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Review

Iridium catalysts for the asymmetric hydrogenation of olefins with nontraditional functional substituents

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Contents

Abstract

Chiral iridium catalysts have now been used in the asymmetric hydrogenation of largely unfunctionalized olefins for a decade. Recently, they have also been applied to substrates with more exotic functional groups, including non-coordinating ones. These, unlike coordinating substituents, cannot direct asymmetric hydrogenation by rhodium- or ruthenium-based catalysts. This review discusses several classes of these less familiar substrates, outlines the progress that has been made toward their stereoselective hydrogenation, and highlights the role of iridium complexes in this emerging field. We hope this will inspire researchers to consider iridium-catalyzed asymmetric hydrogenation as a potential route to a broad range of chiral compounds.

Keywords: Asymmetric hydrogenation; Iridium catalysts; Functionalized olefins; Non-coordinating olefins

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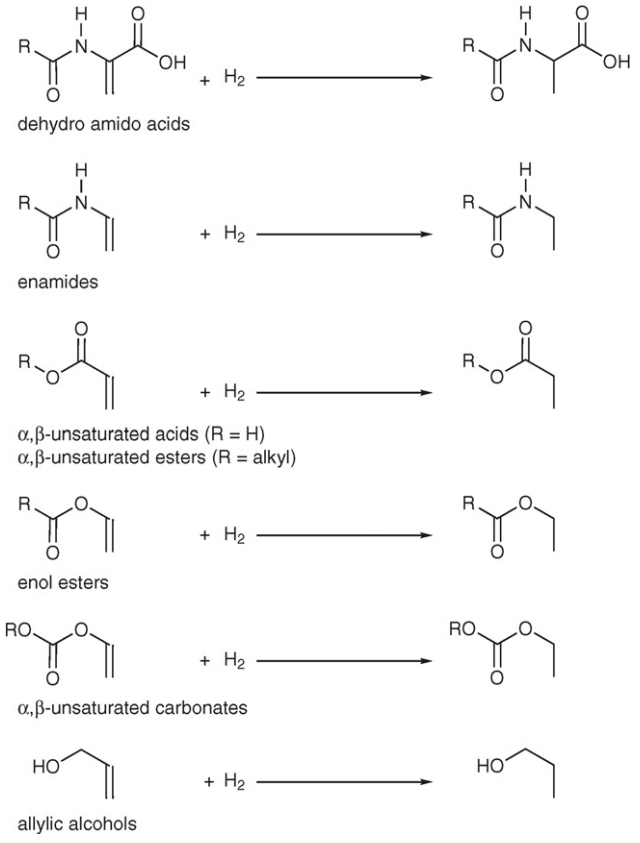
1. Asymmetric hydrogenation of functionalized olefins: a role for iridium?

The importance in modern chemistry of asymmetric hydrogenation by chiral catalysts is well-recognized. In less than 40 years, this class of reactions expanded from initial reports [1] to industrial success [2], and in 2001 garnered the Nobel Prize for two of its pioneers, Knowles [3] and Noyori [4]. However, asymmetric hydrogenation is by no means a "mature science"; new catalysts and applications for the reaction are reported frequently.

The first substrates of catalytic asymmetric hydrogenation were functionalized olefins [5], and these have dominated the field for most of its lifetime. The excellent stereoselectivity of rhodium- and ruthenium-catalyzed olefin hydrogenations usually relies upon the availability of a coordinating moiety, such as a carbonyl or alcohol group, on the olefin (Scheme 1). These functional groups collaborate with the olefin π-bond to form a chelate ring that is pivotal in directing the stereochemistry of the hydrogenation reaction [3,4,6,7]. Additionally, the products formed from the asymmetric hydrogenation of functionalized olefins can be very attractive. For example, the asymmetric hydrogenation of α,β-dehydro-α-amido acids provides a chemical route to chiral α-amido acids (Scheme 1, top); these are easily converted to desirable chiral α-amino acids.

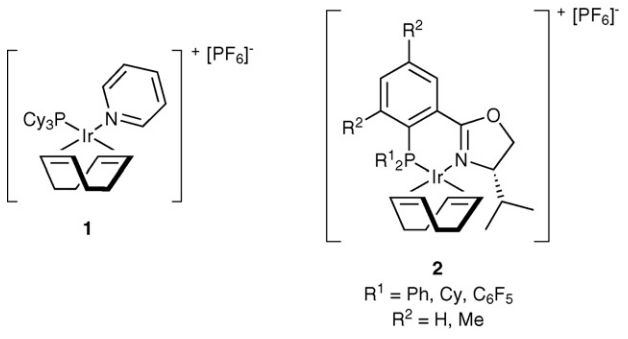


Scheme 1. Olefins with coordinating substituents as substrates for rhodium- or ruthenium-catalyzed asymmetric hydrogenation. Additional substituents are omitted for clarity, however, the new asymmetric center may be formed α or β to the coordinating group (or both).

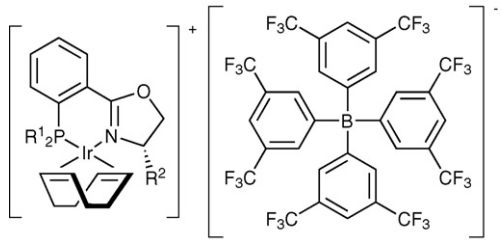
The rhodium- and/or ruthenium-catalyzed asymmetric hydrogenations of dehydro amido acids, enamides, allylic alcohols, enol esters, and α,β-unsaturated acids and carbamates are well-developed. High ee values (>90%) have been achieved for all of these substrates, as well as for α,β-unsaturated ketones. Though some rhodium- and ruthenium-phosphine complexes can hydrogenate unfunctionalized olefins stereoselectively [8], they achieve lower ee values in these reactions than in analogous reactions with functionalized substrates [9].

Compared to their rhodium- and ruthenium-based cohorts, iridium catalysts are new to the asymmetric hydrogenation of olefins. Using an achiral catalyst, Crabtree and co-workers established the ability of iridium compounds to rapidly hydrogenate olefins [10,11]. Crabtree's catalyst, $[(COD)Ir(PCy_3)(py)]^+[PF_6]^-$ (**1**, Scheme 2, COD = 1,5-cyclooctadiene, py = pyridine), catalyzes the hydrogenation of 1-hexene 100× faster than $[RhCl(PPh_3)_3]$ (Wilkinson's catalyst). It also hydrogenates tri- and even tetrasubstituted olefins; Wilkinson's catalyst is inactive towards the latter [11]. Crabtree's catalyst also excels in the diastereoselective, functional-group-directed hydrogenation of cyclic alkenes, consistently controlling the stereochemistry of the new stereocenter relative to the directing group better than related rhodium catalysts can [12].

In the late 1990s, Lightfoot, Pfaltz and co-workers recognized that a chiral analogue of Crabtree's catalyst would have significant potential for asymmetric hydrogenation. They replaced the phosphine and pyridine ligands of Crabtree's catalyst with phosphinooxazoline (PHOX) ligands [13] to form a series of chiral, cationic iridium complexes (**2**, Scheme 2) that hydrogenated prochiral imines to amines in a broad range of ee values (0–89%) [14,15] Though the complexes **2** also catalyzed the hydrogenation of olefins with impressive ee values (75–97%), they formed inactive tri-iridium species over the course of the reaction [16]. This propensity to trimerize, a reaction also observed with Crabtree's catalyst **1** [11], meant that high catalyst loadings of catalysts **2** (4 mol%) were necessary for complete conversion of the olefin [17]. Hoping to increase the catalyst's stability, Pfaltz and co-workers screened a range of reaction conditions, but found little improvement. However, upon changing the counterion to the weakly coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($[BAr^F]^-$), they obtained a highly active and selective olefin hydrogenation cat-



Scheme 2. Crabtree's achiral catalyst for olefin hydrogenation (**1**) [10,11]; Pfaltz's chiral catalysts for the asymmetric hydrogenation of imines (**2**) [14].



3
R^1 = Ph, *o*-Tol
R^2 = ^{i}Pr, ^{t}Bu, Np

Scheme 3. Pfaltz and Lightfoot's chiral catalysts for the asymmetric hydrogenation of olefins (**3**) [17,18].

alyst (**3**, Scheme 3) that was stable to the reaction conditions, and even to air and moisture [17,18]. Using kinetic [19] and pulsed-gradient spin-echo NMR spectroscopic diffusion [20] data, Pfaltz, Pregosin and co-workers have examined the effect of the anion in (PHOX)Ir-catalyzed hydrogenation, and found large, poorly coordinating anions to be crucial for activity. Further, Pfaltz showed that the catalyst anion does not impact the stereoselectivity of hydrogenation [19]. Almost all of the numerous iridium catalysts of the form $[L^*Ir(COD)]^+[X]^-$ for asymmetric olefin hydrogenation that appeared after **3** featured modifications of the cation; $[BAr^F]^-$ is the anion of choice [21].

Though Pfaltz and co-workers showed that the catalysts **3** were active toward some functionalized olefins, these were not the most notable substrates reduced. Rather, several unfunctionalized olefins were hydrogenated with excellent stereoselectivity (≥94% ee) using low catalyst loadings (0.l–4 mol%). Prior to the development of catalysts **3**, there had been few reports of highly enantioselective (≥94% ee) hydrogenations of unfunctionalized olefins [22], and these either had low turnover frequencies or required very low temperature (≤−75 °C) to be selective. The success of **3** in stereoselectively hydrogenating unfunctionalized olefins therefore triggered intense efforts to design other chiral iridium complexes for this purpose, which quickly became the niche of iridium-catalyzed olefin hydrogenation. Developments in this field have been the subject of several reviews [21,23–26], including a very comprehensive article by Cui and Burgess [21], and have been considered in books about asymmetric catalysis [9,27]. Iridium-catalyzed hydrogenation of unfunctionalized olefins has also been examined in the contexts of hydrogenation for the synthesis of fine chemicals [28] and pharmaceutically interesting substrates [29], of the relationship between selective catalysis and nanoscience [30], of enantioselective catalysis from the industrial viewpoint [31], and of green chemistry from the perspective of pharmaceutical manufacturers [32]. Finally, it has been discussed in reviews covering the uses of various ligand classes (*N*-heterocyclic carbenes [33], mixed oxazoline-carbenes [34], nitrogen-containing ligands [35], bidentate N∩P ligands [25,36], phosphorus ligands [37], carbohydrate-derived ligands [38], and chiral ferrocenes [39]) in asymmetric catalysis.

Given that the highly stereoselective hydrogenation of functionalized olefins by rhodium and ruthenium catalysts is well-developed, and that most research on chiral iridium hydrogenation catalysts has addressed the reduction of unfunctionalized olefins, a discussion of the iridium-catalyzed hydrogenation of functionalized olefins may seem peculiar. However, rhodium- and ruthenium-based catalysts are extremely selective for substrates with *coordinating* functionality; substrates with functional groups that do not coordinate well to the metal remain challenging for these catalysts. Iridium catalysts, conversely, achieve very high selectivity for unfunctionalized substrates. Therefore, they have potential for the asymmetric hydrogenation of olefins with poorly coordinating functional substituents, such as electrophilic groups. Though several such reactions have already been reported, none are highly developed, and there remain numerous vinyl-heteroatom moieties whose asymmetric hydrogenation has yet to be reported. In their 2005 review, Burgess and Cui noted that the future of iridium-catalyzed asymmetric hydrogenation lay in the broadening of substrate scope [21]. Olefins with non-coordinating functionality offer tantalizing prospects for expansion. The present review aims to provide an early account of this emerging field [40]. We will discuss examples that have been reported, highlight the advantages of iridium catalysts for these substrates, and identify areas in which further research is warranted.

