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Evolution and Prospects of the Asymmetric Hydrogenation of Unfunctionalized Olefins

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ABSTRACT: The catalytic enantioselective hydrogenation of prochiral olefins is a key reaction in asymmetric synthesis. Its relevance applies to both industry and academia as an inherently direct and sustainable strategy to induce chirality. Here we briefly recount the early breakthroughs concerning the asymmetric hydrogenation of largely unfunctionalized olefins, from the first reports to the advent of chiral Crabtree-like catalysts. The mechanism and its implications on the enantioselectivity are shortly discussed. The main focus of this Perspective lies on the more recent advances in the field, such as the latest developed classes of ligands and the opportunity to employ more Earth-abundant metals. Therefore, separate sections consider iridium N,P-, NHC-, P,S-, and O,P-catalysts, and rhodium, palladium, cobalt, and iron catalysts. Finally, the remaining unsolved challenges are examined, and the potential directions of forthcoming research are outlined.

INTRODUCTION

The enantioselective hydrogenation of olefins is currently recognized as one of the most fundamental transformations in asymmetric catalysis and represents an expedient strategy for the creation of stereogenic centers in target molecules. The process can rely on advantageous features such as excellent atom economy, quantitative yields, and high levels of enantioselectivity for a wide range of alkene substrates.[1] All these factors contribute to the method's attractiveness for both industrial applications and academic research. The field has seen an impressive degree of development since the early reports of successful asymmetric hydrogenation mediated by Rh(I)- and Ru(II)-diphosphine chiral catalysts,[2] a discovery leading up to the 2001 Nobel Prize awards to Noyori[3] and Knowles,[2i] and it has continued to draw the interest of numerous research groups to date. The Rh(I) and Ru(II) catalytic systems have since been applied extensively to diversely functionalized olefins. They still constitute the optimal choice for the synthesis of optically active α-amino acids and many pharmaceutically relevant compounds. However, they have mainly exhibited high efficiency and stereocontrol on substrates possessing a coordinating group in proximity of the C=C bond. With only a few exceptions,[4] they resulted prevalently in low activity and enantioselectivity when tested on minimally functionalized olefins, which can be defined as those not containing any coordinating functional group directly connected to the double bond.[5] In order to overcome these limitations and open the field of asymmetric hydrogenation to more general classes of olefins, different catalytic systems have been developed and evaluated for alkenes lacking metal-chelating functional groups. Among other purposes, the interest in the enantioselective reduction of minimally decorated double bonds is related to the possibility of stereocontrol on remote alkyl regions in the synthesis of natural and biologically active compounds.

The first promising reports of chiral catalysts able to selectively handle unfunctionalized olefins involved metallocenes[6] and organolanthanide[7] complexes. They could hydrogenate 2-phenyl-1-butene up to 96% enantiomeric excess (ee) but required very low temperatures, a base for catalyst activation, and complicated ligand preparation, which greatly inhibited their further development. Nevertheless, outstanding examples of metallocene catalysts were described by Buchwald, who first reported on the use of a titanocene catalyst[6h] for the hydrogenation of trisubstituted nonfunctionalized olefins in up to 99% ee, and later developed a zirconocene catalyst[6m] for the hydrogenation of the even more challenging class of tetrasubstituted olefins with ee's exceeding 90%.

The central role that iridium currently plays in homogeneous catalytic hydrogenation can be traced back to the development of Crabtree's catalyst **1**, $[Ir(cod)(PCy_3)(py)]^+PF_6^-$ (Figure 1,

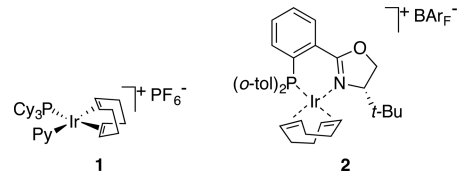

Figure 1. Crabtree's catalyst and Pfaltz's Ir-PHOX catalyst.

cod = 1,5-cyclooctadiene),[8] an achiral cationic complex which demonstrated exceptionally high activity toward olefins lacking neighboring coordinating groups, surprisingly including also tetrasubstituted olefins. The catalyst, employed as a crystalline salt, showed good stability against oxidation, making it easier to handle than most air-sensitive organometallic compounds, despite its impressive reactivity. Crabtree's work opened the possibility for further development of this kind of system in an asymmetric version.

EARLY DEVELOPMENTS

In 1993, the groups of Helmchen,[9] Williams,[10] and Pfaltz[11] introduced the use of chiral phosphinooxazoline N,P-ligands (PHOX) in asymmetric catalysis. In 1997, Pfaltz used PHOX ligands to generate the first series of chiral counterparts of

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Crabtree's catalyst (**2**, Figure 1) and successfully applied it to the asymmetric hydrogenation of imines.[12] Eventually, the catalysts were also employed in a number of aryl-substituted prochiral olefins, resulting in excellent enantioselectivity (98% ee for (*E*)-α-methylstilbene).[13] At the same time, some important issues related to the catalyst stability were solved. It had already been observed by Crabtree that the Ir cationic catalyst suffered from deactivation due to the formation of hydride-bridged trimers. This problem was solved by Pfaltz, replacing the counteranion PF_6^- with the more weakly coordinating species tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (BAr_F^-). This variation granted a dramatic increase in the reaction rate,[14] and it also allowed lowering the catalyst loadings to less than 1 mol%.

These findings prompted enormous attention to the design of chiral Ir complexes with the purpose of expanding the substrate scope to include a broader variety of olefins, resulting in the preparation and screening of a large variety of Ir-N,P-ligated catalysts. It still constitutes a prioritized research goal for the enantioselective hydrogenation of unfunctionalized alkenes.

The Pfaltz group continued to study and develop new versions of the PHOX complexes, modifying the ligand backbone, and built a library of very efficient catalysts for a variety of minimally functionalized olefins.[15] Successive work included pyridine and quinoline rings in ligands' structures and allowed the remarkable asymmetric hydrogenation of purely alkyl-substituted substrates in high ee.[16] An excellent application of these systems to total synthesis provided γ-tocopherol as a single diastereoisomer in 98% ee, controlling two stereocenters in one reductive step.[16b] The various developed ligands also enabled the asymmetric hydrogenation of different classes of substrates, including allylic alcohols, α,β-unsaturated esters,[17] furan derivatives,[18] boronic esters,[19] and tetrasubstituted olefins.[20]

Another class of notably effective catalysts involve C,N-ligands such as **3** (Figure 2), developed by Burgess.[21] They

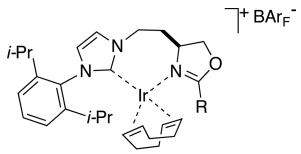

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Figure 2. An example of Burgess's N-heterocyclic carbene catalysts.

contain an N-heterocyclic carbene (NHC) as coordination site in place of phosphines and provide high enantioselectivities for a range of trisubstituted minimally functionalized olefins and vinyl ethers.[22]

