2	X	%ee
S97	Me	Ac	NMe(OMe)	74
S98	Me	TBDPS	NMe(OMe)	94
S99	Me	TBDPS	OMe	75
S100	Bn	TBDPS	NMe(OMe)	90



	R^1	%ee
S101	$CO_2{}^t$Bu	9
S77	CO_2H	23
S102	CH_2OH	61
S103	CH_2OTBDP	52

Figure 15 Representative enantioselectivities for the hydrogenation of alkyl enol ethers using Ir-**26a** catalyst.

3.4 Silyl enol ethers

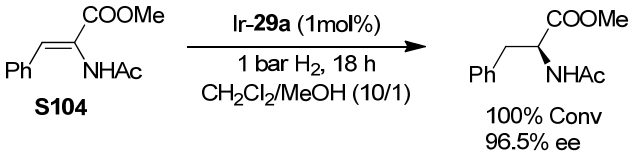
Silyl enol ethers are non-coordinative substrates of varying sensitivity towards acid-degradation. Silyl enol ethers have been hydrogenated using Rh-catalysts, though in the absence of an additional coordinating functionality, the enantioselectivities were extremely low (ee's up to 10%).[127] Andersson's group have also tried to hydrogenate this substrate class using Ir-Crabtree's analogues containing ligands **18** (Figure 4), **43** and **44** (Figure 6), but as for alkyl enol ethers complex mixtures were obtained.[62b] So, it is expected that, although no data has been reported yet, the use of Ir-catalysts modified with carbene-oxazoline ligands would be more appropriate in the asymmetric hydrogenation of silyl enol ethers.

4 Enamides and enamines

Traditionally, the asymmetric hydrogenation of enamines and enamides has been subject of interest as an alternative method to the asymmetric hydrogenation of imines for the preparation of chiral amines that can be used as resolving reagents, chiral auxiliaries, and intermediates for the synthesis of a variety of biologically active molecules.[128]

The hydrogenation of enamides is dominated by Rh- and Ru-catalysts modified with chiral phosphorus ligands mainly because of the coordinative ability of the amide group to the metal center.[128a] However, Knochel's group have demonstrated that chiral Crabtree's catalyst analogues can be successfully used in the asymmetric hydrogenation of enamides.[75] They found out that [Ir(cod)(**29a**)][BAr_F] catalytic precursor (Figure 5) can hydrogenate (*Z*)-methyl 2-acetylamino-3-phenylacrylate **S104** in high enantiomeric excess (up to 96.5%; Scheme 19) under mild reaction conditions

(1 bar H_2). Despite this early success in the synthesis of chiral amino acids, the use of other Ir-complexes has not yet been reported.



Scheme 19 Asymmetric hydrogenation of enamide **S104** using Ir-**29** catalysts

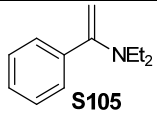
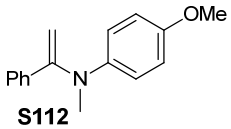
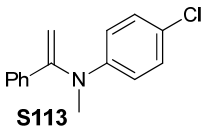
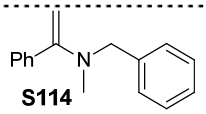
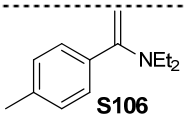
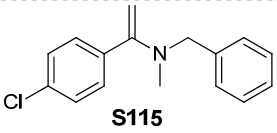
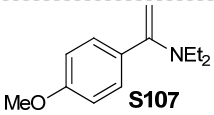
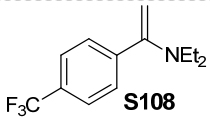
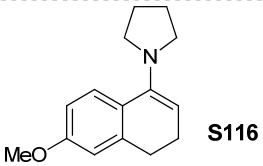
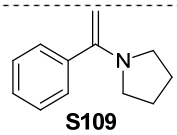
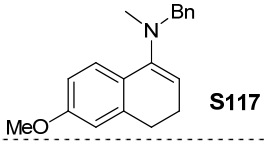
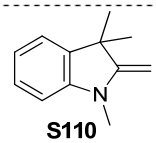
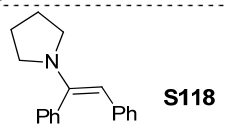
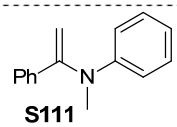
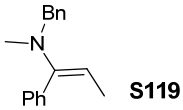
In contrast with the hydrogenation of enamides, there are very few examples of successful enantioselective hydrogenation of *N*,*N*-dialkyl enamines, which provides a direct approach to chiral tertiary amines. Enamines are electron-rich and moisture sensitive, thus poor substrates,[128a] but the low coordinative ability of the enamines still makes them an attractive class of alkenes for the enantioselective hydrogenation using Crabtree's analogues. Despite this, to the best of our knowledge, only two reports have been published.[129]

In 2008, Andersson's group was able to identify *N*-phosphine-oxazoline ligand **18b** (Figure 4) as a suitable ligand for the hydrogenation of enamines after screening the group ligand's portfolio (Table 6, entries 2-3 and 5-7).[129a] Moderate-to-high enantioselectivities (ee's up to 84%) were achieved in the asymmetric reduction of terminal 1-amino-1-aryl alkenes with no β-substituents (Table 6, entries 2-3, 5-9, 10, 12, 14, 16). Interestingly, complete conversion to product tertiary amine was observed at room temperature using 50 bar H_2, but enantioselectivities were highly substrate dependent. The results indicate that enantioselectivities decreased considerably when the amino group was cyclic (i.e. ee's reduced from 84% to 33% by replacing the diethylamine group by a pyrrolidino group; Table 6, entries 2 vs 12) and for *exo*-cyclic enamines (i.e. Table 6, entry 14).

In 2009, Pfaltz's group reported the use of phosphine-oxazoline (**8**, Figure 3 and **15**, Figure 4), phosphinite-oxazoline (**20**, Figure 4) and phosphinite-pyridine (**33**, Figure 5) ligands in the asymmetric hydrogenation of several terminal 1-aryl-enamines as well as several *endo*-cyclic and *E*-acyclic enamines.[129b] The best results were achieved with 1-amino-1-aryl alkenes bearing an aryl (ee's up to 91%; Table 6, entries 15, 18 and 20) or a benzyl (ee's up to 92.5%; Table 6, entries 23 and 25) substituent on the nitrogen atom, which were hydrogenated with good enantiomeric excesses using phosphine-oxazoline ligand **8d** (Figure 3) and the phosphinite-oxazoline ligand **20a** (Figure 4), respectively. Enantioselectivities in the hydrogenation of *endo*-cyclic and *E*-acyclic enamines were lower (ee's ranging 67-87%; Table 6, entries 26-29).

Table 6 Selected results for the asymmetric hydrogenation of enamines.

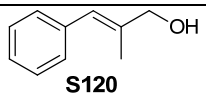
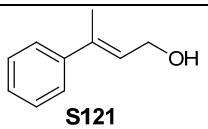
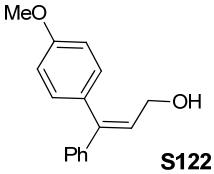
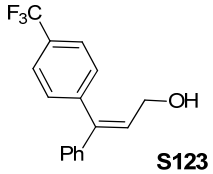
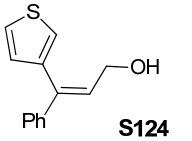
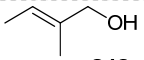
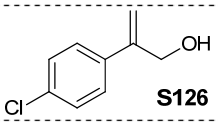
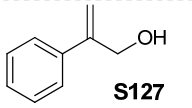
Entry	Substrate	[M]/L	%	Ref	Entry	Substrate	[M]/L	%	Ref.

			ee					ee	
1	 **S105**	Ir-**8d**	18	131b	18	 **S112**	Ir-**8d**	90	131b
2		Ir-**18a**	84	131a	19		Ir-**20a**	20	131b
3		Ir-**18b**	54	131a					
4		Ir-**20a**	54	131b					
5		Ir-**42a**	0	131a	20	 **S113**	Ir-**8d**	90.5	131b
6		Ir-**44a**	14	131a	21		Ir-**20a**	55	131b
7		Ir-**50a**	0	131a					
					22	 **S114**	Ir-**8d**	56	131b
8	 **S106**	Ir-**18b**	87	131a	23		Ir-**20a**	92.5	131b
					24	 **S115**	Ir-**8d**	27	131b
9	 **S107**	Ir-**18b**	64	131a	25		Ir-**20a**	76	131b
10	 **S108**	Ir-**18b**	77	131a	26	 **S116**	Ir-**20a**	87	131b
11	 **S109**	Ir-**8d**	44	131b					
12		Ir-**18b**	33	131a	27	 **S117**	Ir-**33a**	71	131b
13		Ir-**20a**	8	131b					
14	 **S110**	Ir-**18b**	20	131b	28	 **S118**	Ir-**15c**	69	131b
15	 **S111**	Ir-**8d**	91	131b					
16		Ir-**18b**	79	131a	29	 **S119**	Ir-**15c**	67	131b
17		Ir-**20a**	13	131b					

5 Allylic and homoallylic alcohols and ethers

The asymmetric hydrogenation of allylic alcohols is of interest because they are abundant in natural sources such as essential oils, and widely used as starting materials and/or major components in food, fragrance and pharmaceutical industries.[130] The hydrogenation of allylic alcohols have been traditionally been dominated by Ru-complexes modified with chiral diphosphines.[131] However, from the early reports on the use of chiral Ir-Crabtree's analogues using the PHOX ligands **8** (Figure 3), it was clear that this substrate class can be hydrogenated with high enantioselectivity.[26] Thus, *trans*-2-methyl-3-phenyl-2-propen-1-ol **S120** was hydrogenated in excellent enantioselectivities (ee's up to 96%; Table 7, entry 1). Since then the commercially available substrate **S120** has been used as a benchmark to test new Ir-catalysts (Table 7). The best enantioselectivities have been achieved using ligands **13a**[56] (Figure 4) and **44a**[90] (Figure 6) ligands (ee's up to 99%; Table 7, entries 3 and 16).

Table 7 Selected results for the asymmetric hydrogenation of allylic alcohols

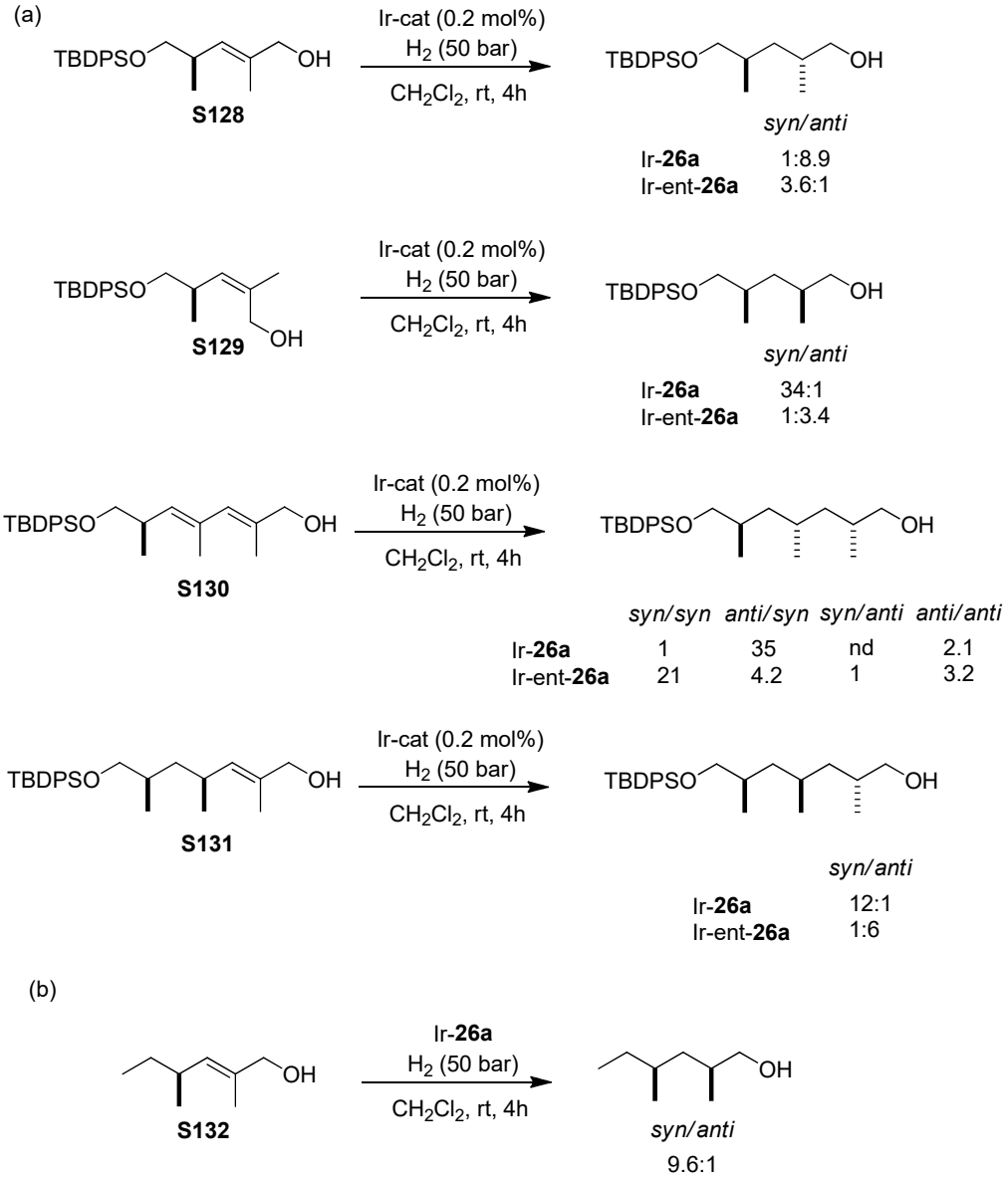
Entry	Substrate	[M]/L	% ee	Ref	Entry	Substrate	[M]/L	% ee	Ref.
1	 **S120**	Ir-**8a**	96	26					
2		Ir-**10b**	67	54	25	 **S121**	Ir-**49a**	97	63
3		Ir-**13a**	98.8	57	26		Ir-**36**	90	96
4		Ir-**14a**	90	58					
5		Ir-**15b**	96	44					
6		Ir-**16c**	95	60	27	 **S122**	Ir-**42b**	92	63
7		Ir-**20d**	97	68a					
8		Ir-**24a**	92	74a					
9		Ir-**25a**	93	75a					
10		Ir-**29a**	69	77					
11		Ir-**32b**	96	79	28	 **S123**	Ir-**42b**	92	63
12		Ir-**33a**	97	81a					
13		Ir-**35**	42	84					
14		Ir-**39**	95	86					
15		Ir-**43a**	98	91	29	 **S124**	Ir-**42b**	90	63
16		Ir-**44a**	99	92					
17		Ir-**46b**	96	93					
18		Ir-**49a**	91	63	30	 **S125**	Ir-**20d**	91	81c
19		Ir-**50a**	93	96	31		Ir-**33a**	91	81c
20		Ir-**52a**	70	99					
21		Ir-**53a**	49	100	32	 **S126**	Ir-**20a**	88	69
22		Ir-**54**	20	101					
23		Ir-**59b**	90	104c	33	 **S127**	Ir-**25b**	95	75b
24		Ir-**62c**[g]	81	105	34		Ir-**46b**	90	93
					35		Ir-**59b**	83	104c

[g] R^1= ^{t}Bu; R^2= NCy_2.