2. Important considerations

2.1. Iridium-catalyzed asymmetric hydrogenation: mechanistic overview

Though non-coordinating functional groups do not direct the hydrogenation of an olefin *via* chelate formation, they may nevertheless influence the stereoselectivity of the reaction. Many of the substrates we will discuss bear electrophilic substituents on the olefin, resulting in a polarized double bond. As iridium catalysts have most frequently been applied to unfunctionalized olefins, the impact of substrate electronics on the enantioselectivity of the reaction is largely unknown. Certainly, a strongly polarized double bond could affect the reaction. Therefore, prior to discussing these substrates, we must inspect the origin of stereoselection in non-chelation-assisted asymmetric hydrogenation. Unfortunately, despite the numerous studies that have addressed the mechanism of the iridium-catalyzed asymmetric hydrogenation of olefins [41–48], it remains a poorly understood reaction. Our discussion of stereoselection is thus preceded by a strong caveat: the mechanism of iridium-catalyzed asymmetric hydrogenation, be it of functionalized or unfunctionalized substrates, is far from understood. Any selectivity model based on the information collected to date should be considered with caution [49]. Nevertheless, the available data has led to selectivity models that successfully predict the sense of stereoselection in the reaction, and these are discussed below [50].

In the early stages of catalytic olefin hydrogenation by complexes of the type $[(A^{\cap}B)Ir(COD)]^+[BAr^F]^-$ ($A^{\cap}B$ = chiral, chelating ligand that binds through A and B atoms), the COD ligand is hydrogenated to cyclooctane and lost from the catalyst precursor, leaving behind a coordinatively unsaturated iridium cation. To induce asymmetry in subsequent hydrogenations, this cation must be transformed into one bearing both the olefin substrate and at least one hydrogen atom. Thus it

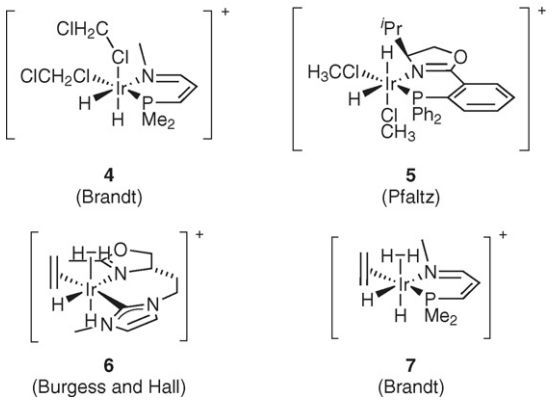
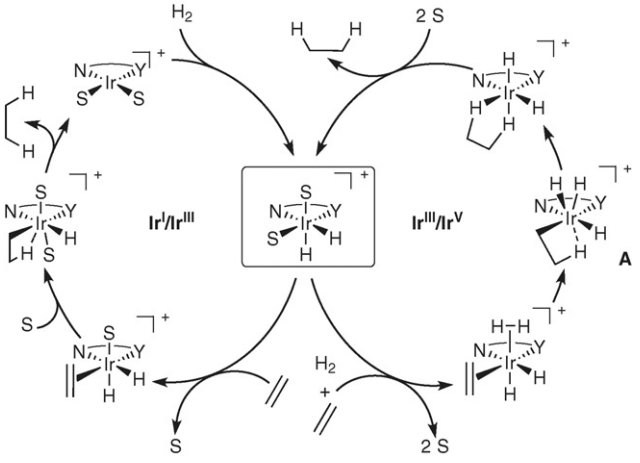


Fig. 1. Most stable configurations for iridium (III) dihydride complexes, as calculated by Brandt (**4** and **7**) [43], Pfaltz (**5**) [46], and Burgess and Hall (**6**) [47].

must react with H_2 and substrate to form a cationic iridium (III) dihydride complex with a bound olefin. As the first H-atom transfer from metal to olefin will occur from this dihydride complex, its structure is crucial for stereoselection [51]. Computational studies dealing with iridium-catalyzed asymmetric hydrogenation have concluded that electronic effects, in particular the trans influence, dictate the structure of this dihydride complex, and that sterics play a secondary role [43,46,47]. The hydrides, being very strong σ-donors, cannot be trans to one another. Therefore they must be mutually cis, and prefer not to be trans to next strongest trans-influence ligand (generally a phosphine or carbene in these systems) [52]. Calculations on N∩P complexes of iridium with chlorocarbon solvent (iridium-catalyzed asymmetric hydrogenation is generally most successful in CH_2Cl_2) led Brandt [43] and Pfaltz [46] to minimized structures for solvated dihydride complexes (**4** and **5**, respectively, Fig. 1) that had mutually cis hydrides cis to the phosphine (the stronger trans-influence terminus of the N∩P ligand). This cis-dihydride arrangement is consistent with the X-ray crystal structure of the chlorocarbon-solvated iridium compound $[Ir(H)_2(PPh_3)_2(ClCH_2CH_2Cl)]^+[BAr^F]^-$, which also has mutually cis dihydrides positioned cis to phosphine [53]. In THF-d_8 solution, Pfaltz studied $[(N^{\cap}P)Ir(H)_2(solvent)_2]^+$ by NMR spectroscopy, and found the calculated species to be the major isomer. However, a complex mixture of hydrido species was obtained in CD_2Cl_2, suggesting that under catalytic conditions, the situation may be quite complicated.

Unlike the structure of the iridium (III) dihydride complex, its fate in the mechanism of asymmetric hydrogenation is an issue of some contention. Both Brandt and Burgess and Hall (who examined their oxazoline-carbene-ligated catalysts) [47], have used complexes with truncated ligand sets to calculate lowest-energy reaction paths for iridium-catalyzed asymmetric hydrogenation. Both groups then re-optimized all intermediate and transition state structures on their energetically favoured reaction paths, using full ligand sets. The iridium (III) dihydride intermediates calculated in each study (**6** and **7**, Fig. 1) are similar despite being calculated using different ligands. In each, the olefin substrate occupies the coordination site trans to the stronger trans-influence terminus of the chiral ligand (in Brandt's system, a phosphine; in Burgess and Hall's system, a carbene). These intermediates, computed with full ligand sets, were used to develop selectivity models for asymmetric hydrogenation (vide infra).



Scheme 4. Two possible catalytic cycles for olefin hydrogenation by chiral iridium complexes, with a common Ir^{III} dihydride complex (in box). At left, a cycle with Ir^I and Ir^{III} intermediates, based upon those drawn by Chen [44] and Pfaltz [26b]. At right, a cycle with Ir^{III} and Ir^V intermediates, generalized from those drawn by Brandt [43] and Burgess and Hall [47]. S = solvent; Y = phosphine or carbene.

The mechanistic pathways computed by Brandt and by Burgess and Hall pass through Ir^{III} and Ir^V intermediates. Though slightly different, these mechanisms are generalized as shown in Scheme 4 (at right). Alternatively, the groups of Buriak [54] and Chen [44] have published data in support of catalytic cycles with Ir^I and Ir^{III} intermediates (Scheme 4, at left). Buriak and co-workers used *para*-hydrogen induced polarization (PHIP) NMR spectroscopy to study the hydrogenation of styrene-d_8 by an achiral N-heterocyclic carbene–phosphine iridium complex in CD_2Cl_2. The ethylbenzene-d_8 product showed PHIP enhancements for the added protons, indicating that hydrogen atoms were added pairwise to the olefin. As noted by its authors, this study does not exclude the action of parallel, non-pairwise H_2 additions. Dietiker and Chen used gas-phase MS to study the hydrogenation of styrene by the Pfaltz catalyst **3** (R^1 = Ph, $R^2 = {}^i$Pr). They used the mass spectrometer to select one ion that had a mass consistent with the formulation [L*Ir(styrene)]$^+$ and that was present during the hydrogenation of styrene, and to react it with D_2. The collision frequency of iridium species with D_2 was estimated to be similar to that in solution. Un-, mono-, and di-deuterated ions (i.e. having masses consistent with [L*Ir(styrene)]$^+$, [L*Ir(styrene)]$^+$-d_1, and [L*Ir(styrene)]$^+$-d_2, respectively) were detected, but trideuterated products were not. As they had shown the insertion of olefin into the metal hydride to be reversible in the MS, Dietiker and Chen concluded that an intermediate having the mass of [L*Ir(styrene)$(D_2)_2$]$^+$, three chemically equivalent deuterides, and a monodeuterated alkyl group could not be part of a favourable catalytic cycle. However, the trihydride intermediates calculated for Ir^{III}/Ir^V cycles (**A**, Scheme 4, at right) have hydrides that are trans to different groups and diastereomerically inequivalent; the rates of their

interconversions relative to those of the insertion are not discussed. Also, though insertion clearly occurs reversibly (evinced by the formation of a monodeuterated ion), the kinetic isotope effect on the insertion/elimination process is not known.

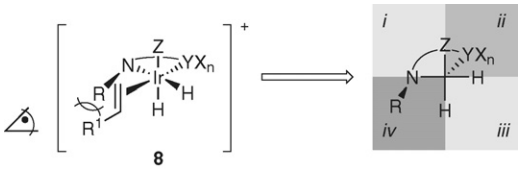
Unfortunately, each experimental and theoretical study on iridium-catalyzed asymmetric hydrogenation has been performed on a different system; various catalysts, unfunctionalized substrates, and reaction conditions have been used. The possibility that changes in catalyst, substrate (particularly to functionalized substrates), or reaction conditions alter the energy of the system enough to bias it toward a different mechanism, or that multiple pathways are available to a single system, cannot be dismissed. However, the Ir^{I}/Ir^{III} and Ir^{III}/Ir^{V} cycles are united by the intermediacy of iridium (III) dihydride complexes from which H transfer to olefin occurs, and examining the geometry of these complexes produces a useful model for predicting the sense of enantioselection in these catalysts [55,56]. Thus, although Brandt, Andersson, and Burgess and Hall have developed selectivity models for the asymmetric hydrogenation of alkenes based on Ir^{III}/Ir^{V} cycles [43,45,47,48], a similar analysis can be considered for Ir^{I}/Ir^{III} cycles.

2.2. General selectivity model based on an iridium (III) dihydride

In the calculated structures for solvated iridium dihydride complexes (**4** and **5**), the mutually cis hydride ligands lie cis to the stronger trans-influence terminus of the chiral ligand. Olefin coordination can therefore occur at two sites: (1) in the plane of the chelate, trans to the stronger trans-influence terminus of the chiral ligand; or (2) in the remaining axial position, cis to the chiral ligand. For two cases in which an olefin and a dihydrogen ligand bind to the metal, calculations predict that the olefin will lie in the equatorial plane (**6** and **7**). Though no data is available for monosolvated olefin dihydride complexes (such as the one in Scheme 4, bottom left), an olefin in these cases should also prefer the equatorial site over the axial one, which is crowded by the chiral ligand [57]. Therefore an olefin-ligated iridium (III) dihydride complex that is consistent with either mechanism can be drawn (**8**, Scheme 5, left). In it, the olefin lies in the same coordination plane as the chiral ligand, and is cis to the weaker trans-influence terminus of the ligand.

The facial selectivity of olefin binding can be rationalized by examining **8** from the perspective of the olefin-binding site (Scheme 5, right) [43,45,47,48]. The olefin is cis to the nitrogen terminus of the ligand, so it prefers to bind to the metal with its smallest substituent pointing toward the bulky group on that part of the ligand (quadrant *iv* as drawn in Scheme 5). As the substrates for asymmetric olefin hydrogenation are most commonly trisubstituted, the smallest substituent is generally a hydrogen atom. The next smallest substituent will, if possible, be placed in quadrant *ii*, which is partly hindered by the other end of the chiral ligand. The larger substituents can then be situated in the relatively unhindered quadrants *i* and *iii*. Based on this model, trisubstituted olefins that have their largest substituents trans to one another should fit perfectly into the olefin binding sites of these catalysts and be reduced very selectively. This is borne out experimentally, with *E*-trisubstituted olefins generally being hydrogenated more selectively than their *Z*-counterparts, and 1,1-disubstituted olefins being particularly difficult for iridium-catalyzed asymmetric hydrogenation. Tetrasubstituted olefins, which have no H-atom substituent, are also difficult substrates.