Various classes of chiral N,P-ligands have been developed by the Andersson group. The investigation of different bicyclic heteroaromatic rings led to highly enantioselective hydrogenations by means of oxazole-,[23] thiazole-,[24] and imidazole-based[25] iridium catalysts **4**, **5**, and **6** (Figure 3). Other successful ligands were constructed around a 2-aza-norbornane chiral backbone (**7**, Figure 3).[26] The diverse nature of the different heterocycles also enables tuning the electron density on the N-donor atom, which in turn affects the electrophilicity of the iridium center. These iridium catalysts perform excellently on the typically tested trisubstituted nonfunctionalized olefins and also allow extending the substrate scope to

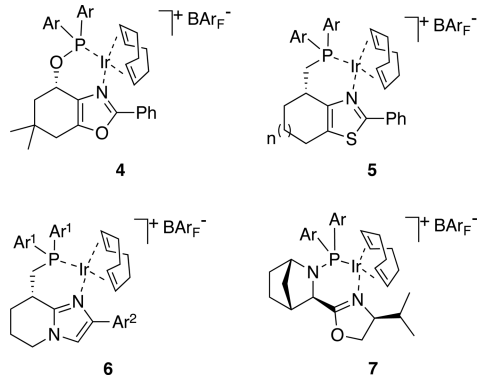

Figure 3. Catalysts developed by the Andersson group.

vinyl silanes,[27] fluorinated olefins,[25,28] vinyl boronates[29] and enol phosphinates.[30]

Several comprehensive reviews[5,31] have covered these major advances in the asymmetric hydrogenation of nonfunctionalized olefins; hence, this Perspective is mainly focused on the recent reports in the field (up to 2016) and the potential future directions of research.

To evaluate the efficiency and selectivity of the catalytic systems in asymmetric hydrogenation, unfunctionalized trisubstituted olefins have generally been employed as benchmark substrates, especially 1,2-diarylalkenes. In some cases disubstituted terminal olefins are also included in the screening, but reaching high enantioselectivity for these compounds has normally shown to be more problematic and might require more substrate-specific catalysts. Finally, exclusively alkyl-substituted and tetrasubstituted alkenes represent even more challenging substrates, appearing only in a limited number of reports.[6m,20,32]

MECHANISM AND SELECTIVITY

The advent of iridium Crabtree-type chiral catalysts started the evolution of the hydrogenation of hindered alkenes without coordinating functional groups. The mechanistic aspects of the Ir-catalyzed hydrogenation and the origin of stereoselectivity have been studied and discussed by various contributors.[33] This section will shortly describe the proposed catalytic cycle most widely accepted today.

In 2003, Brandt and co-workers carried out density functional theory studies employing a truncated model for an Ir-N,P-catalyst and proposed the mechanism to involve an Ir(III)/Ir(V) catalytic cycle.[34] In that study, starting from complexes $[Ir\text{-}(H)_2(N,P)(alkene)S]^+$ (alkene = ethane, S = solvent), the coordinated solvent molecule was replaced by a H_2 molecule, forming intermediate **A** (Figure 4). The migratory insertion step, which was identified as rate-determining due to the significant calculated energy barrier, occurred simultaneously and was also facilitated by the oxidative addition of the coordinated dihydrogen molecule to form the Ir(V) species **B**. Reductive elimination, liberating the alkane product, and coordination of new dihydrogen and alkene molecules regenerated species **A**. Kinetic studies have shown that the reaction is first-order in hydrogen pressure, but this could be related to H_2 diffusion in the solution, which can become rate-limiting when alkene hydrogenation is fast. It has been shown for Ir(PHOX) catalysts that the reaction is diffusion-limited at room temperature.[14,15b,35] Successive extended calculations on the full structure of a reported Ir-N,P-catalyst further reinforced

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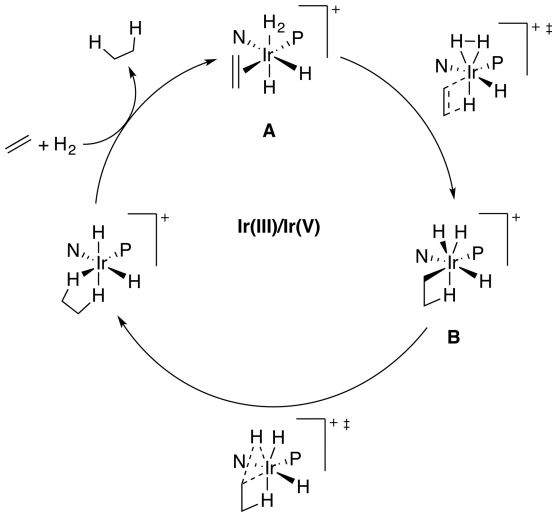

Figure 4. Proposed Ir(III)/Ir(V) catalytic cycle.

the proposed Ir(III)/Ir(V) mechanism as the lowest energy path for the reaction, investigating both gas-phase and solvent field conditions.[36]

This reaction pathway has been also supported by other recent computational investigations[37] and experimental findings. NMR studies by Pfaltz[38] led to the identification of a fundamental intermediate, an Ir(III) dihydride alkene complex. This species was defined as a resting state of the catalyst, and it demonstrated the requirement of the coordination of an additional dihydrogen molecule prior to the migratory insertion step.

The catalytic cycle shown in Figure 4 is proposed to be operating for most unfunctionalized olefins, with few exceptions.

In order to rationalize the stereoselectivity of the hydrogenation, the steric environment around the incoming olefin, which is coordinated *trans* to phosphorus, must be taken into account. The possibility for the olefin to coordinate is determined by the orientation of the R group near the nitrogen of the N,P-ligand (commonly an aryl or a bulky alkyl), which points to the alkene coordination site. The position of this steric bulk in the chiral N,P-ligands can be visualized by means of a quadrant selectivity model, indicating which areas will be more hindered, depicted from the perspective of the incoming olefin (Figure 5a). Gray quadrants represent the most occupied areas, which dictate the preferential coordination of one face of the alkene in order to minimize sterical interactions, with the R group occupying the lower left quadrant (i) or the upper one (ii), depending on the ligand structure and absolute configuration.

This quadrant model can be used to predict the stereochemical outcome of the majority of the N,P-Ir-catalyzed hydrogenations of prochiral olefins. It has proven reliable for a wide range of substrates,[36] where the stereoselection is mainly directed by steric hindrance rather than dominated by electronic effects or coordinating groups. Since the preferential coordination depends on the position of the smallest substituent (H) on the substrate, olefins are not discriminated based on the prochiral carbon atom, and this results in the formation of opposite enantiomers upon hydrogenation of an (*E*)- or (*Z*)-olefin. This is shown in Figure 5b for the case of a catalyst having the lower left quadrant (i) as the most occupied.