The substrate scope has been recently extended to include 1,1-aryl/alkyl-, 1,1-diaryl- and 1,3-dialkyl trisubstituted allylic alcohols and also more challenging terminal allylic alcohols. For 1,1-aryl/alkyl and 1,1-diaryl trisubstituted olefins **S121**-**S124** the best enantioselectivities have been achieved using phosphine-thiazole **49a** (Figure 6) and phosphine-imidazole **42b** (Figure 6) ligands, respectively (Table 7, entries 25 and 27-29).[61,94] For the alkyl allylic alcohol **S125** the Pfaltz's group has demonstrated that the use of phosphinite-oxazoline **20d** (Figure 4) and phosphinite-pyridine **33a** (Figure 5) ligands lead to high enantiomeric excess (ee's up to 91%; Table 7, entries 30-31).[79c] This later finding was further exploited to hydrogenate all four stereoisomers of farnesol (Section 2.1.2, Scheme 14b).[132] For terminal allylic alcohols, the Ir-catalyzed asymmetric hydrogenation has achieved ee's up to 88% in the hydrogenation of **S126** using phosphinite-oxazoline **20a** (Figure 4) ligand (Table 7, entry 32).[67] Introducing a phosphite moiety in the ligand design is advantageous, achieving enantioselectivities up to 95% in the reduction of **S127** (Table 7, entry 33).[73b]

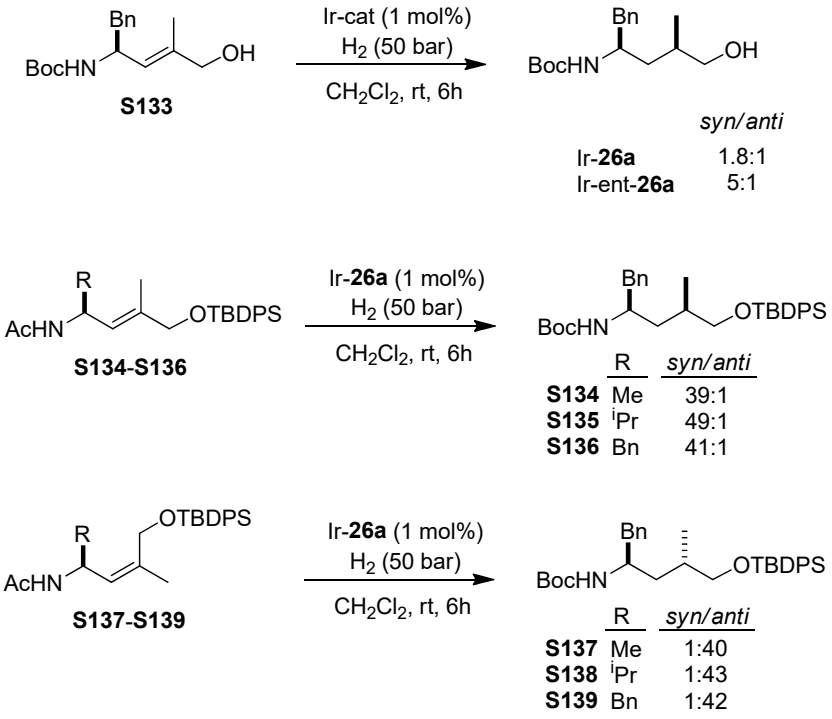
In 2007, Burgess and co-workers demonstrated that diastereoselective hydrogenation of allylic alcohols can be efficiently used to construct α,ω-functionalized 1,3-dimethyl and 1,3,5-trimethyl fragments (Scheme 20a).[133] This finding constitutes an alternative to the diastereoselective

hydrogenations of chiral homoallylic alcohols achieved mainly using Rh- and Ir-diphosphine catalysts, which takes advantage of the chelating ability of the homoallylic substrate to achieve high diastereoselectivities.[134] They showed that the chiral Crabtree analogue containing carbene-oxazoline ligand **26a** (Figure 4) efficiently hydrogenated substrates **S128**-**S131** to achieve the α,ω-difunctionalized 2,4-dimethylpentane and 2,4,6-trimethylheptane in high diastereoselectivity. Interestingly, catalyst Ir-ent-**26a** gave appreciable selectivity in the opposite diastereoisomer, which illustrates that catalyst control is operative in these reactions. However, the geometry of the allylic alcohol is significant for optimizing the selectivity of the process. Thus, while for the reduction of *E*-allylic alcohol **S128**, the Ir-**26a** catalyst favored the *anti* product (*syn*/*anti*= 1:8.9), the use of *Z*-allylic alcohol **S129** favors the *syn* product (*syn*/*anti*= 34:1) using Ir-**26a** (Scheme 20a).[133a,135] The potential application of this methodology has been demonstrated with the preparation of (*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-hexamethyldocosane, a putative sex pheromone from an Australian beetle, for which the diastereoselective hydrogenation of **S129** is the key step.[133b] Additionally, the same authors proved that α-monofunctionalized 1,3-dimethyl chiral fragments can be achieved albeit with lower stereocontrol compared with the α,ω-difunctionalized (Scheme 20b).[136]



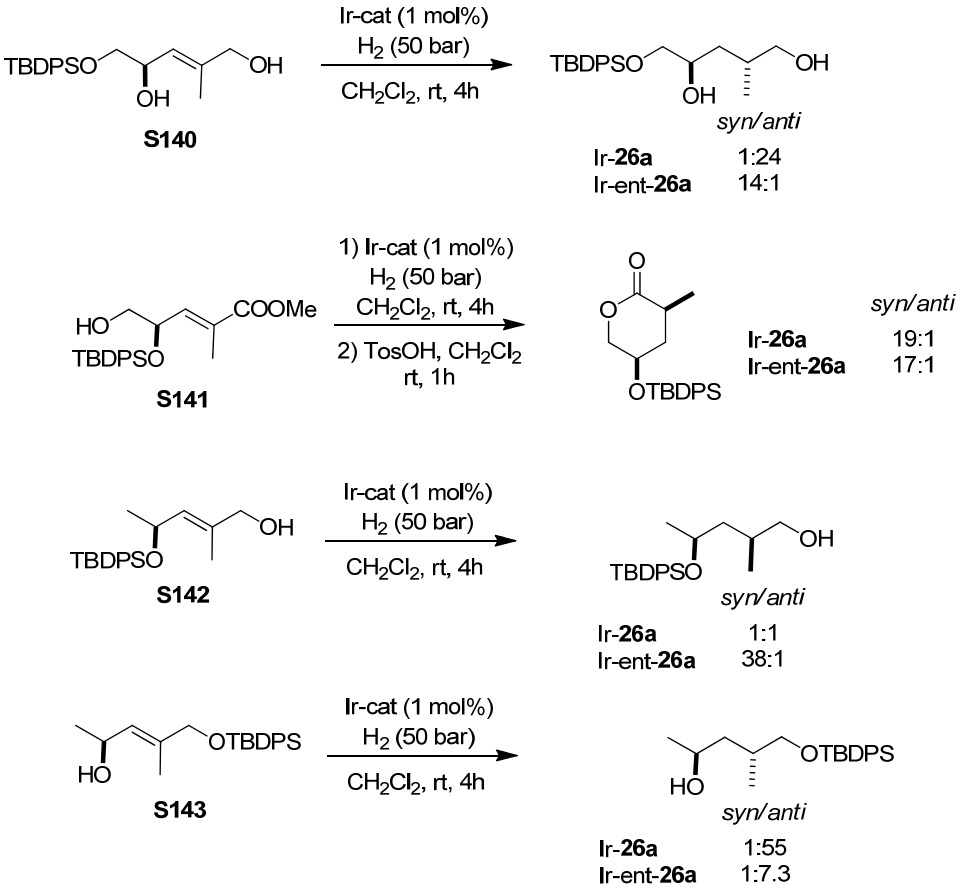
Scheme 20 Hydrogenation of allylic alcohols **S128-S132**.

More recently, Burgess's group has further exploited this methodology for the preparation of α-methyl-γ-aminoacid derivatives from *N*-acetyl protected allylic alcohols (*syn*/*anti* up to >19:1; Scheme 21).[137] However, the stereoselectivity can be improved by protecting the alcohol using a *tert*-butyldiphenylsilyl protecting group (*syn*/*anti* up to 49:1).



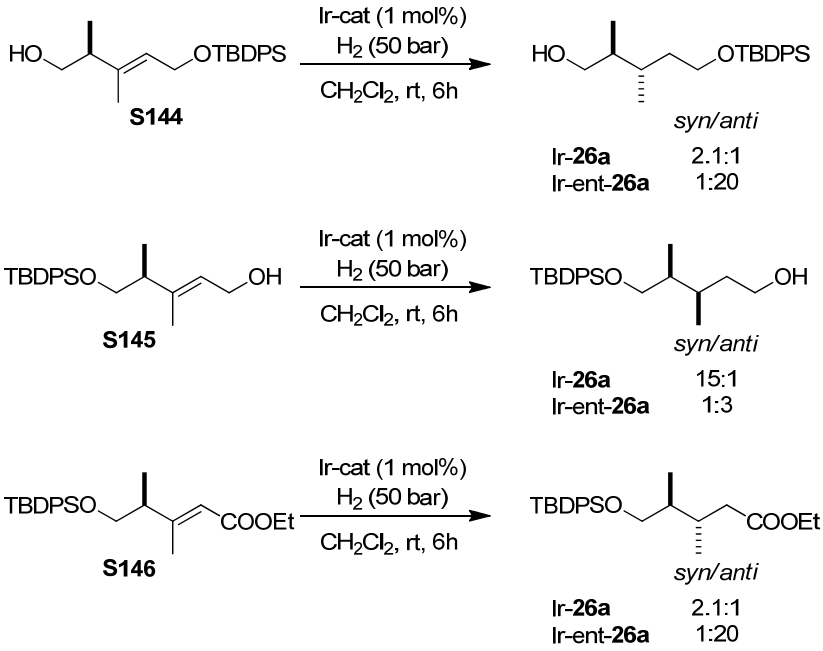
Scheme 21 Hydrogenation of *N*- or *O*-protected amino alcohol derivatives **S133**-**S139**.

In 2008, the Burgess group disclosed that diastereoselective reduction of allylic alcohols can be used as an efficient alternative for the preparation of 1,3-hydroxymethyl fragments.[138] The hydrogenation of the allylic alcohol **S140** is catalyst controlled, which allows the preparation of both *syn* and *anti* stereoisomers with high stereocontrol (Scheme 22). This behavior contrast to the one observed in the hydrogenation of the related homoallylic alcohol **S141**, which proceeds via substrate control and therefore only one isomer is preferentially formed (Scheme 22). The same authors also explored alkenes derived from lactic acid (substrates **S142** and **S143**, Scheme 22) and they found that while the hydrogenation of **S142** proceeds via catalyst control, the reduction of **S143**, in which the protecting group has been swapped from the secondary alcohol to the primary one, proceeds via substrate control.[138] The latter has been attributed to the coordination of the allylic alcohol to iridium, which can occur via direct oxygen coordination to iridium or via hydrogen bonding from an Ir-hydride to the allylic alcohol oxygen. The authors illustrated the potential utility of this methodolgy in the total syntheses of (–)-dihydromyoporone[138] and (–)-spongidepsin.[139]



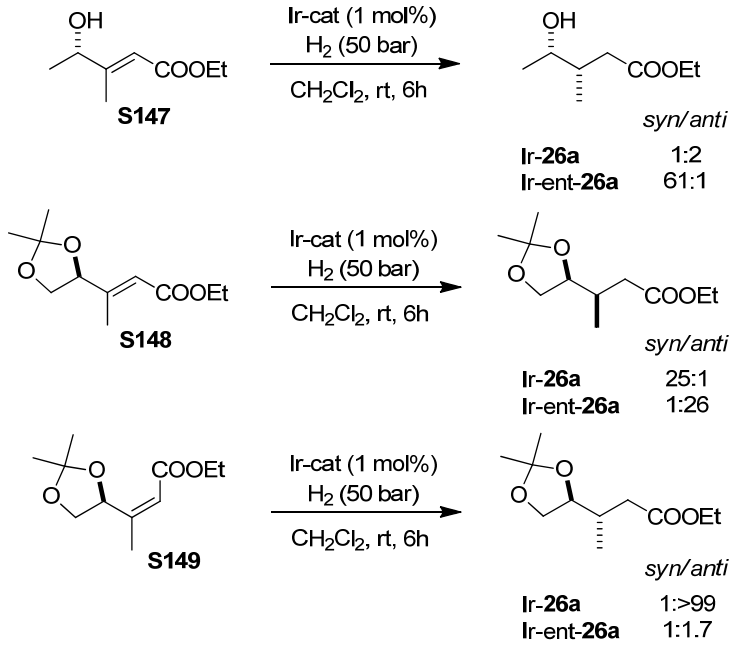
Scheme 22 Hydrogenation of allylic and homoallylic alcohols **S140**-**S143**.

More recently, Burgess and co-workers demonstrated that chiral Crabtree-type catalysts could be used to prepare 1,2-dimethyl fragments very efficiently from chiral allylic and homoallylic alcohols (Scheme 23). In all cases studied the hydrogenation proceeds with catalyst control rather than substrate control, which allows the formation of both diastereoisomers.[140] However, the substrate also has a small but important effect on the stereoselectivities. Thus, while coordination effects are significant for homoallylic alcohols (i.e. substrate **S144**) the steric factors are important for the homoallylic silyl ethers (i.e. substrate **S145**). This methodology was used in the synthesis of the central region of the neurotoxin (+)-kalkitoxin, and in the total synthesis of (–)-lasitol, a substance isolated from *Lasius meridionalis* ants.[140]



Scheme 23 Hydrogenation of allylic and homoallylic alcohols **S144**-**S146**

Similarly, chiral aldol-type 1,2-hydroxymethyl fragments were efficiently synthesized from trisubstituted allylic alcohols using chiral analogues of Crabtree's catalyst allowing both the *syn*- and *anti*-isomers to be obtained (Scheme 24).[141] This methodology contrasts with those developed using terminal allylic alcohols with metal-diphosphine catalysts that mostly proceeds under substrate control.[142] It is interesting to note that the best *syn*-selectivity was achieved using allylic alcohol **S147** (Scheme 24). The same authors successfully reduced glucitol derivatives **S148**-**S149**, which gives access to α,ω-difunctional fragments (Scheme 24).



Scheme 24 Hydrogenation of allylic alcohol derivatives **S147**-**S149**.

