

Iridium-Catalyzed Asymmetric Hydrogenation of Olefins

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ABSTRACT

Asymmetric hydrogenation is one of the most important catalytic methods for the preparation of optically active compounds. For a long time the range of olefins that could be hydrogenated with high enantiomeric excess was limited to substrates bearing a coordinating group next to the C=C bond. We have found a new class of catalysts, iridium complexes with chiral P, N ligands, that overcome these limitations. For a wide range of unfunctionalized olefins, excellent enantioselectivities could be achieved. Because these catalysts do not require the presence of any particular functional group in the substrate, they considerably broaden the scope of asymmetric hydrogenation. In addition, promising results were also obtained with certain functionalized alkenes, furans, and benzofurans.

Introduction

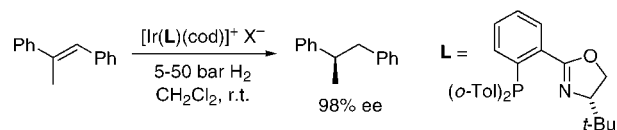
The development of highly enantioselective rhodium-diphosphine catalysts around 1970 marked the beginning of a new era in asymmetric synthesis. For the first time, practically useful enantioselectivities could be obtained with synthetic chiral catalysts. The well-known L-Dopa process, which was established at Monsanto at that time,¹ demonstrated that these catalysts can be applied on an industrial scale, and since then, hydrogenation has played a dominant role in industrial asymmetric catalysis.² Today, asymmetric hydrogenation is still one of the most widely used, most reliable catalytic methods for the preparation of optically active compounds.³ High enantioselectivity, low catalyst loadings, essentially quantitative yields, perfect atom economy, and mild conditions are attractive features of this transformation.

An impressive number of chiral phosphine ligands are known, which induce very high enantioselectivity in rhodium- and ruthenium-catalyzed hydrogenations. However, the range of olefins that can be hydrogenated with

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Andreas Pfaltz was born in Basel, Switzerland, in 1948. He received a diploma in natural sciences and a PhD degree from the ETH in Zürich. After completing his thesis under the direction of Albert Eschenmoser in 1978, he joined the research group of Gilbert Stork at Columbia University as a postdoctoral fellow. In 1980 he returned to the ETH where he was appointed "Privatdozent" (Lecturer) in 1987. From 1990 to 1995 he was Professor of Organic Chemistry at the University of Basel and from 1995 to 1998 director at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany. In 1999 he returned to the University of Basel where he is currently Professor of Chemistry.

Scheme 1. Asymmetric Hydrogenation of 1,2-Diphenyl-1-propene



high enantiomeric excess is still limited. Both rhodium and ruthenium catalysts require the presence of a coordinating group next to the C=C bond, hydrogenation of dehydro-amino acid derivatives or allylic alcohols being typical examples. With unfunctionalized olefins, these catalysts generally show low reactivity and unsatisfactory enantioselectivity. Thus, their application is restricted to certain classes of properly functionalized substrates.

Some years ago, we found a new class of hydrogenation catalysts, iridium complexes with chiral P, N ligands, which overcome these limitations.⁴ For a wide range of unfunctionalized olefins, excellent enantioselectivities could be achieved with these catalysts.⁵ Moreover, they showed exceptionally high activity in the hydrogenation of unfunctionalized trisubstituted and even tetrasubstituted olefins. In this respect, they resembled the Crabtree catalyst, [(Cy₃P)(pyridine)Ir(COD)]PF₆ (Cy = cyclohexyl, COD = cyclooctadiene),⁶ which provided the stimulus for our work. In addition, promising results were also obtained with certain functionalized alkenes for which no suitable catalysts were available yet. In this Account, we discuss the special properties and scope of these catalysts with special emphasis on recent developments.⁷

Initial Studies: An Unexpected Anion Effect

First tests with iridium complexes derived from chiral phosphino-oxazolines (PHOX ligands)⁸ and (*E*)-1,2-diphenyl-1-propene as substrate gave encouraging results (Scheme 1).^{4a} With 4 mol % of catalyst (X = PF₆) at 10–50 bar hydrogen pressure up to 98% ee could be obtained. However, the turnover numbers were disappointingly low.

Kinetic studies showed that with 4 mol % of catalyst in a 0.3 M solution of olefin at 7 bar hydrogen pressure the reaction was extremely fast and reached completion within less than 1 min.⁹ Lower catalyst loadings resulted in decreased conversion. Although the initial rate was still high at 1 mol % catalyst loading, rapid and essentially complete deactivation of the catalyst was observed before 50% of the olefin was consumed. Deactivation is a known problem of the Crabtree catalyst, which is attributed to the formation of inactive hydride-bridged trinuclear complexes.⁶ In our case, too, NMR analysis of deactivated reaction mixtures suggested the presence of such hydride-bridged species. In subsequent studies a trinuclear Ir-(PHOX)-hydride complex was isolated and characterized by NMR and X-ray analysis.¹⁰ This complex proved to be remarkably stable, and all experiments to convert it back into a catalytically active species failed.

Attempts to increase conversion by variation of the solvent, hydrogen pressure, or the catalyst and substrate

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concentration were unsuccessful. Coordinating solvents and additives such as amines or coordinating anions such as halides, carboxylates, and even the very weakly coordinating triflate ion were found to deactivate the catalyst. The best results were obtained in anhydrous dichloromethane or 1,2-dichloroethane using cationic Ir-PHOX complexes with hexafluorophosphate as counterion. Rigorous exclusion of moisture and oxygen resulted in increased conversion. When the reaction was set up in carefully dried dichloromethane in a glovebox, full conversion could be achieved with only 0.5 mol % of catalyst. However, reactions at such low catalyst loadings were difficult to reproduce.

After a long and quite frustrating period of fruitless experiments, Andrew Lightfoot in our laboratory finally found a surprisingly simple solution for avoiding catalyst deactivation, when he tested an Ir-PHOX catalyst with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAR_F^-) as counterion.^{4a} Iridium complexes with this bulky, apolar, and extremely weakly coordinating anion did not suffer from deactivation, and full conversion could be routinely obtained with catalyst loadings as low as 0.02 mol %.^{11,12} In addition, the BAR_F^- salts proved to be much less sensitive to moisture than the corresponding hexafluorophosphates. Tetrakis(pentafluorophenyl)borate and tetrakis(perfluoro-*tert*-butoxy)aluminate were equally effective, whereas catalysts with tetraphenylborate and tetrafluoroborate gave only low conversion.