In their computational study, Burgess and Hall used their minimized intermediate and transition-state structures to predict the enantioselectivity of hydrogenation for three simple substrates. In each case, they correctly predicted the sense and approximate magnitude of the enantioselectivity, demonstrating predictive value for this type of analysis. Though **8** is generally a useful model for predicting the sense of stereoselection in iridium-catalyzed hydrogenation, there are two factors that may complicate its use in analyzing the reaction. Deuterium-labelling experiments by Burgess and co-workers have demonstrated that significant olefin isomerization occurs on the timescale of hydro-



Scheme 5. Generalized iridium (III) dihydride complex **8** with bound olefin (left), and a view of the sterics about iridium from the perspective of the olefin ligand (right). R^1 = smallest olefin substituent; NR = chiral N-containing ligand (frequently oxazoline); YX_n = strong *trans*-influence ligand (phosphine, carbene, etc.); Z = H_2 or solvent.

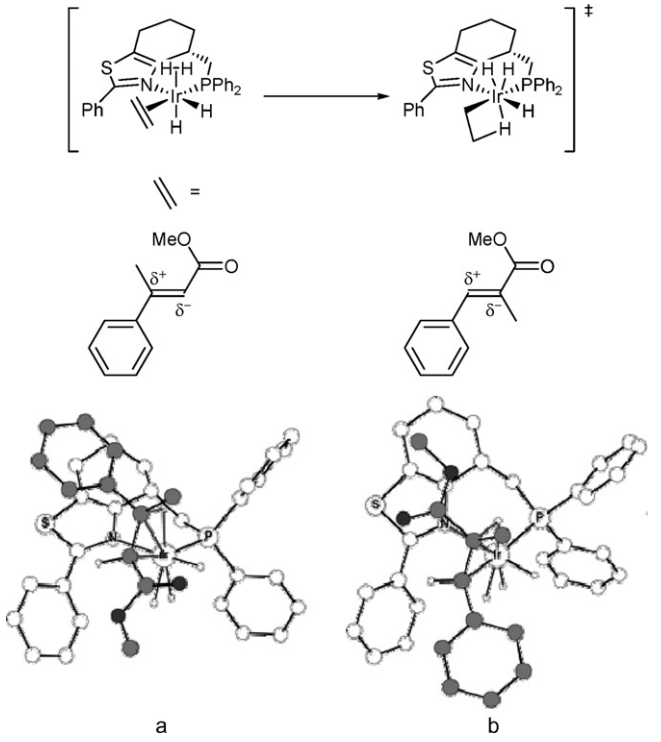


Fig. 2. Transition states for the first H transfer in the iridium-catalyzed hydrogenation of (a) methyl β-methylcinnamate, and (b) methyl α-methylcinnamate [48]. Only the lower-energy transition state (of two possibilities) is shown for each compound.

genation, particularly for terminal and *Z*-trisubstituted alkenes [42]. This process can affect the enantioselectivity of the reaction, and is likely responsible to some degree for the lower ee values obtained in the hydrogenation of terminal and *Z*-trisubstituted substrates. Additionally, calculations have found that in some cases, the lowest-energy reaction path for iridium-catalyzed hydrogenation does not pass through the most stable olefin-ligated iridium (III) dihydride. Thus, analysis of the most stable form of **8** may not permit a complete understanding of asymmetric hydrogenation by these complexes.

2.3. Effect of double-bond polarization

Only one computational study has treated the hydrogenation of strongly polarized olefins by chiral iridium catalysts. In an investigation of ligand structure on olefin hydrogenation, our group consistently observed lower enantioselectivity for the hydrogenation of *trans*-α-methylcinnamic esters than for their isomers, *trans*-β-methylcinnamic esters, by a given catalyst. Using a thiazole-phosphine-ligated iridium cation of the type **8** ($RN^{\cap}YX_n$ = (*S*)-4-((diphenylphosphino)methyl)-2-phenyl-4,5,6,7-tetrahydrobenzo[*d*]thiazole, Z = H_2), we examined the transition states for the reduction of methyl *trans*-α-methylcinnamate and methyl *trans*-β-methylcinnamate [48]. We found that polarized double bonds added an electronic effect to the energy of these transition states (Fig. 2). When the double bond to be reduced is polarized, hydride addition to the δ^+ carbon is electronically favoured. In the transition state for the migration of hydride to olefin, the olefin is tilted toward the hydride; this process is sterically favoured if the olefin tilts away from the ligand bulk, and disfavoured if the olefin tilts toward it. These steric and electronic effects may reinforce one another, as is the case for methyl *trans*-β-methylcinnamate, or counteract one another, as for methyl *trans*-α-methylcinnamate. In the latter case, the lower-energy transition state is sterically favoured, tilting the olefin away from the phenyl group protruding from the thiazole portion of the ligand. However, it is electronically disfavoured, as the hydride is transferred to the α-carbon rather than the Michael-acceptor β-carbon. To our knowledge, the $\Delta\Delta G^{\ddagger}$ for hydrogenation of the two enantiofaces of an olefin by any particular catalyst has not been determined, so it is not clear whether this destabilization of the favoured transition state for migratory insertion is sufficient to directly affect the selectivity of the reduction. Regardless, it may slow the reaction enough to allow other processes (such as olefin isomerization) to occur, thus lowering the stereoselectivity of hydrogenation.

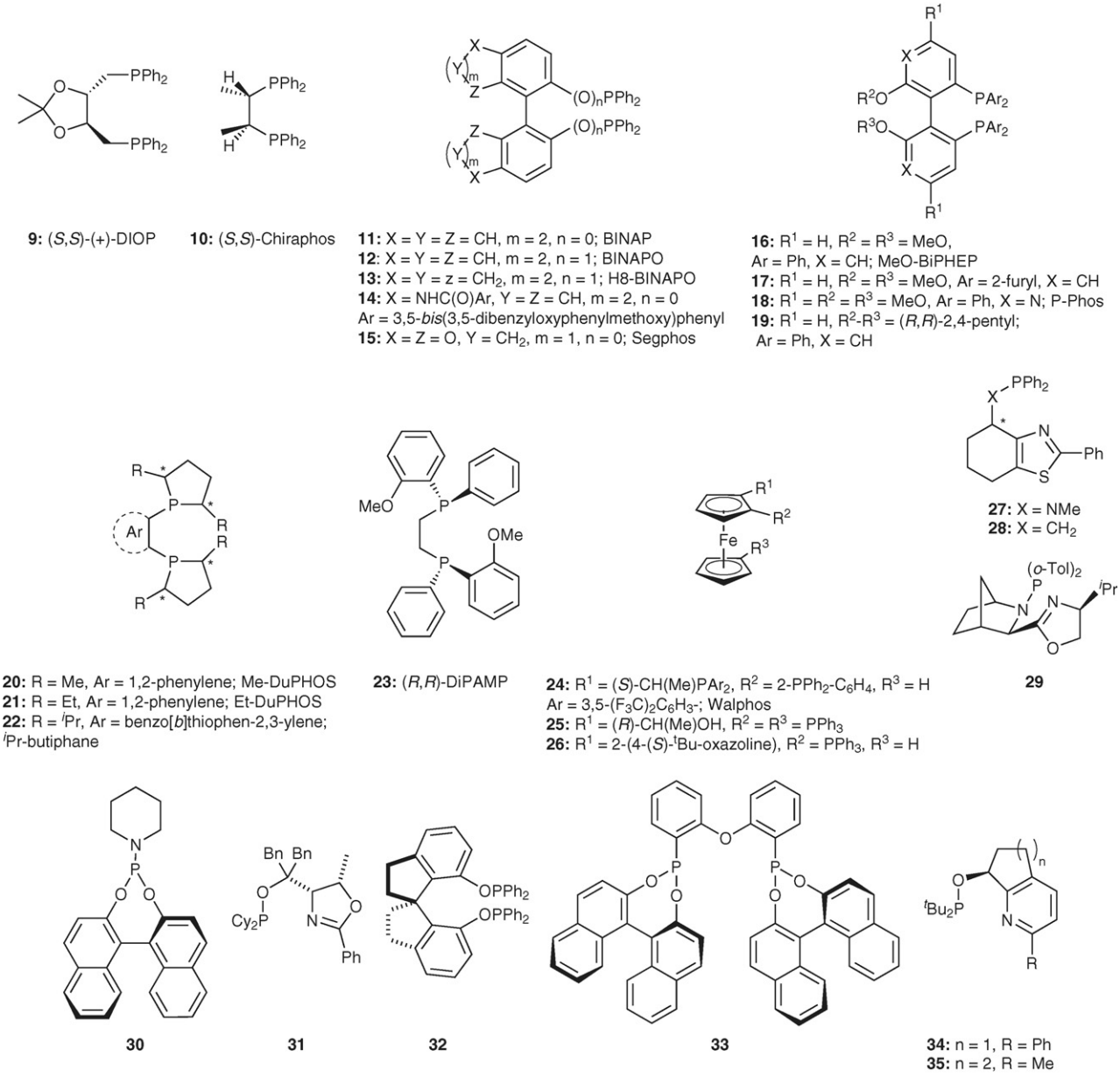
3. Asymmetric hydrogenations of nontraditional substrate classes

3.1. Vinyl phosphonates

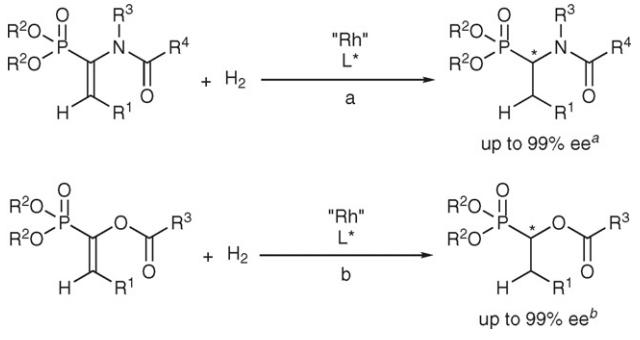
α-Amino alkylphosphonic acids, the phosphonic analogues of α-amino acids, display a range of useful biological activities including bacterial-growth inhibition, analgesic properties, and ACE inhibition [58]. Thus their alkyl esters, α-amino alkylphosphonates, are attractive targets for enantioselective synthesis. Just as α-amido acids have been prepared in chiral form by the asymmetric hydrogenation of dehydro amido acids, chiral α-amido alkylphosphonates have been prepared by the rhodium-catalyzed reduction of α-amido alkenylphosphonates (Scheme 7, a) [59–61]. In an early example of this reaction, Schöllkopf et al. used $[Rh(NBD)Cl]_2$ (NBD = norbornadiene) and (+)-DIOP (**9**, Scheme 6) to catalyze the hydrogenation of two α-formamido alkenylphophonates, yielding the corresponding alkyl phosphonates [59]. α-Acyloxy alkenylphosphonates have also been hydrogenated using chiral rhodium catalysts, yielding chiral α-acyloxy alkylphosphates (Scheme 7b) [61,62]. These reactions have been explored using a variety of chiral $P^{\cap}P$ ligands, often with excellent ee values.