6 α,β-Unsaturated carbonyls

6.1 α,β-Unsaturated carboxylic acids

Asymmetric hydrogenation of α,β-unsaturated carboxylic acids using [Ru(BINAP)(OAc)$_2$] was described by Noyori in 1987[11] and has since been thoroughly developed to include a variety of di- and trisubstituted alkenes (Figure 16).[122a,b,143] The reaction has also proven to be feasible using rhodium-diphosphine or phosphoramidite catalysts although with somewhat limited substrate scope.[122c,d,144]

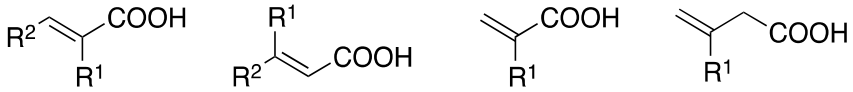
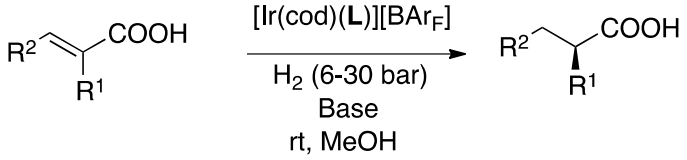


Figure 16 Typical substrates for the Rh and Ru catalyzed hydrogenation.

During the past few years, chiral analogues of Crabtree's catalyst have been used, mainly by Zhou and co-workers, to enantioselectively reduce these types of alkenes. α-Substituted cinnamic acids, which have served as the benchmark substrates for the ruthenium-catalyzed reaction are also the most studied with [Ir(cod)(N,P)][BAr$_F$] complexes. Unlike hydrogenation of weakly-functionalized olefins, the asymmetric hydrogenation of α,β-unsaturated carboxylic acids is commonly performed in methanol and thus similar to the traditional P,P-ligated rhodium catalytic systems. Analogous to the ruthenium and rhodium case, coordination of the carboxylate ion to form a chelate with iridium is likely and has been suggested.

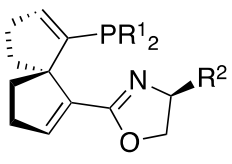
Using their spirocyclic ligand **69a** (Figure 13, R^1=3,5-^{t}Bu$_2$-Ph and R^2= Bn), Zhou and co-workers could reduce several α-alkyl substituted cinnamic acids (**S150** and **S151**) in excellent enantioselectivity (Table 8, entries 1 and 2).[145] The reaction featured high catalytic activity under mild conditions but addition of base was crucial for high catalytic activity. A slightly modified ligand **69c** (Figure 13, R^1=3,5-^{t}Bu$_2$-Ph and R^2= ^{i}Pr) was used when targeting alkyl-alkyl substituted alkenes (i.e. substrates **S152**-**S153**; Table 8, entries 3 and 4).

Table 8 Representative results from the asymmetric hydrogenation of α,β-disubstituted α,β-unsaturated carboxylic acids using spirocyclic ligands **69** and **70**.



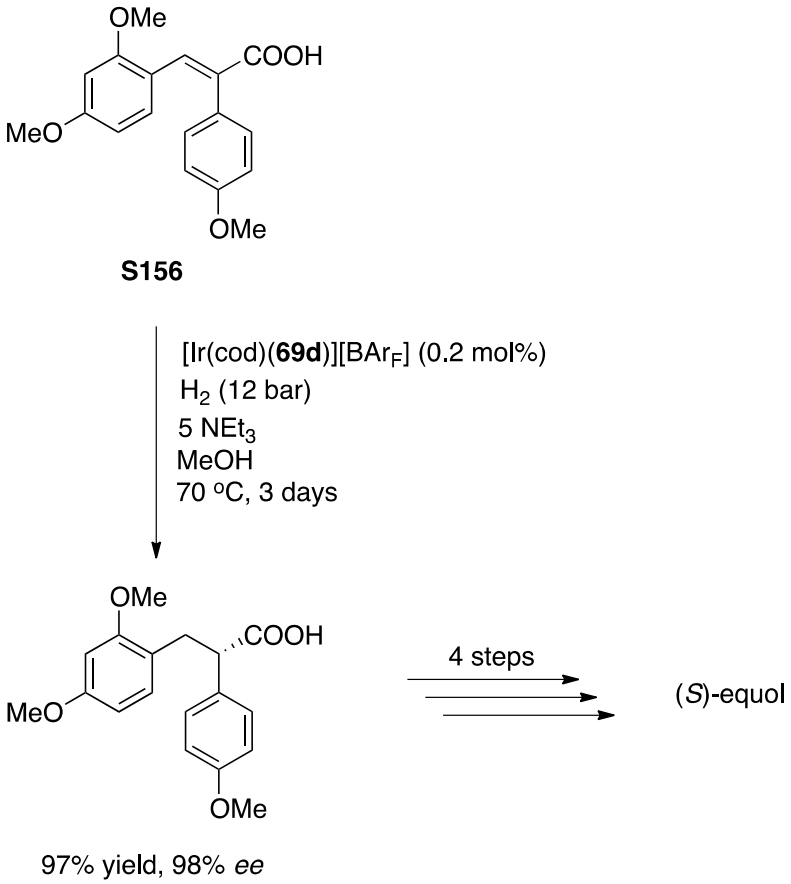
Entry		R^1	R^2	Ir-cat. (mol%)	L	Base	ee (%)	Ref.
1	**S150**	Me	Ph	0.25	**69a**	0.5 NEt_3	>99	147
2	**S151**	^{i}Pr	Ph	0.25	**69a**	0.5 NEt_3	99	147
3	**S152**	Me	Et	0.25	**69c**	0.5 Cs_2CO_3	98	147
4	**S153**	^{n}Pr	Me	0.25	**69c**	0.5 Cs_2CO_3	98	147
5	**S154**	Ph	Me	1.0	**70a**	1.0 NEt_3	94	148
6[a]	**S155**	Ph	Ph	1.0	**70a**	1.0 NEt_3	94	148
7[b]	**S155**	Ph	Ph	0.25	**69d**	0.5 Cs_2CO_3	95	149

[a] Reaction performed at 50 °C. [b] Reaction performed at 45 °C.



70

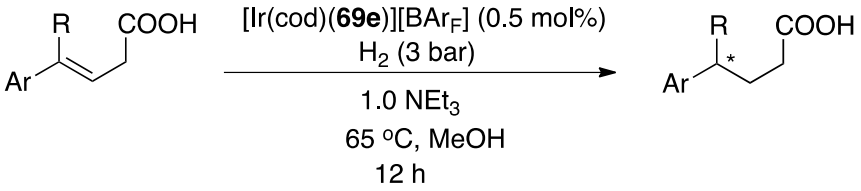
Another spirocyclic phosphine-oxazoline ligand, **70a** (Table 8, R^1= o-tol, R^2= Ph), was utilized by Ding and Zhang in the asymmetric hydrogenation of α-aryl substituted unsaturated carboxylates **S154** and **S155**.[146] Under somewhat more forceful conditions, enantioselectivities >90% ee were obtained for a series of substrates (Table entries 5 and 6). Ligand **69d** (Figure 13, R^1=3,5-^{t}Bu$_2$-Ph and R^2= H), which contains an unsubstituted oxazoline ring, was the best ligand from this family in the reduction of these bulky alkene substrates (Table 8, entry 7).[147] The reaction could be performed under one atmosphere of H_2 and enantioselectivities over 90% were consistently obtained. Synthesis of the isoflavane derivative (*S*)-equol using this methodology as the enantiodetermining step resulted in conversion of **S156** in 97% yield and 98% ee (Scheme 25). By increasing the reaction time and temperature a substrate to catalyst ratio of 5000:1 could be used.



Scheme 25 The enantiodetermining step in the preparation of (*S*)-equol from **S156** is catalyzed by [Ir(cod)(**69d**)][BAr$_F$].

As mentioned in section 3.3, Zhou and co-workers also performed asymmetric hydrogenations of a variety α-aryloxy and α-alkyloxy crotonic and cinnamic acids using Ir-catalysts based on ligand **69** (Figure 13).[145] The catalytic system tolerated variation of the ether-group but more importantly, the β-substituent could be changed from Ph to Me to H while retaining good enantioselectivity.[123]

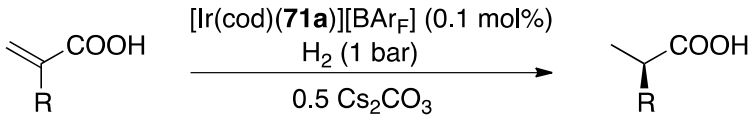
The successful asymmetric hydrogenations of crotonic- and cinnamic-acid derivatives using iridium catalysts based on the spirocyclic oxazoline backbones prompted Zhou to further expand the substrate scope. At 65 °C, *E*-4-methyl-4-phenyl-3-butenoic acid **S157** could be effectively reduced by [Ir(cod)(**69**)][BAr$_F$] in 60 % ee provided that one equivalent of triethylamine or a similar amine base was present.[148] Enantioselectivities above 90% ee required changing the phosphine substituents to 3,5-dimethylphenyl and when exchanging the benzyl substituent on the oxazoline to α-methylnaphthyl (ligand **69e**, Figure 13, R^1=3,5-Me$_2$-Ph and R^2= CH$_2$-1-naphthyl) ee's around 95% were obtained. With [Ir(cod)(**69e**)][BAr$_F$], a series of 4,4-disubstituted 3-butenoic acids could be hydrogenated with good enantioselectivities (Scheme 26).



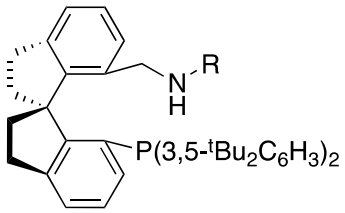
	Ar	R	ee (%)
S157	Ph	Me	95
S158	4-MeO-C_6H_4	Et	92
S159	4-MeO-C_6H_4	^{i}Pr	88

Scheme 26 Asymmetric hydrogenation of some β,β-disubstituted-α,β-unsaturated acids **S157-S159**.

Yet another type of α,β-unsaturated carboxylic acids, α-substituted acrylic acids, were reduced only slowly and in modest enantioselectivity using [Ir(cod)(**69**)][BAr$_F$], under reaction conditions similar to those described above. Instead, spirocyclic ligands where the oxazoline N-donor had been replaced by a primary or secondary amine proved to consistently give enantioselectivities >90% ee.[149] Ligands **71a** and **71b** both exhibited high selectivity but the former was significantly faster and thus used for further studies of both alkyl- (**S161**-**163**) and aryl-substituted (**S160**) derivatives (Scheme 27). Using 0.1 mol% of [Ir(cod)(**71a**)][BAr$_F$] under an atmosphere of hydrogen for 4 h brought about quantitative yields and excellent enantioselectivities for a range of aryl- and alkyl-substituted substrates.



	R	ee (%)
S160	Ph	98
S161	^{i}Pr	96
S162	^{n}Hex	98
S163	CH_2COOMe	97



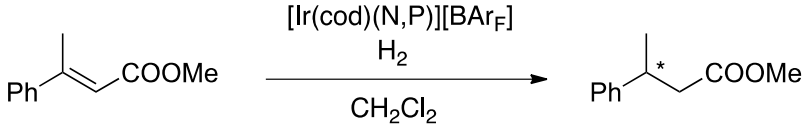
71a R = H
71b R = Me

Scheme 27 Asymmetric hydrogenation of some α-substituted acrylic acids using phosphine-primary amine catalyst Ir-**71a**.

6.2 α,β-Unsaturated esters

While (deprotonated) carboxylic acids are excellent coordinating functional groups, α,β-unsaturated esters are less so, and the α- and especially *trans*-β-

methyl cinnamate esters such as **S164** (Scheme 28) are typical test substrates for the asymmetric hydrogenation using [Ir(cod)(N,P)][BAr_F] complexes in CH_2Cl_2. The hydrogenation product have been obtained in >95% ee using several ligands (Scheme 28).[43,71c,77,90,94-95,98,103a]



S164

>95 ee
Many examples

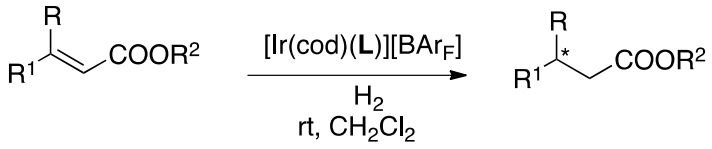
Scheme 28 *trans*-β-Methyl cinnamate ester **S164** has been hydrogenated in excellent enantioselectivity by a large number of N,P-ligated Ir-complexes.

Other β,β-disubstituted acrylate esters than **S164** have been less explored but recently chiral mimics of Crabtree's catalyst proven to be a general method for the asymmetric hydrogenation of these alkenes. Both the *E*- and *Z*- isomer of the challenging methyl/phenethyl derivatives **S165** and **S166** (Table 9, entries 1 and 2) could be reduced in good enantioselectivity using the successful pyridine-phosphinite ligands **33a** and **33b** (Figure 5), developed in Pfaltz group.[79a]

As described in section 3.3, Zhu and Burgess performed the asymmetric hydrogenation of unsaturated esters that also contain vinylic ethers with good results using ligand **26a** (Figure 4).[126a] Hou and co-workers used ligand **14a** (Figure 4) to obtain enantioselectivities over 90% for several β,β-substituted α,β-unsaturated esters.[57] Both the β-methyl (**S167**) and β-ethyl (**S168**) derivative could be reduced highly selectively (Table 9, entries 3 and 4), but more significantly, the *Z*-alkene **S169** could be reduced in 92% enantioselectivity (entry 5).

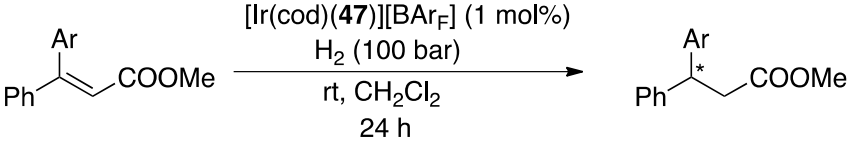
Very recently, one of us decided to perform a comprehensive screening of α,β-unsaturated esters in the Ir-catalyzed asymmetric hydrogenation in order to thoroughly establish the substrate scope.[150] Previously developed bicyclic ligands **18b** (Figure 4) and **50b** (Figure 6), which give excellent enantioselectivity in the asymmetric hydrogenation of both *E*- and *Z*- β-methyl cinnamate esters were used.[60a,95] A range of structurally different substrates (**S170**-**S173**) could be reduced with excellent enantioselectivity (Table 9, entries 6–9).[150] In all cases, when changing between the *E*- and *Z*- isomers, products with opposite absolute configuration were obtained using catalysts with the same configuration (Table 9, **S170** vs. **S171** and **S172** vs. **S173**).

Table 9 Representative results from the asymmetric hydrogenation of β,β-disubstituted acrylate esters.