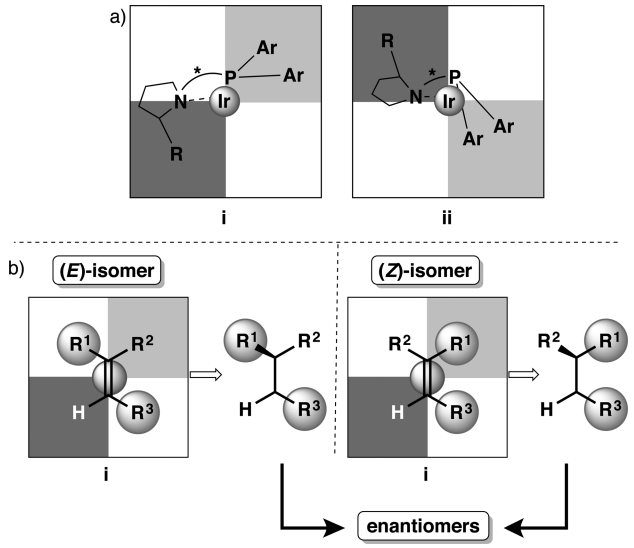

Figure 5. (a) Quadrant selectivity model. (b) Hydrogenation of isomeric alkenes.

LATEST RESULTS

It might seem that most issues have been largely overcome during decades of research on the asymmetric hydrogenation of olefins. This is certainly true in the sense that the large number of very efficient catalysts now available make it possible to achieve high enantioselectivities for a wide range of olefin classes, generally operating under mild conditions and at low catalyst loadings. Optimization efforts have predominantly revolved around the now well-established, wide variety of Ir-based catalysts, which continue to provide optimal results in the hydrogenation of various classes of substrates. However, some unsolved limitations in the applicability of these catalytic systems can still be found and will be analyzed herein after a discussion of recently published results. The selected reports regard exclusively catalytic systems that were applied to largely unfunctionalized olefins. Results on some unusual non-coordinating groups such as boronates are also covered. A very interesting part of the most recent advances involves the use of cheaper bulk metals as alternatives to iridium; therefore, successful examples of cobalt and iron catalysis are presented and arranged in separate sections.

The vast majority of reported research in asymmetric hydrogenation still concerns the use of Crabtree-type catalysts. Considerable advancements in the design of chiral ligands for iridium complexes have generated many innovative classes of catalysts, exploring diverse possibilities of tuning sterics and donor properties. For this reason, the large number of reports in iridium catalysis are grouped according to the donor atoms in the ligand coordination sites.

Iridium N,P-Catalysts. Recent advances in the development of ligands for Ir catalysis have been made by several research groups. For example, the group of Pàmies and Diéguez has lately been very active in the preparation of sugar-based ligands.[39] In particular, pyranoside phosphite-oxazoline structures **8** (Figure 6) were investigated, evaluating rigid biarylic moieties on the phosphorus to modularly generate a ligand library.

This approach afforded chiral iridium catalysts with improved substrate versatility, which achieved excellent ee's (up to 99%) for a broad range of unfunctionalized model alkenes: diaryl,

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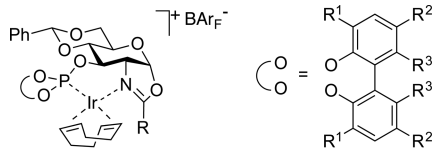

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Figure 6. Pyranoside-based catalysts.

dialkyl, and cyclic trisubstituted, triaryl-substituted, and also 1,1-disubstituted terminal olefins. Similarly, good results (>90% ee) were obtained for some of these substrates when using a simpler version of the ligands, having an *ortho*-tolyl phosphinite function.[40] The group also explored the possibility to carry out the hydrogenation of some olefins in propylene carbonate (PC) as an alternative, environmentally friendly solvent, still maintaining the excellent enantioselectivities. Another contribution by Pàmies and Diéguez showed that modification of previously developed phosphite-oxazoline catalysts to thiazoline-containing analogues **9** (Figure 7) was beneficial for the

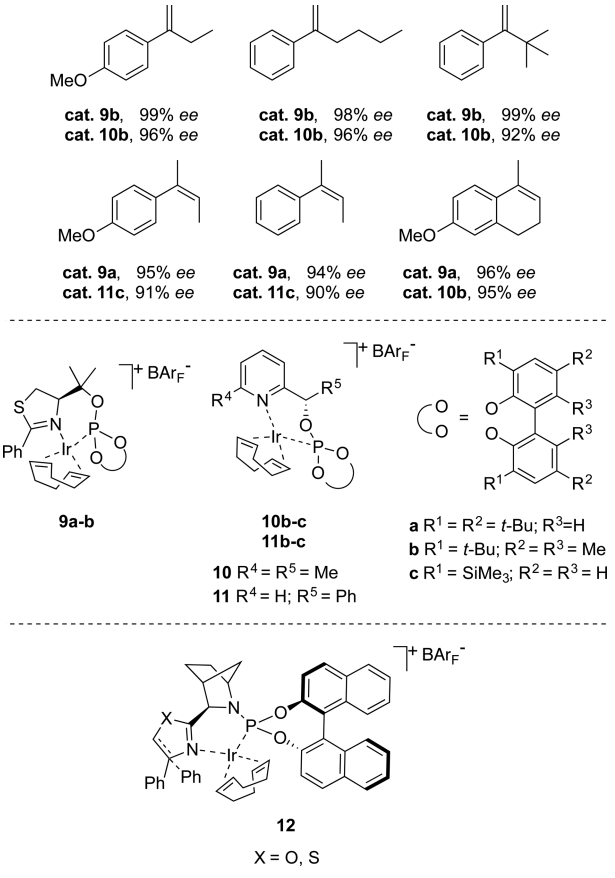

Figure 7. Selected results for biaryl-phosphite pyridine, phosphite-thiazoline, and phosphoramidite-based catalysts.

substrate scope.[41] The hydrogenation of (*E*)- and (*Z*)-trisubstituted olefins resulted in high enantioselectivities as expected, but it was moreover possible to achieve exceptional ee's, in the range of 90−99%, for 1,1-disubstituted terminal olefins. Later studies implemented biaryl phosphites on pyridine-containing ligands, without the use of sugar fragments.[42] This generated iridium catalysts **10** and **11** (Figure 7), whose structures resemble more closely Pfaltz's pyridine-based ligands[16−19] and were found to give high stereoselectivity toward both (*E*)- and (*Z*)-trisubstituted olefins, as well as more demanding dihydronaphthalenes and triaryl-substituted substrates (95−98% ee). Excellent results (90−99% ee) could also be achieved on several vinyl boronates and terminal olefins (>90% ee).

An interesting example of ligand design was reported when the Diéguez and Andersson groups collaborated to prepare and evaluate a library of catalysts containing the 2-aza-norbornane framework, an oxazoline or thiazole ring, and a biaryl phosphite moiety.[43] The resulting phosphoramidite-based ligands **12** (Figure 7) showed good versatility and resulted in hydrogenated products in higher ee's than the first generation of this type of ligands. Demanding terminal olefins were also well tolerated, and improved enantioselectivities were reached for a number of these compounds; however, some of the aryl-alkyl-substituted ones were still hydrogenated in moderate ee's due to competitive isomerization to the (*E*)-isomers.