How can these bulky, extremely weakly coordinating anions prevent catalyst deactivation? A comparative kinetic study of catalysts with different anions provided a plausible answer.¹² With PF_6^- as counterion the rate dependence on olefin concentration was first order, whereas the rate order observed for the corresponding BAR_F^- salt was close to zero. This striking difference may be explained by the stronger coordination of PF_6^- or formation of a tight anion pair, which slows down the addition of the olefin to the catalyst to such an extent that it becomes rate-limiting. The essentially noncoordinating BAR_F^- ion, on the other hand, does not interfere with olefin coordination, and therefore, the catalyst remains saturated with olefin even at low substrate concentration. The slower reaction of the PF_6^- salt with the olefin could explain its higher tendency to undergo deactivation. If we assume that deactivation is caused by the formation of hydride bridged species leading to an inactive trinuclear complex, then the critical step in the catalytic cycle is the reaction of the Ir-hydride intermediate with the olefin. If olefin insertion is very fast, as in case of the BAR_F^- salt, hydrogenation dominates over the deactivation pathway, whereas with the PF_6^- salt the olefin reacts more slowly and, therefore, deactivation becomes a significant competing process.

Practical Aspects

Iridium(COD) complexes with PHOX or related P, N ligands, which are used as precatalysts, are readily prepared by refluxing a solution of $[\text{Ir}(\text{COD})\text{Cl}]_2$ and P, N

ligand in dichloromethane. For the exchange of the chloride ion with BAR_F^- , the complexes are treated with NaBAR_F in a two-phase dichloromethane-water system, and if necessary, the resulting orange BAR_F^- salts can be purified by column chromatography on silica gel. The complexes are stable against oxygen and moisture and, therefore, can be easily handled in the laboratory atmosphere.

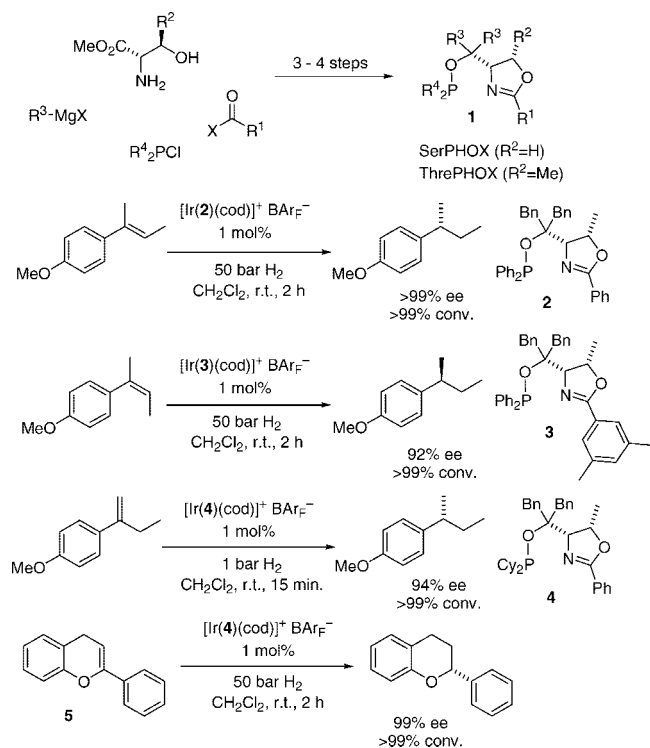
Hydrogenations are usually carried out in dichloromethane at room temperature at 5–50 bar hydrogen pressure.⁴ 1,2-Dichloroethane, toluene, and *tert*-butyl methyl ether have also been used with similar results. For most substrates, the enantioselectivity shows only a moderate to weak dependence on hydrogen pressure, with the exception of terminal olefins which give much higher enantiomeric excesses at 1 bar than at elevated pressures. Typically, 0.02–1 mol % of catalyst is used in a 0.1–2 M solution of substrate, using anhydrous solvents. Kinetic studies with (*E*)-1,2-diphenyl-1-propene showed that the reaction is very fast at room temperature.¹² Under the experimental conditions used, the rate was found to be limited by hydrogen diffusion between the gas and liquid phase. Therefore, the TOF of 7200 h^{-1} , measured under these conditions, should be taken as a lower limit. At 4 °C with less than 0.1 mol % of catalyst, the reaction was no longer diffusion-limited, and relevant kinetic data, indicating a TOF of 5500 h^{-1} , could be recorded.

New P, N Ligands with Broader Scope

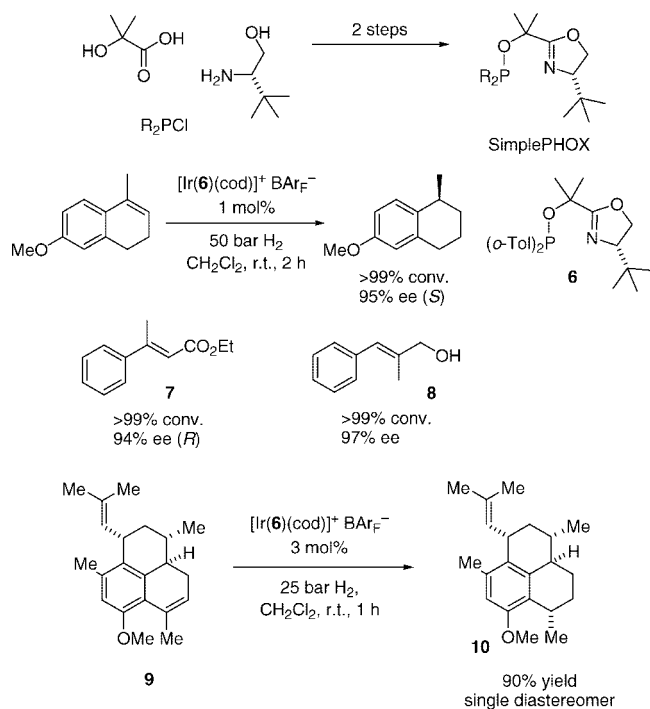
Although very high enantioselectivities could be obtained in the hydrogenation of (*E*)-1,2-diphenyl-1-propene and related trisubstituted diarylalkenes using Ir(PHOX) catalysts, the range of substrates proved to be limited. Therefore, we decided to extend our studies to other types of oxazoline-based P, N ligands with different backbones. The phosphinite-oxazolines which are derived from serine and threonine (**1**) proved to be an especially promising class of ligands.¹³ In contrast to the PHOX ligands, the phosphorus unit is attached to the stereogenic center next to the oxazoline nitrogen atom. Starting from different carboxylic acid derivatives, chlorophosphines, and Grignard reagents, a highly diverse library of ligands can be prepared (Scheme 2).