Although rhodium catalysts are very effective for the enantioselective hydrogenation of alkenylphosphonates with α-amido and α-acyloxy substituents, they have not been used for other alkenylphosphonates. Chiral phosphonates without additional α-heteroatom functionality are also interesting compounds. For example, they have been converted to chiral phosphine ligands [63,64] using Horner and Balzer's method [65]. Phosphonates are transition-state analogues for acyl transferase enzymes [66]. 1-Arylethylphosphinic acids are analogues of the nonsteroidal anti-inflammatory drug Naproxen [67], and have known biological activity [67,68]. Given the potential utility of the products, the enantioselective hydrogenation of alkenylphosphonates with chiral ruthenium-based catalysts has been explored. The groups of Genet and Beletskaya have used complexes of the form $[(P^{\cap}P)RuBr_2]$ to hydrogenate a range of vinylphophonates to alkylphosphonates (Scheme 8) [69]. In all cases, the substrates were terminal alkenes with one aryl and one phosphonate substituent. The reactions were found to yield the best ee values at 80 °C and 10 bar H_2, and required 23–28 h for completion under these conditions. Matteoli et al. have used ruthenium-based catalysts for the asymmetric hydrogenation of 2,3-bis(diphenylphosphinoyl)-buta-1,3-diene, forming the Chiraphos (**10**, Scheme 6) precursor (1*S*,2*S*)-bis(diphenylphosphinoyl)-butane [63]. This difficult substrate contains two prochiral vinylphosphonates, and thus can form three products (two chiral and one *meso*) upon hydrogenation. Using $[((S)\text{-}\mathbf{11})Ru(OAc)_2]$ under harsh conditions (10 mol% catalyst, 99 bar H_2, 100 °C for 310 h), the authors obtained (*S*,*S*)-bis(diphenylphosphinoyl)butane in 70% de and 42% ee.

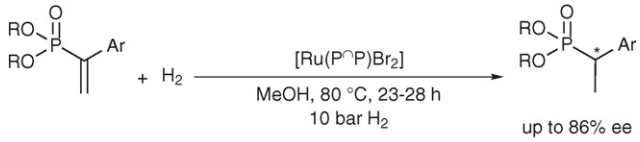
To date, only one publication has described the iridium-catalyzed reduction of vinylphosphonates [70]. Beletskaya, Pfaltz and co-workers used a (PHOX)Ir complex to hydrogenate α-aryl vinylphosphonates. This reaction was performed under milder conditions (see Table 1) than the reported ruthenium-catalyzed reactions, and returned highly enantiopure hydrogenation products (ee = 92–95% under optimized conditions), in most cases without sacrificing conversion. There were two substrates that posed difficulties for the reaction. Consistent with the sensitivity of iridium hydrogenation catalysts to strongly coordinating groups, the reaction was unsuccessful for Ar = py. The 2-(6-MeO-naphthyl)-substituted vinyl phosphonate was hydrogenated very slowly. As iridium catalysts (including **3**) are known to hydrogenate olefins with methoxyaryl substituents, this was a puzzling result. As the authors



Scheme 6. Ligands discussed in this article. Only ligands with no variants, and ligands **34** and **35**, are shown in chiral form. See text for stereochemical information regarding ligands having variants.

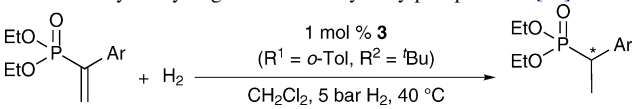


Scheme 7. Asymmetric hydrogenation of α-amido and α-acyloxy alkenylphosphonates by rhodium-based catalysts. "Rh" = rhodium complex (chiral or achiral precursor); L* = chiral ligand, as part of the Rh complex or as an additive. (a) See Ref. [60d]. (b) See Ref. [61a].



Scheme 8. Asymmetric hydrogenation α-aryl vinylphosphonates by ruthenium-based catalysts. P⌒P = (*S*)-**11**, **16**, **17**, **20** [69].

Table 1
Iridium-catalyzed hydrogenation of α-aryl vinylphosphonates [70]



Entry	Ar	Time	Conversion (%)	ee (%)
1	Ph	6	100	94[a]
2	4-Ph-C_6H_4	6	95	94
3	1-Naphth	24	93[b]	92
4	2-Naphth	6	96	93
5	2-(6-MeO-Naphth)	115	78[c]	95
6	Py		0	–[d]

[a] Absolute configuration of the major product was (*R*).
[b] This substrate was already 90% hydrogenated after 5 h. The ee was not determined at that time.
[c] An additional 1 mol% of catalyst was added after 27 h.
[d] Not applicable.

suggest, a trace impurity in this substrate could be causing its unusual behaviour.

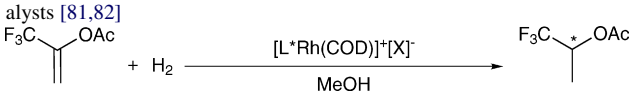
The successful use of **3** for the asymmetric hydrogenation of vinylphosphonates, coupled with the diverse methods for preparing these compounds [71,72], makes this a promising method for the preparation of optically active alkylphosphonates, and an area in which iridium catalysts may be very useful in the future. For example, the asymmetric hydrogenation of tri- and tetrasubstituted vinylphosphonates remains completely unexplored.

3.2. Fluoro- and trifluoromethyl-substituted olefins

Fluorine-containing molecules are popular in the chemical industry, making up some 30–40% of agrochemicals and 20% of pharmaceuticals on the market [73]. The effects of fluorine substitution on a compound's physicochemical properties have been reviewed [74,75] and discussed within the context of bioactivity [75]. Additionally, fluorinated groups are frequently incorporated in liquid-crystalline materials, and fluorine substituents at chiral centers are commonly used in the design of antiferroelectric liquid crystals [76,77]. Therefore, the synthesis of optically active fluorinated compounds is an area of interest, and has been reviewed [78].

The fluoro and trifluoromethyl substituents are both highly electronegative. For example, the trifluoromethyl group has Hammett parameters of $\sigma_m = 0.43$ and $\sigma_p = 0.54$, higher than those for nonfluorinated alkyl groups. These values are also higher than those for some common electron-withdrawing groups, such as simple carboxylic acids and esters [79]. Though the Hammett parameters for fluorine are lower ($\sigma_m = 0.34$ and $\sigma_p = 0.06$), the protean nature of its effects on physical properties has been noted [74]. In fact, the often-surprising behaviour of fluorinated organics, combined with their popularity, prompted Seebach to describe them as 'flustrates' [80]. Not surprisingly, the asymmetric hydrogenation of fluorine- and trifluoromethyl-substituted olefins displays some interesting features.

Table 2
Asymmetric hydrogenation of α-(trifluoromethyl)vinyl acetate by rhodium catalysts [81,82]



Entry	L*	X	Configuration[a]	ee (%)
1	(*R*,*R*)-**23**[b]	$^-BF_4$	S	77
2	(*S*,*S*)-**10**[b]	$^-BF_4$	*R*	38
3	(*S*,*S*)-**20**[c]	^-OTf	*S*	94
4	(*R*,*R*)-**21**[c]	^-OTf	*R*	>95

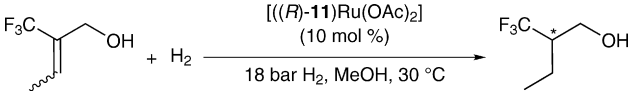
[a] Absolute configuration of the product.
[b] From Ref. [81].
[c] From Ref. [82].

3.2.1. Trifluoromethyl-substituted olefins

In 1980, Koenig and co-workers achieved the enantioselective hydrogenation of α-(trifluoromethyl)vinyl acetate (Table 2, entries 1 and 2) [81]. They screened several chiral-diphosphine-ligated rhodium complexes for the reaction, and found [((*R*,*R*)-**23**)Rh(COD)]$^+$[BF_4]$^-$ to be the most effective, producing (*S*)-1-(trifluoromethyl)ethyl acetate in 77% ee (100% completion was measured by H_2 uptake). They were also able to obtain the *R* enantiomer of the product, albeit in only 38% ee, using (*S*,*S*)-**10** as the chiral ligand. Burk was later able to obtain both of these enantiomers in high ee (Table 2, entries 3 and 4) [82] using the Me- and Et-DuPHOS ligands (**20**, **21**) developed in his laboratory [83].

Following the reports from Koenig and Burk, other olefins having both a trifluoromethyl and a coordinating functional group have been hydrogenated by chiral ruthenium and rhodium catalysts. In a particularly interesting series of experiments, Iseki, Kobayashi, and co-workers hydrogenated the *E* and *Z* isomers of the allylic alcohol 2-(trifluoromethyl)-undec-2-en-1-ol (Table 3), as well as an *E*/*Z* mixture, using [((*R*)-**11**)Ru(OAc)$_2$] [84,85]. They found that the *E* isomer was hydrogenated faster and more selectively than the *Z* isomer, but that *both isomers yielded the same major product* [86]. This is in stark contrast to the case of nonfluorinated olefins. For instance, *E*- and *Z*-2-methyl-2-butenoic acid (tiglic and angelic acid, respectively) are hydrogenated by this same catalyst to give products of opposite configuration [87,88]. Clearly, the –CF_3 moiety affects the enantioselectivity of the hydrogenation reaction. It appears that

Table 3
Stereoselectivity in the ruthenium-catalyzed asymmetric hydrogenation of 2-trifluoromethyl-but-2-en-1-ol [84,85]



Entry	Olefin geometry	Time (h)	Conversion (%)[a]	ee (%)[b]
1	*E*	240	94	83
2	*Z*	48	21	15
3	*E* + *Z* (45:55)	72	44[c]	68

[a] Conversion to saturated product, determined by GLC analysis.
[b] Determined by GLC analysis of the Mosher ester. The major enantiomer was the same in all cases, though absolute configuration was not assigned.
[c] The unreacted olefin had an *E*:*Z* ratio of 14:86.

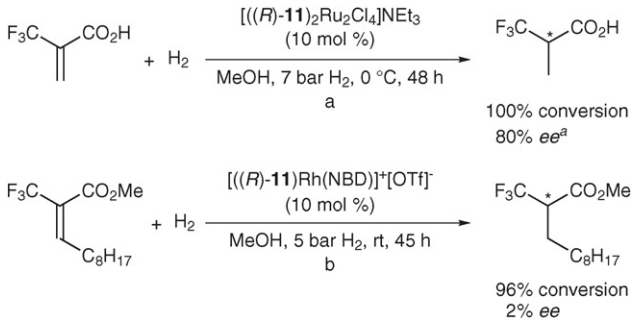


Fig. 3. Hydrogenation of a trifluoromethyl-substituted acid and ester [84,85]. (a) After derivatization to 2-(trifluoromethyl)propan-1-ol.

in the case of the *E* olefin, the effects exerted by the olefin geometry and by the $–CF_3$ group reinforce one another, resulting in rapid and selective catalysis. For the *Z* olefin, the $–CF_3$ effect opposes that of the olefin geometry, causing the reaction to be slower and less selective. In the end, the $–CF_3$ group dominates.

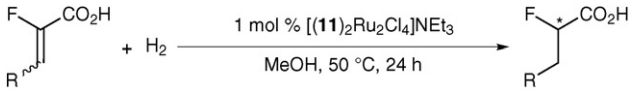
Iseki, Kobayashi, and co-workers have also used chiral rhodium and ruthenium catalysts to hydrogenate a $–CF_3$ substituted carboxylic acid (Fig. 3a) [84,85] and a $–CF_3$ substituted ester (Fig. 3b) [85]. The former was hydrogenated with good enantioselectivity (80% ee after derivatization with CH_2N_2 and reduction by $LiAlH_4$) using [((*R*)-**11**)$_2$Ru$_2$Cl$_4$]NEt$_3$. The ester, on the contrary, was hydrogenated using [((*R*)-**11**)Rh(NBD)]$^+$[OTf]$^-$ as the catalyst, producing the saturated ester in only 2% ee. Unfortunately, the different catalysts used for the reactions, as well as the different reaction conditions and olefin substitution patterns, preclude speculation on the reasons for this large disparity in enantioselection.

