Catalytic Homogeneous Asymmetric Hydrogenations of Largely Unfunctionalized Alkenes

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Received May 3, 2005

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1. Introduction

Despite decades of research on homogeneous catalysts for asymmetric hydrogenations, most of the alkenes studied have some functionality that can coordinate strongly to a metal. Comparatively few "largely unfunctionalized alkenes" have been examined, and the ones that have can be classified in a few narrowly defined categories. Consequently, no practical methods have been developed for asymmetric hydrogenations for a large group of alkene types.

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Before going further, we must define the term "largely unfunctionalized alkene" in the context of this review. Interpretations of this term hinge around how rigorously the word "unfunctionalized" is defined. Purists would argue these are alkenes in which the carbon−carbon double bonds are connected only to totally aliphatic groups, for example, **A** and **B**

10.1021/cr0500131 CCC: $53.50
Published on Web 08/24/2005

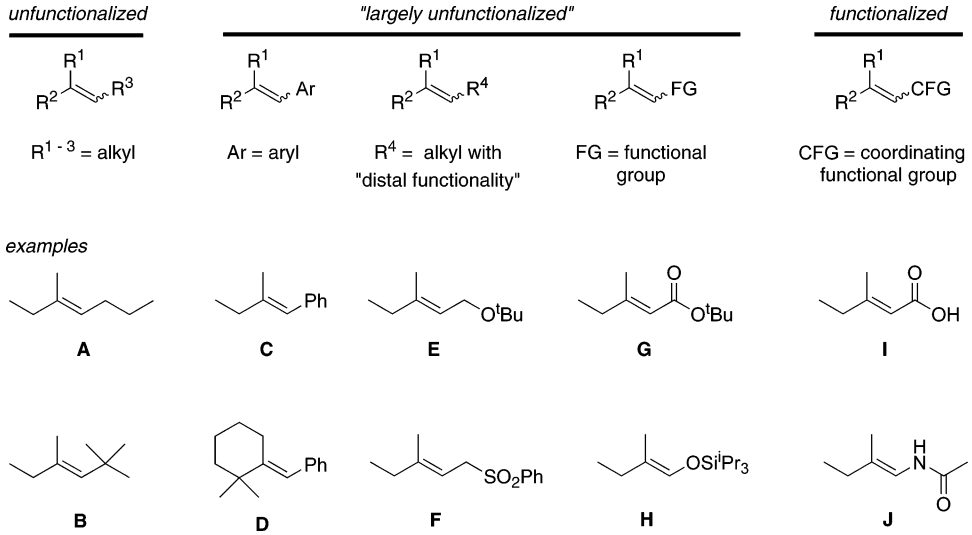


Figure 1. "Functionalized alkene" is not a "black and white" expression that either applies or does not. Many alkenes fall into a gray area.

(Figure 1). If that interpretation were adopted here, this review would be very short, because no practical methods based on homogeneous catalysts have been developed for asymmetric hydrogenations of such alkenes. What if the definition of "largely unfunctionalized" were relaxed to include phenyl groups and other benzenoid rings, for example, **C** and **D**? Of course, aromatic units are functional groups, and they can form stable complexes with organometallic catalyst precursors. However, in most catalytic hydrogenation reactions, aryl-substituents do not form stable, well-defined bonds with metal centers, so from the perspective of catalytic cycles, aryl groups are usually not functional. They certainly occupy space and sometimes become involved in relatively weak interactions (e.g., π-stacking), but usually they are not intimately involved with the metal. Somewhat more functionalized alkenes have other groups that are not strongly coordinating and that occupy positions where they do not significantly influence the electronic nature of the alkene, for example, **E** and **F**. If a functional group is directly conjugated with an alkene and does affect its reactivity, as in **G** and **H**, then the olefin is more functionalized. Alkenes such as **I** and **J** have functional groups that often do bind to metal centers and orient the substrates about metal centers in catalytic intermediates; from the standpoint of catalytic hydrogenations, they are definitely functionalized.

The term "largely unfunctionalized alkenes" is dangerously vague to use in a *Chemical Review* because it can encompass a vast range of substrates. That, however, is the point. It is only at the level of functionality of alkenes such as **I** and **J** that chemists currently tend to recognize good substrates for asymmetric hydrogenation reactions. Alkenes **A**−**H**, and many compounds like them, cannot be regarded as routine substrates for homogeneous asymmetric hydrogenation reactions. There is an intellectual vacuum in the literature with respect to asymmetric hydrogenations of largely unfunctionalized alkenes. This review is to outline the true substrate scope for those alkenes in asymmetric hydrogenations and to highlight areas for which further research is justified. The closest review to this one is by Halterman in *Comprehensive Asymmetric Catalysis.*[1]

The fact that asymmetric hydrogenations of largely unfunctionalized alkenes are not as well explored as functionalized ones should not be interpreted to mean they are less important. It is true that totally unfunctionalized alkenes can only be hydrogenated to chiral hydrocarbons, there are not a vast number of valuable molecules of this kind, and chiral hydrocarbons usually cannot be used as chirons to prepare other materials because there is no functional group to build on. However, the real significance is that methods are required for asymmetric hydrogenations of alkene functionalities that are either remote or are proximal only to functional groups that have weak coordinating characteristics. If there were a general solution to this problem then that would be a major contribution to synthetic methodology.

2. General Challenges with Respect to Asymmetric Hydrogenations of Largely Unfunctionalized Alkenes

2.1. Determination of Enantioselectivities

Convenient, accurate methods for determination of product enantiomeric excesses are required if asymmetric hydrogenations of largely unfunctionalized alkenes are to be investigated. Chiral gas chromatography (GC), high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), or NMR shift reagents tend to separate enantiomers of organic compounds that have polar groups and even ones that have only aromatic substituents. Consequently, determination of enantiomeric excesses is not a serious problem for hydrogenation of many types of functionalized and some largely unfunctionalized alkenes. It is, however, a problem for chiral alkanes derived from alkenes that have only aliphatic substituents. There are some reports of separations of enantiomers of a few selected chiral alkanes,[2] but these tend to be from analytical researchers who focus on such difficult problems and to feature

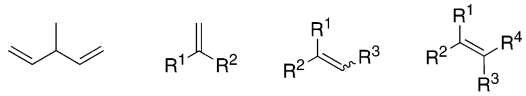


Figure 2. Common prochiral alkenes.

apparatus and techniques that most organic chemists would not regard as convenient. This is certainly a major reason why reports of attempted enantioselective hydrogenations of truly unfunctionalized alkenes rarely emerge in the open literature.