This ligand class allowed (*E*)- and (*Z*)-2-aryl-2-butenes to be hydrogenated with very high enantioselectivities for the first time. By variation of the substituents at the oxazoline ring and ligand backbone, it was possible to systematically optimize the enantioselectivity for each substrate. Thus, for (*E*)-2-(4-methoxyphenyl)-2-butene the enantiomeric excess could be increased to >99% ee using ligand **2**. For the corresponding (*Z*)-isomer ligand **3**, with a 3,5-dimethylphenyl group at the oxazoline ring, gave the best results. The (*E*)- and (*Z*)-isomers afforded products of opposite configuration. Further fine-tuning allowed terminal olefins to be hydrogenated with high enantiomeric excess using complex **4**, incorporating a dicyclohexylphosphinite ligand. Carrying out the hydrogenation at 1 bar hydrogen pressure was critical to obtain high enantioselectivities, in contrast to hydrogenation of trisub-

Scheme 2. Applications of ThrePHOX Ligands



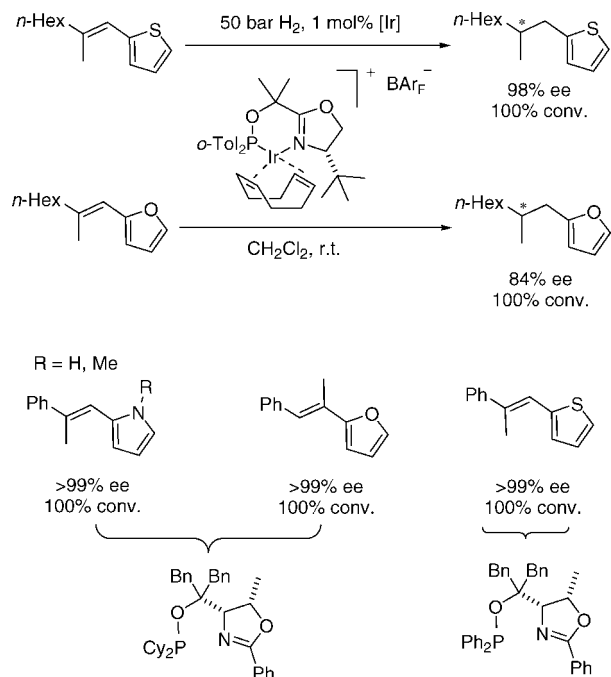
Scheme 3. Applications of SimplePHOX Ligands



stituted olefins which showed only moderate to weak pressure dependence.¹⁴ The same ligand also induced very high ee in the hydrogenation of flavene **5**.¹⁵

Another very useful, readily available class of phosphinite-oxazoline ligands is shown in Scheme 3. The synthesis is very short and convenient: refluxing *tert*-leucinol and 2-hydroxy-2-methylpropionic acid in xylene leads to the corresponding oxazoliny alcohol in high yield,

Scheme 4. Hydrogenation of Alkenes Bearing Heteroaromatic Substituents

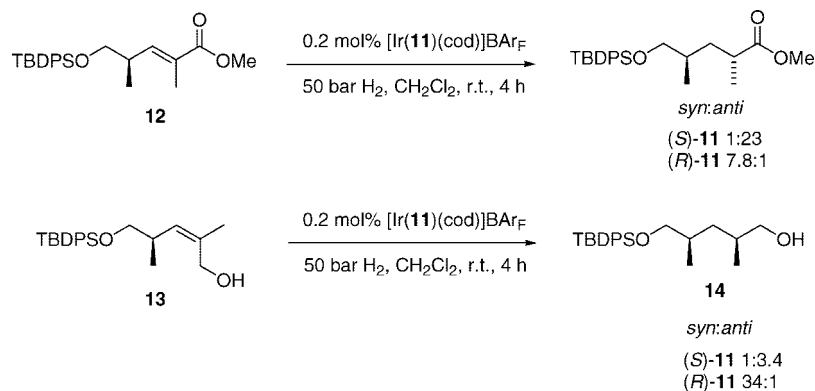


which has been converted to a series of SimplePHOX ligands by deprotonation and reaction with chlorophosphines.¹⁶

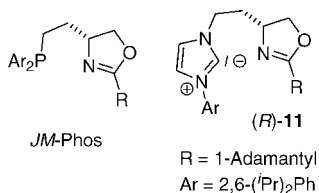
In the hydrogenation of the cyclic substrate 6-methoxy-1-methyl-3,4-dihydronaphthalene, ligand **6** was most effective among the SimplePHOX derivatives; the observed ee of 95% is one of the best values recorded for this substrate. The same complex also proved to be an excellent catalyst for the hydrogenation of the trisubstituted acrylic ester **7** and allylic alcohol **8**. Harmata and Hong have applied this catalyst in a total synthesis of the antibiotic pseudopteroxazole. A key intermediate in the synthesis was the tricycle **9**, which was hydrogenated with near perfect regioselectivity to give **10** with complete control of stereochemistry in 90% yield, along with only traces of over-hydrogenated product. That the exocyclic C=C bond was not hydrogenated was attributed to the preferred conformation of the substrate **9**, in which the methyl group on the benzene ring blocks the face of the adjacent alkenyl substituent that should be preferred by the chiral catalyst. So the catalyst would have to approach the disfavored face, and therefore, reduction of this double bond is inhibited (Scheme 3).¹⁷