To date, the asymmetric hydrogenation of trifluoromethyl-substituted olefins has only been accomplished by rhodium- and ruthenium-based catalysts, and always with the assistance of an additional coordinating group on the olefin. Further, the coordinating group has been geminal to the $–CF_3$ group in all cases. The application of iridium catalysts to the enantioselective hydrogenation of trifluoromethyl-substituted (and higher C_nF_{n+1} alkyl-substituted) olefins having no additional functionality could broaden the scope of the reaction and provide a more general route to chiral trifluoromethylalkyls. Additionally, because of their polarized double bonds, $–CF_3$ substituted olefins could prove useful in probing the effect of substrate electronics on asymmetric hydrogenation.

3.2.2. *Fluorine-substituted olefins*

Olefins with fluorine substituents have also been hydrogenated asymmetrically to give alkanes with fluorine atoms bonded directly to a chiral center. Saburi and co-workers used ruthenium-BINAP catalysts to hydrogenate the 2-fluoro-2-alkenoic acids shown in Table 4 [89]. Variation of the reaction conditions showed that both conversion and ee were insensitive to the form of the pre-catalyst ([(**11**)$_2$Ru$_2$Cl$_4$], [(**11**)$_2$Ru$_2$Cl$_4$]NEt$_3$, or [(**11**)Ru(OC(O)(CH$_3$)$_3$)$_2$]) and only slightly sensitive to the reaction temperature over the range 35–80 °C. Hydrogen pressure had a greater effect on ee, with better selectivity being observed at 5 bar than at 50 bar. Very

Table 4
Asymmetric hydrogenation of 2-fluoro-2-alkenoic acids by Saburi and co-workers [89]



Entry	R	Olefin	**11**	ee (%)[a]	Product[b]
1	C_3H_7	Z	*R*	90	*R*
2	C_3H_7	Z	*S*	89	*S*
3	C_3H_7	*E*[c]	*R*	83	*R*
4	C_3H_7	*E*[c]	*S*	88[d]	*S*
5	C_5H_{11}	*Z*	*R*	89[e]	*R*
6	C_5H_{11}	*Z*	*S*	89	*S*
7	C_6H_5	*Z*	*S*	56[d]	S

[a] Determined by HPLC of the anilide. Hydrogenation occurred to completion in all cases.
[b] Determined from optical rotation.
[c] *E*/*Z* = 8:2.
[d] 50 bar H_2.
[e] 60 °C, 10 bar H_2, amine-free catalyst.

good selectivity was achieved for 3-alkyl-substituted substrates (Table 4, entries 1–6), whereas a phenyl group in the 3-position reduced the activity and selectivity of the system (Table 4, entry 7).

The olefin geometry of the 2-fluoro-2-alkenoic acids had no discernable effect on the stereoselectivity. Not only was the same enantiomer formed preferentially from the hydrogenations of *Z*- and *E*-2-fluoro-2-hexenoic acid, but the magnitude of the ee was also the same in both cases (Table 4, compare entry 1 vs. 3 and entry 2 vs. 4). This is distinct from the case of *E*- and *Z*-isomers of trifluoromethyl-substituted olefins, which gave the same product but in very different ee values (vide supra). In the present case, the practical consequence of this unusual selectivity is welcome; as asymmetric hydrogenation of an *E*/*Z* mixture gives the same result as that of pure *Z* olefin, no separation of isomers is required before reduction. Hydrogenation of an olefin with catalysts of opposite stereochemistry yielded products of opposite configuration, again regardless of olefin geometry (Table 4, compare entry 1 vs. 2 and entry 3 vs. 4) [89]. Thus either enantiomer of the fluoroalkane can be obtained from an *E*/*Z* mixture of fluoroolefins.

In a recent patent, Nelson et al. have applied Rh-Walphos catalysts to the hydrogenation of substituted tetrahydropyridinium derivatives, including **36** in Fig. 4 [90]. HPLC analysis of the reaction mixture immediately after hydrogenation showed 99.3% ee, and the final product **37** was isolated in 74% yield. This reaction is particularly remarkable because excellent ee is achieved for the hydrogenation of a tetrasubstituted olefin (**36**).

Iridium catalysts have been applied to the asymmetric hydrogenation of fluoroolefins only in the past year [91]. Our group published the enantioselective hydrogenation of several fluoroolefins by a series of cationic iridium complexes with N$^\cap$P ligands. In some cases, very high ee values were obtained. The main difficulty encountered in this study was the propensity of the olefins to undergo defluorination prior to hydrogenation, yielding alkane side products (**39**) in addition to the desired fluoroalkanes (**38**, Table 5). We found that defluorination could

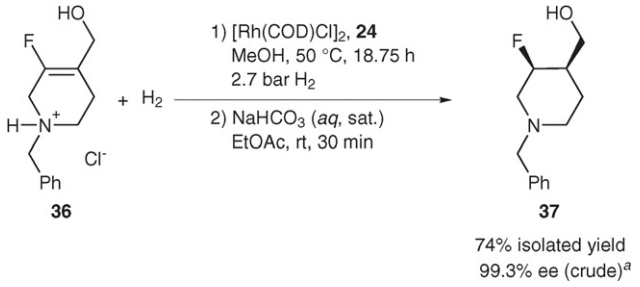
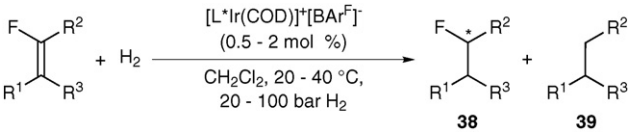


Fig. 4. Extremely enantioselective rhodium-catalyzed hydrogenation of a fluorine-substituted heterocycle [90]. (a) Determined by HPLC of the reaction mixture after hydrogenation.

be suppressed, sometimes completely, by varying the reaction catalyst and solvent. The best solvent for avoiding defluorination was CH_2Cl_2. After screening several catalysts for the reaction, we found that no single catalyst produced the best results for all substrates. For example, [(**27**)Ir(COD)]$^+$[BAr^F]$^-$ hydrogenated two substrates in excellent ee values (Table 5, entries 1 and 2), but was completely inactive toward a third substrate, ethyl α-fluorocinnamate (entry 3). This olefin could be hydrogenated in high yield and with excellent chemoselectivity by [(**29**)Ir(COD)]$^+$[BAr^F]$^-$, though in modest ee (entry 4). Three tetrasubstituted olefins, which are generally challenging substrates for asymmetric olefin hydrogenation, were hydrogenated with moderate-to-good selectivity (entries 5–7) by [(**29**)Ir(COD)]$^+$[BAr^F]$^-$. Notably, the hydrogenations of an *E*/*Z* isomer pair yielded products of *opposite configuration* (entries 5 and 6); this is consistent with results obtained in other iridium-catalyzed hydrogenations but opposite to those from the rhodium-catalyzed hydrogenation of fluoroolefins. The hydrogenations in this study are encouraging but preliminary; a broader study of fluorine-substituted olefins will be required before clear trends in their reactivity emerge.

Table 5
Asymmetric hydrogenation of fluoroolefins using iridium catalysts [91]



Entry	R^1	R^2	R^3	L*	Conversion **38** (%)[a]	Conversion **39** (%)[a]	ee **38** (%)[b]
1	Ph	CH_2OAc	H	**27**	78	4	>99[c]
2	Ph	CH_2OH	H	**27**	97	0	>99[c]
3	Ph	CO_2Et	H	**27**	0	0	–[d]
4	Ph	CO_2Et	H	**29**	97	2	29[c]
5	Ph	CO_2Et	Me	**29**	21	0	57[e]
6	Me	CO_2Et	Ph	**29**	25	0	74[f]
7	Me	CH_2OH	Ph	**29**	17	7	90[g]

[a] Determined by ^{1}H NMR spectroscopy.
[b] Determined by chiral GC–MS or HPLC. Absolute configurations were determined by comparison of the optical rotation or Chiral HPLC retention time to literature values. Esters were reduced to the alcohol for comparison to literature compounds.
[c] Absolute configuration of the major product was *R*.
[d] Not applicable.
[e] Relative configuration of the major product was (−)-(2*R**,3*S**).
[f] Relative configuration of the major product was (+)-(2*S**,3*S**).
[g] Absolute configuration of the major product was (+)-(2*S*,3*S*).

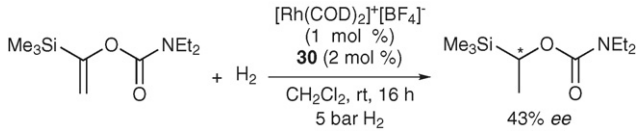


Fig. 5. Asymmetric rhodium-catalyzed hydrogenation of a 1-(trimethylsilyl)ethenyl carbamate [95].

To our knowledge, there are no reports of the asymmetric hydrogenation of fluoroolefins (or other haloolefins [92]) without additional functionality (i.e. carboxylic acid or ester, allyl alcohol). As only iridium complexes are capable of hydrogenating unsubstituted olefins with high stereoselectivity and low catalyst loadings, we believe they are mostly likely to yield results for these substrates.

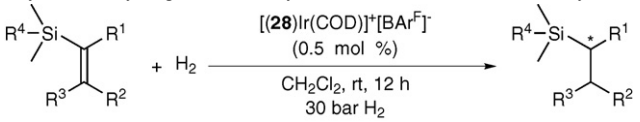
3.3. Vinyl silanes

As an isostere of carbon, silicon has been substituted into pharmaceuticals to yield compounds with modified bioactivity. Additionally, the replacement of carbon with silicon atoms often yields compounds that are not covered by existing patents. Several reviews have been written on this topic in recent years, documenting its rapid growth in popularity [93]. This 'silicon switch' concept depends critically on the availability of organosilicon compounds in stereopure form, and the asymmetric hydrogenation of vinyl silanes would offer an attractive route to α-chiral silanes. However, there exist very few published instances of this reaction.

The diastereoselective hydrogenation of 3-silyl- and 3-stannyl-allyl alcohols was first accomplished in 1992 [94]. This report demonstrated the controlled hydrogenation of olefins bearing silyl and stannyl substituents using homogeneous transition-metal catalysts, and set the stage for enantioselective reductions of these substrates. A rhodium-based catalyst was also used in the first enantioselective hydrogenation of a silyl-substituted olefin. Studying the asymmetric hydrogenation of enol acetates and enol carbamates, Panella et al. prepared and hydrogenated the 1-(trimethylsilyl)ethenyl carbamate shown in Fig. 5 [95]. Complete conversion was achieved, and the major enantiomer was obtained in 43% ee [86]. Presumably, the carbamate group directs this hydrogenation. However, the reduction of related substrates by the same catalyst under the same conditions gave much better ee values (63–98%). The origin of the markedly lower selectivity observed for this substrate was not discussed.