Entry		R	R^1	R^2	L	ee (%)	Ref.
1	**S165**	Me	CH_2Bn	Et	**33a**	89	81a
2	**S166**	CH_2Bn	Me	Et	**33b**	93	81a
3	**S167**	Me	4-MeO-C_6H_4	Et	**14a**	98	58
4	**S168**	Et	4-MeO-C_6H_4	Et	**14a**	98	58
5	**S169**	4-MeO-C_6H_4	Me	Et	**14a**	92	58
6	**S170**	^{i}Pr	Ph	Et	**18b**	>99 (*S*)	152
7	**S171**	Ph	^{i}Pr	Et	**50b**	>99 (*R*)	152
8	**S172**	Me	CH_2Ph	Et	**18b**	93 (+)	152
9	**S173**	CH_2Ph	Me	Et	**50b**	85 (–)	152

β,β-Diaryl methyl acrylates (β-aryl cinnamate esters) have been reduced using N,P-ligated iridium complexes, albeit less enantioselectively. With 1 mol% [Ir(cod)(**47**)][BAr_F] under 100 bar H_2, three of these sterically very demanding alkenes (**S174-S176**) could be hydrogenated in moderate enantioselectivity (Scheme 29).[61]

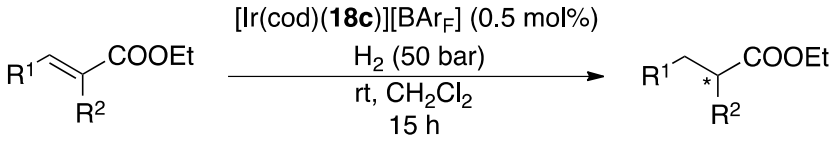


	Ar	ee (%)
S174	4-MeO-C_6H_4	69
S175	3-thiophenyl	87
S176	3-furyl	80

Scheme 29 Asymmetric hydrogenation of some β-aryl cinnamate esters using [Ir(cod)(**47**)][BAr_F].

trans-α-Methyl cinnamates have also been used as substrates for asymmetric hydrogenation with chiral analogues of Crabtree's catalyst but has given high enantioselectivity less frequently than its β-substituted counterpart.[60a,71c,95,103a]

During attempts to identify suitable ligands for the asymmetric hydrogenation of α,β-substituted ethyl acrylates, bicyclic oxazoline **18c** (Figure 4) was identified as an especially selective ligand.[150] Using 0.5 mol% [Ir(cod)(**18c**)][BAr_F], both alkyl and aryl-substituted alkenes could be reduced in excellent enantioselectivity (Scheme 30).

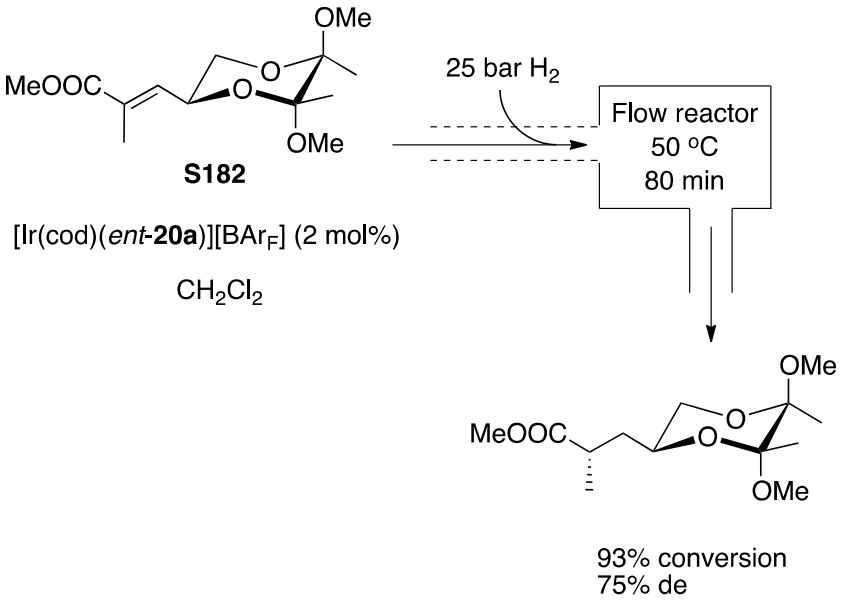


	R^1	R^2	ee (%)
S177	Me	Me	97
S178	Ph	Me	95
S179	Ph	Et	96
S180	Ph	^{i}Bu	90
S181	^{n}Pr	Me	93

Scheme 30 Asymmetric hydrogenation of α,β-substituted ethyl acrylates **S177**-**S181**.

In addition to varying the alkene substituents, different tiglate and α-methyl cinnamate esters were also compared. Both achiral (Et, Bn and ^{i}Pr) and chiral (*rac*- and (+)-1-phenylethyl) esters had modest influence on the outcome of the reaction with a difference in enantioselectivity of +/– 4% ee.

Newton, Ley and co-workers performed the diastereoselective hydrogenation of the α,β-unsaturated ester **S182** by co-feeding it together with 2 mol% [Ir(cod)(*ent*-**20a**)][BAr_F] (Figure 4) and CH_2Cl_2 into a flow-reactor.[151] Hydrogen was added by a tube-in-tube diffusion system and by heating the flow to 50 °C for 80 min, the product could be obtained in 75% diastereomeric excess (Scheme 31). By modifying the setup, the catalyst loading could be decreased but, although several catalysts were tested, the diastereomeric excess could not be significantly improved.

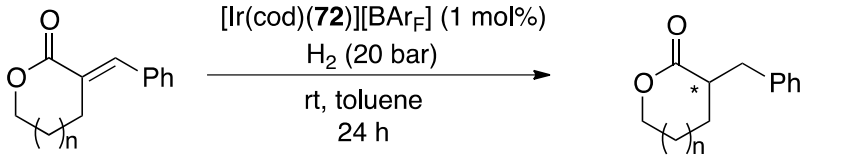


Scheme 31 Diastereoselective hydrogenation of **S182** performed in a flow reactor setup.

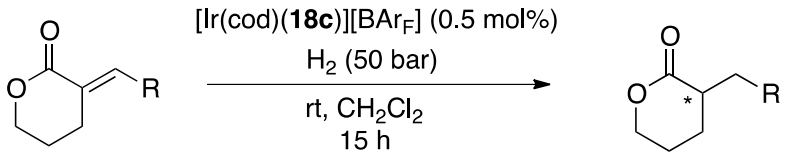
Ir-catalyzed asymmetric hydrogenation of α,β-unsaturated lactones has been studied by Zhang and co-workers who, while also studying ketones and lactams, attempted the reduction of five- and six-membered α,β-unsaturated

lactones with exocyclic double bonds.[152] [Ir(cod)(**72**)][BAr_F], under 20 bar H_2 in toluene, reduced the unsaturated five-membered lactone **S183** in 95% ee and the unsaturated six-membered lactone **S184** in 71% ee (Scheme 32).

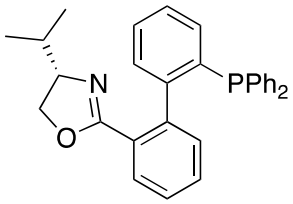
Ir-**18c** (Figure 4), which formed an excellent catalyst for the enantioselective reduction of α,β-substituted acyclic esters, also reduced the six-membered phenyl- and methyl-substituted alkenes **S184** and **S185**, giving the saturated lactones in excellent ee (Scheme 32).[150]



	n	conv. (%)	ee (%)
S183	0	100	95
S184	1	100	71



	R	conv. (%)	ee (%)
S184	Ph	>99	99
S185	Me	>99	96



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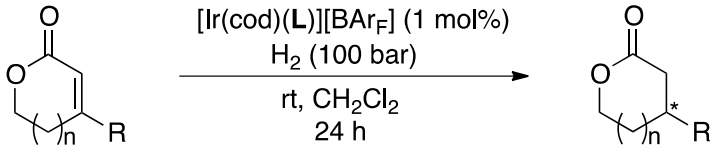
Scheme 32 Asymmetric hydrogenation of some α,β-unsaturated lactones with exocyclic alkenes, **S183**-**S185**.

While the asymmetric hydrogenation of exocyclic alkenes in α,β-unsaturated lactones gives, by necessity, products with an α-CH_2R substituent, the reduction of α,β-unsaturated lactones with a β-substituted internal alkene gives more useful products. Unfortunately, the reduction of such alkenes has been shown to proceed only very slowly using ligands developed by the Andersson group.[153] Five-membered methyl- and phenyl-substituted alkenes **S186** and **S187** were reduced in good enantioselectivity but only to 20% conversion after 24h under 100 bar H_2 using catalysts based on bicyclic ligands **18b** (Figure 4) and **50b** (Figure 6) (Scheme 33). For the six-membered variants, phosphine-imidazole ligand **42b** (Figure 6) gave similar selectivity and conversion for the phenyl-derivative **S188** while the methyl-substituted alkene **S189** was completely reduced.[153]

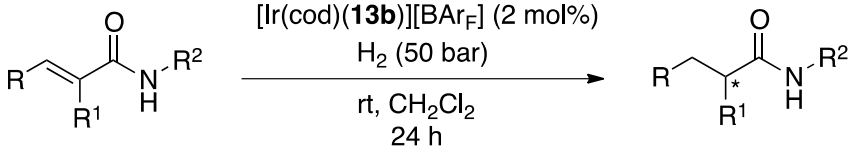


	n	R	L	conv. (%)	ee (%)
S186	0	Ph	**18b**	20	92
S187	0	Me	**50b**	24	85
S188	1	Ph	**42b**	15	93
S189	1	Me	**42b**	99	79

Scheme 33 Asymmetric hydrogenation of α,β-unsaturated lactones with endocyclic alkenes, **S186**-**S189**.

6.3 α,β-Unsaturated amides

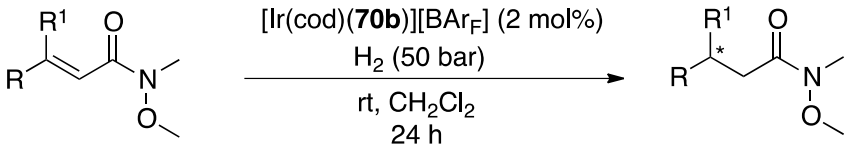
A few examples of asymmetric hydrogenation of acrylic amides, catalyzed by chiral analogues of Crabtree's catalyst, have also appeared. Lu and Hou[154] found that the ferrocene-based PHOX-mimic **13b** (Figure 4) was the best ligand for the asymmetric hydrogenation of α,β-disubstituted acrylamides (Scheme 34). While the α-substituent was either methyl or methylene throughout, the β-substituent could be either aryl (**S190**-**S192**) or alkyl (**S193**-**S195**). As in the case of the corresponding esters, changing the amide substituents only moderately affected the enantioselectivity. It was however shown, that for the *trans*-α-methyl, β-phenyl derivatives such as **S190**, primary amides gave higher enantioselectivity than their secondary counterparts, and ^{i}Bu was the *N*-substituent that gave the highest ee.



	R	R^1	R^2	ee (%)
S190	Ph	Me	^{i}Bu	93
S191	Ph	CH_2Bn	^{i}Bu	97
S192	Ph	CH_2OMe	^{i}Bu	95
S193	Me	Me	Ph	98
S194	^{n}Pr	Me	Bn	84
S195	^{i}Pr	Me	Bn	93

Scheme 34 Representative results from the asymmetric hydrogenation of α,β-disubstituted acrylamides using [Ir(cod)(**13b**)][BArF].

Recently, Ding and co-workers performed asymmetric hydrogenations of β,β-disubstituted acrylic Weinreb amides.[155] Using [Ir(cod)(**70b**)][BArF] (ligand **70b**; see Table 8, R^1= Ph, R^2= Bn) under 50 bar H_2, high enantioselectivity could be obtained for several alkenes (Scheme 35). While high enantioselectivities were maintained as long as the *trans*-substituent remained a bulky or aryl group (R = Ph, Bn, ^{t}Bu), aliphatic *trans*-substituents such as in **S200** gave significantly lower selectivity (R = ^{n}Bu).



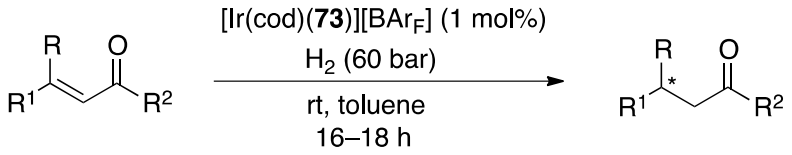
	R	R^1	ee (%)
S196	Ph	Me	95
S197	Ph	^{i}Pr	82
S198	2-MeC_6H_4	Me	91
S199	Bn	Me	90
S200	^{n}Bu	Me	65

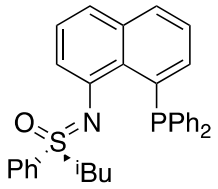
Scheme 35 Asymmetric hydrogenation of β,β-disubstituted acrylamides.

6.4 α,β-Unsaturated ketones

The asymmetric hydrogenation of α,β-unsaturated ketones has been the subject of several studies. While the selective hydrogenation of the carbonyl function is best realized using the P,P-ligated Noyori-type catalytic systems,[156] Takaya and co-workers showed that [Ir(cod)(BINAP)][BF_4] could be chemoselective either towards the carbonyl- or alkene-function of *E*-4-phenyl-3-butene-2-one depending on the addition of auxiliary aminophosphine ligands.[157] Alkene-selective asymmetric hydrogenation of enones has been achieved using various systems; P,P-ligated Ru-[124,158] Rh-[159] and Pd-catalysts[160] have proven efficient. Organocatalytic transfer-hydrogenation[161] and auxiliary assisted heterogeneous systems[162] have also shown to be advantageous. The majority of the above-mentioned catalytic systems are highly enantioselective for cyclic substrates but not as useful for the reduction of linear alkenes, and here, chiral mimics of Crabtree's catalyst have proven valuable.

Lu and Bolm found that iridium complex [Ir(cod)(**73**)][BAr_F] based on sulphoximine-phosphine ligand **73** gave only trace amounts of carbonyl reduction in the asymmetric hydrogenation of acyclic β,β-disubstituted enones.[163] Thus, using [(**73**)][BAr_F] under 60 bar H_2 in toluene, the saturated ketone products could be obtained in good yield and enantioselectivity after 16–18 hours (Scheme 36). No change in selectivity was observed when exchanging the ketone substituent (R^2) from phenyl (**S201**) to methyl (**S202**) and the *E*- and *Z*- isomers of the phenyl/*iso*-propyl derivative (**S204** and **S205**) both gave excellent enantioselectivity but different absolute configurations of the product.





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	R	R^1	R^2	ee (%)
S201	Me	Ph	Ph	81
S202	Me	Ph	Me	79
S203	Me	CH_2Bn	Ph	81
S204	^{i}Pr	Ph	Ph	97
S205	Ph	^{i}Pr	Ph	92

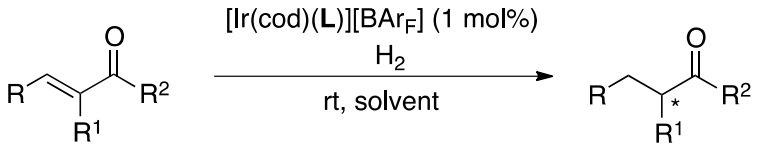
Scheme 36 Representative results from the asymmetric hydrogenation of β,β-disubstituted α,β-unsaturated ketones using [Ir(cod)(**73**)][BAr_F].