The same catalyst gave high enantioselectivities for a range of trisubstituted alkenes bearing heteroaromatic rings at the C=C bond. The ThrePHOX ligands also proved highly effective for this class of substrate (Scheme 4).^{4b}

Closely related ligands have been reported by Burgess (JM-Phos)¹⁸ and Richards (structure **1** with R² = R³ = H).¹⁹ Although these ligands are structurally very similar, the enantioselectivities they induce in Ir-catalyzed hydrogenations are not as high as those obtained with the most effective derivatives of structure **1** (R³ = alkyl). A new class of phosphinooxazoline analogues, in which the phosphine group has been replaced by a heterocyclic carbene, has

Scheme 5. Diastereoselective Hydrogenations with $[\text{Ir}(\mathbf{11})(\text{cod})]\text{BAR}_F^{21}$ 

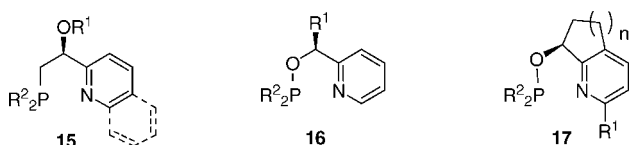
been developed by Burgess and used in Ir-catalyzed hydrogenations.²⁰ The best results have been obtained with the (1-adamantyl)oxazoline ligand **11**. For the standard substrate, (*E*)-1,2-diphenyl-1-propene, this ligand induced 98% ee, while for monoarylalkenes the ee values were lower than those recorded for the best phosphinites-oxazolines.



Using catalyst **11**, allylic alcohols and enoates bearing a stereogenic center adjacent to the C=C bond were converted to versatile precursors for the synthesis of deoxypolyketides. Hydrogenation of enoate **12** occurs with high diastereoselectivity (*anti:syn* 23:1). Using the opposite enantiomer of the catalyst, the product was formed with inverse, but lower diastereoselectivity (*syn:anti* 7.8:1). To access the *syn* stereochemistry with high selectivity, *Z*-allylic alcohol **13** was hydrogenated using (*R*)-**11** to give alcohol **14** with a *syn:anti* ratio of 34:1 (Scheme 5).²¹

Stereochemical triads could also be formed selectively by diastereoselective hydrogenation after homologation of the chain, and this method has been applied to the synthesis of a polydeoxyketide natural product.²² Burgess and co-workers also studied the hydrogenation of conjugated dienes and investigated the complex kinetics of the reaction of 2,4-diphenyl-1,3-butadiene in detail.²³

With the intention of mimicking the coordination sphere of the Crabtree catalyst more closely, we investigated a series of pyridine- and quinoline-derived ligands **15** and **16**.²⁴ As the results were encouraging, we decided to extend our studies to bicyclic analogues of type **17** because we thought that the more rigid conformation imposed by the additional ring could result in even higher enantioselectivities.



Indeed, iridium complexes incorporating the five- and six-membered ring derivatives **17** ($n = 1, 2$) proved to be efficient catalysts. Catalysts **18** and **19** with *tert*-butyl or *o*-tolyl groups on the P atom and a 2-phenylpyridine ring induced high enantioselectivities with complete conversion across a range of test substrates (Figure 1).²⁵ More importantly, we found that these catalysts are useful for enantioselective hydrogenation of purely alkyl-substituted olefins and furans (see below). The synthesis of similar ligands and application to iridium-catalyzed hydrogenation of olefins has been reported by Zhou et al.²⁶

Andersson and co-workers have investigated chiral P, N ligands **20**²⁷ and **21**,²⁸ which incorporate a rigid bicyclic backbone and an oxazole or thiazole moiety, and 2-azanobornane-oxazoline derivatives **22**.²⁹ Ligands **20** and **21** gave excellent enantioselectivities for a series of test substrates, which were in the same range as those achieved with the best oxazoline-based ligands and pyridine-phosphinites **17**. More recently, the Andersson group has extended the range of substrates to vinylsilanes,³⁰ fluorinated olefins,³¹ and enol phosphinates (Scheme 6).³²

Knochel et al. applied pyridine-based P, N ligands in the hydrogenation of methyl α -acetamidocinnamate with encouraging enantioselectivities of up to 97% ee (Scheme

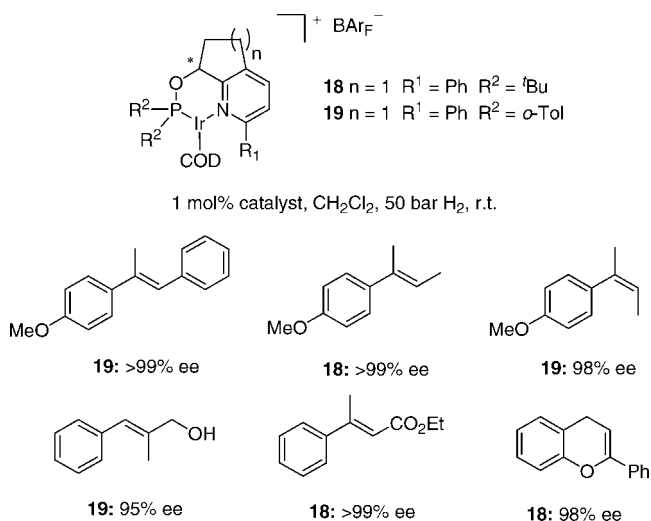
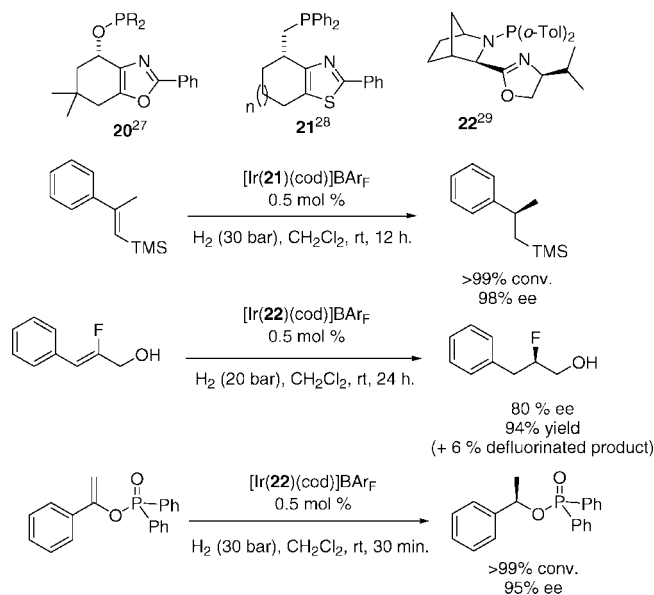


FIGURE 1. Hydrogenation with catalysts **18** and **19**.