Our group has enantioselectively hydrogenated silyl-substituted olefins without additional functional groups (Table 6) [96]. We found that the chiral thiazole-supported iridium complex [(**28**)Ir(COD)]$^+$[BAr^F]$^-$ hydrogenated several silyl-substituted olefins in high yield (≥99% in all cases) with ee values that ranged from modest (28%, Table 6, entry 1) to excellent (98%, entry 2). The size of the silyl group did not affect the ee of the reaction, as the substrate bearing a –$SiMe_2Ph$ substituent (entry 5) was hydrogenated with an ee that was average

Table 6
Asymmetric hydrogenation of silyl-substituted olefins iridium catalysts [96]



Entry	R^1	R^2	R^3	R^4	Conversion (%)[a]	ee (%)[b]	Configuration[c]
1	Ph	H	Me	Me	>99	28	*S*
2	H	Ph	Me	Me	>99	98	*R*
3	Ph	H	H	Me	>99	58	*S*
4	H	$(CH_2)_3Cl$	Me	Me	>99	55	nd[d]
5	Me	Ph	H	Ph	>99	55	S

[a] Determined by ^{1}H NMR spectroscopy.
[b] Determined by chiral GC or by comparison of optical rotation with literature data.
[c] Absolute configuration of the major enantiomer.
[d] Not determined.

compared to those with –$SiMe_3$ groups (entries 1–4). The size of the other olefin substituents also appeared inconsequential, as an olefin with only methyl or primary alkyl substituents (entry 4) was hydrogenated with average selectivity, as was the comparatively bulky (3,4-dihydro-1-naphthalenyl)trimethylsilane (Fig. 6). In fact, most substrates were hydrogenated with moderate enantioselectivity; only two displayed remarkable reactivity. *Z*-α-Trimethylsilyl-β-methylstyrene (entry 1) was hydrogenated in anomalously low enantioselectivity, whereas its isomer, *E*-α-methyl-β-trimethylsilylstyrene was hydrogenated in exceptionally high ee (entry 2). In the latter, the sterically favoured transition state for migratory insertion is further stabilized because the hydride is added to the olefin terminus bearing the electron-withdrawing silyl group (see Section 2.3). However, another olefin with this favoured geometry was also hydrogenated (entry 4), with only moderate enantioselectivity. That olefin bore no aryl substituents, and this may have affected the selectivity of hydrogenation; the paucity of asymmetric hydrogenations of purely alkyl-substituted olefins means that little is known about the reaction [97]. Additionally, the occurrence of olefin isomerization in vinyl silane hydrogenation has not been examined, and may be important for some substrates. Given the burgeoning popularity of silicon in pharmaceutical applications, the enantioselective hydrogenation of vinyl silanes has the potential to be an important reaction. However, more research is needed to improve its substrate scope and selectivity, as well as our understanding of it.

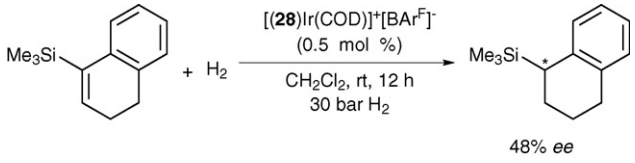


Fig. 6. Enantioselective hydrogenation of 3,4-dihydro-1-naphthalenyl)trimethylsilane [96]. The absolute configuration of the major isomer was not determined.

3.4. Enol ethers and enol phosphinate esters

Early interest in the asymmetric hydrogenation of enol ethers aimed to find a suitable alternative to the asymmetric hydrogenation of ketones, before that reaction was well-developed and general. However, the hydrogenation of enol ethers is not merely a substitute for ketone hydrogenation. Rather, it can lead to products that are difficult or impossible to access directly from the hydrogenation of ketones, such as chiral cyclic ethers. Additionally, some enol ethers can be converted to products other than alcohols. Finally, the selective asymmetric hydrogenation of an enol ether forms a protected chiral alcohol that can be deprotected at any later point in a synthesis. Enol ethers have proven difficult substrates though, and the search for general catalysts for their asymmetric hydrogenation continues.

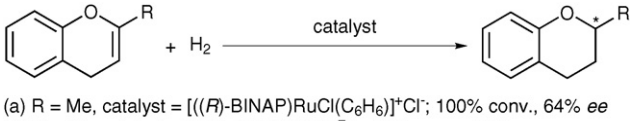
3.4.1. Alkyl enol ethers

Most asymmetric hydrogenations of alkyl enol ethers that have been reported feature 1-amido-2-alkoxy [98] or 1-homoamido-2-alkoxy [99] olefins that could be hydrogenated by rhodium catalysts; however, a few cyclic enol ethers with no additional coordinating functionality have been hydrogenated stereoselectively. Silyl enol ethers have been hydrogenated using rhodium catalysts, though in the absence of additional coordinating functionality, the ee values were limited to 10% [100]. In 1995, Takaya and co-workers reported the ruthenium-BINAP-catalyzed asymmetric hydrogenation of several enol ethers [101]. They hydrogenated the isomers 2-methylenetetrahydrofuran and 2-methyl-4,5-dihydrofuran to 2-methyltetrahydrofuran in high ee, and also enantioselectively reduced 2-methylfuran (see Section 3.5.3). 2-Methyl-1,4-benzopyran (Scheme 9, a) and α-phenoxystyrene were hydrogenated in moderate enantioselectivity.

Pfaltz and co-workers used an iridium catalyst, [(**31**)Ir(COD)]$^+$[BAr^F]$^-$, to hydrogenate 2-phenyl-1,4-benzopyran (Scheme 9b) [24]. This reaction proceeded to complete conversion and yielded 98% ee using lower temperature and H_2 pressure than the ruthenium-BINAP-catalyzed hydrogenation. Thus iridium catalysts have considerable potential for the asymmetric hydrogenation of cyclic enol ethers.

3.4.2. Enol phosphinate esters

Kumada and co-workers were among the first researchers who attempted to access chiral alcohols *via* asymmetric hydrogenation of olefins [102]. Noting that the successful substrates for this reaction bore a carbonyl oxygen three atoms away from the olefin, they reasoned that enol phosphinate esters



(a) R = Me, catalyst = [((*R*)-BINAP)RuCl(C_6H_6)]$^+$$Cl^-$; 100% conv., 64% *ee*
(b) R = Ph, catalyst = [(**31**)Ir(COD)]$^+$[BAr^F]$^-$; >99% conv., 99% *ee*

Scheme 9. Enantioselective hydrogenation of 2-substituted 1,4-benzopyrans. (a) THF solution, 50 °C, 101 bar H_2, 0.2–1 mol% catalyst, 20–60 h [101]; (b) CH_2Cl_2 solution, r.t., 50 bar H_2, 1 mol% catalyst [24b].

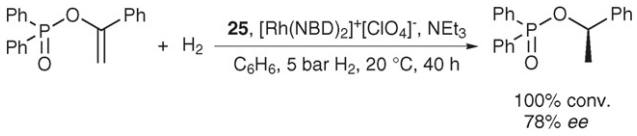


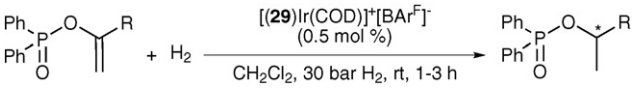
Fig. 7. Enantioselective hydrogenation of an enol phosphinate ester using a chiral rhodium catalyst [102]. Only the best example is shown.

might be stereoselectively reduced to alkyl phosphinate esters, which could be deprotected to chiral secondary alcohols. Using a catalyst system composed of $[Rh(NBD)_2]^+[ClO_4]^-$, a chiral ferrocenylphosphine (**25**), and triethylamine, they achieved the asymmetric hydrogenation of enol phosphinates in 16–80% ee (Fig. 7); these were higher values than those achieved in contemporary ketone hydrogenations.

Following the work of Kumada and co-workers, the asymmetric hydrogenation of enol phosphinates was set aside for some time. In 2005, Berens reported a process for converting chiral alkyl phosphinate esters to chiral phosphines [103], thereby increasing the value of chiral alkyl phophinate esters. Our group has revisited the asymmetric hydrogenation of enol phosphinate esters [104]. We applied our iridium catalysts to several types of enol ethers, and found that the catalyst $[(\mathbf{29})Ir(COD)]^+[BAr^F]^-$ [105] hydrogenated enol phosphinate esters with excellent stereoselectivity (Table 7). Both 1-alkyl- and 1-aryl-enol phosphinate esters were reduced, reaching high conversion after a few hours at room temperature, and the ee values of the products ranged from 85% to >99%. Only the 4-methoxyphenyl-substituted substrate proved challenging. Notably, the same type of substituent produced anomalously poor results in Pfaltz' vinylphosphonate hydrogenation (Section 3.1). In the enol phosphinate ester case, we detected diphenylphosphinic acid in the ^{31}P NMR spectrum of the hydrogenation mixture. This suggested that the phosphinate group was being lost from the olefin, which was rendered electron-rich by the *para*-methoxy group. The reaction could be driven to 48% conversion using harsher conditions and a resin to scavenge the diphenylphosphinic acid. Fortunately, this treatment had no ill effects on stereoselectivity.

Though excellent conversions and ee values have been obtained for the asymmetric hydrogenation of terminal enol phosphinate esters, no studies have addressed the related reaction with tri- or tetrasubstituted olefins, and we expect that iridium catalysts could also be useful for these substrates.

Table 7
Asymmetric hydrogenation of enol phosphinate esters by an iridium catalyst [104]



Entry	R	Conversion (%)[a]	ee (%)[b]
1	Ph	>99	95
2	4-Me-C_6H_4	97	96
3	4-^{t}Bu-C_6H_4	93	94
4[c]	4-MeO-C_6H_4	48	98
5	4-Br-C_6H_4	>99	>99
6	4-F_3C-C_6H_4	>99	99
7	4-O_2N-C_6H_4	>99	92
8	2-Naphth	>99	85
9	Cy	>99	92
10	^{t}Bu	>99	>99

[a] Determined by ^1H NMR spectroscopy.
[b] Determined by chiral GC or HPLC. Absolute configuration of the product was *R* in all cases.
[c] 50 bar H_2, 2 mol% catalyst, 100 bar H_2, in the presence of poly(4-vinylpyridine) resin.

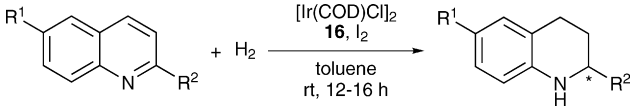
3.5. Heteroaromatic substrates

The omnipresence of substituted heterocycles in Nature can hardly be exaggerated. Thus their chiral synthesis is highly desirable, and the atom-economic catalytic asymmetric hydrogenation reaction would be a useful implement for this purpose. Unfortunately, there are few examples of very stereoselective, high-yielding hydrogenation catalysts for these substrates. It has been suggested [106–109] that the special resonance stability of heteroaromatics could hamper this reaction, and there is experimental evidence supporting this assertion (vide infra) [110]. Additionally, the hydrogenation of heteroaromatics has traditionally been the province of heterogeneous catalysts, whereas most asymmetric hydrogenation catalysts are homogeneous. Only recently have these two fields intersected in the asymmetric hydrogenation of heteroaromatics. Though they prove challenging substrates for the reaction, the past few years have seen a few classes of heteroaromatics hydrogenated in excellent yields and ee values.

3.5.1. Quinolines

Consistent with the idea that aromaticity can be an obstacle to the hydrogenation of heteroaromatics, the first of these substrates to be reduced asymmetrically were benzo-fused compounds, in which the heteroaromatic rings are less stabilized than their monocyclic analogues [106,111,112]. In 2003, Zhou and co-workers published the first highly enantioselective hydrogenation of substituted quinolines [107]. Prompted by the success of iridium catalysts in imine hydrogenations [15] and by the utility of 1,2,3,4-tetrahydroquinolines [113], they attempted the hydrogenation of 2-methyl quinoline (Table 8) with a catalyst generated *in situ* from $[Ir(COD)Cl]_2$ and (*R*)-MeO-Biphep ((*R*)-**16**, Scheme 6). The result was a poor catalyst for the reaction—after 18 h, it produced a trace of 2-methyl-1,2,3,4-tetrahydroquinoline in low ee. Fortunately, the authors were inspired by reports of improvements in the yields and selectivities of some catalytic systems through the use of achiral additives [114]. They screened a number of additives in the iridium-catalyzed hydrogenation of 2-methylquinoline, and found that adding iodine (I_2/Ir = 10) and changing the solvent from CH_2Cl_2 to toluene transformed the poorly selective, barely catalytic system into a rapid and selective one. Though they did not speculate on the role of I_2 in the reaction, Zhou and co-workers were able to hydrogenate quinolines with a variety of substituents in the two and six positions (Table 8) in high yields, with very good ee values. However, almost no stereoinduction was observed when 3- and 4-substituted quinolines were reduced.