2.2. Substrate and Catalyst Scope

The second general challenge in this area is related to the structures of the substrates themselves and the types of catalysts available. However, the nature of that challenge varies with the substrate type. Common prochiral alkenes can be classified as symmetrical, 1,1-di-, tri-, and tetrasubstituted alkenes, **K**−**N** (Figure 2).

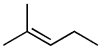
Dienes that contain the core structure **K**, and similar prochiral dienes, are intriguing potential substrates for asymmetric hydrogenations, but they have not been explored. Lack of research on asymmetric hydrogenations of these substrates is almost certainly a reflection of the degree of difficulty of the problem. Effective catalysts would have to react significantly faster with one enantiotopic alkene unit, and hydrogenation of the other alkene group has to be slow enough to enable the reaction to be stopped near the half-reduction stage. This would require a very special catalyst, particularly if the substrate has no other functionality to preferentially bring one enantiotopic alkene into the proximity of the metal.

For 1,1-disubsituted alkenes, **L**, the problem is similar: these tend to be quite difficult substrates for asymmetric transformations. One way to rationalize this is to imagine that if the methylene group can freely exchange positions with one of the substituents R^1 or R^2 in the chiral environment formed by a catalyst, then the face selectivity is reversed. This factor is more important if the substituents R^1 and R^2 have no coordinating functionalities. Consequently, just as for substrates **K**, special catalyst structures are required to achieve this; some *are* available, however.

The major problem for asymmetric hydrogenation of tri- and tetrasubstituted alkenes **M** and **N** is different. These are relatively hindered alkenes. In the absence of coordinating functionality to direct catalysts to the reactive site, alkenes such as these tend to be too sterically shielded by their own substituents to allow access of homogeneous metal complexes. A consequence of this is that even for *achiral* systems there are only a few types of homogeneous catalysts that will mediate hydrogenation of largely unfunctionalized tri- and tetrasubstituted alkenes. Thus, there are relatively few conceptual starting points for chiral modifications. This is important because probably most, and certainly a large proportion, of the useful largely unfunctionalized alkene substrates for asymmetric hydrogenations will be tri- and tetrasubstituted alkenes. The next section is devoted to *achiral* catalysts for homogeneous hydrogenations of tri- and tetrasubstituted alkenes, to outline what these starting points may be.

Table 1. Hydrogenation of Tri- and Tetrasubstituted Alkenes with $Co(CH_3(CH_2)_2CHEtCO_2)_2$, 1a

alkene $\xrightarrow{3.4\ atm\ H_2}$ alkane

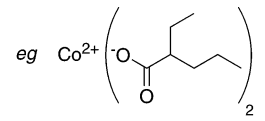
alkene	catalyst (mol %)	conversion (%)	time (min)	TOF (h^{-1})
	0.2	44	90	146
	0.5	92	60	184
	0.5	37	90	42

3. Achiral Catalysts for Homogeneous Hydrogenations of Tri- and Tetrasubstituted Alkenes

There are relatively few homogeneous catalysts that will hydrogenate largely unfunctionalized tri- and tetrasubstituted alkenes. The main ones that will be considered in this section are catalysts **1**−**8** (see subsequent text for diagrams). Briefly, these include Ziegler-type systems **1** formed from transition-metal species activated with alkyl-lithium or aluminum compounds, some iridium complexes, notably Crabtree's catalyst **2**, and the *N*-heterocyclic carbene analogues **3** and **4**. Less important examples are derivatives of Wilkinson's catalyst **5**, notably the rhodium diphosphine complex with a carborane counterion **6**, some rhodium and iridium diiminate complexes **7**, and Shvo's ruthenium complex **8**. Hydrogenation activity for trisubstituted alkenes has also been mentioned for $(Cp^*IrCl)_2$[3] and the cluster compound $Pt_2Ir_2(\mu\text{-}CO)_3(CO)_4(PPh_3)_3$;[4] however, the data for these catalysts are limited and what is available is markedly inferior to Crabtree's catalyst.

"Ziegler-type" systems, ie transition-metal salt and metal-alkyl reducing agent

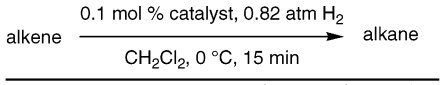
1

eg Co^{2+}  / ^{n}BuLi

1a

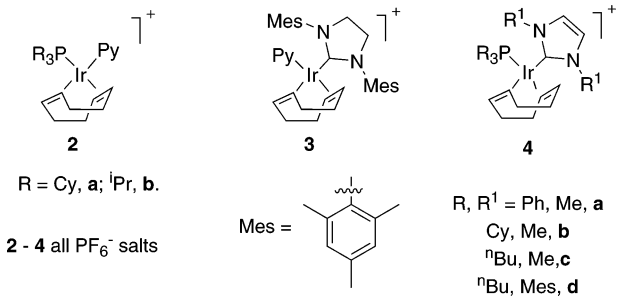
Most Ziegler-type catalysts[5] are only effective for hydrogenations of less hindered mono- and disubstituted alkenes and have little activity toward tri- and tetrasubstituted alkenes.[6,7] However, the cobalt salt, $Co(CH_3(CH_2)_2CHEtCO_2)_2$, **1a**, has been reported to catalyze hydrogenation of tri- and tetrasubstituted alkenes with moderate to high conversions under mild reaction conditions when organic lithium reagents were used as the cocatalyst (Table 1).[8] It is tempting to speculate that many of these catalysts might be heterogeneous. In many cases this may be so, but Buchwald's work on chiral titanium and zirconium cyclopentadienyl derivatives (see next section) is similar and affords high enantioselectivities that are uncharacteristic of heterogeneous reactions.