Scheme 6. Hydrogenation of Vinylsilanes, Fluorinated Olefins, and Enol Phosphinates

7).³³ Several other groups have also developed chiral P, N ligands and applied them in Ir-catalyzed hydrogenation of olefins.^{7,34}

Tetrasubstituted olefins remain a challenging class of substrates. Buchwald and co-workers have shown that chiral zirconocene complexes can catalyze the hydrogenation of tetrasubstituted olefins with high enantioselectivity.^{5b} However, high catalyst loadings, long reaction times, and high pressures are a disadvantage of this system. We have recently identified a number of P, N ligands which have given encouraging results for this class of substrate.³⁵ Surprisingly, the structurally simple, readily accessible phosphinooxazoline **23** originally reported by Sprinz and Helmchen,³⁶ and derivatives thereof, proved to be the most efficient ligands for several substrates (Scheme 8). In other cases, ThrePHOX and SimplePHOX derivatives and for the cyclic alkene **24** the simple commercially available PHOX ligand **25** with an isopropyl substituent and a Ph₂P group were the ligands of choice. Importantly, no isomerization at the benzylic position was observed, so the relative configuration of the products was exclusively *cis*. For some substrates, the catalyst loading could be reduced to 0.1 mol % without affecting conversion and ee.

Purely Alkyl-Substituted Olefins

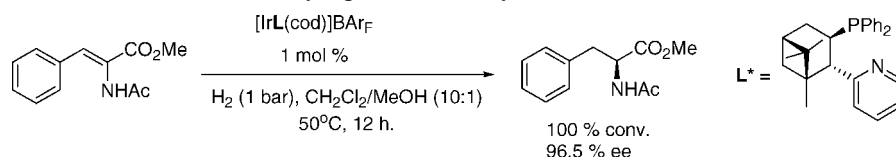
The development of catalysts that allow highly enantioselective hydrogenation of purely alkyl-substituted olefins has been a long-term goal of our research because such catalysts would considerably expand the scope of asymmetric hydrogenation as they do not require the

presence of any specific functional group or aryl substituent. With the many classes of catalysts in hand, which have been discussed in the previous sections, we decided to screen the (*E*)- and (*Z*)-olefins **28** as test substrates, the methoxyphenyl group having been introduced to facilitate product analysis by GC or HPLC on chiral columns. Most ligands that had given high enantioselectivities with alkenes containing an aryl substituent at the C=C bond performed poorly with (*E*)- and (*Z*)-**28**. However, bicyclic pyridine–phosphinite **29** gave enantioselectivities of >94% ee under optimized conditions. Consistent with previous studies, the (*E*)- and (*Z*)-isomers were converted to the products having opposite configurations (Scheme 9).³⁷

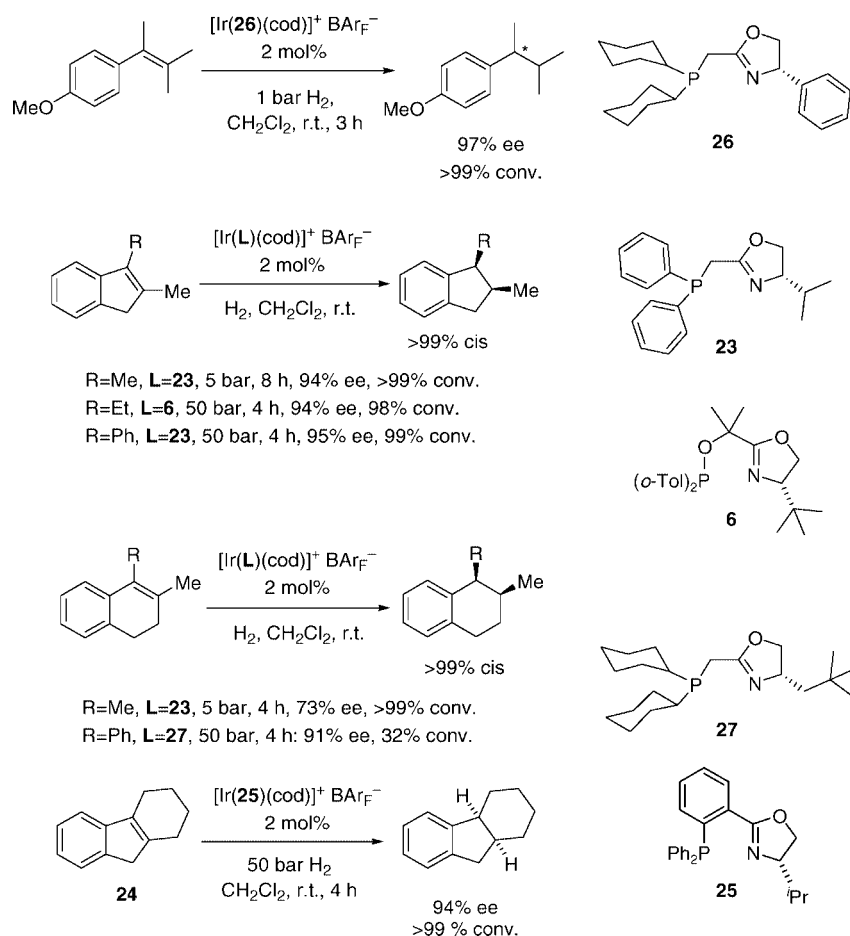
These results encouraged us to search for a suitable substrate devoid of any heteroatom or aryl group but still allowing reliable determination of the enantioselectivity after hydrogenation. Cyclohexylalkene **30** was found to meet these requirements: it was readily prepared in high isomeric purity (*E/Z* > 99:1) following published procedures, and the ee of the hydrogenation product **31** could be determined by GC on a chiral column.^{37a} This substrate proved to be more demanding than alkenes (*E*)- and (*Z*)-**28**, and most ligands studied gave ee values below 30%. We identified only two ligands, both bicyclic pyridine–phosphinites, that induced enantioselectivities of >80% ee. The ee value of 97% obtained with ligand **18** under optimized conditions clearly shows that highly enantioselective hydrogenation of purely alkyl-substituted olefins is possible.