Table 8
Asymmetric hydrogenation of some substituted quinolines by iridium catalysts [107]



Entry	R^1	R^2	Yield (%)[a]	ee (%)[b]	Configuration[c]
1	H	Me	94	94	*R*
2	H	CH_2CPh_2OH	94	91	*S*
3	H	Ph	95	72	*S*
4	F	Me	88	96	*R*
5	Me	Me	91	81	*R*
6	MeO	Me	89	84	*R*

Conditions: 48 bar H_2, substrate/Ir/**16**/I_2 = 100:1:1.1:10.
[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] Determined by comparison of optical rotation to literature compound or analogue.

Zhou and co-workers applied their catalyst system to the enantioselective total synthesis of (−)-galipeine [115], a biologically active tetrahydroquinone alkaloid isolated from the bark of the *Galipea officinalis* tree in 1999 [116]. The seven-step synthesis (Fig. 8), which featured the iridium-catalyzed hydrogenation of a 2-substituted quinoline as the key step, furnished (−)-galipeine in 54% overall yield and 96% ee from commercially available, achiral isovanillin.

Subsequently, Zhou and co-workers used an iridium catalyst with the chiral, ferrocene-based N∩P ligand **26** to hydrogenate quinolines (Table 9, entry 2) [117]. Again using toluene solvent and I_2 as an additive, they reduced a number of 2- and 6-substituted substrates. For most substituents, this new catalyst system gave comparable yields, but slightly (5–10%) lower ee values than the earlier system. For 2-phenylquinoline, and for substrates with bulky groups in the two-position, the Ir/**26**/I_2 system performed significantly worse than the Ir/**16**/I_2 variant.

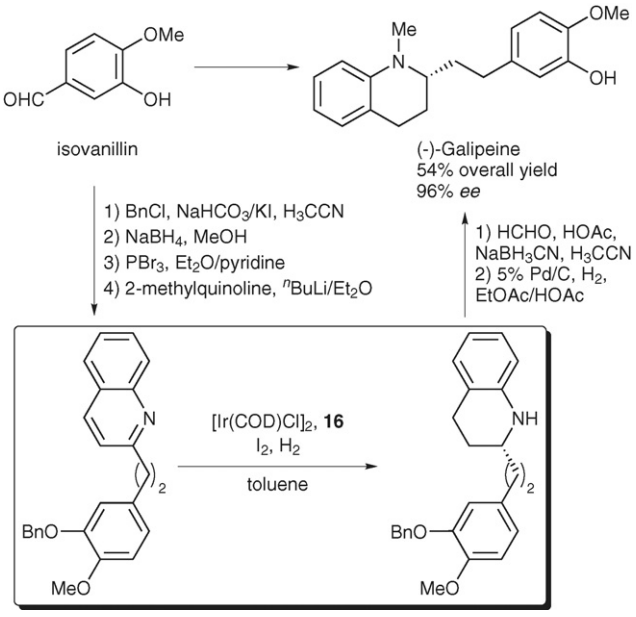
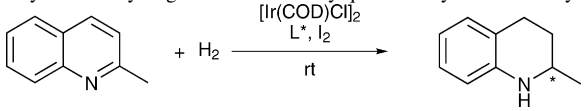


Fig. 8. Enantioselective total synthesis of the alkaloid (−)-galipeine, with iridium-catalyzed asymmetric hydrogenation of a quinoline as the key step [115].

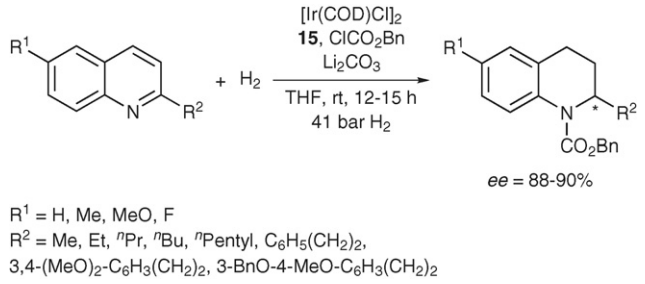
Following the success of Zhou and co-workers, several other groups combined chiral diphosphines with $[Ir(COD)Cl]_2$ and I_2 to form active and selective catalysts for the asymmetric hydrogenation of substituted quinolines, and these are summarized in Table 9 (using the substrate 2-methylquinoline as a standard) [112i,118–121]. Chan, Fan, Xu, and co-workers applied catalysts based on (*R*)-P-Phos (**18**, entries 3 and 4) [118], BINAPO (**12**, **13**, entries 5 and 6) [119], and atropisomeric (**19**, entry 7) [112i] ligands to the reaction. They also performed the reaction in biphasic dmpeg/hexane (dmpeg = dimethyl poly(ethylene glycol)) mixtures, which allowed them extract the reaction products, then recover and reuse the catalyst. After 8 uses, no attrition in the efficiency or enantioselectivity of $[Ir(COD)Cl]_2$/**18**/I_2 was

Table 9
Asymmetric hydrogenation of 2-methylquinoline by iridium catalysts with P∩P and P∩N ligands



Entry	L* [Ref.]	P(H_2) (bar)	*t* (h)	Solvent	Ir (mol%)[a]	Conversion (%)[b]	ee (%)[c]
1	**16** [107]	48	15	Toluene	1	94	94
2	**26** [117]	41	12	Toluene	1	>95	90
3	**18** [118a]	48	20	dmpeg/hexane[d]	1	98	89
4[e]	**18** [118a]	48	20	dmpeg/hexane[d]	1	99	88
5	**12** [119]	48	20	THF	1	>99	81
6	**13** [119]	48	20	THF	1	>99	95
7	**19** [112i]	48	20	Toluene	1	>99	92
8	**32** [120]	48	20	THF	0.02	91	92
9	**33** [121]	41	20	Toluene	1	>96	92
10	**14** [122]	46	1.5	THF	0.25	>95	90

[a] Amount of Ir with respect to substrate. The catalyst systems were composed Ir/L*/I_2 in the ratio 1/1/(4–10).
[b] Conversion, determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral HPLC.
[d] dmpeg = dimethyl poly(ethylene glycol).
[e] Upon recycling the catalyst eight times.



Scheme 10. Hydrogenation of quinolines by an iridium-diphosphine catalyst in the presence of benzyl chloroformate [109].

observed (entries 3 and 4). They also used a phosphine with a *spiro*-biindane backbone (**32**, entry 8) to achieve efficient asymmetric hydrogenation at very low catalyst loading [120]. Reetz and Li found high enantioselectivities using BINOL-derived phosphinites as ligands (**33**, entry 9) [121]. Further, they examined the effect of achiral phosphine and phosphate additives on the reaction, and found them to be helpful for difficult substrates. Fan and co-workers employed catalysts based on the dendritic diphosphine ligand **14** and higher- and lower-order dendrimers for the asymmetric hydrogenation of quinolines [122], and found these catalysts to be active even at low catalyst loadings (entry 10). They also recycled the catalysts with minimal loss of enantioselectivity, though catalyst activity suffered after ∼4 uses. Finally, Genet, Mashima and co-workers hydrogenated 2-phenylquinoline to (*S*)-2-phenyl-1,2,3,4-tetrahydroquinoline using phosphine-supported, iodo-bridged diiridium complexes [123]. These catalysts gave moderate ee values for this reaction, but were more useful for the enantioselective hydrogenation of nonaromatic cyclic imines.

Zhou and co-workers have also accomplished the asymmetric hydrogenation of quinolines in the absence of I_2 [109]. In this case, the substrates were activated by *in situ* reaction with benzyl chloroformate, and hydrogenated in 88–90% ee using an iridium–diphosphine complex. The carbobenzyloxy group was attached to the nitrogen atom in the hydrogenation product (Scheme 10), but could be removed by hydrogenation over Pd/C. A non-coordinating base was required to scavenge HCl formed from the benzyl chloroformate. In the presence of 4-Å molecular sieves, low conversion and a reversal of the product configuration were observed.

In addition to providing an alternative to using I_2 in the reduction of quinolines, the alkyl chloroformate system allowed Zhou and co-workers to hydrogenate 1-substituted isoquinolines enantioselectively (Table 10). Contrary to the case of quinolines, only the imine bonds of the isoquinolines were reduced, forming 1,2-dihydroisoquinolines. In an observation that is not yet understood, adding lithium salts increased the reaction's enantioselectivity. Although the yield and ee values for these isoquinoline reductions were lower than for the quinoline reductions, they were good in many cases, and this is to our knowledge the only asymmetric hydrogenation of isoquinolines reported to date.

Though iridium-based catalysts are now available to hydrogenate 2-substituted quinolines to chiral 1,2,3,4-tetrahydroquinolines with good enantioselectivity, there remains considerable progress to be made in this area. Few 2-substituted quinolines can be hydrogenated in >95% ee, and some substrates, such as 2-phenylquinoline, give considerably lower values. More importantly, none of the catalyst systems that hydrogenate quinolines with high stereoselectivity have been demonstrated for substrates with more than one substituent on the heterocyclic ring. Asymmetric hydrogenation of the related isoquinolines is largely unexplored.

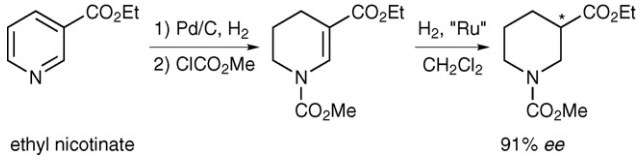
Table 10
Asymmetric hydrogenation of isoquinolines by an iridium-diphosphine catalyst in the presence of alkyl chloroformate [109]

Entry	R^1	R^2	R^3	Yield (%)[a]	ee (%)[b]	Configuration[c]
1	H	Me	Me	85	80	*S*
2	H	Me	Bn	87	83	*S*
3	H	Bu	Me	87	60[d]	*S*
4	H	Bn	Me	83	10[d]	*S*
5	H	Ph	Me	57	82	*S*
6	MeO	Me	Me	57	63	*S*

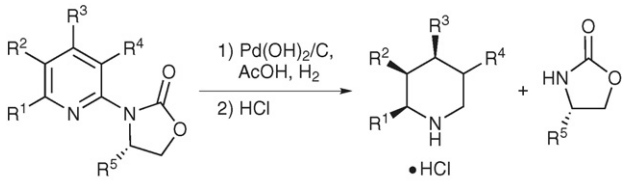
[a] Isolated yield based on isoquinoline.
[b] Determined by chiral HPLC.
[c] Determined by comparison of optical rotation to literature value or analogue.
[d] Determined following conversion of the product to the corresponding tetrahydroisoquinoline.

3.5.2. Pyridines

The asymmetric hydrogenation of pyridines produces chiral piperidine moieties, which are found in many biologically active compounds [124]. As many pyridine derivatives are commercially available, the asymmetric hydrogenation of pyridines is highly desirable, and has been the focus of a short review [108]. However, the direct asymmetric hydrogenation of pyridines to piperidines with a chiral catalyst has proven difficult. Several groups have accomplished the asymmetric reduction of ethyl nicotinate to ethyl nipecotinate [125,126]. Unfortunately, the only highly selective method for the reduction of ethyl nicotinate derivative requires three reaction steps: the hydrogenation to ethyl 1,4,5,6-tetrahydro-3-pyridinecarboxylate over Pd/C, the protection of the new enamine with methyl chloroformate, and finally the rhodium-catalyzed asymmetric hydrogenation of the resulting carbamate (Scheme 11) [127]. The one-step reduction



Scheme 11. Asymmetric hydrogenation of an ethyl nicotinate derivative by a chiral rhodium catalyst [127]. "Ru": chiral-diphosphine-ligated ruthenium catalyst.