Table 2. Hydrogenation with $Ir(COD)(P^iPr_3)Py\cdot PF_6$, 2b



alkenes	conversion (%)	maximum TOF (h^{-1})
	100	8300
	100	4500
	35	3800
	< 40	4000

The most important homogeneous achiral catalysts for hydrogenation of hindered unfunctionalized alkenes are Crabtree's catalysts, **2**: $Ir(COD)L_1L_2\cdot PF_6$, where L_1 = tertiary phosphine, L_2 = pyridine, or $L_1 = L_2$ = tertiary phosphine.[9,10] Complex **2a** is often called "Crabtree's catalyst", but this understates his contributions since Crabtree was instrumental in the development of several effective iridium complexes. When complex **2b** was subjected to atmospheric H_2 in nonpolar solvents such as CH_2Cl_2 at room temperature, it was efficient for hydrogenation of mono-, di-, tri-, and tetrasubstituted alkenes (Table 2). Turnover frequencies (TOFs) of up to 4000 h^{-1} were obtained for 2,3-dimethylbut-2-ene (0 °C and just under 1 atm H_2 pressure). This is remarkable considering that tetrasubstituted alkenes are very difficult to hydrogenate due to steric hindrance. The disadvantage of this catalyst is competitive degradation to inactive dimer or trimer in the presence of H_2, especially when hindered substrates are used. This explains how low conversion of tri- or tetrasubstituted alkenes were reported even when very high *initial* TOFs were observed. This problem can be partially solved by addition of catalyst in batches.

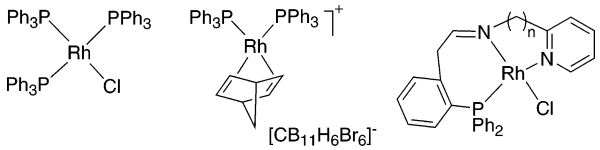


Recently, analogues of Crabtree's catalyst have been produced in which either the phosphines or the pyridine ligand have been substituted with electron-rich *N*-heterocyclic carbenes.[11,12] Catalyst **3**, which represents a phosphine-for-carbene switch, was somewhat less active than Crabtree's **2a**. However, the thermostability of the catalyst was improved, which enabled the hydrogenation of hindered substrates with high conversions at elevated temperature.[12] Complexes with comparable activities were identified when the pyridine was substituted with a carbene, this time of the aromatic imidazolylidine kind.[11]

Table 3. Hydrogenation of Two Alkenes Using $Rh(PPh_3)_2(NBD)\cdot CB_{11}H_6Br_5$, 6, or $Ir(Py)(PCy_3)(Cod)\cdot PF_6$, 2a

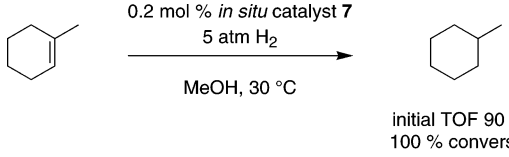
alkenes	catalyst	time (h)	yield (%)	TOF (h^{-1})
	**6**	5	95	19
	2a	5	100	20
	**6**	24	68	3
	2a	16	95	6

Wilkinson's catalyst **5**[13−15] is ineffective for hydrogenations of tri- and tetrasubstituted alkenes. For instance, relative reaction rates for this catalyst relative to cyclohexene have been reported to be 34 times less for 1-methylcyclohexene, and 100 times slower for 1,4-dimethylcyclohexene. No reactivity was observed for tetrasubstituted unfunctionalized alkenes.



Complex **6** is a distant relative of Wilkinson's catalyst that is positively charged and has a large, poorly coordinating counterion. Counterions can influence the reactivity of hydrogenation catalysts. Rifat et al. reported that **6** is an effective catalyst for hydrogenation of tri- and tetrasubstituted alkenes.[16] Comparable yields were observed for hydrogenation of 1-methycyclohexane and 2,3-dimethylbut-2-ene relative to Crabtree's catalyst $Ir(Py)(PCy_3)(COD)\cdot PF_6$ **2a** under the same conditions (Table 3).

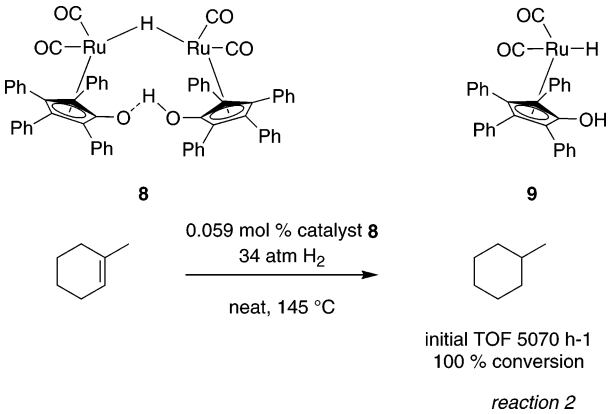
Osborn and co-workers reported that complexes **7** were active for hydrogenation of 1-methylcyclohexene.[17] The catalyst prepared in situ by using $\{Rh(COE)_2Cl\}_2$ and corresponding ligand was more reactive; an initial TOF of 90 h^{-1} and complete conversion were observed (reaction 1). Catalyst **7a** was more reactive than the homologous chelate **7b**, and the corresponding iridium systems were described as significantly less active. We regard these complexes as a useful starting point for the design of chiral analogues for asymmetric hydrogenations.