To evaluate our catalysts in the reaction of a structurally more complex substrate, we studied the hydrogenation of γ -tocotrienyl acetate (**32**).³⁷ This reaction involves reduction of three C=C bonds and creates two new stereocenters in a single step. Because the two prochiral C=C units are both (*E*)-configured, the sense of asymmetric induction at the two reaction sites is expected to be the same, leading to either the (*RR*)- or (*SS*)-configuration depending on the absolute configuration of the catalyst. Whereas oxazoline-based ligands showed disappointingly low stereoselectivities, imidazolines and pyridine-phosphinites gave encouraging results. The best stereoselectivity was achieved with the iridium catalyst derived from pyridine–phosphinite ligand **29**, which gave almost exclusively the natural (*RRR*)-isomer of γ -tocopheryl acetate (**33**) (Scheme 10).

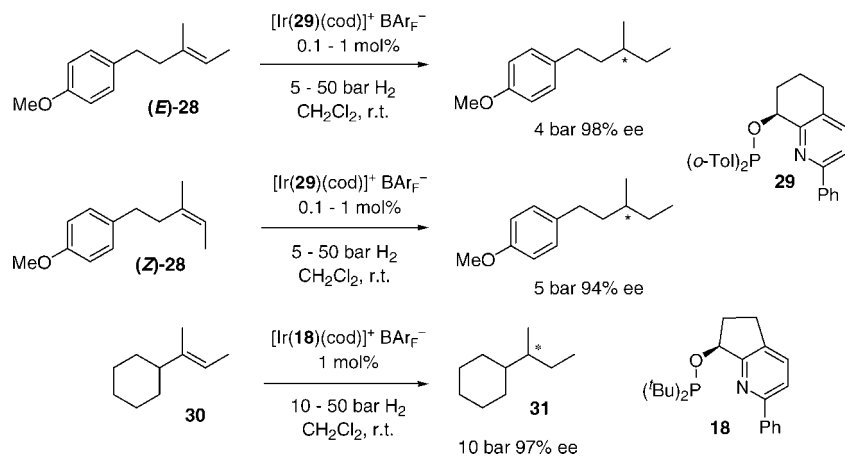
This transformation that generates two stereogenic centers in a single step with virtually perfect stereocontrol demonstrates the potential of this class of catalysts for the stereoselective synthesis of complex molecules. Moreover, because these catalysts do not require the presence of any particular substituents near the C=C bond, they should be applicable to a much wider range of olefins than Rh

Scheme 7. Hydrogenation of Methyl α -Acetamidocinnamate

Scheme 8. Hydrogenation of Tetrasubstituted Olefins



Scheme 9. Hydrogenation of Purely Alkyl-Substituted Olefins



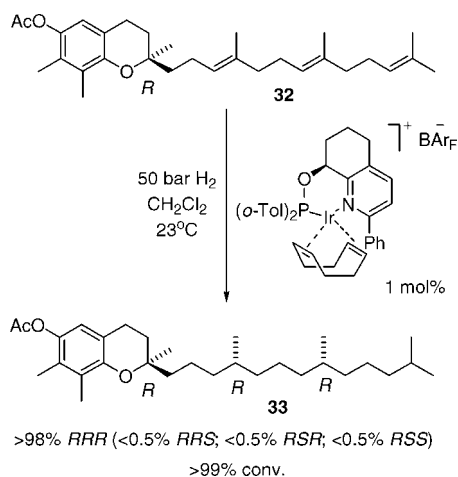
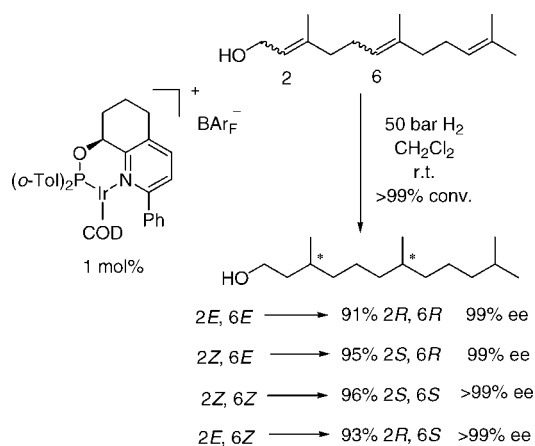
or Ru catalysts. The functional group tolerance has not been studied in detail yet, but from the range of olefins we have investigated, we know that keto, ester and amide functions may be present in the substrate and do not react. However, strongly coordinating groups such as pyridyl or amino substituents inhibit the reaction.