A direct and powerful strategy to access chiral cyclohexanes by asymmetric hydrogenation of diversely functionalized 1,4-cyclohexadienes has been studied and optimized by the Andersson group.[44] Among the hydrogenation substrates, many examples of purely alkyl-substituted dienes can be found, for which thiazole- or imidazole-based iridium catalysts produced excellent enantioselectivities (up to 99%). The predominant formation of the *trans* isomer was observed for 1,3-substituted carbocycles. Successively, the scope of this methodology has been further improved by fine variation of aryl substituents on the imidazole-type ligands (**6**, Figure 8), which afforded even more efficient, versatile, and enantioselective catalysts.[45]

An important feature to consider in this work lies in the possibility to preserve some of the double bonds on the cyclic structures, leaving room for further synthetic manipulations. This has proven to be consistently attainable in the case of

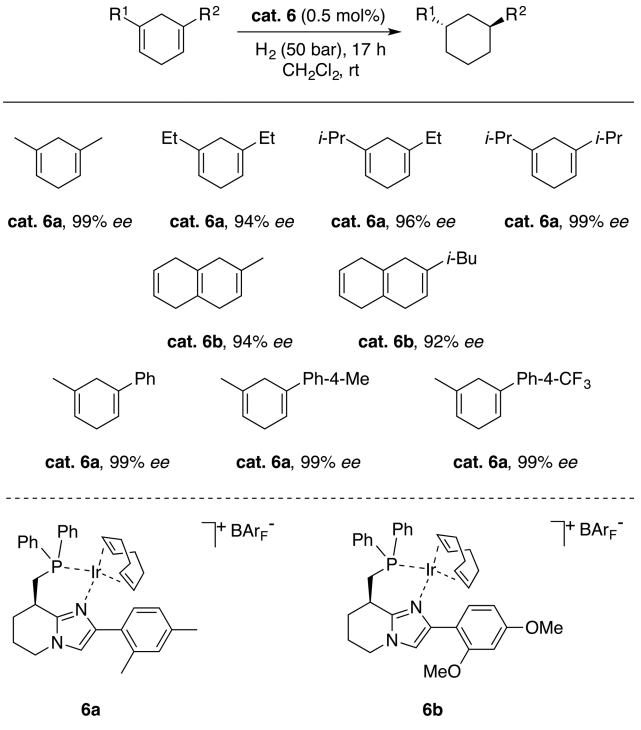

Figure 8. New generation of imidazole-based catalysts for the asymmetric hydrogenation of cyclohexadienes (selected results).

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tetrasubstituted olefins. In addition, it was also found possible to discriminate between two differently trisubstituted olefins on some aryl-containing cyclohexadienes, and they could be converted to either monohydrogenated products or fully saturated chiral cyclohexanes, depending on hydrogen pressure and reaction time; in both cases, 99% ee was maintained (Figure 9).

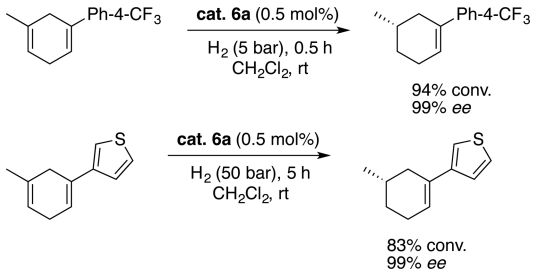

Figure 9. Regioselective hydrogenation of cyclohexadienes.

In 2014, the synthesis of new pyridine-based N,P-ligands with a five-membered fused carbocycle (**13**, Figure 10) was

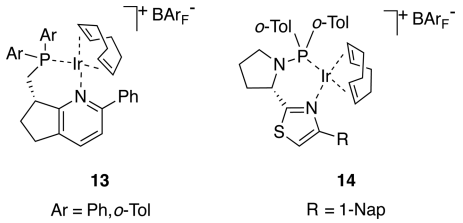

Figure 10. Examples of new pyridine- and proline-based catalysts.

described by Andersson and co-workers.[46] This group of catalysts differs from previous generations employing pyridine as a N-donor since they contain a carbon atom instead of oxygen as a linker between the ligand chiral backbone and the phosphorus. Earlier ligands with a P−O bond are generally less stable.[16a] The results obtained in the asymmetric hydrogenation of some typically tested trisubstituted olefins proved the catalysts' efficiency, reaching full conversion and ee's in the range of other heterocyclic ligands (>90% ee). Thiazole-substituted ligands **14** (Figure 10) derived from proline also showed high activity and good enantioselectivities when used in the Ir-catalyzed hydrogenation of certain trisubstituted and endocyclic nonfunctionalized alkenes (84−97% ee).[47]

Using the BIPI ligands class (**15**, Figure 11), which had already performed successfully in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins, a set of novel iridium catalysts was developed by Busacca, Qu, and Senanayake.[48] In order to apply this system to unfunctionalized olefins, a ligand optimization study was carried out, varying the substituents at the phosphorus and on the imidazoline ring. Having cyclohexyl groups on both functions and a fluorine atom on the naphthyl *peri*-position provided a very efficient catalyst for hydrogenating challenging tetrasubstituted olefins, yielding an excellent 96% ee for the model substrate 2,3-dimethylindene using 1 bar of H_2 (2 mol% of catalyst). A 90% ee was obtained for dimethyl dihydronaphthalene, and high selectivity was also achieved for two representative trisubstituted olefins. Pyridyl-dihydrobenzooxaphosphole (BoQPhos) ligands **16** (Figure 11) were also evaluated in the Ir-catalyzed hydrogenations of unfunctionalized olefins.[49]

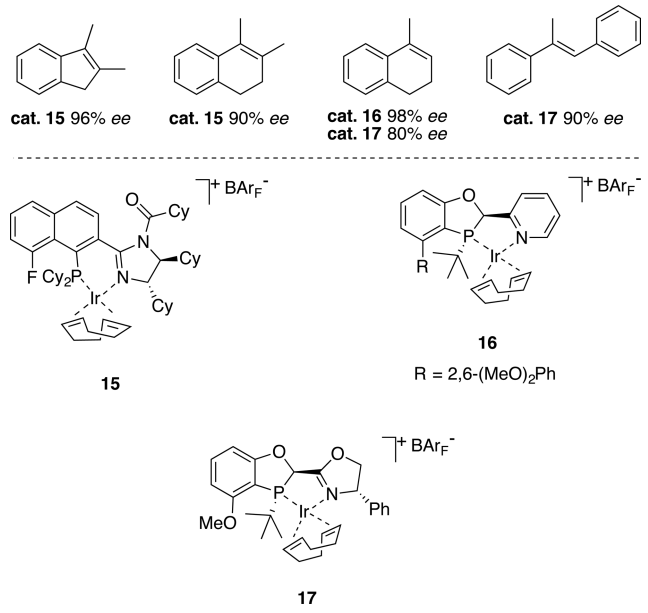

Figure 11. BIPI, BoQPhos, and LalithPhos catalysts.