reaction 1

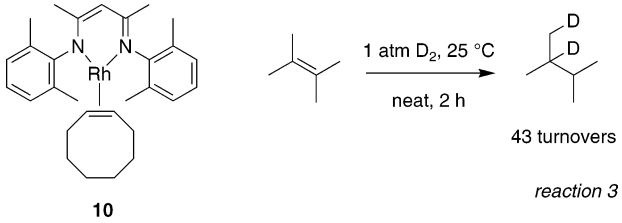
Shvo's complex **8**[18] is best known for hydrogenations of ketones and aldehydes, but some data for catalytic hydrogenations have been reported. This robust, air-stable complex was shown to reduce 1-methylcyclohexane under elevated dihydrogen pres-

sures and high temperature (reaction 2). At temperatures less than 145 °C, the reaction rate of the hydrogenation is diminished, probably because the reactive monomers **9** recombine into the inactive dimeric complex **8**.



reaction 2

One study illustrates pitfalls that may be encountered when trying to modify achiral hydrogenation catalysts to find effective asymmetric ones. The rhodium β-diiminate complex **10** catalyzes the hydrogenation of 1-methylcyclohexene and 2,3-dimethylbut-2-ene.[19] However, the 1,2-dideutero-alkane was formed *exclusively* when the latter substrate was deuterated (reaction 3). This indicates, at least for that particular substrate, that double bond migration may precede the reduction step, so what is really observed is addition of H_2 to a less hindered alkene than the starting material. For scientists wishing to design asymmetric hydrogenation catalysts, this is critical information. However, for those investigating achiral catalysts, this type of observation is somewhat less important, and tests for double bond migration are not usually performed.



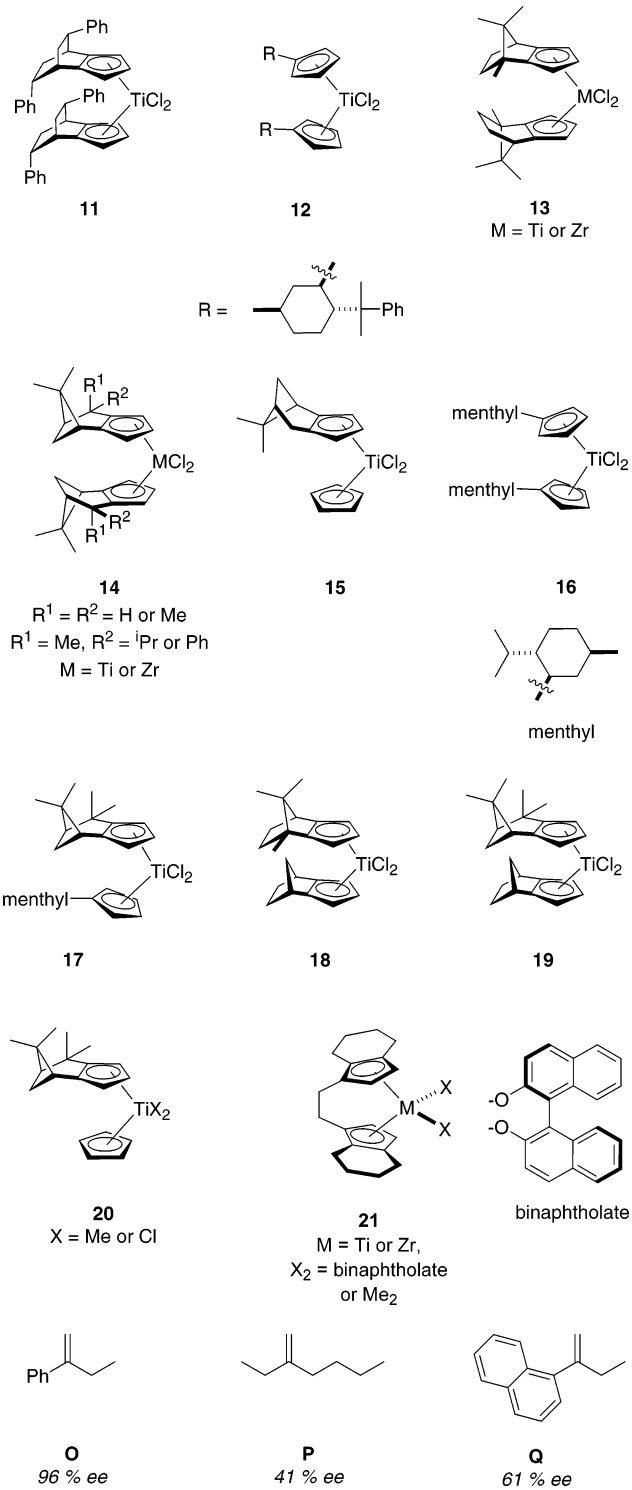
reaction 3

The next section describes how catalysts loosely related to the Ziegler-type were applied in asymmetric hydrogenations of unfunctionalized alkenes, and the one after that discusses chiral analogues of Crabtree's catalysts. We have noted that the rhodium complexes **7** appear to be useful leads for development of asymmetric catalysts. It might also be possible to prepare chiral analogues of the Shvo's system **8**, but if the rate-limiting step in applications of this catalyst is dissociation of the dimer, then very little enantioface discrimination may be possible at temperatures around 145 °C. In any case, salient tests for double bond migration have not been reported for catalysts **2** and **8**. One conclusion therefore emerges at this stage: there are very few achiral catalysts that mediate hydrogenations of tri- and tetrasubstituted alkenes, and fewer still that are unexplored with respect to chiral modifications.