By changing the geometry at the double bonds in di- or polyenes, it is possible to control both the absolute and relative configuration. This is demonstrated by the hydrogenation of the four stereoisomers of farnesol. Hydrogenation of (*2E,6E*)-farnesol using catalyst **29** gives 91%

of the (*2R,6R*) product with 99% ee. By changing the double-bond geometry, the opposite absolute configuration can be established due to the high inverse facial selectivity of the catalyst. In this way all four stereoisomers of the product are accessible with high levels of selectivity using the same catalyst (Scheme 11).³⁸

Hydrogenation of Heteroaromatic Substrates

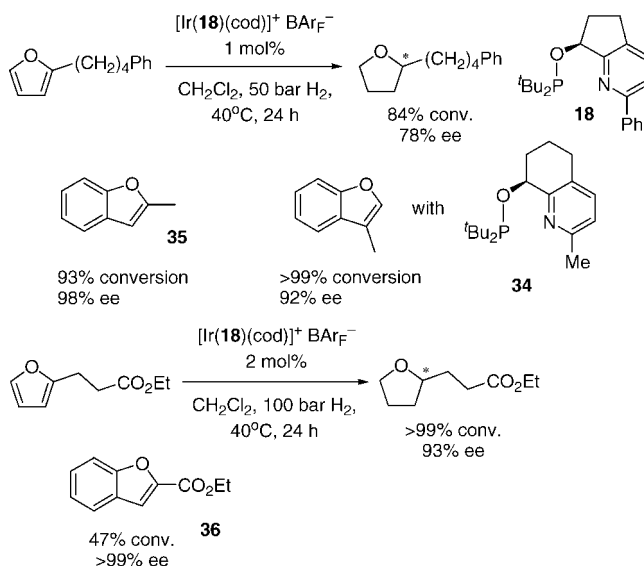
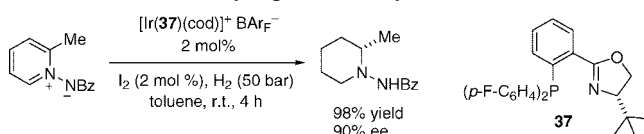
During previous investigations of furyl-substituted alkenes, we had found that with certain Ir complexes derived from

Scheme 10. Hydrogenation of γ -Tocotrienyl Acetate**Scheme 11. Enantio- and Diastereoselective Hydrogenation of Farnesol Stereoisomers**

oxazoline–dialkylphosphinites both the olefinic C=C bond and the furan π system were reduced.^{37b} The stereoselectivities were, however, moderate. Catalysts incorporating ligands **18** and **34** proved to be more efficient and induced good to excellent enantioselectivities in the hydrogenation of a series of substituted furans and benzofurans. As expected, the benzene ring of substrates **35** and **36** was not reduced (Scheme 12).³⁹

Ligands with bulky, electron-rich (^tBu)₂P groups were found to be best suited for this class of substrates. Because of the low reactivity of the furan and benzofuran π systems, elevated temperatures and relatively long reaction times were necessary. The benzofuran carboxylate ester **36**, in particular, reacted only sluggishly, albeit with near perfect enantioselectivity. Overall, ligands like **18** and **34** open up an attractive enantioselective route to tetrahydrofuran and benzodihydrofuran systems, which are structural motifs found in many natural products and biologically active compounds.

Charette and Legault⁴⁰ have reported the enantioselective hydrogenation of *N*-iminopyridinium ylides as an approach to chiral piperidine derivatives. Initial experiments using an Ir–BINAP catalyst in the presence of a catalytic amount of iodine gave high conversion, albeit with low enantioselectivity. Catalyst screening showed that

Scheme 12. Hydrogenation of Furans and Benzofurans**Scheme 13. Hydrogenation of Pyridine Derivatives**

iridium complexes derived from PHOX ligands were the most promising in terms of enantioselectivity. The di(4-fluorophenyl)phosphino derivative **37** was found to be optimal in terms of enantioselectivity and yield (Scheme 13).

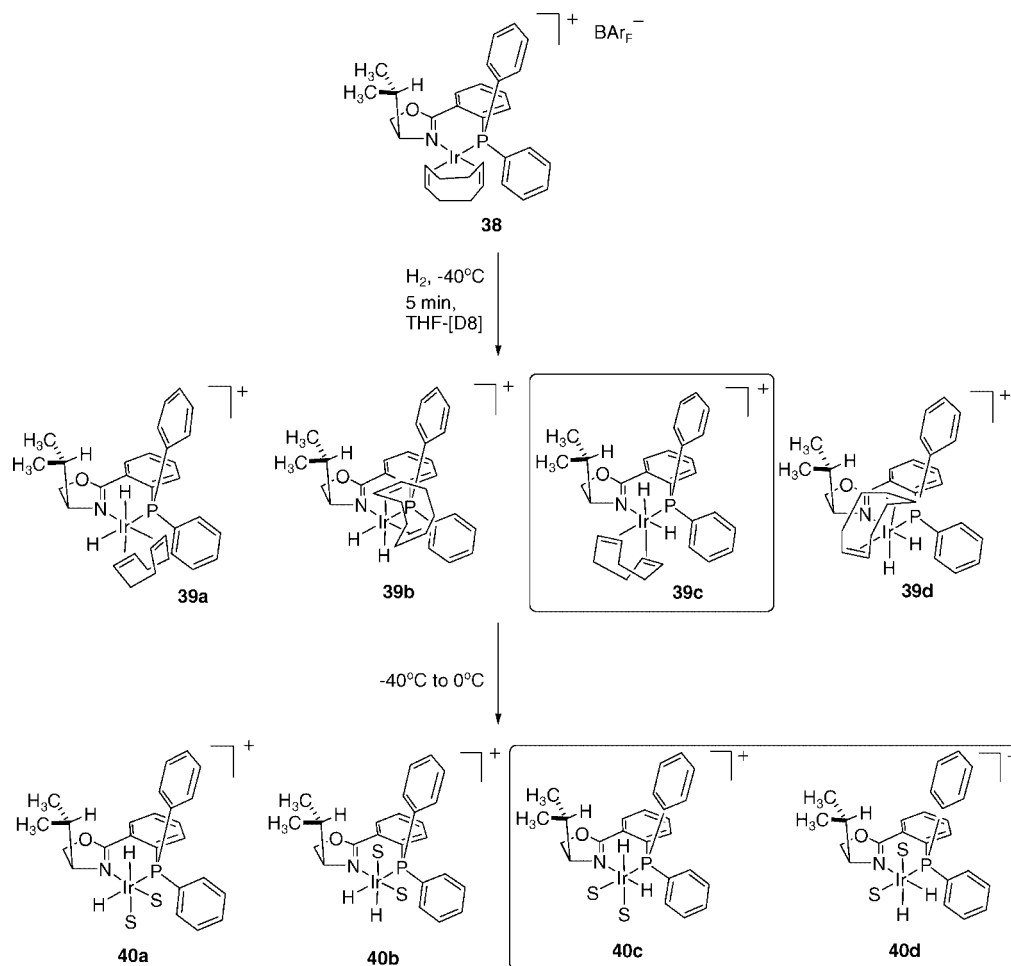
The products can be converted to the corresponding piperidine derivatives by a facile N–N bond cleavage (>85% yield) using either Raney nickel or lithium in ammonia. Although enantioselectivity and scope need to be improved, these results are important, as for the first time a promising chiral catalyst has been found for the asymmetric hydrogenation of prochiral pyridine derivatives.