Although high conversions and good enantioselectivities (76−90% ee) were obtained for different substrates (Figure 11), the BIPI-derived catalysts **15** provided better results. The hydrogenation of prochiral unfunctionalized dihydronaphthalenes was improved with the design of new phosphine-oxazoline ligands **17** (LalithPhos, Figure 11), and various 1-aryltetralins were thus obtained in ee's higher than 90% using 1 atm of H_2.[50]

The group of Van der Eycken has investigated chiral ferrocene-derived N,P-ligands **18** (Figure 12), whose iridium

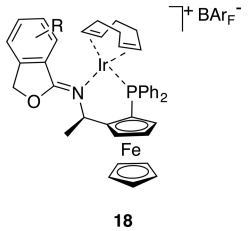

Figure 12. Ferrocene N,P-catalysts.

complexes were tested in the hydrogenation of unfunctionalized olefins.[51] A 91% ee was observed for (*E*)-*α*-methylstilbene at 50 bar of H_2. Moderate enantioselectivities were found for dihydronaphthalene substrates and 2,3-dimethylindene, while an excellent result was achieved for *α*-ethylstyrene (>99% ee).

Sigman recently reported a novel strategy for the enantioselective hydrogenation of 1,1-diaryl-substituted olefins, which relies on a remote coordinating effect deriving from a *meta* substituent on one of the aromatic rings.[52] In particular, methoxy functionalities were studied as *meta* directing groups, providing an expansion of the substrate scope compared to the Ru and Rh catalytic systems, which required oxygen directing groups in the *ortho* position. The use of the new proline-derived phosphoramidite (PhosPrOx) ligands **19** (Figure 13) afforded remarkable ee's (up to 93%) in the hydrogenation of 1,1-diaryl-substituted olefins without an *ortho* substituent. However, the requirement for a 3,5-dimethoxy substitution on one of the aryls in the substrate in order to reach high enantioselectivity is still limiting the scope of this new

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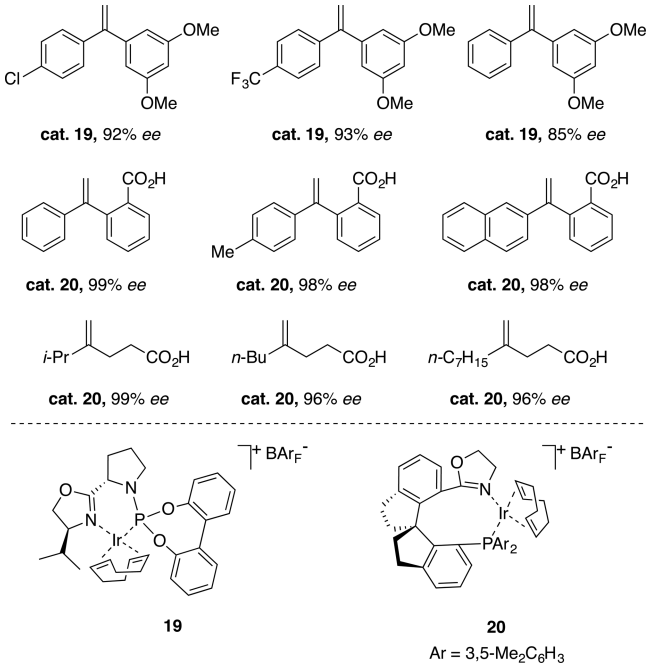


Figure 13. Remotely directed asymmetric hydrogenation of 1,1-diaryl- and 1,1-dialkyl-alkenes.

methodology. Zhou applied the same concept via remote carboxyl group coordination in the hydrogenation of 1,1-diaryl- and 1,1-dialkylethenes.[53] For the former, the directing COOH group was placed in the *ortho* position of one of the aryl substituents and could be readily removed by one-pot decarboxylation, accessing chiral unfunctionalized 1,1-diarylethanes in high yields and excellent enantioselectivity. These structures are the core of many biologically active compounds. The catalysts contained spiro phosphine-oxazoline ligands **20** (Figure 13) and successfully operated at 0.25 mol% loading and 6 atm of H_2 on a broad scope of diarylethene acids (96 to >99% ee). Also for dialkyl substrates, high enantioselectivities were achieved (89−99% ee), resulting in useful chiral γ-methyl fatty acids. Asymmetric iridium-catalyzed hydrogenations have generally relied on steric differentiation in order to reach high stereoselectivity, while the coordination strategy had been a prerogative of Rh- and Ru-mediated processes. Insight into this interesting new strategy in asymmetric hydrogenation and its potential has been highlighted by Reek.[54]

The synthesis of chiral benzimidazole-based ligands **21** (Figure 14) was reported in 2014 by Müller, and their first

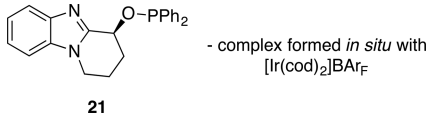
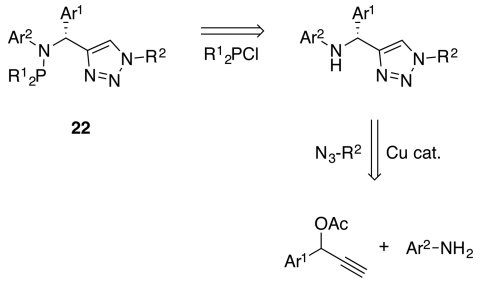


Figure 14. Benzimidazole-derived N,P-ligand.

application in the asymmetric hydrogenation of (*E*)-α-methylstilbene provided encouraging results (up to 90% ee).[55] Optimization of the ligands structure is still to be accomplished, but it could lead to a new competitive class of catalysts in the future.

An alternative strategy involving one-pot Cu-catalyzed cycloadditions for the facile preparation of tunable triazole-containing N,P-ligands **22** (Clickphine, Scheme 1) was

Scheme 1. Retrosynthesis of Clickphine N,P-Ligands



developed in 2015 by Reek and van Maarseveen.[56] Chirality is induced to the ligand libraries from a single copper catalyst, and the process allows the variation of up to four substituents on the triazole-phosphine structure in two reaction steps. These iridium complexes were evaluated in the hydrogenation of largely unfunctionalized olefins; while good ee's were obtained for both examples of (*E*)-trisubstituted (90%) and terminal aryl-alkyl-disubstituted subtrates (75%), they could not equal the excellent results obtained with other classes of Ir-N,P-catalysts. On the other hand, a promising enantioselectivity of 87% was achieved in the case of a more demanding tetrasubstituted substrate, with very few higher values reported so far.

Iridium N-Heterocyclic Carbene (NHC) Catalysts. In a recent study comparing different NHC,N-ligands,[57] Burgess concluded that imidazolinylidene **23**, imidazolylidine **3**, and benzimidazolylidene **24** structures (Figure 15) show negligible

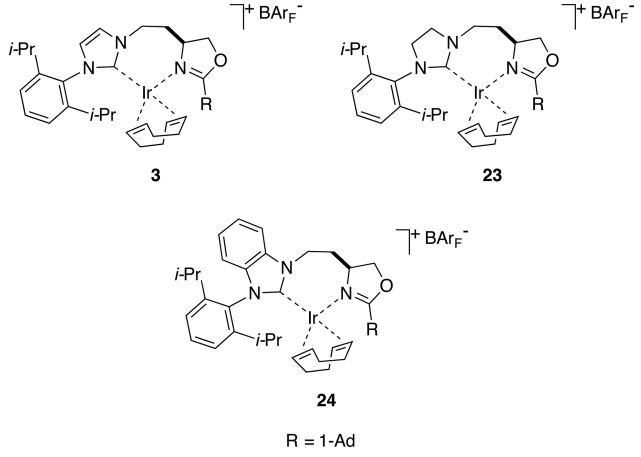


Figure 15. Comparison of NHC,N-catalysts.

differences in catalytic performance in the Ir-catalyzed asymmetric hydrogenation of largely unfunctionalized alkenes. The test substrates were reduced with enantioselectivities comparable to those previously reported for this class of ligands, obtaining excellent results (up to 99% ee) in the case of (*E*)-trisubstituted olefins.