4. Titanium-, Zirconium-, and Lanthanide-Based Metallocene Catalysts

4.1. Titanocene- and Zirconocene-Based Catalysts

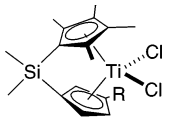
Early work on chiral metallocene catalysts for asymmetric hydrogenations features work from the groups of Kagan,[20] Vollhardt (**11**, **12**, and **13** (M = Zr or Ti),[21,22] Paquette (**13** − **20**),[23,24] Waymouth (**21**)[25]



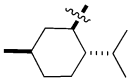
and others.[26,27] Typically, these catalyst precursors were activated using *n*-butyllithium to generate low-valent Ti or Zr, though Waymouth and co-workers

used methyl aluminoxane.[25] Throughout these studies, only three prochiral alkenes were studied; specifically, substrates **O**−**Q**. The best enantioselectivities reported are up to 96% as indicated; however, in every case these were *determined via optical rotations.* In some cases, the specific rotations of the alkanes are small and nearly always much less than those of the complexes. Consequently, if the samples were contaminated with a trace of the catalyst, this would skew the data considerably. Even in the absence of such contamination, optical rotations are notoriously capricious and inaccurate. In most of these studies, turnover number (TON), TOF, and conversions were not determined, but the data that were given indicate that these parameters were not exceptionally good. However, the conversion data by Waymouth et al. for the Brintzinger-type[28] systems, M(EBTHI)X_2, **21** (where M = Zr and EBTHI = ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl), seem to indicate that these catalysts were perhaps the most active in the series **11**−**21**. Waymouth observed that monosubstituted alkenes undergo polymerization in the presence of these catalysts, whereas more hindered alkenes are hydrogenated. They were unable to find conditions under which the corresponding dichlorides, that is, X = Cl, could be used as a catalyst precursor.

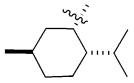
Interest in titanocene and zirconocene hydrogenation catalysts diminished after Buchwald's studies, but there has been some activity more recently. Thus, White and co-workers used the titanocene complexes **22** to hydrogenate substrate **O** (ee's up to 60% determined by rotation).[29]



22
R = menthyl or neomenthyl



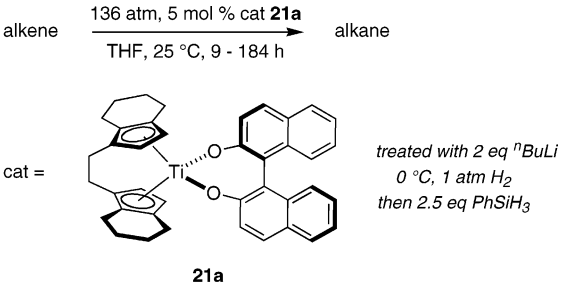
(-)-menthyl



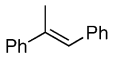
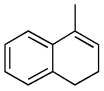
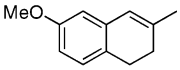
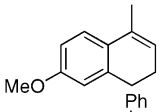
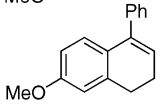
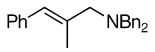
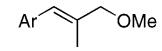
(+)-neomenthyl

Buchwald and co-workers have made important contributions in this area.[30,31] Their first main discovery related to the titanocene complex **21** where X_2 = binaphtholate as indicated. As noted above, Waymouth et al. had previously used the corresponding *zirconocene activated by methylaluminoxane*; their study was restricted to deuteration of monosubstituted alkenes (which were mostly polymerized anyway) and 2-phenyl-1-butene, **O**, which did not polymerize to any significant extent, but only gave 36% ee. Buchwald et al. made two modifications to the protocols used in these hydrogenation reactions: they used the *titanocene* analogue (**21**, M = Ti, X_2 = binaphtholate), activated with *n*-butyllithium and stabilized with phenylsilane, and they focused on trisubstituted alkenes. Further, in eight of nine cases, they managed to determine enantioselectivities via analytical HPLC using a chiral support. Table 4 outlines a comprehensive list of thesubstrates reported.[30] The substrates were primarily *E*- and cyclo-*Z*-alkenes. It was observed that the *E*-alkenes are reduced faster, under less H_2 pressure, and usually

Table 4. Hydrogenation of Trisubstituted Alkenes Using A Chiral Titanocene Catalyst, 21a



21a

entry	alkene[a]	yield (%)	*ee* (%)
1		94	> 99
2[a]		79	95
3[a]	 *E*/*Z* 64/36	80	31
4		70	83
5		77	92
6[b]		70	93
7		87	87
8		75	95
9[a,c]		86	94

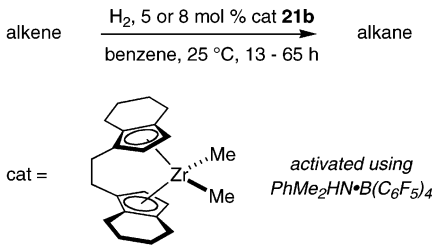
[a] Ar = 4-$MeOC_6H_4$. [b] 122 atm H_2. [c] 163 atm H_2.

with higher enantioselectivities. The methoxy-substituents in many of the substrates were included to facilitate chiral HPLC analyses but were not thought to be necessary for the high enantioselectivities. Corresponding deuteration studies on the *E*-1,2-diphenylpropene substrate (cf. entry 1) proved that the hydrogens from the silane were not delivered to this alkene to any significant extent and that deuterium added to the alkene carbons, that is, double bond migration events, did not precede the addition.

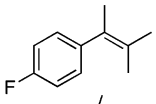
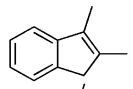
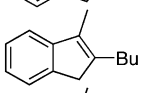
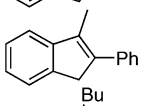
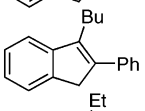
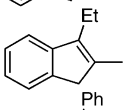
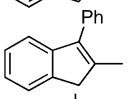
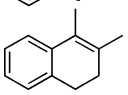
Later Buchwald's group returned to the zirconocene systems, similar to those originally used by Waymouth,[25,32] but activated with an ammonium tetra(pentafluorophenyl) group as indicated in Table 5.[31] Table 5 is a comprehensive list of the substrates reported. Seven of the eight substrates were cyclic tetrasubstituted systems. In one case, entry 8, a significant amount (9%) of *cis*-hydrogenation of the aromatic rings was observed.