Lu and Bolm also used [Ir(cod)(**73**)][BAr_F] in the asymmetric hydrogenation of the α,β-disubstituted enone *E*-3-methyl-4-phenyl-3-buten-2-one but the product was obtained in only 55% ee.[164] Instead, the PHOX ligand **8d**, (Figure 3) developed by Pfaltz proved to be highly selective for the reaction and gave the saturated ketone as the only product. Interestingly, when β,β-disubstituted enones were reduced by the same complex significant amounts of the saturated alcohol was obtained.[163] Using [Ir(cod)(**8d**)][BAr_F], several, both aryl- and alkyl-substituted alkenes could be reduced over 3 hours under 2 bar H_2 (Table 10, entries 1–6). Good-to-excellent enantioselectivity was observed for all substrates tested with even one 1,1-disubstituted alkene (**S210**, entry 6) giving 86% ee.

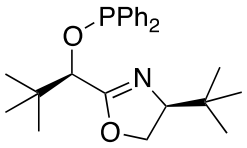
While Lu and Bolm observed slightly higher enantioselectivities in toluene, Hou and co-workers used [(**8d**)][BAr_F] for the reduction of **S207** and **S206** with dichloromethane as the solvent with close to identical results (Table 10, entries 7 and 8).[165]

Recently, a catalytic system featuring phosphinite-oxazoline ligand **74**, developed by Kazmaier and co-workers, was shown to give excellent enantioselecivities (>99% ee) in the hydrogenation of two α,β-disubstituted enones (Table 10, entries 9 and 10).[166]

Table 10 Representative results from the asymmetric hydrogenation of α,β-disubstituted enones.

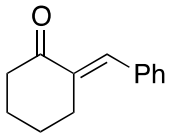


Entry		R	R^1	R^2	Ligand	Solvent	ee (%)	Ref.
1	**S206**	Ph	Me	Ph	**8d**	toluene	99 (*S*)	52a
2	**S207**	Ph	Me	Me	**8d**	toluene	98 (*S*)	52a
4	**S208**	Ph	Ph	Ph	**8d**	toluene	99 (*R*)	52a
5	**S209**	Et	Me	Ph	**8d**	toluene	87 (*S*)	52a
6	**S210**	H	Bn	Ph	**8d**	toluene	86 (*S*)	52a
7	**S207**	Ph	Me	Me	**8d**	CH_2Cl_2	98	59
8	**S206**	Ph	Me	Ph	**8d**	CH_2Cl_2	97	59
9	**S207**	Ph	Me	Me	**74**	CH_2Cl_2	>99	166
10	**S211**	Ph	Et	Me	**74**	CH_2Cl_2	>99	166

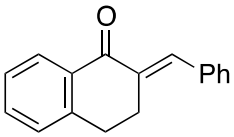


74

The exocyclic enones **S212** and **S213** are popular substrates for N,P-ligated Ir-catalyzed hydrogenation systems and have been reduced effectively and in high enantioselectivity by several catalytic systems.[152,164-166]



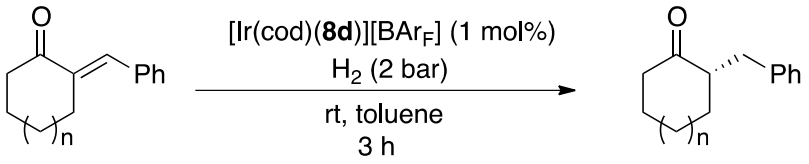
S212



S213

Figure 17 α,β-Disubstituted enones **S212** and **S213** are reduced in high enantioselectivity by several complexes of the type [Ir(cod)(N,P)][BAr_F].

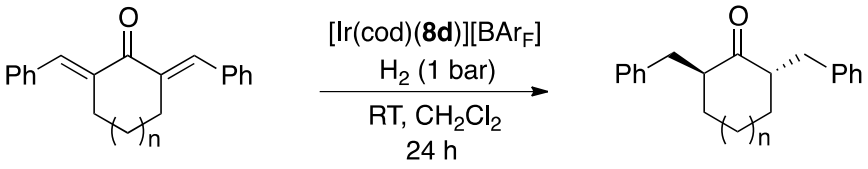
During their studies of linear alkenes, Lu and Bolm also applied [Ir(cod)(**8d**)][BAr_F] to the asymmetric hydrogenation of cyclic substrates and the catalytic system was shown to reduce the five-, six-, seven-, and eight-membered cyclic enones with exocyclic double bonds (**S214**-**S217**) in excellent enantioselectivity (Scheme 37).[164]



	n	ee (%)
S214	0	92
S215	1	94
S216	2	99
S217	3	97

Scheme 37 Asymmetric hydrogenation of cyclic enones **S214**-**S217** using [Ir(cod)(**8d**)][BAr$_F$].

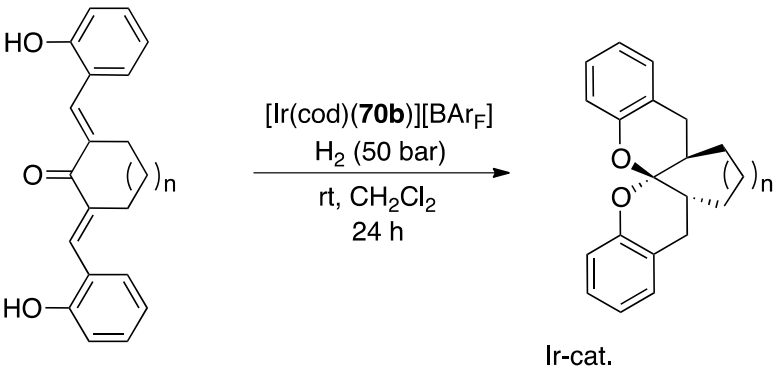
Very high diastereo- and enantioselectivities were also observed by Hou and co-workers for the reduction of enones **S218** and **S219** using [Ir(cod)(**8d**)][BAr$_F$] (Scheme 38).[165]



	n	Ir-cat. (mol%)	*cis*:*trans*	ee (%)
S218	0	5	1 : 38	>99
S219	1	3	1 : >50	>99

Scheme 38 Asymmetric hydrogenation of **S218** and **S219** using [Ir(cod)(**8d**)][BAr$_F$].

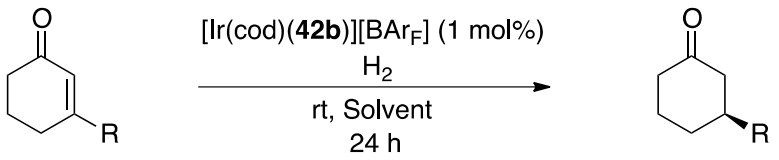
The results obtained by Hou, and especially the high distereoselectivities achieved, inspired Wang, Ding and co-workers to perform the asymmetric hydrogenation of cyclic enones carrying 2-hydroxy groups **S220**-**S222** (Scheme 39).[167] Probably due to the acidity of the catalytic system, *in situ* cyclization of the product ketones gave spiroketals, which were isolated in good yields. Using ligand **70b** (Table 8, R^1= Ph, R^2= Bn), the five-membered cyclic ketone **S220** was reduced in very low enantioselectivity while the six-membered ketones such as **S221** gave product spiroketals in excellent enantio- and diastereoselectivity. Seven-membered ketone **S222** was also reduced in excellent ee but with a poor *cis*:*trans* ratio (Scheme 39).



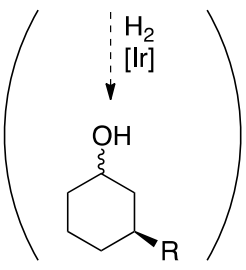
	n	Ir-cat. (mol%)	*cis*:*trans*	ee (%)
S220	0	3	17 : 33	26
S221	1	1	1 : 49	>99
S222	2	3	17 : 33	>99

Scheme 39 Representative results from the asymmetric hydrogenation of enones with tandem spiroketalization.

As in the case of lactones, cyclic enones containing internal alkenes are reduced considerably slower and only one successful N,P-ligated iridium catalytic system has been presented as of yet. Andersson and co-workers performed the asymmetric hydrogenation of three β-substituted cyclohex-2-enones using [Ir(cod)(**42b**)][BArF], (Figure 6) which also performed best in the reduction of the corresponding lactones (*vide supra*).[153] Both the methyl- (**S223**) and butyl-derivative (**S224**) could be completely reduced in good enantioselectivity in CH_2Cl_2 but the reaction time and hydrogen pressure had to be carefully controlled since prolonged reaction time led to reduction of the product ketone to the saturated alcohol (Scheme 40). While the carbonyl reduction did not start until the alkene had been consumed for R = Me and ^{n}Bu, the phenyl derivative (**S225**) gave a mixture of saturated alcohols and ketone when performed in CH_2Cl_2. Although the degree of carbonyl reduction could be controlled somewhat by adjusting the H_2 pressure, a better alternative was to perform the reaction in 2,2,2-trifluoroethanol (TFE). Reduction of 3-phenyl-cyclohex-2-enone in this solvent under 100 bar H_2 gave the product cleanly and in 94% ee (Scheme 40).



	R	solvent	H_2 (bar)	ee (%)
S223	Me	CH_2Cl_2	50	92
S224	^{n}Bu	CH_2Cl_2	50	88
S225	Ph	TFE	100	94



Scheme 40 The asymmetric hydrogenation of cyclic enones with [Ir(cod)(**42b**)][BAr_F]. The reaction conditions have to be controlled to avoid reduction of the product carbonyl.

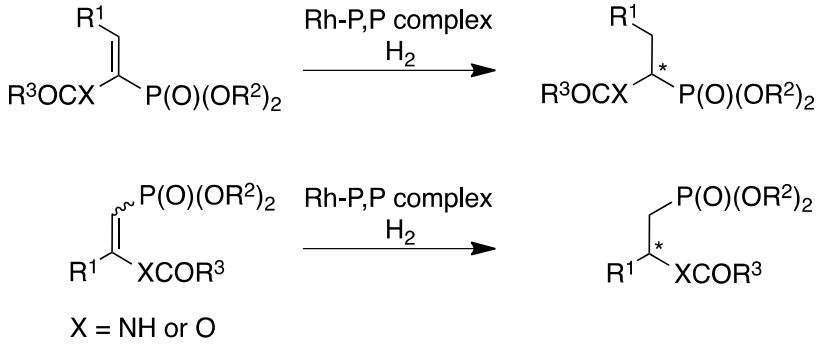
The enantioselectivities in CH_2Cl_2 and TFE were comparable but slightly better in TFE for R = Ph and Me and somewhat better in CH_2Cl_2 for R = ^{n}Bu. N,P-ligated iridium species can be a source of significant acidity,[125] and it is likely that the alcoholic solvent acts as a buffer, preventing the carbonyl reduction either by removing formed protons or hydrogen bonding to the C=O thus inhibiting bonding of Lewis acidic iridium species.

7 Alkenes bearing other heteroatoms

Chiral centres bearing heteroatoms other than nitrogen or oxygen have also been prepared by asymmetric hydrogenation. Yet, with the exception of phosphorus as vinyl phosphonates, relatively few reports exist. The asymmetric hydrogenation of trisubstituted vinyl silanes has been performed exclusively using iridium N,P-catalysts,[63] and the hydrogenation of thio-enol-ethers has only been reported using Rh-diphosphine catalytic system.[168] Vinyl fluorides and boronates have been enantioselectivly reduced using different metal-ligand complexes and will be discussed.

7.1 Phosphorus

Vinyl phosphonates have frequently been used as substrates for asymmetric hydrogenation using rhodium-catalyzed systems. The majority of the reports however, focus on alkenes that, in addition to the phosphonate, also bear coordinating functional groups such as enamido- or enol ester-functionalities in α or β position (Scheme 41).[14,169] The products of these reactions are valuable as they are easily manipulated into α or β amino- or hydroxy-phosphonic acids which, as amino acid isosters, have various effects in biological systems.



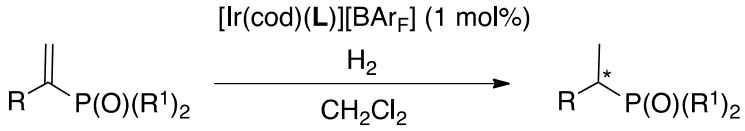
Scheme 41 Asymmetric hydrogenation of α-enolbenzo- and α-acetamido-phosphonates are frequently performed with P,P-ligated rhodium catalysts.

Less functionalized vinyl phosphonates lacks very good coordinating groups like acetamides or enol esters but still have the potential to coordinate through the $P(O)(OR)_2$ function and is an interesting class of substrates for metal-catalyzed hydrogenation. 1-Aryl-ethenylphosphonates have been used as substrates for asymmetric hydrogenation using ruthenium-diphosphine

catalysts.[170] For rhodium, only one example of ee's above 90% have been reported using a BoPhoz type ligand.[171]

With N,P-ligated Ir-catalysts, Beletskaya and Pfaltz obtained 94, 92 and 93% ee for the phenyl- and two naphthyl-derivatives **S226**, **S227** and **S228** (Table 11, entries 1, 3 and 4) using [Ir(cod)(**8a**)][BAr_F] (PHOX-ligand **8a**; Figure 3, R^1= *o*-Tol and R^2= ^{t}Bu).[172] Under similar conditions, Andersson and co-workers obtained the phenyl-substituted product from **S226** in >99 % ee using [Ir(cod)(**47**)][BAr_F] (ligand **47**; Figure 6).[173] In addition to phosphonate esters, the corresponding diphenylphosphine oxides **S229**-**S234** were evaluated in asymmetric hydrogenation reactions using [Ir(cod)(**47**)][BAr_F]. Aromatic (**S229-S231**) and aliphatic (**S232**-**S234**) 1,1-disubstituted diphenylvinylphosphine oxides could be reduced, often in >99 % ee, using this catalytic system (Table, entries 5-10).[173] Hence, it seems that replacement of the $P(O)(OEt)_2$-group with the bulkier $P(O)Ph_2$ fits as well for hydrogenation using chiral mimics of Crabtree's catalyst.

Table 11 Representative results from the asymmetric hydrogenation of 1-substituted ethenylphosphonates using [Ir(cod)(**L**)][BAr_F].