In 2013, Pfaltz developed a series of NHC-pyridine ligands (**25**, Figure 16) containing five-, six-, and seven-membered carbocycles.[58] These structures combine the features of some of the most successful ligands available to date, and their iridium catalysts proved to be very efficient in the hydrogenation of different unfunctionalized olefins.

High levels of enantioselectivity (>90%) were observed, even for (*Z*)-trisubstituted (94% ee) and endocyclic substrates (96% ee). Although they did not outperform Burgess's system **3** in

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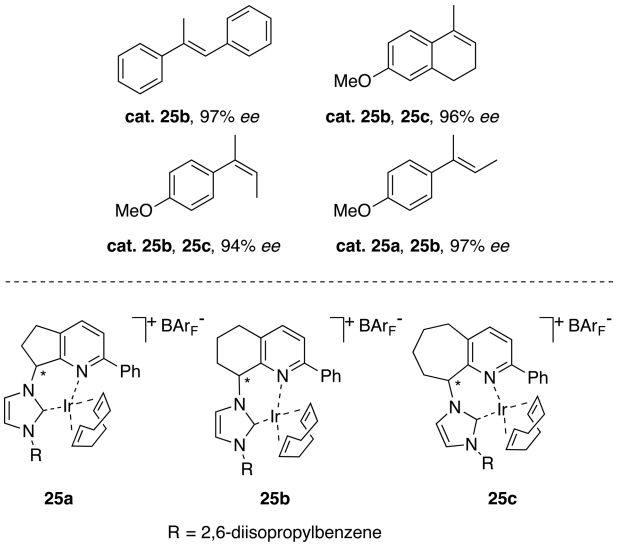

Figure 16. Application of NHC-pyridine catalysts (selected results).

the case of terminal disubstituted olefins, these catalysts clearly improve the application range of NHC-iridium ligands to some difficult classes of alkenes. It is worth mentioning that an important advantage of NHC-catalysts compared to their phosphine analogues concerns their better tolerance of acid-sensitive substrates.

Iridium P,S-Catalysts. Sulfur offers the opportunity to create stereogenic centers on the sulfur atom upon coordination with a metal, bringing chirality closer to the metal, and also leading to increased stability of the ligands compared to some commonly employed N-donors. Recent investigations by the group of Pàmies and Diéguez involved the synthesis of various furanoside thioether-phosphite, -phosphinite, and -phosphine ligands **26** (Figure 17), derived from easily accessible D-(+)-xylose.[59] Structures containing bulky biaryl phosphite moieties afforded highly efficient and enantioselective iridium catalysts, which have been evaluated in the hydrogenation of a wide series of minimally functionalized olefins. Excellent ee's (up to 99%) were obtained for different trisubstituted alkenes, including interesting triaryl-substituted substrates. High enantioselectivities could also be obtained for acyclic (*Z*)-olefins (94% ee), while cyclic substrates were found to result in good but somewhat lower selectivities (75−86% ee). High ee could be achieved for vinylboronates (91%). Challenging 1,1-disubstituted terminal olefins gave low to moderate results when minimally functionalized, depending on the nature of the substrate alkyl substituents. A simpler class of phosphite-phosphinite-thioether ligands (**27**, Figure 17) derived from cyclohexene oxide was also prepared and evaluated in the asymmetric hydrogenation of various minimally functionalized olefins.[60] Excellent ee's were reported for several interesting substrates, including trisubstituted alkenylboronic esters (85−88% ee) and *tert*-butyl-substituted terminal olefins (up to 99% ee). Furthermore, the catalytic system proved to be highly efficient on terminal aryl-substituted boronic esters (up to 98% ee), extending the scope of successful asymmetric hydrogenations to this class of olefins. Ferrocene-based P,S-ligands **28** (Figure 17) have been also studied and evaluated in analogous hydrogenation experiments.[61] However, the best enantioselectivities for non-functionalized olefins were obtained with the classes of iridium P,S-catalysts based on structures **26** and **27**.

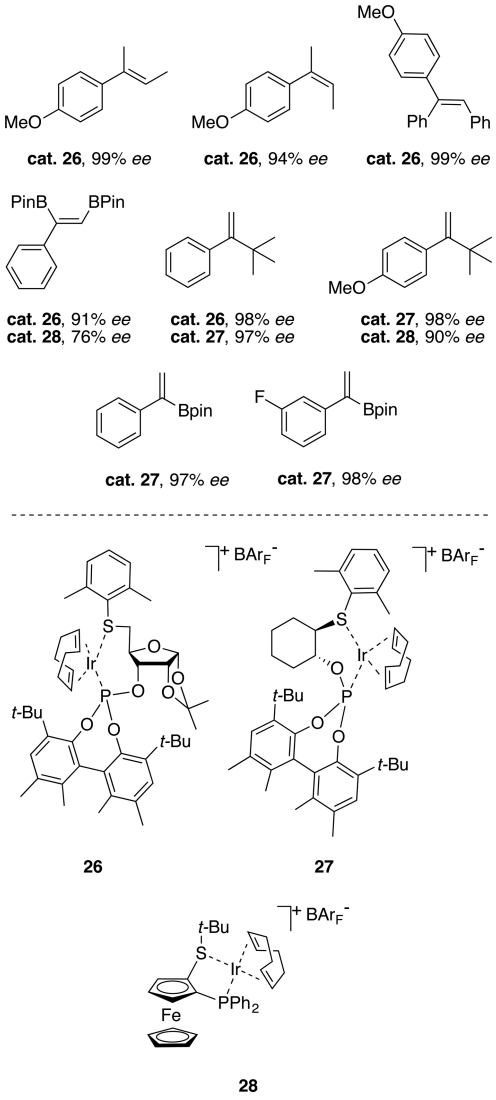

Figure 17. Examples of application of P,S-catalysts.