Buchwald's work with the titanocene and zirconocene systems **21a** and **21b** stands alone among all those performed with chiral metallocene complexes because an extensive number of substrates was studied with reliably determined enantiomeric excesses. The hydrogenations shown for the tetrasubstituted alkenes (Table 5) are, to this date, the

Table 5. Hydrogenation of Tetrasubstituted Alkenes Using A Chiral Zirconocene Catalyst, (EBTHI)$ZrMe_2$ (21b)/$PhMe_2NH{\cdot}B(C_6F_5)_4$[31]



21b

entry	alkene	P (H_2) (atm)	yield (%)	*ee* (%)
1		116	77	96
2		116	87	93
3		5.4	96	92
4[a]		68	89	99
5		108	94	98
6[b]		116	95	52
7		136	94	78
8		136	91	92

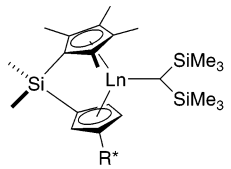
[a] cis/trans = 98:2. [b] cis/trans = 95:5.

best data set reported for that particular substrate type. However, the methodology as it stands is unlikely to find widespread applications, for several reasons. First, the catalyst loadings are high, typically in the 5 mol % range; hence the approach is not economical for larger scale work and separation from catalyst residues becomes a consideration. Second, the catalyst systems are extremely air sensitive (requiring glovebox techniques), so they are inconvenient to use. Third, high pressures and long reaction times tend to be involved. The H_2 pressures used mostly exceed those that are safely held in simple stainless steel reactors; hence the equipment required is somewhat less widely available, especially since the reactors must be loaded under rigorously anaerobic conditions. Finally, even though a total of 17 substrates were reported, it is hard to make the case that these particular products are frequently required in organic syntheses.

Buchwald and co-workers proposed that their catalysts operate via formation of metallocene hydrides, insertion of alkenes to give metal alkyls, then hydrogenolysis to regenerate the metal hydrides and form the products. That model is consistent with the configuration of the products for which absolute stereochemistries were determined, but it was not supported by any other evidence. Almost simultaneously, however, Marks and co-workers were studying metallocenes based on lanthanides, and focusing on mechanistic issues. Their work, though on a different system, leads to conclusions similar to the ones Buchwald outlined for his catalysts.

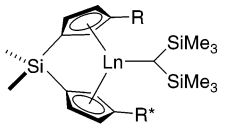
4.2. Lanthanide-Based Catalysts

Marks' group reported two kinds of asymmetric lanthanide complexes, **23** and **24**, for hydrogenation of unfunctionalized alkenes[33−36] based on their prior work with achiral systems.[37] These complexes have two bridged Cp rings. Optically pure menthyl or neomenthyl groups were attached to one of the Cp rings, so the planar chirality in these structures formed diastereomeric relationships with the Cp-attachment; this facilitated separation of the different stereoisomers.



23

Ln = Sm, Y, La, Nd or Lu
R* = (-)-menthyl or (+)-neomenthyl



24

Ln = Y or Lu
R* = (-)-menthyl, R = TMS or
R* = (+)-neomenthyl, R = ^{t}Bu

These lanthanide catalysts are highly active toward hydrogenation of monosubstituted and disubstituted alkenes. Turnover frequencies of up to 26 000 h^{-1} were observed for hydrogenation of 2-phenylbut-1-ene **O** using **23** (where Ln = Sm, R* = (+)-neomenthyl). The best enantiomeric excess reported for that substrate was 96% at −78 °C and 1 atm H_2. This was determined via optical rotations, but the authors stressed that these were reproducible.

Some interesting trends were noted in the studies of the lanthanide complexes. For instance, the enantioselectivities within a series of hydrogenations decrease with metal radius and with increased temperature. Complexes **24** are about 1 order of magnitude less reactive than **23** and give lower face selectivities, for example, the best ee for hydrogenation of 2-phenylbut-1-ene is 45% using the complex **24** where Ln= Y, R = $SiMe_3$, and R* = (−)-menthyl.[35]

Marks et al. performed a detailed study of the mechanisms of hydrogenation reactions mediated by complexes **23** and **24**. The mechanisms of these reactions are ligand- and substrate-dependent. In the particular case of hydrogenation of 2-phenyl-1-butene **O** using **23** (Ln = Sm), the reactions may be envisioned to proceed via hydrogenolysis of the Ln−alkyl bond to form a Ln−H complex. These undergo rapid insertion of alkene followed by turnover-limiting ($k_H/k_D = \sim 2.0$) hydrogenolysis of the new Ln−alkyl bond. In the absence of sufficient substrate, hydride-bridged dimers will form, and these are less reactive, so in situ generated catalysts tend to be superior. No hydrogen scrambling was observed when D_2 was used with illustrative members of either complex type, so

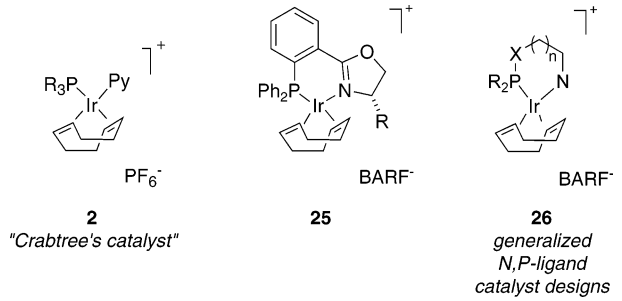
the reaction does not appear to be complicated by migration reactions.

In summary, the lanthanide catalysts developed by Marks et al. have high catalytic activities for hydrogenations of disubstituted alkenes, but on the basis of data with achiral catalysts,[37] they are unlikely to mediate reduction of tri- and tetra-substituted alkenes. Unfortunately, the complexes are extremely air-sensitive and quite difficult to prepare; that is work for experts in manipulation of air-sensitive compounds. In fact, asymmetric hydrogenations with these lanthanide complexes encompass *only* the two 1,1-disubstituted ones, **O** and **P**, and asymmetric *deuterations* of styrene and 1-pentene. Of the two 1,1-disubstituted substrates, only 2-phenyl-1-butene **O** gives good ee; the catalysts are unable to give good enantioface selectivities for **P** where the substituents, ethyl and *n*-butyl, are of a similar size.