Entry		R	R^1	**L**	temp (°C)	H_2 (bar)	time (h)	ee (%)	Ref.
1	**S226**	Ph	OEt	**8a**	40	5	6	94	172
2	**S226**	Ph	OEt	**47**	rt	50	15	>99	94
3	**S227**	1-naphtyl	OEt	**8a**	40	5	6	92	172
4	**S228**	2-naphtyl	OEt	**8a**	40	5	6	93	172
5	**S229**	Ph	Ph	**47**	rt	50	15	>99	94
6	**S230**	4-F-C_6H_4	Ph	**47**	rt	50	15	93	94
7	**S231**	4-MeO-C_6H_4	Ph	**47**	rt	50	15	>99	94
8	**S232**	^{t}Bu	Ph	**47**	rt	50	15	90	94
9	**S233**	CH_2Bn	Ph	**47**	rt	50	15	>99	94
10	**S234**	CH_2CH_2OH	Ph	**47**	rt	100	15	>99	94

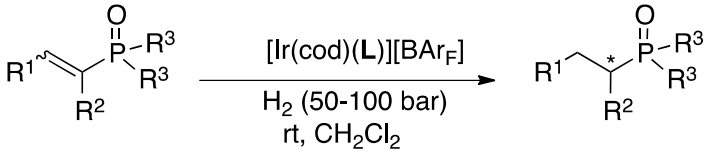
As for the asymmetric hydrogenation of weakly functionalized trisubstituted vinylphosphonates, a few catalytic systems utilizing rhodium-diphosphine and rhodium-phosphoramidite complexes have proven suitable. In 1999, Kadyrov and co-workers used [Rh(cod)(DIOP)][BF_4] to reduce *E*-β-methylphosphonatocrotonate in 42% ee by stirring the reaction under an atmosphere of hydrogen for 78 hours without solvent.[174] The authors reasoned that the poor selectivity was due to lack of good coordinating functional groups, but the reaction was not studied in more depth. Minnaard and co-workers evaluated several diphosphine ligands together with [$Rh(cod)_2$][BF_4] in the asymmetric hydrogenation of (*E*)-carboxymethyl vinylphosphonates.[175] Ligands from the Josiphos family turned out to be the most effective, reducing both alkyl and aryl substituted alkenes in high

selectivity. A high (5 mol%) catalyst loading was needed to ensure full conversion of the alkenes in 24 hours. Zheng and co-workers showed that *E*-(2-aryl-1-propene)phosphonates could be reduced in excellent enantioselectivity by a rhodium-phosphoramidite catalytic system.[176]

The [Ir(cod)(N,P)][BAr_F] catalytic system has also proved useful in this reaction; iridium complexes derived from ligand **47** (Figure 6), that reduced 1,1-disubstituted vinyl phosphonates, gave high enantioselectivities in the reduction of two (*E*)-carboxyethyl vinylphosphonates **S235** and **S236** (Table 12, entries 1–2).[173] Interestingly, the *Z*-isomer of the phenyl-substituted derivative (**S237**) was reduced faster than the *E*-isomer (**S235**), and in higher enantioselectivity but yielded the product with the same absolute configuration. This effect has sometimes been observed in the rhodium-catalyzed asymmetric hydrogenation of functionalized vinylphosphonates,[177] and can be attributed to substrate chelation. To our knowledge, this effect has not previously been observed in the Ir-catalyzed hydrogenation of alkenes. In contrast, in the hydrogenation of a β,β-disubstituted-α,β-unsaturated vinyl phosphonates using a rhodium-phosphoramidite catalytic system, both the *E*- and the *Z*-alkene gave excellent selectivity but of different enantiomers.[176] Taken together these results illustrate the intermediate nature of the weakly functionalized vinyl phosphonates and the fact that in some cases chelation takes place while in other cases not.

The phosphite-oxazole ligand **45a** (Figure 6) has also been used to obtain high enantioselectivity in the reduction of two trisubstituted vinylphosphonates with *Z*-configuration (Table 12, entries 4 and 5).[92]

Table 12 Asymmetric hydrogenation of some trisubstituted vinyl phosphonates.



Entry		*Z* / *E*	R^1	R^2	R^3	Ir-cat. (mol%)	**L**	ee (%)	Ref.
1	**S235**	*E*	COOEt	Ph	OEt	1	**47**	90	94
2	**S236**	*E*	COOEt	Bn	OEt	1	**47**	>99	94
3	**S237**	*Z*	COOEt	Ph	OEt	1	**47**	>99	94
4	**S238**	*Z*	COOEt	Ph	Ph	0.2	**45a**	92	93
5	**S239**	*Z*	Me	Ph	Ph	0.2	**45a**	91	93

7.2 Boron

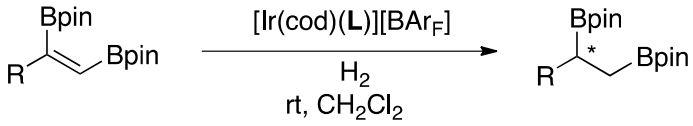
Asymmetric hydrogenation of trisubstituted vinylboronates was first performed in 2004 by Morgan and Morken.[178] In a screen using *E*-1,2-bis(Bpin)styrene **S240** (Bpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl) as substrate, rhodium was superior to iridium with the P,P-ligands that were evaluated. Walphos type ligands were the most selective and the highest enantiomeric

excess (93%) was obtained when the reaction was performed in toluene using 2 mol% Rh. Interestingly, a 2:1 ratio of ligand-to-metal gave the highest selectivity, while a 1:1 or lower, ligand:metal ratio gave reversed, and poor, enantioselectivity. 1,2-Bis(boronates) carrying aliphatic substituents could also be reduced in high enantioselectivity using a slightly modified ligand, but again relatively high loadings of rhodium and ligand were required.

Curious to see if chiral mimics of Crabtree's catalyst could perform well in this reaction, Andersson and co-workers also attempted hydrogenation of *E*-1,2-bis(Bpin)styrenes.[65] When the reaction was performed under 1 bar of H_2, using 0.5 mol% [Ir(cod)(**50a**)][BAr_F] as pre-catalyst (**50a**; Figure 6), 1,2-di(Bpin)-1-phenyl-ethane was obtained in 96% ee from **S240** and the *para*-methoxy derivative in 88% ee from **S242** (Table 13, entries 1 and 5). Using **18d** (Figure 4) as chiral ligand in the asymmetric hydrogenation of these alkenes gave close to racemic product mixtures and higher hydrogen pressure resulted in significantly lower selectivity.[65] For the *n*-butyl derivative (**S243**, entry 6), the highest enantioselectivity obtained was 48% when [Ir(cod)(**18d**)][BAr_F] was used as pre-catalyst.

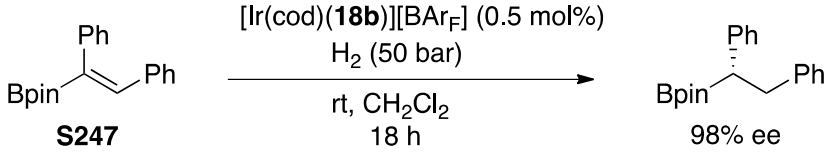
Recently, ligands **24b** (Figure 4) and **33b** (Figure 5), were applied in the iridium catalyzed asymmetric hydrogenation of 1,2-bis(boronates). While [Ir(cod)(**24b**)][BAr_F] gave excellent results for two *E*-1,2-bis(Bpin)styrenes (Table 13, entries 2 and 4),[72b] [Ir(cod)(**33b**)][BAr_F] could reduce the phenyl-derivative (**S240**, entry 3) as well as the bulky cyclohexyl (**S245**, entry 8) and *tert*-butyl (**S246**, entry 9) derivatives highly selectively.[179] The *n*-hexyl derivative **S244** was reduced in 72% ee by this complex (entry 7).

Table 13 Representative results from the asymmetric hydrogenation of vinyl-1,2-bis(boronates) using complexes of the type [Ir(cod)(N,P)][BAr_F].



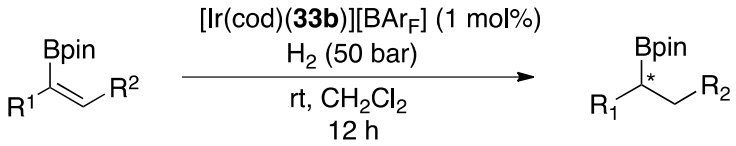
Entry		R	Ir-cat. (mol%)	L	H_2 (bar)	time (h)	ee (%)	Ref.
1	**S240**	Ph	0.5	**50a**	1	18	96	67
2	**S240**	Ph	1	**24b**	50	2	>99	74b
3	**S240**	Ph	1	**33b**	50	12	98	178
4	**S241**	4-F-H_4C_6	1	**24b**	50	2	92	74b
5	**S242**	4-OMe-H_4C_6	0.5	**50a**	1	18	88	67
6	**S243**	^{n}Bu	0.5	**18d**	1	18	48	67
7	**S244**	Hex	1	**33b**	50	12	72	178
8	**S245**	Cy	1	**33b**	50	12	95	178
9	**S246**	^{t}Bu	1	**33b**	50	12	85	178

In addition to 1,2-bis(boronates), several trisubstituted alkenes containing only one boronic ester function have been subjected to Ir-catalyzed asymmetric hydrogenation with good results. For instance, the quite sterically demanding *cis*-stilbene boronate **S247** could be reduced using 0.5 mol% [Ir(cod)(**18b**)][BAr_F] (ligand **18b**; Figure 4) under 50 bar H_2 (Scheme 42).[65]



Scheme 42 Asymmetric reduction of **S247** using [Ir(cod)(**18b**)][BAr_F].

Ganić and Pfaltz recently prepared a range of chiral boronic esters by asymmetric hydrogenation of trisubstituted vinyl boronates using the Ir-complex of ligand **33b** (Figure 5), which also was used for bis(boronates).[179] Under 50 bar H_2 in CH_2Cl_2, alkenes carrying various aliphatic and aromatic groups (**S248**-**S254**) could be reduced in very high enantioselectivities (Scheme 43). In all cases the substituent on the prochiral carbon atom (R^1) was a relatively bulky aliphatic group, indicating that this is a prerequisite for high enantiomeric excess.

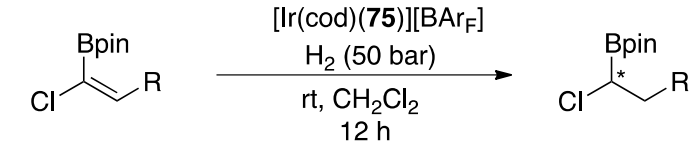


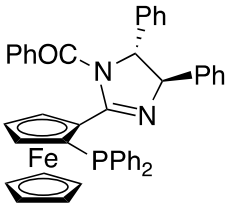
	R^1	R^2	ee (%)
S248	Cy	Ph	96
S249	Cy	4-MeO-C_6H_4	97
S250	Cy	4-F_3C-C_6H_4	98
S251	Cy	Bn	96
S252	Cy	Et	97
S253	Hex	4-H_3C-C_6H_4	95
S254	^{t}Bu	4-H_3C-C_6H_4	96

Scheme 43 Asymmetric hydrogenation of trisubstituted vinyl boronates using [Ir(cod)(**33b**)][BAr_F].

Even 1-chloro-1-alkenyl boronates can be reduced selectively using N,P-ligated Ir-complexes;[180] H_2 with [Ir(cod)(**75**)][BAr_F] reduced several alkyl- (**S255**-**S257**) and aryl-substituted (**S258**-**S260**) derivatives with high enantioselectivity and without significant de-chlorination, although a high (4–14 mol%) catalyst loading was required (Scheme 44). Several P,P-ligated rhodium complexes, as well as one ruthenium complex, were also tested in this reaction. The ruthenium complex gave the dechlorination product almost exclusively, while the rhodium-catalysts were both slow and unselective compared to the chiral analogues of Crabtree's catalyst.

These results demonstrate the high catalytic activity and uniquely high tolerance of chiral Crabtree mimics to functional groups, even on the double bond, in asymmetric hydrogenation.





75

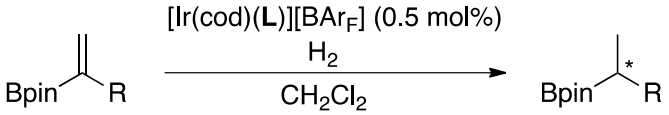
	R	Ir-cat. (mol%)	yield (%)	ee (%)
S255	Me	4	73	46
S256	^{n}Pr	4	75	83
S257	^{i}Pr	4	85	93
S258	Ph	10	89	90
S259	4-MeO-C$_6$H$_4$	10	73	88
S260	4-F$_3$C-C$_6$H$_4$	10	65	94

Scheme 44 Asymmetric hydrogenation of 1-chloro-1-alkenyl boronates.

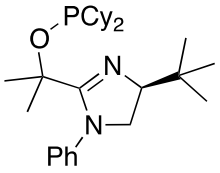
The rhodium-Walphos system utilized by Moran and Morken for the hydrogenation of 1,2-bis(boronates) also proved useful for the reduction of 1,1-disubstituted vinyl boronates. Several 1-alkyl-1-(Bpin)-ethenes could be hydrogenated in high enantioselectivity using their catalytic system but the reduction required high catalyst loadings and low reaction temperature and was selective for long chain and cyclic aliphatics as well as for homoallylic ethers and esters.[181] Prior to the the work by Moran and Morken, Miyaura and co-workers presented the first hydrogenation of 1-phenylethenyl boronic esters using 3 mol% [Rh(cod)(BINAP)][BF$_4$] as catalyst precursor.[182] The best selectivity (80 % ee) was obtained using simple 1,3,2,-dioxaborolane as the boronate function and stirring the reaction at –20 °C for 7 days. With the pinacol ester in the boronate function and at room temperature, the reaction only required 24 hours to go to completion but the enantioselectivity was poor.

Iridium catalysts have proven very useful in the hydrogenation of this type of prochiral alkenes. Andersson and co-workers attempted hydrogenation of the phenyl- and hexyl-substituted vinyl pinacol-boronates **S261** and **S262** using the iridium complex of ligand **18d** (Figure 4) as catalyst and obtained good enantioselectivity for the phenyl derivative (Table 14, entry 1) but very low selectivity for the *n*-hexyl derivative (entry 3).[65] As in the case of trisubstituted vinyl-(bis)boronates, significantly lower catalyst loading was required when using chiral versions of Crabtree's catalyst as compared to the rhodium-P,P-systems.

Table 14 Asymmetric hydrogenation of 1,1-disubstituted vinyl boronates.



Entry		R	L	temp (°C)	H_2 (bar)	time (h)	ee (%)	Ref.
1	**S261**	Ph	**18d**	rt	50	18	89	67
2	**S261**	Ph	**76**	–20	2	4	4	178
3	**S262**	^{n}Hex	**18d**	rt	50	18	18	67
4	**S262**	^{n}Hex	**76**	–20	2	4	96	178
5	**S263**	Cy	**76**	–20	2	4	33	178
6	**S264**	CH_2Bn	**76**	–20	2	4	94	178
7	**S265**	Bn	**76**	–20	2	4	94	178
8	**S266**	$CH_2OTBDMS$	**76**	–20	2	4	88	178

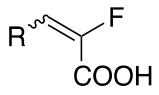


76

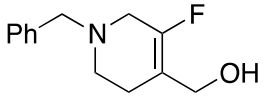
Ganić and Pfaltz optimized their catalytic system for the *n*-hexyl substituted alkene **S262** and used [Ir(cod)(**76**)][BAr_F] as precatalyst to obtain excellent selectivity in the asymmetric hydrogenation of several substrates of this kind (Table 14, entries 4, 6, 7 and 8).[179] At –20 °C and under 2 bar of hydrogen, the reactions were complete after 4 hours using only 0.5 mol% catalyst. Surprisingly, with R = Ph (**S261**), an essentially racemic mixture of products was obtained. Also the cyclohexyl derivative **S263** (entry 5) gave low enantioselectivity, indicating that this catalytic system is most efficient for alkenes in which the substituents are linked by a CH_2-function.