Iridium O,P-Catalysts. In 2011, Pfaltz and co-workers reported the synthesis and evaluation of L-proline-based O,P-ligands **29** (Figure 18) in Ir-catalyzed hydrogenations.[62] These

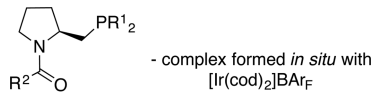

Figure 18. Proline-derived O,P-ligands.

chiral amido- and ureaphosphines can coordinate transition metals through the carbonyl oxygen atom and can be prepared from inexpensive precursors. It was shown that full conversion and excellent enantioselectivities (up to 99% ee) could be obtained, for example, in the hydrogenation of (*E*)-α-methylstilbene, with a performance comparable to that of the best N,P-systems. These O,P-complexes proved, however, to be less stable than proline-based N,P-catalysts and were therefore generated *in situ* prior to the hydrogenation reaction. These catalysts did not outperform other highly enantioselective N,P-iridium complexes in the case of minimally functionalized trisubstituted olefins, but they have been successfully applied to

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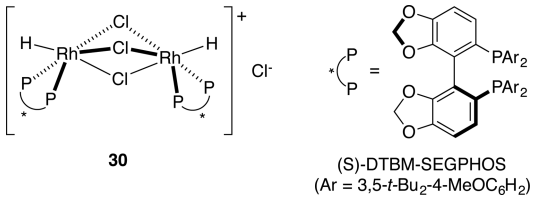
the hydrogenation of some functionalized olefins, such as α,β-unsaturated esters and ketones.[63]

Rhodium. A dinuclear Rh(III) complex (**30**, Figure 19) derived from chiral diphosphine ligands was reported for the

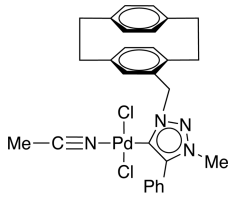


30 (S)-DTBM-SEGPHOS (Ar = 3,5-*t*-Bu_2-4-$MeOC_6H_2$)

Figure 19. Dinuclear Rh(III) hydrogenation catalyst.

hydrogenation of olefins without directing groups, in contrast to conventional results for Rh(I) species.[64] The approach relies on the dissociation into the corresponding mononuclear monohydride Rh(III) as active species. The precatalyst is a chloride-bridged dinuclear rhodium complex, and a number of structures were generated from a series of chiral diphosphine ligands. Employing bulkier diphosphine ligands resulted in higher activity and selectivity in the hydrogenation of (*E*)-α-methylstilbene (up to 95% ee) using 30 bar of H_2 at 80 °C in toluene, with 1 mol% catalyst loading and 2 mol% of *n*-Bu_4NCl as additive. Excellent results (87−98% ee) were also obtained for a range of methylstilbene derivatives with various aryl substituents. High enantioselectivity could also be achieved in the hydrogenation of alkenyl boranes (85 and 93% ee).

Palladium. An interesting report in palladium catalysis involves a chiral [2,2]paracyclophane-based 1,2,3-triazol-5-ylidene Pd complex (**31**, Figure 20) containing a labile



31

Figure 20. Chiral [2,2]paracyclophane-based Pd catalyst.

acetonitrile ligand.[65] It was employed to hydrogenate prochiral olefins under mild conditions in methanol (1 atm H_2, 30−35 °C). When tested on (*E*)-α-methylstilbene and a naphthalene-substituted terminal alkene, it produced nearly quantitative yields and promising levels of enantioselectivity (84−87% ee). Ligand improvement and screening could result in a substrate scope expansion for this type of catalytic system.

Cobalt. An early report by Pfaltz had presented an efficient cobalt catalyst for the enantioselective reduction of α,β-unsaturated esters.[66] More recently, Chirik's work made an important contribution to the asymmetric hydrogenation of largely unfunctionalized olefins using cobalt catalysis. This paves the road for the use of more Earth-abundant metals; an obviously attractive option in terms of cost and environmental advantages. Cobalt bis(imino)pyridine complexes **32** (Figure 21) have also been successfully employed in the asymmetric hydrogenation of challenging terminal aryl,alkyl-substituted olefins and furnished the corresponding saturated products in high enantioselectivity (>90% ee).[67] A particularly remarkable result is the excellent 96% ee observed in the formation of 1-

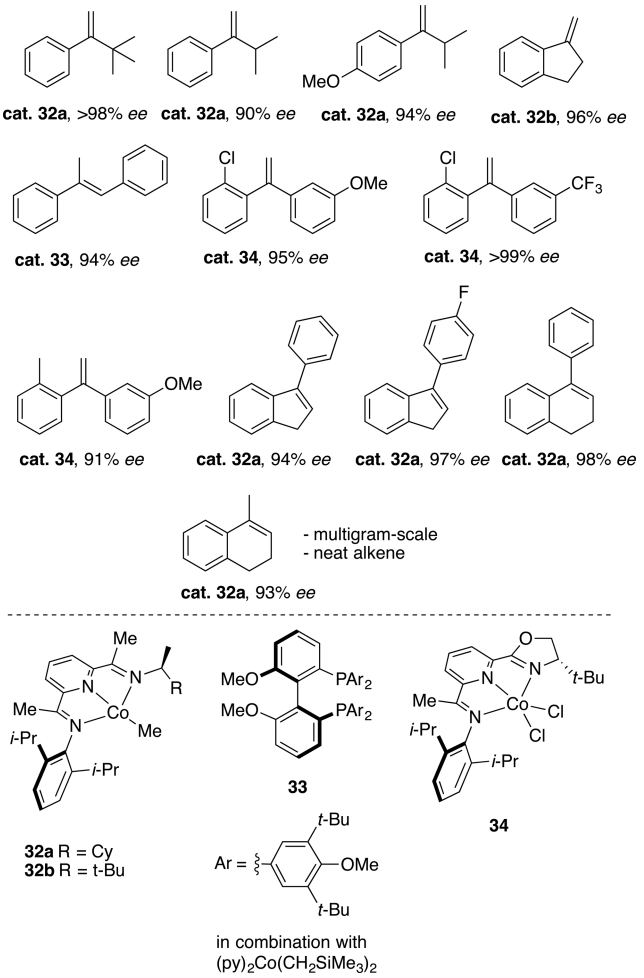


Figure 21. Cobalt-catalyzed asymmetric hydrogenation of unfunctionalized olefins (selected results).

methylindane. Hopmann recently presented a quantum mechanical study of the chiral CoBIP catalysts, providing information about their properties, activation paths and asymmetric hydrogenation mechanism.[68] Competitive alkene isomerization was shown to play a role in the overall process, affecting also the observed enantioselectivities.

Successively, high-throughput screening of numerous chiral bidentate phosphine ligands in combination with different cobalt precursors allowed the identification of a suitable catalytic system for the asymmetric hydrogenation of (*E*)-α-methylstilbene.[69] Ultimately, a Biphep derivative (ligand **33**, Figure 21) was found to be highly stereoselective, resulting in 83% conversion and 94% ee, after 20 h using 34 atm of H_2. The catalyst loadings are higher (10 or 5 mol%) than those commonly used for iridium catalysts (1 mol% or less), but these results certainly prove cobalt to be a valuable asset for efficient and versatile hydrogenation of largely unfunctionalized olefins.

Both Lu and Chirik reported the Co-catalyzed enantioselective hydrogenation of several 1,1-diarylethenes in 2016. In Lu's case,[70] a stable cobalt complex containing an oxazoline iminopyridine chiral ligand (**34**, Figure 21) was used as precatalyst. In the presence of $NaBHEt_3$ in toluene and using 1 atm of H_2 at room temperature, it was possible to reach full conversion and 90% ee for substrates with an *ortho*-Cl group, which provided a unique effect to achieve high enantioselectivities. When the alkene scope was evaluated, enantio-

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selectivities up to 95% ee were observed for α-alkylstyrenes. The Cl group could then be removed or used for further functionalizations with excellent yields, describing a convenient way to obtain various chiral 1,1-diarylethanes.