5. Iridium-Based Catalysts

5.1. Introduction

The Pfaltz group recognized that ligands containing chelating phosphine and oxazoline groups were structurally similar to the PR_3/pyridine ligand set in Crabtree's catalysts **2** and, in 1998, reported enantioselective hydrogenation of unfunctionalized alkenes with the iridium complexes **25**.[38] These complexes have a coordination environment similar to that of Crabtree's catalysts: a cationic iridium center with a phosphine and a pyridine as the ligands. Significantly, the most widely applied counterion for the Pfaltz catalysts is BARF {tetrakis(3,5-bis(trifluoromethyl)phenyl)borate} as opposed to Crabtree's PF_6^- systems.



2 "Crabtree's catalyst" **25** **26** generalized N,P-ligand catalyst designs

Like Crabtree's catalyst, complexes **25** are catalytically reactive in hydrogenations of largely unfunctionalized alkenes; many trisubstituted aryl alkenes were completely hydrogenated under 50 bar H_2 pressure at low catalyst loading (typically 0.1−1.0 mol %) within 2 h in a noncoordinating solvent CH_2Cl_2. More importantly, the hydrogenations were highly enantioselective, giving alkanes in over 90% ee for most trisubstituted aryl alkenes. The tetrasubstituted alkene 2-methyl-3-phenylbut-2-ene was also hydrogenated quantitatively with 81% ee.

Since the milestone Pfaltz paper described above, many more iridium complexes with *N,P*-ligands **26** have been designed and successfully applied to hydrogenation reactions. Today, most of the work on enantioselective catalysts for hydrogenation of unfunctionalized alkenes is centered around this approach.[39]

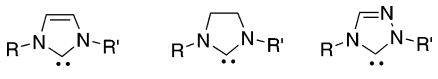
5.2. *N,P*-Ligands for Asymmetric Hydrogenations[40]

All the *N,P*-iridium catalysts reported for asymmetric hydrogenation to date have a cationic iridium as the central metal, an *N,P*-ligand, a 1,5-cyclooctadiene ligand, and a BARF counterion (though on occasion PF_6^- has been used). In most cases, a six-member ring is formed from the *N,P*-ligand and the iridium center (**26**, $n = 1$). The *P*-center is most frequently a phosphine (Figure 3, **27**,[38,41] **28**,[42] **29**,[43] **30**,[44] **31**,[44] **32**,[45] **33**,[46] **34**,[47] **35**,[48] **39**,[49] **43**,[50] **44**[51]), but phosphinites (**36**,[52,53] **37**,[54,55] **40**,[56] **41**,[56] **42**[57]) and phosphites **38**[58,59] have also been prepared and tested. All the early *N,P*-ligands featured oxazoline or structurally similar five-membered rings such as imidazoline as the *N*-ligating fragment, and the chirality of the ligand was set by an asymmetric center in that heterocyclic ring. Where oxazoline rings were involved, the chirality was usually derived from amino alcohols (from amino acids), and the rest of the ligand was then attached via the 2-position on the oxazoline using condensations with P-containing carboxylic acids. For ligands **29**, **34**, and **37**, however, the R^2 oxazoline substituent could be derived from common carboxylic acids. An advantage of the latter route is that a greater diversity of R^2 substituents can be used. Some of the ligands that have been explored have both endocyclic oxazoline chirality and other asymmetric centers (e.g., **32**, **33**, **37**, and **38**). However, trends observed for the ligands published so far indicate that most often, but not always,[59] the asymmetric centers that are peripheral to the oxazoline ring tend to be less important in asymmetric hydrogenations than the oxazoline-based chirality.

The most recent trends in this area reflect a greater sense of adventure with respect to the position of the chiral center and the heterocycles used. In systems **40**−**44**, the chirality is outside the heterocyclic fragment.

Syntheses of most of these ligands shown in Figure 3 have been reviewed.[60,61] Preparations of these systems are not discussed further here.

5.3. *C,N*-Ligands



R **S** **T**

Electron-rich *N*-heterocyclic carbenes,[62] including those based on the imidazolylidenes, **R**, imidazolinylidenes, **S**, and 1,2,4-triazolylidiene, **T**, frameworks, have emerged as useful ligands for organometallics.[63−68] They are often compared to phosphines because of their strong σ-donating ability, but complexes containing these carbene ligands tend to be more thermostable than their phosphine analogues.[69] These carbene complexes have been successfully used in many catalytic transformations, particularly metathesis and C−C and C−heteroatom coupling reactions.