Mechanistic Studies

In early work of Crabtree and co-workers, olefin dihydride intermediates formed during hydrogenation of cyclooctadiene using [Ir(pyridine)(PCy₃)(COD)]PF₆ in dichloromethane at 0 °C were detected by NMR spectroscopy.⁴¹ In a more recent, complementary study we found that when [Ir(PHOX)(COD)]BAR_F complex **38** was treated with hydrogen at –40 °C for 5 min in [D₆]-THF, olefin dihydride intermediates were formed which were characterized by NMR spectroscopy. Two new signals appeared in the hydride region that were assigned to a single dihydride complex **39c** formulated as [Ir(PHOX)(H)₂(COD)]BAR_F (Scheme 14).⁴²

The predominance of isomer **39c** over **39a** or **39b** is consistent with Crabtree's findings, who convincingly demonstrated that in the reaction of H₂ with [Ir(pyridine)(PR₃)(COD)]PF₆ the formation of an Ir–H bond trans to the N ligand is electronically favored.⁴³ Highly selective formation of isomer **39c** results from H₂ addition

Scheme 14. Hydrogenation of Complex 38



to the more sterically encumbered face of the starting complex because dihydrogen addition to the sterically more accessible face, leading to isomer **39d**, would build up steric strain between the chelating COD ligand and the isopropyl group in the oxazoline ring and the pseudoaxial *P*-phenyl group. When the solution containing complex **39c** was warmed to 0°C under hydrogen, gradual consumption of isomer **39c** was observed, accompanied by the appearance of two new hydride complexes **40c** and **40d** with concomitant formation of cyclooctane.

We have carried out DFT (density functional theory) calculations on the complete structures of complexes shown in Scheme 14. The fully minimized structures of the four possible *cis*-dihydrides, which can be formed by oxidative addition of H_2 to $[\text{Ir}(\text{PHOX})(\text{COD})]^+$, were calculated. The most stable structure corresponded to the reaction product **39c** that was shown to be formed exclusively in the NMR experiment. Isomers **39a** and **39d** were 10.6 and 4.9 kcal/mol higher in energy, whereas for isomer **39b** no stable chelate structure could be located due to severe steric interactions which prevent the formation of an Ir–N bond. The four possible $[\text{Ir}(\text{PHOX})(\text{H})_2(\text{solvent})_2]^+$ complexes **40** resulting from hydrogenation of the cyclooctadiene ligand were also examined, and again the two most stable structures corresponded to the isomers observed in the NMR experiments. These results show that steric interactions are very

important and may dominate over electronic factors. Consequently, computational studies of potential reaction pathways should be based on full catalyst and substrate structures rather than simple model systems.

Brandt, Hedberg, and Andersson proposed a catalytic cycle via Ir^{III} and Ir^{V} intermediates, in which an additional dihydrogen molecule, coordinated to an Ir–dihydride, undergoes oxidative addition during migratory insertion.⁴⁴ Since an extremely truncated model for the ligand and substrate (ethylene) was used, which neglected the severe steric interactions present in the actual catalysts, it seems dangerous to rule out an Ir^{I} – Ir^{III} cycle. From subsequent calculations on the full catalyst and substrate structures, which were based on the postulated Ir^{III} – Ir^{V} cycle, a simple qualitative quadrant model was derived for rationalizing the observed enantioselectivities. Burgess, Hall, and co-workers⁴⁵ also reported DFT calculations on the complete ligand and substrate structures for an Ir^{III} – Ir^{V} catalytic cycle which reproduced the correct selectivity order for three different substrates. On the other hand, Chen and Dietiker reported an experimental investigation of the hydrogenation of styrene with $[\text{Ir}(\text{PHOX})(\text{COD})]\text{BAR}_f$ in the gas phase by means of electrospray ionization tandem mass spectrometry, which suggests that the catalytic cycle proceeds by way of Ir^{I} and Ir^{III} intermediates.⁴⁶

Taking into account the available computational and experimental data, it is still too early to draw definitive

conclusions regarding the mechanism of Ir-catalyzed asymmetric hydrogenation. Further experimental work, especially on reactions in solution under real catalytic conditions, is clearly desirable.

Conclusion

Iridium catalysts with chiral P, N ligands have emerged as a new class of highly efficient catalysts for asymmetric hydrogenation, which are largely complementary to rhodium- and ruthenium-diphosphine catalysts. A variety of substrates, for which no suitable catalysts were available before, can now be hydrogenated with excellent enantioselectivity. So far, iridium catalysts have been mainly applied to aryl-substituted unfunctionalized olefins. However, high enantioselectivities have also been obtained with α,β -unsaturated carboxylic esters. Ruthenium and rhodium complexes, on the other hand, are the catalysts of choice for α,β -unsaturated carboxylic acids. For allylic alcohols, both Ru and Ir complexes are suitable catalysts, whereas allylic acetates and other protected allylic alcohols are the domain of Ir catalysts. In addition, Ir catalysts have also proved suitable for the asymmetric hydrogenation of certain enol ethers like flavenes and the enantioselective reduction of imines,⁴⁷ a reaction which is not covered in this Account. Asymmetric hydrogenation of furans, benzofurans, and pyridine derivatives is another promising area of application, which deserves further investigation. Most importantly, the discovery of Ir catalysts for the enantioselective hydrogenation of purely alkyl-substituted olefins has substantially expanded the application range of asymmetric hydrogenation and opened up new possibilities for the synthesis of chiral compounds.

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