In Chirik's report, cobalt bis(imino)pyridine complexes **32** proved very successful in the asymmetric hydrogenation of cyclic unfunctionalized olefins, such as aryl-substituted indenes and dialins (up to 99% ee).[71] In a comparative study, both isomeric exo- and endocyclic alkenes were hydrogenated in good to high enantioselectivity (up to 95% ee), with a tendency to show opposite stereochemical outcomes. Moderate ee's (up to 77%) were obtained for 1,1-diarylethenes when *ortho* substitution was present. A remarkable application of the catalytic system is the multigram-scale reduction of 4-methyl-1,2-dihydronaphthalene (93% ee), carried out in neat alkene using 0.1 mol% of chiral cobalt complex. Co-hydride species were rapidly generated in the presence of H_2 and were identified by means of NMR and X-ray diffraction, providing some information about the chiral environment around the cobalt.

Iron. Aryl-substituted bis(imino)pyridine iron dinitrogen complexes **35** (Figure 22) were described as efficient base metal

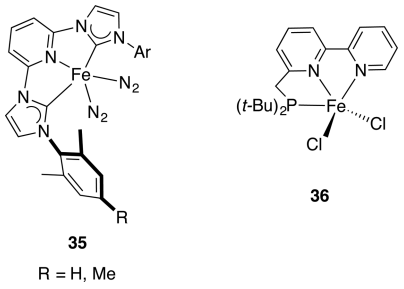

Figure 22. Iron catalysts for the hydrogenation of simple olefins.

catalysts, exhibiting high turnover frequencies for the hydrogenation of unfunctionalized trisubstituted and challenging tetrasubstituted olefins, employing iron loadings as low as 0.3 mol% at room temperature.[72] Recent optimization of the ligand design using more electron-rich structures improved the performance.[73] This work could furnish valuable insight for the development of an asymmetric version of iron catalytic systems.

Another class of iron catalysts was reported where the active species are generated *in situ* by reduction of stable Fe(II) complexes with $LiAlH_4$.[74] The use of bidentate N,N-ligands resulted in excellent activity in the hydrogenation of styrene, which was fully saturated in less than 1 h using 30 atm of H_2 with 0.1 mol% catalyst loading. A particularly efficient catalyst was then obtained using a pincer bipyridine ligand (**36**, Figure 22), which provided full conversion after 3 h using 10 atm of H_2, at 0.01 mol% catalyst loading. Styrenes and aliphatic terminal olefins were also hydrogenated with high reaction rates; however, it was necessary to increase the temperature to 50 °C in the case of disubstituted olefins. This contribution also makes it possible to envision further developments toward Fe-based asymmetric hydrogenation catalysts.

■ CONCLUSIONS AND OPEN CHALLENGES

The development of chiral Crabtree-type catalysts has notably expanded the field of homogeneous asymmetric hydrogenation of nonfunctionalized olefins, providing complementarity to Rh and Ru systems. Examining the scope of the catalysts that are currently available for the asymmetric hydrogenation of largely unfunctionalized olefins, it seems clear that careful ligand optimization and control of the reaction conditions allow reaching high enantioselectivities for many different substrate classes. One drawback of this approach is the lack of generality of the catalysts; it is still difficult to generate a single catalyst that would tolerate a large number of olefins bearing substituents of diverse nature. However, recent investigations, especially in iridium catalysis, continue to produce new powerful systems, advancing toward the goal of increased functional group tolerance. The main limitation that still concerns the majority of asymmetric hydrogenations is the necessity to operate on pure geometrical isomers; (*E*)- and (*Z*)-trisubstituted olefins are generally found to produce opposite enantiomers of the alkane products, canceling the chance of achieving high stereoselectivity when both are present. The reason for this undesired behavior lies in the mode the catalysts are discriminating between the prochiral faces of the olefin, with the favored coordination being dictated by the less substituted carbon atom rather than the prochiral center. Therefore, a catalytic system that would be able to select directly on the prochiral carbon, regardless of alkene geometry, is much sought after, as it would enable the asymmetric hydrogenation of *E*/*Z* mixtures to yield enantiomerically pure products. This issue is even more relevant in the case of unfunctionalized olefins, since the presence of functional groups on the substrates facilitates both the stereoselective synthesis of either (*E*)- or (*Z*)-isomers and also their separation.

Another open challenge concerns the development of efficient systems for hindered tetrasubstituted olefins. This class of substrates has always proved very demanding, and reports of highly enantioselective hydrogenations are still scarce. One interesting feature of tetrasubstituted olefins is certainly the opportunity to generate two contiguous stereocenters in a single reaction; thus, efforts in the development of improved catalysts for these sterically challenging compounds are easy to foresee.

Other demanding substrates are also represented by olefins that contain non-coordinating groups such as silanes or halides. In the latter case, the hydrogenation is further complicated by competing dehalogenation processes, an issue still to be overcome by development of new catalytic systems.

In addition to handling these difficult classes of alkenes, it would also be highly desirable to directly saturate aromatic rings, which would be one of the most interesting opportunities for the asymmetric hydrogenation of minimally functionalized substrates. Several efficient catalysts have been developed for the asymmetric hydrogenation of various classes of heteroarenes, and these advances have been reviewed in detail by Zhou and Glorius.[75] Some examples of catalytic hydrogenation of benzene rings have been reported,[76] but still the substrate scope remains very narrow, and this research area is also likely to expand in the future.

The formation of multiple stereocenters from the asymmetric hydrogenation of polyene substrates is of undoubtable interest, and the usefulness of this strategy has been elegantly demonstrated in natural products preparation.[16b,77] On the other hand, polyenes can also offer many other interesting post-hydrogenation synthetic possibilities if the catalytic system can be tuned to react with one olefin while leaving others untouched and available for further functionalization. It

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would represent a powerful synthetic tool to induce chirality, especially in complex structures containing many double bonds. Examples of regioselective iridium catalysts have been recently reported[45] and can surely offer a hint for future studies on this subject.

Finally, a fundamental area of investigation lies in the search for catalysts based on more cost-effective and environmentally friendly Earth-abundant metals, exemplified by recent works in cobalt and iron catalysis. In the former case, some excellent results for the asymmetric hydrogenation of unfunctionalized olefins have already been reported, and the optimization of catalytic activity and stability are plausible lines of forthcoming development. In the case of Fe-catalyzed hydrogenation of olefins, the challenge is instead to design an efficient asymmetric variant of the newly developed achiral systems.

Taking the above-mentioned considerations into account, one can conclude that many fascinating aspects and opportunities of the asymmetric hydrogenation of minimally functionalized olefins remain to be explored and that the design of innovative catalysts capable of overcoming the remaining issues would provide fundamental contributions to the field.

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Notes

The authors declare no competing financial interest.

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