Scheme 12. Chiral-auxiliary-directed hydrogenation of pyridines [128].

of ethyl nicotinate by rhodium or palladium catalysts provides ethyl nipecotinate in only 17% ee [126].

Glorius and co-workers extended the scope of highly enantioselective pyridine reduction by using chiral 1,3-oxazolidin-2-ones as auxilliaries to direct the hydrogenation of these substrates by achiral heterogeneous catalysts (Scheme 12) [128]. Though the use of an auxiliary is not ideal from the standpoint of atom-economy, the 1,3-oxazolidin-2-one was removed during the hydrogenation, avoiding the need for a separate removal step. Additionally, it could be recovered and recycled, which greatly improves the atom-economy of the process. Glorius was able to install up to three stereocenters simultaneously; only the substituent in the 3-position (R^4 in Scheme 12) was racemic in the final product.

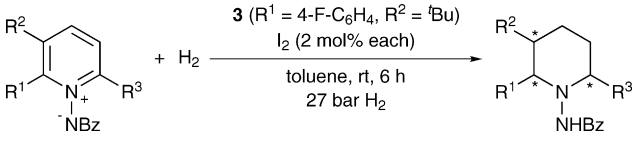
Iridium catalysts entered the field of asymmetric pyridine hydrogenation in 2005. Legault and Charette [129] used *O*-(2,4-dinitrophenyl)hydroxylamine to activate a series of substituted pyridines, forming *N*-iminopyridinium ylides. These could be hydrogenated in very good yields and ee values using the Pfaltz-type catalyst **3** (R^1 = 4-F-C_6H_4, R^2 = ^{t}Bu) in the presence of catalytic amounts I_2 (Table 11). The specific catalyst used was found to strongly affect the outcome of the reaction. Additionally, the reaction did not take place in the absence of I_2, which the authors speculated was serving to oxidize the Ir^I pre-catalyst to an active Ir^{III} catalyst. The hydrogenation products were crystalline solids whose enantiopurity could easily be improved by a single recrystallization. Further, they can be converted to the corresponding piperidines using Raney nickel or lithium/ammonia. Therefore, this reaction provides a route to chiral piperidines from pyridines, using a chiral catalyst to impart stereoselectivity and an achiral auxiliary to activate the substrate. The main limitations of Legault and Charette's system came in the hydrogenation of disubstituted substrates, and in particular substrates with substituents in the 3-position. Future developments in the area of asymmetric pyridine hydrogenation (by iridium catalysts or otherwise) should include methods to control the stereochemistry at the 3-position, which has proven difficult for existing catalyst systems.

3.5.3. Furans

Furans are another class of heteroaromatic substrates that iridium catalysts hydrogenate enantioselectively. Similarly to that of other aromatic substrates, the hydrogenation of furans in high yield and ee is quite challenging. In an early example of this reaction, Takaya and co-workers hydrogenated 2-methylfuran using [((*R*)-**11**)$_2$Ru$_2$Cl$_4$](NEt$_3$) [101]. The product, (*S*)-2-methyltetrahydrofuran, was obtained in lower ee than most of the substrates studied in that report (see Section 3.4.1), prompting the authors to describe the reaction as giving 'only 50% ee'; however, it was an excellent start in the asymmetric hydrogenation of a difficult substrate (Eq. (1)).

A series of rhodium complexes were also tested in the hydrogenation of a specific substituted furan. Albert and co-workers studied the reduction of **40** to the 2′,3′-dideoxynucleoside **41** (Eq. (2)) [130]. Given the origin of enantioselectivity in most rhodium-phosphine catalysts for asymmetric hydrogenation, it is likely that the imide and/or ester groups of **40** directed the stereochemistry of this reaction.

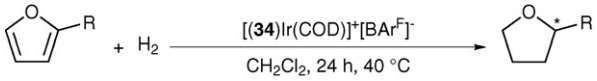
Table 11
Asymmetric hydrogenation *N*-benzoyliminopyridinium ylides using an N∩P-ligated iridium catalyst [129]



Entry	R^1	R^2	R^3	Yield (%)[a]	*dr*[b]	ee (%)[c]	Configuration[d]
1	Me	H	H	98	–[e]	90	2*S*
2	Et	H	H	96	–[e]	83	2*S*
3	^{n}Pr	H	H	98	–[e]	84	2*S*
4	Bn	H	H	97	–[e]	58	2*R*
5	CH_2OBn	H	H	85	–[e]	76	2*R*
6	$(CH_2)_3OBn$	H	H	88	–[e]	88	2*R*
7	Me	Me	H	91	>95:5	54	2*S*, 3*S*
8	Me	H	Me	92	57/43	86/84	2*S*, 5*R*

[a] All product mixtures were subjected to H_2 and Pd/C for 1 h to remove traces of partially hydrogenated product. Yield given is the isolated yield of product following this procedure and filtration through silica.
[b] Diastereomeric ratio of *cis*:*trans* products.
[c] Determined by chiral HPLC.
[d] Absolute configuration for entry 1 was determined by derivatization and comparison to a literature compound. Subsequent configurations were determined by analogy from HPLC elution order. In entries 7 and 8, the configuration of the major product is given. Note that the different configurations for entries 1–3 vs. entries 4–6 reflect a change in substituent priority, not in the sense of enantioselectivity.
[e] Not applicable.

Table 12
Asymmetric hydrogenation of furans by an iridium catalyst [134]



Entry	R^1	Conversion (%)[a]	ee (%)[b]
1[c]	$(CH_2)_4Ph$	84	78
2[d]	$(CH_2)_2CO_2Et$	>99	93

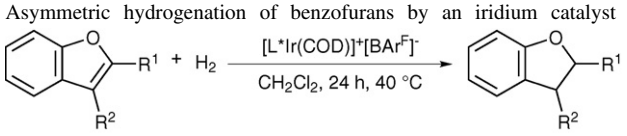
[a] Determined by GC.
[b] Determined by chiral HPLC. Absolute configurations were not assigned.
[c] 1 mol% catalyst, 50 bar H_2.
[d] 2 mol% catalyst, 100 bar H_2.

Recently, a few heterogeneous catalysts have hydrogenated furan substrates enantioselectively. A wool-Rh complex hydrogenated 2-methylfuran in 76.9% ee [131], and a silica-supported alginic acid-amino acid-Pt complex gave an excellent result – 98.3% ee – for the hydrogenation of furfuryl alcohol [132]. Thus far, these systems have been demonstrated on only one substrate each, so their scope as asymmetric hydrogenation catalysts remains unknown. Several 2-furancarboxylic acids have been hydrogenated using Pd/Al_2O_3 in the presence of chiral modifiers, with modest ee values (10–45%) [133].

In 2006, Pfaltz and co-workers reported the highly successful iridium-catalyzed asymmetric hydrogenation of furans [134]. With their new bicyclic pyridine-phosphinites providing the chiral environment on iridium, Pfaltz and co-workers hydrogenated several substituted furans (Table 12) and benzofurans (Table 13) in ee values that ranged from 78% to >99%. In the case of benzofurans, high selectivity could be achieved for both 2- and 3-methylbenzofuran, with the phenyl rings being unaffected.

Interestingly, these authors previously reported that alkenes with furan and other heteroaromatic substituents could be hydrogenated using complexes of iridium with oxazoline–phosphine and oxazoline–phosphite ligands, without reduction of (or interference from) these substituents [23,25]. Thus, both the hydrogenation of a furan ring and the hydrogenation of an olefin without altering a furan ring in the same molecule are possible; the course of the reaction is determined by careful choice of catalyst and reaction conditions. Quantitative comparisons between the relevant catalysts are not possible because few experimental details were provided. Nevertheless, the high conversion and stereoselectivity displayed in the asymmetric hydrogenation of furans and benzofurans by bicyclic-phosphinite-ligated iridium catalysts make them the best catalysts known for this reaction.

Table 13
Asymmetric hydrogenation of benzofurans by an iridium catalyst [134]



Entry	R^1	R^2	L*	Conversion (%)[a]	ee (%)[b]
1[c]	H	Me	**35**	>99	92
2[c]	Me	H	**34**	93	98
3[d]	CO_2Et	H	**34**	47	>99

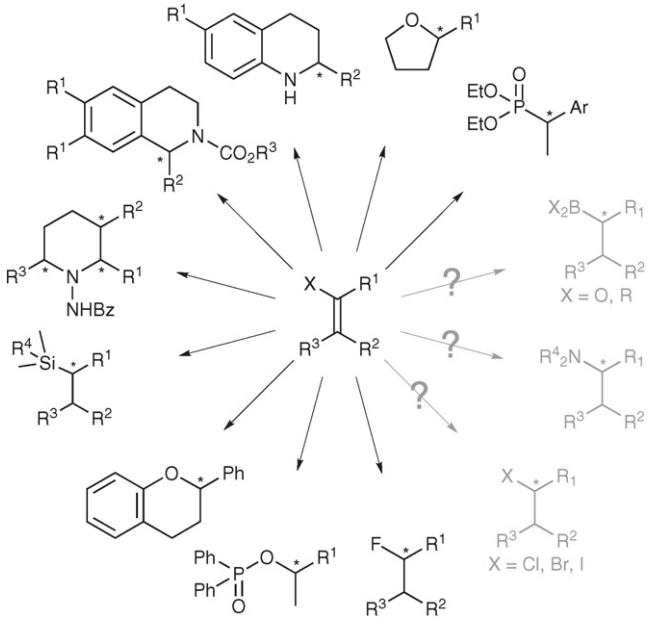
[a] Determined by GC.
[b] Determined by chiral HPLC. Absolute configurations were not assigned.
[c] 1 mol% catalyst, 50 bar H_2.
[d] 2 mol% catalyst, 100 bar H_2.

4. Conclusion

The asymmetric hydrogenation of olefins is a synthetic technique applied widely in both academic and industrial research. It is an atom-economic and often highly selective way to install a chiral center. Chiral iridium catalysts have for some time been used to enantioselectively hydrogenate olefins without coordinating functionality; specifically, they are extremely popular for the hydrogenation of unfunctionalized olefins. However, because iridium hydrogenation catalysts do not rely on a coordinating group to direct the reaction, they are also uniquely suited to certain types of functionalized olefins—those with non-coordinating functional groups. Therefore these catalysts allow the asymmetric hydrogenation of olefins to traverse new ground, and improve its utility for established substrates.

Iridium catalysts been applied to the hydrogenation of olefins with non-coordinating functional groups only in the past few years. In that short time, many high-yielding and highly selective reactions of this type have been developed. The range of chiral functional groups accessible by this method is impressive, though others remain inaccessible (Scheme 13). Some substrates that may be interesting for future study include those with electrophilic substituents, such as alkenyl chlorides, bromides, or iodides, alkenyl boranes or borates, and enamines.

Even in the iridium-catalyzed asymmetric hydrogenation of the functionalized substrates discussed in this review, challenges linger. Most notably, these new substrate classes have been examined only briefly, and will require further investigation before the scope of this catalytic reaction can be ascertained.



Scheme 13.

The unique properties of non-coordinating functional groups, particularly their ability to polarize double bonds, likely affect the catalytic asymmetric hydrogenation reaction, but more research is needed to understand their impact. Finally, some substrate classes display specific selectivity problems. However, auspicious results have been obtained in the asymmetric iridium-catalyzed reduction of olefins with nontraditional functionality, and we believe that continued incursions into this field will provide useful protocols for the asymmetric hydrogenation of a range of compounds while broadening the substrate scope of iridium catalysts for olefin hydrogenation.

Acknowledgements

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