7.3 Fluorine

Vinyl fluorides are another challenging alkene type whose enantioselective reduction has been only briefly assessed. A few examples involving fluorinated olefins carrying coordinating functional groups exist. Both the *E*- and *Z*-isomer of the α,β-unsaturated carboxylic acid **S267** where R = ^{n}Pr could be reduced in 88–90% ee by Ru-BINAP.[183] The reaction proceeded smoothly at 50 °C in methanol, p(H_2) = 5–50 bar, for these two substrates but the scope of the reaction was not much extended. For the *Z*-phenyl derivative enantioselectivity dropped significantly to 56%.



S267



S268

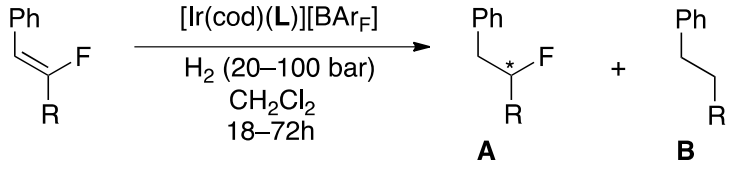
Figure 18 Vinyl fluorides **S267** and **S268**, carrying coordinating functional groups have been subjected to asymmetric hydrogenation using P,P-ligated ruthenium and rhodium complexes.

The tetrasubstituted vinyl fluoride **S268**, which is also an allylic alcohol, has been hydrogenated to its chiral product with *cis*-configuration in very high enantioselectivity.[184] Several chiral diphosphine ligands were screened with the metal precursors $[Ir(cod)_2][BF_4]$ and $[Rh(nbd)_2][BF_4]$ in CH_2Cl_2 and MeOH but the major product was the defluorinated compound in most cases. One N,P-ligand (PHOX), was also tested as ligand to iridium in dichloromethane but also in this case defluorination was a problem. One P,P-ligated ruthenium and some rhodium catalysts exhibited significantly less defluorination and were studied further. Optimization of the reaction conditions eventually gave the product in 99% ee (with only a few per cent defluorination) using a rhodium-Walphos system.[184]

Andersson and co-workers wanted to use chiral mimics of Crabtree's catalyst to prepare fluorine-bearing chiral centres by asymmetric hydrogenation of vinyl fluorides. Thus, trisubstituted alkenes bearing fluorine atoms were prepared and subjected to asymmetric hydrogenation using ligands developed in the Andersson group.[64] While significant amounts of defluorinated products were obtained using phosphine-oxazole and phosphine-thiazole ligands (**43** and **44**, Figure 6), azaphosphine P-donors (N–PAr_2), in general, appeared to give less defluorination than their phosphine counterparts. Thus, a thiazole N-donor ligand carrying an azadiarylphosphine, **47** (Figure 6), was prepared in hope of obtaining low defluorination and high enantioselectivity. Indeed, using [Ir(cod)(**47**)][BAr_F] only a few per cent defluorination and excellent ee's for the two alkenes **S269** and **S271** were obtained (Table 15, entries 1a and 2a).[64]

In a subsequent study, imidazole-phosphine ligand **42a** (Figure 6) was prepared as a more basic ligand than the corresponding oxazoles and thiazoles.[87] Even though a slight improvement in both selectivity and enantioselectivity was observed, the effect was not very pronounced, suggesting that defluorination is affected mainly by other factors than ligand acidity. [Ir(cod)(**42a**)][BAr_F] was tested in the asymmetric hydrogenation of a set of vinyl fluorides (**S269**-**S274**) with varying results (Table 15). Unsurprisingly, *Z*-alkenes (i.e. sterically *trans* alkenes) **S269** and **S271** were reduced faster and more selectively than the *E*-isomers **S270** and **S272**. Less electron-poor alkenes **S269**-**S272** (R = CH_2OH and CH_2OAc) were also reduced faster than the very electron-deficient α,β-unsaturated esters **S273** and **S274**.[87]

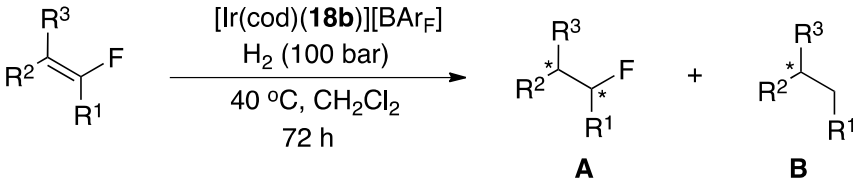
Table 15 Asymmetric hydrogenation of trisubstituted vinyl fluorides.



Entry			R	*Z*/*E*	temp (°C)	Ir-cat. (mol%)	L	A : B	ee (%)	Ref.
1	a	**S269**	CH_2OAc	*Z*	25	0.5	**47**	95 : 5	>99	66
	b	**S269**			25	1	**42a**	84 : 16	85	89
	c	**S270**		*E*	25	1	**42a**	50 : 50	17	89
2	a	**S271**	CH_2OH	*Z*	25	0.5	**47**	100 : 0	99	66
	b	**S271**			25	1	**42a**	92 : 8	80	89
	c	**S272**		*E*	25	1	**42a**	43 : 57	52	89
3	a	**S273**	COOEt	*Z*	40	1	**42a**	66 : 34	46	89
	b	**S274**		*E*[a]	40	1	**42a**	83 : 17	72	89

[a] 10:1 *E*:*Z*

In addition to trisubstituted alkenes, a few tetrasubstituted vinyl fluorides could also be reduced using chiral mimics of Crabtree's catalyst. This is surprising, given that electron-poor alkenes are usually reduced more slowly using these catalytic systems. Using the bicyclic N-linked oxazoline ligand **18b** (Figure 4) previously developed in Andersson's group, three tetrasubstituted alkenes **S275-S277** were reduced in ee's between 57 and 90% (Scheme 45).



	R^1	R^2	R^3	Ir-cat. (mol%)	A : B	ee (%)
S275	COOEt	Me	Ph	0.5	100 : 0	57
S276	COOEt	Ph	Me	0.5	100 : 0	74
S277	CH_2OH	Ph	Me	1	71 : 29	90

Scheme 45 Asymmetric hydrogenation of tetrasubstituted vinyl fluorides.

7.4 Silicon

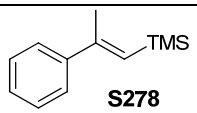
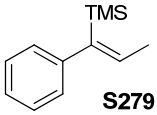
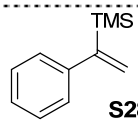
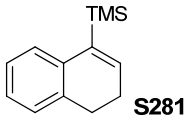
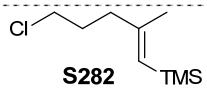
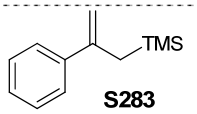
Vinyl silanes are another challenging alkene type whose hydrogenation has hardly been studied, although organosilanes are important organic intermediates and a number of innovative new organosilicon drugs are in development.[185] To the best of our knowledge there is only one example in which a Rh-catalyst was used in the diastereoisomeric hydrogenation of vinylsilanes that also contain a hydroxyl group.[186]

The first example on the highly enantioselective hydrogenation of vinylsilanes was reported by Andersson's group. They found that chiral analogues of Crabtree's catalyst containing *N*-phosphine-oxazoline **18a**

(Figure 4) and phosphine-thiazoline **44a** (Figure 6) were able to hydrogenate (*E*)-trimethyl(2-phenylprop-1-en-1-yl)silane **S278** in high enantioselectivities (96% and 98% ee, respectively; Table 16, entries 1-2).[63] The hydrogenation of substrates containing the TMS group attached to the prochiral carbon led, however, to low-to-moderate enantioselectivities (i.e. substrates **S279**-**S281**; Table 16, entries 5-8). The hydrogenation of alkyl substituted substrate **S282** led also to low enantioselectivity (Table 16, entry 9).

More recently, the use of phosphite-containing ligands have also proved to transfer the chiral information to the hydrogenation product highly effectively (ee's up to 98%; Table 16, entries 3 and 4).[72b,92] As previously mentioned the application of phosphite-containing ligands has also opened the possibility to hydrogenate terminal olefins containing a neighboring trimethylsilyl group (substrate **S283**; Table 16, entries 10-12).[72b,73b,92]

Table 16 Enantioselectivities achieved using chiral Crabtree's analogues in the asymmetric hydrogenation of trimethylsilyl containing substrates **S278**-**S283**

Entry	Substrate	L	ee (%)	Ref.
1	 **S278**	**18a**	96	65
2		**44a**	98	65
3		**24a**	97	74b
4		**46a**	98	93
5	 **S279**	**18a**	26	65
6		**44a**	28	65
7	 **S280**	**44a**	58	65
8	 **S281**	**44a**	48	65
9	 **S282**	**44a**	55	65
10	 **S283**	**24a**	96	74b
11		**25a**	96	75b
12		**46a**	93	93

8 Prediction of the stereochemical outcome

While the amount of available ligands for the [Ir(cod)(N,P*)][BAr_F] catalytic system has grown large, most of the published ligands have proven to give high enantioselectivity only for a narrow type of alkene.[2c,3a] It appears as if the strict sterical requirements put on the ligands to obtain high enantioselectivity also to a degree prevent their generality. Thus in synthesis, for reduction of a specific alkene, one would have to screen a large array of different ligands to find the best one and, because of this, the incentive to provide modular and easily prepared ligands is strong.

The Andersson group has developed two series of ligands that perform well in the asymmetric hydrogenation of a large set of prochiral trisubstituted alkenes.[3c,d] The first system comprises a variable ligand backbone, containing an oxazole, thiazole or imidazole N-donor and a phosphine or phosphinite P-donor (Class **1**, Figure 19).[87,89-90] The second system, based on a 2-aza-norbornane scaffold, consists of an oxazoline N-donor and an azaphosphinite P-donor (Class **2**, Figure 19).[62a,65,129a,187] and has been further modified to contain a thiazole N-donor.[95]

A generalized structure of a successful N,P-ligand as developed by several groups highlighting the individual elements is shown in Figure 19.

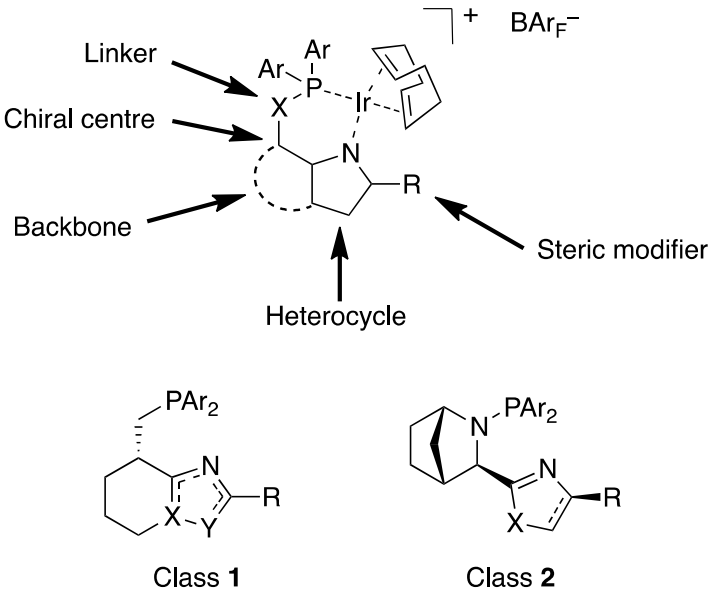


Figure 19 Generalized ligand structure of many successful ligands and the two major ligand classes developed by Andersson and co-workers.

Computational[37,40] and to some extent also experimental[31] studies strongly indicate that for a generalized N,P-ligand (Figure 20, middle) a complex cation $[Ir(H)_2Z(N,P^*)]^+$ (Z = solvent or H_2) is formed upon activation with hydrogen (See also section 1.4). The primary steric environment sensed by the incoming alkene derives from the group R, which points out towards the alkene, which is arriving *trans* to the phosphorus. This situation is illustrated in Figure 20; a) (middle) shows the generalized structure of the complex $[Ir(H)_2Z(N,P^*)(alkene)]^+$ where R is the substituent group attached to the heterocycle. With ligands from classes **1** and **2**, differently shaped coordination pockets are formed. This is illustrated in a) and emphasized in b) where the complex is viewed along the Ir-P-bond i.e. the way that an imaginary alkene is approaching. For Class **1**, the phenyl group on the thiazole ring will point out towards the reader and down. For Class **2** on the other hand, the isopropyl group on the oxazoline moiety will point out towards the reader but up. The situation can be rationalized as presented under c) with a simple quadrant model.

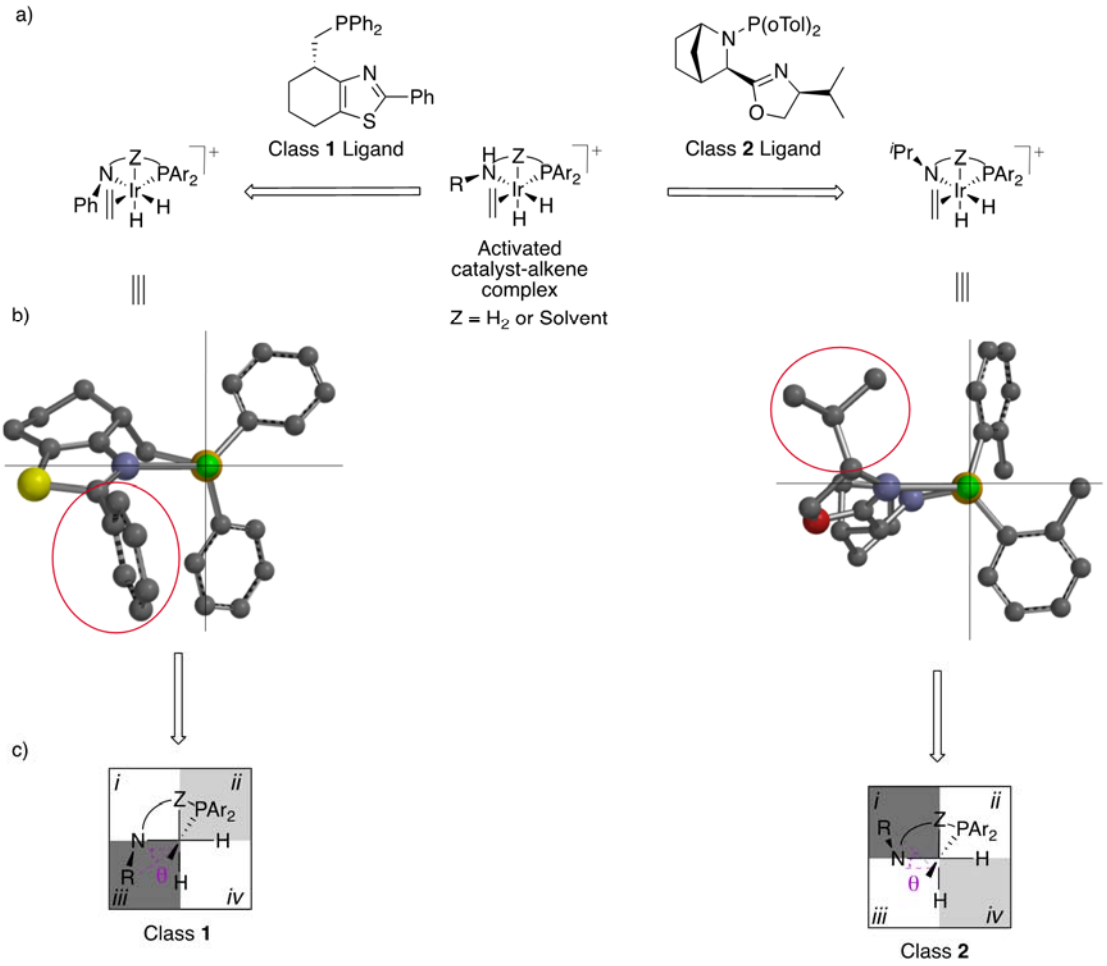


Figure 20 Rationalized view of the steric environment sensed by an alkene approaching a $[Ir(H)_2Z(N,P^*)]^+$ complex. Z = Solvent or H_2.

In Figure 20 c), the situation is again viewed from the perspective of the incoming alkene. The dark-gray quadrants (*iii* for class **1** and *i* for class **2**) represent areas that are occupied by the R-groups and the light-gray quadrants areas that are somewhat encumbered by the presence of an aryl group on the phosphorus (*ii* for Class **1** and *iv* for Class **2**). The other quadrants do not have any significant parts of the ligand pointing up towards the incoming alkene and are thus considered to be completely open.
For any N,P-ligated complex of this kind, the position of the steric bulk can be determined by measuring the angle (θ) from the N-Ir-P plane up to the center of the R-group as shown in Figure 20 c).[41] For ligands of Class **1**, the angle is negative and for ligands of Class **2** it is positive, indicating that the quadrant accommodating the R-group will be in the lower and upper corner respectively. The quadrant system can be used to predict the absolute configuration of the products derived from asymmetric hydrogenation of trisubstituted alkenes using chiral N,P-ligated iridium catalysts. Since a trisubstituted alkene only has one hydrogen substituent, it will be placed in the most crowded quadrant to minimize steric interactions. Since the hydrides are added from "below", Class **1** and Class **2** gives products of opposite absolute configuration upon alkene reduction.

This selectivity model has proven to correctly determine the absolute configuration for almost all substrates studied by the Andersson group to date including non-functionalized tri- and disubstituted alkenes, α,β-unsaturated esters and various cyclic alkenes. Figure 21 depicts the outcome when reducing a) cyclic alkenes (X = NTs or O, R = aryl or alkyl) and b) β,β-disubstituted α,β-unsaturated esters and acids (R = aryl or alkyl, R' = H or alkyl). The absolute configuration changes when reducing a cyclic 2,3-alkene or a 3,4-alkene since they coordinate from different sides (Figure 21, a). For β,β-disubstituted unsaturated esters or acids, the absolute configuration changes when the configuration of the alkene is changed from *E* to *Z* (Figure 21, b).

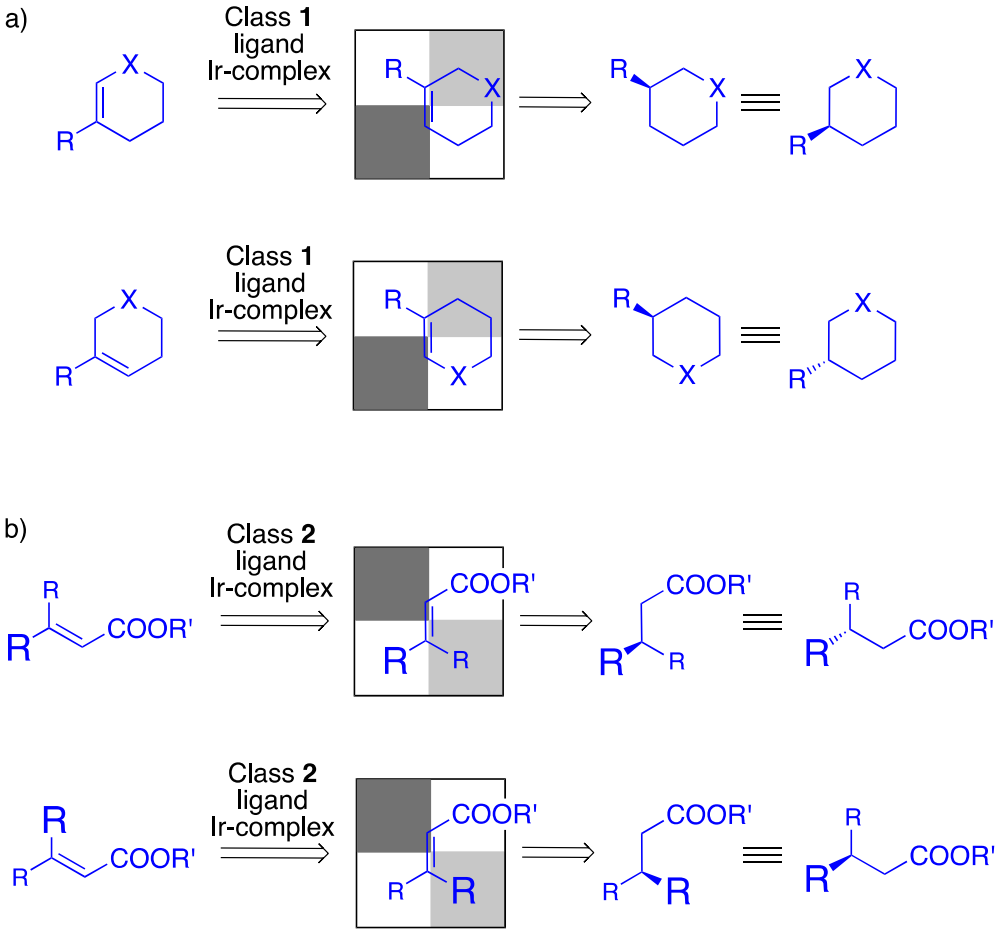


Figure 21 Selectivity model for prediction of the absolute configuration.

Interestingly, although the stereochemical outcome in the hydrogenation of β,β-disubstituted unsaturated esters can be predicted in this fashion, α,β-disubstituted unsaturated esters gives products of the opposite absolute configuration to what is suggested by the model.[150] A possible explanation for why the model fails can be found in the strong polarization of the double bond in this type of substrates. Coordination to the Ir-catalyst followed by tilting of the alkene and concominant hydride transfer to the β-position is feasible for β,β-disubstituted unsaturated esters as depicted in Figure 22 a). Conversly, inserting a α,β-disubstituted unsaturated ester into the quadrant model results in the situation shown in Figure 22 b). Here, β-addition is hampered by steric

interactions between the ligand bulk and the alkene hydrogen while α-addition is electronically unfeasible.

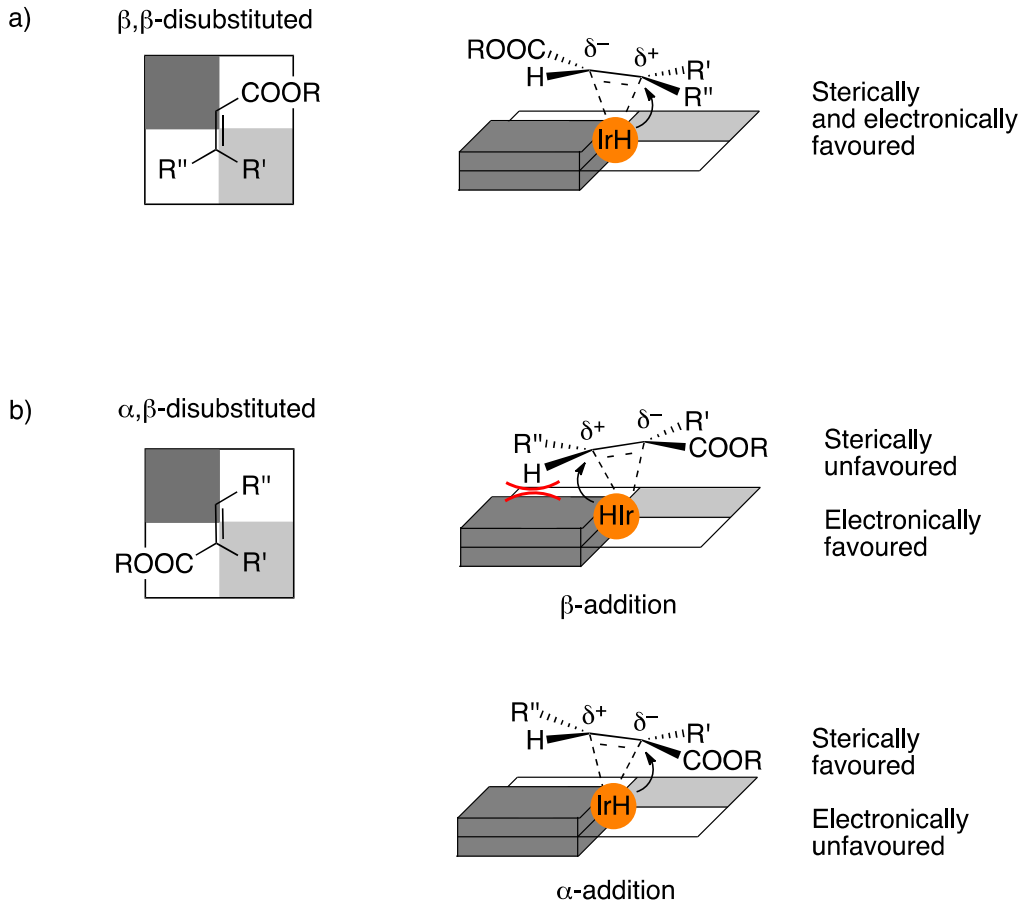


Figure 22

It has also been shown that the angle θ can be used to correctly determine the stereochemical outcome from many other chiral analogues of Crabtree's catalyst.[41] For instance, the ligand *ent*-**10a**[53] (Figure 4) developed in Burgess laboratory has a calculated θ-angle of –34.2° and the hydrogenation of *E*-2-phenyl-2-butene thus gives (*S*)-2-phenylbutane as the major product (96% ee) while *Z*-2-phenyl-2-butene produces mainly (*R*)-2-phenylbutane (87% ee). Correspondingly, the PHOX-ligand **8a**[69,188] (Figure 3, R^1= *o*-Tol and R^2= ^{t}Bu) for which θ was calculated to be +31.5°, the product composition is inverted with *E*-2-phenyl-2-butene producing mainly the (*R*) product (81% ee) and the *Z*-alkene giving mainly the (*S*) product (63% ee). The calculated θ-angle together with the quadrant model can thus serve as a tool to readily predict the stereochemical outcome of hydrogenation reactions.

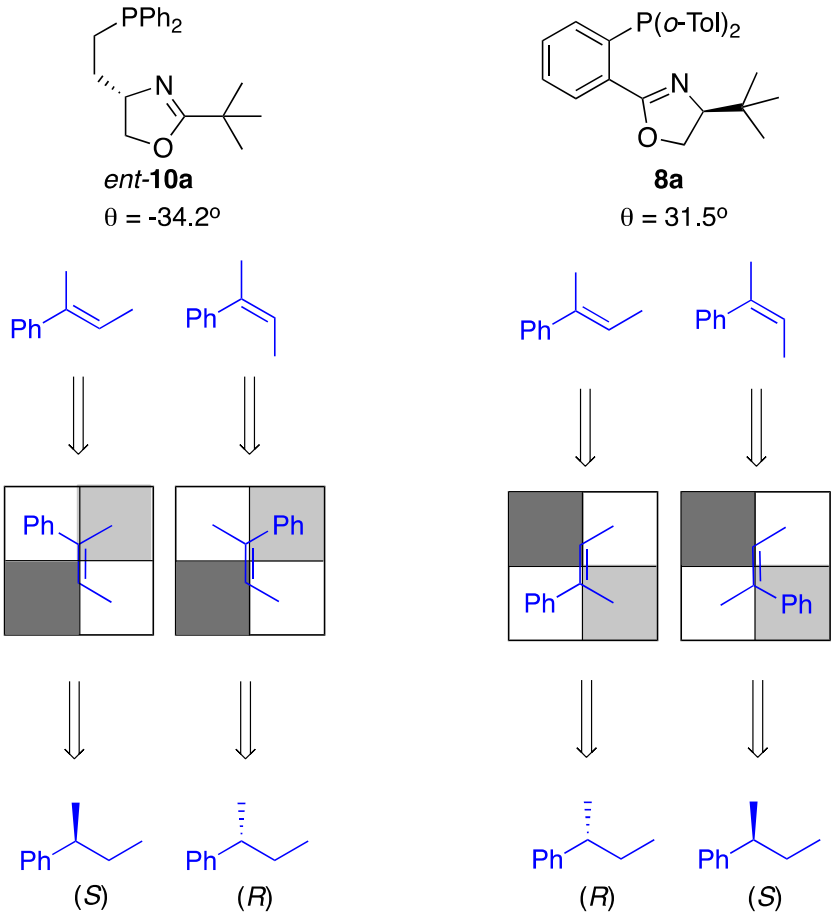


Figure 23 The angle θ (See Figure 20) correctly determines the absolute configuration of the products for a wide range of N,P-ligated iridium complexes.

9 Conclusion and perspective

Both the array of viable ligands for, and the substrate scope of, Ir-catalyzed asymmetric hydrogenation has expanded continuously over the last 10 years. N,P-ligated iridium complexes are now not only the state-of-the-art method for enantioselective reduction of tri-, tetra- and 1,1-disubstituted non-functionalized alkenes, but also for a wide range of other substrates such as allylic alcohols, α,β-unsaturated esters and carboxylic acids, vinyl boronates and vinyl phosphonates. Vinyl fluorides, enol ethers and enamines are alkene classes for which Ir-catalyzed asymmetric hydrogenation have shown great potential but for which truly effective and general reduction methods are lacking.

The use of Ir-catalyzed asymmetric hydrogenation in total synthesis and in industrial settings is still limited by the fact that very few, if any, easily prepared ligands have proven effective for a wide range of alkene substrates. Since the enantioselectivity obtained using a particular ligand is often strongly substrate dependent, ligand development should move towards modular ligands prepared by simple and inexpensive, yet flexible, synthetic routes. Furthermore, although low (<0.5 mol%) catalyst loadings are frequently used for non-functionalized substrates, increased substrate functionalization

typically lowers the turn-over frequency of Crabtree-type catalysts (and thus, in practice, the catalyst loading). Thus, effective methods for catalyst immobilization and/or re-use are highly desirable.

Although both supercritical CO_2 and propylene carbonate have proven to be useful solvents for Ir-catalyzed asymmetric hydrogenation, no solvent system has yet rivaled the environmentally unfriendly dichloromethane as the solvent of choice for reductions using Crabtree-type catalysts.

Finally, although a considerable degree of knowledge about the reaction mechanism has been acquired, mainly through quantum chemical calculations, experimental data are still scarce.

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