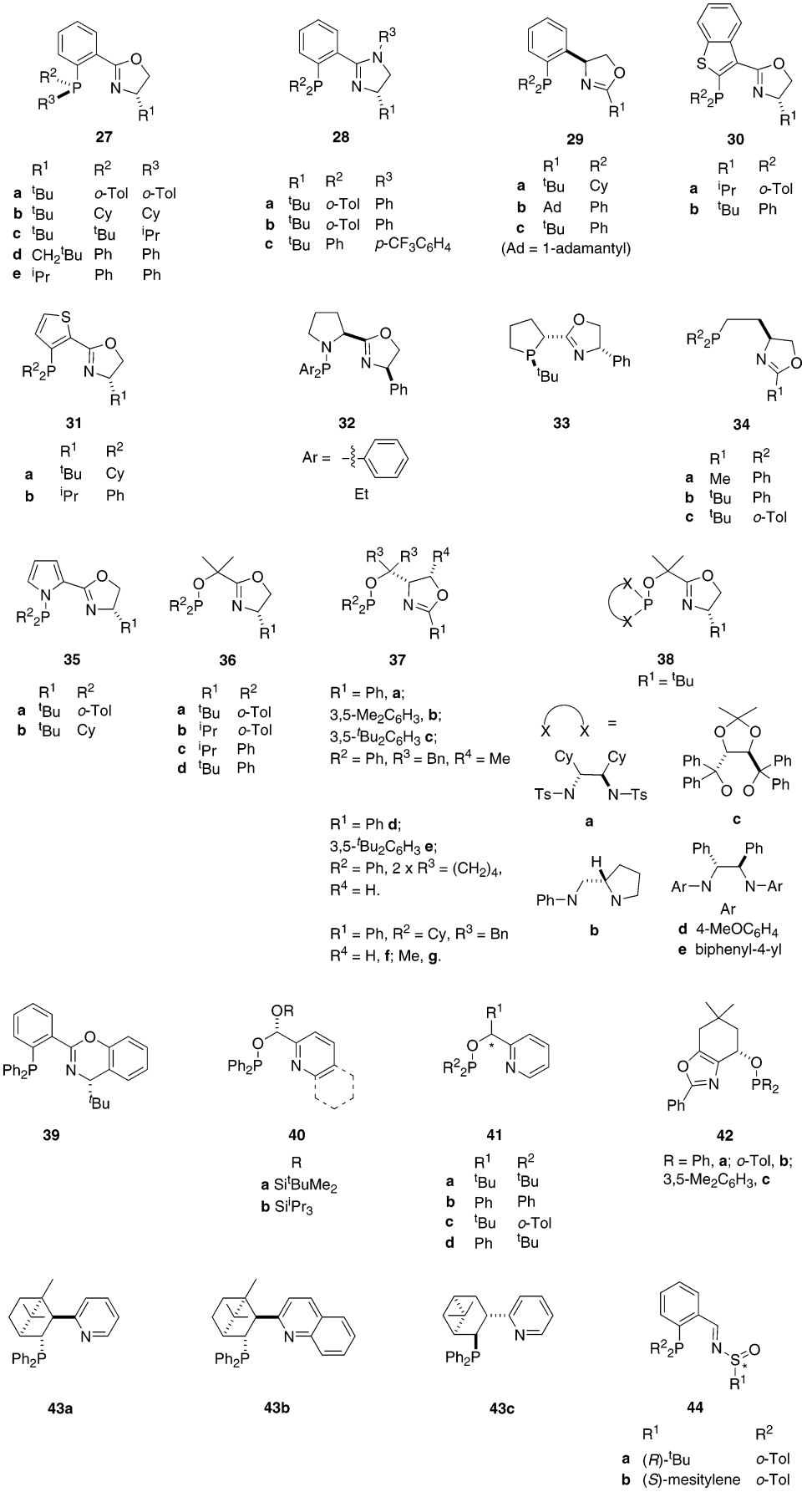
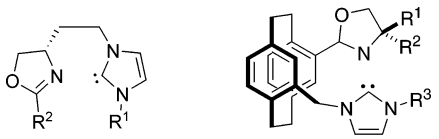


Figure 3. *N*,*P*-Ligands that have been used for asymmetric hydrogenations of largely unfunctionalized alkenes. The list is intended to be comprehensive and to specifically designate the best ligands in each class.

Chiral *N*-heterocyclic carbene ligands have been known for some time.[70−73] Two complexes containing chelating *N*-heterocyclic carbene and *N*-centers, which we have called "*C*,*N*-ligands" in this review, have been applied to catalytic asymmetric hydrogenation of unfunctionalized alkenes. The first *C*,*N*-ligand, **45**,[74,75] is related to the *N*,*P*-ligand **25** by substitution of a phosphine with imidazolylidene. Iridium complexes from these ligands were the first electron-rich carbene complexes discovered to catalyze an asymmetric transformation with high enantioselectivities (>98%);[74,75] the previous best was 76% in an intramolecular cyclization.[76] The *C*,*N*-ligands **46**[77] have chiral centers and planar chirality; they were complexed to iridium and were reported to be relatively unreactive catalysts for hydrogenation of unfunctionalized alkenes, and the enantioselectivities observed were poor (<38% ee for all of several substrates under different conditions).



45
R^1 = 2,6-^{i}Pr$_2$C$_6$H$_3$
R^2 = 1-Ad

46
$R^1 = R^2$ = Me
R^3 = mesityl

5.4. Ir-Mediated Hydrogenations of Trisubstituted Alkenes

Trisubstituted alkenes are the easiest substrate class for Ir-mediated asymmetric hydrogenations. We have attempted to compile the best data for each reported catalyst type as a function of each monoene substrate (Table 6). However, there are two sets of data that are not included in Table 6. First, for some substrates there have been reports of asymmetric Ir-mediated hydrogenations using only one or two catalyst types, so these data are summarized separately in Figure 4. Second, asymmetric hydrogenations of a group of alkenes containing heterocyclic aryl substituents were described in a review.[60] These data are described later in this section.

There are some trends in the alkenes that researchers have selected as substrates for asymmetric hydrogenations. Table 6 and Figure 4 together list a total of 27 alkenes. None of the substrates have totally aliphatic substituents. Many of the alkenes studied have 4-methoxyphenyl substituents to facilitate analytical separations of the product enantiomers on chiral columns. By far the most frequently studied substrate is *E*-1,2-diphenylpropene. *All* the catalyst types have been tested on this alkene; it is becoming a type of "yardstick" in hydrogenation chemistry just as *E*-1-acetoxy-1,3-diphenylpropene became in palladium-mediated allylations. That will prove to be unfortunate if the catalysts most suitable for more difficult substrates are relatively ineffective for *E*-1,2-diphenylpropene.

Trends can also be identified in the data that were obtained when monoenes were subjected to asymmetric Ir-mediated hydrogenations. Generally, high enantioface selectivities were observed more frequently for *trans*-alkenes than their *cis*-isomers. Alkenes with two trans aryl substituents tend to give higher enantioselectivities and, sometimes, higher conversions than those with only one aryl group on the alkene. Almost all the catalyst types hydrogenate *E*-1,2-diphenylpropene with high enantioselectivities and conversions, the only exception being catalyst **46**. Unsurprisingly, structures similar to this substrate tend to give similar data. The fourth substrate shown in Table 6 is a cycloalkene, and on the basis of the data collected, this is a more challenging case. The substrates with alcohol, ester, and acetoxy function-

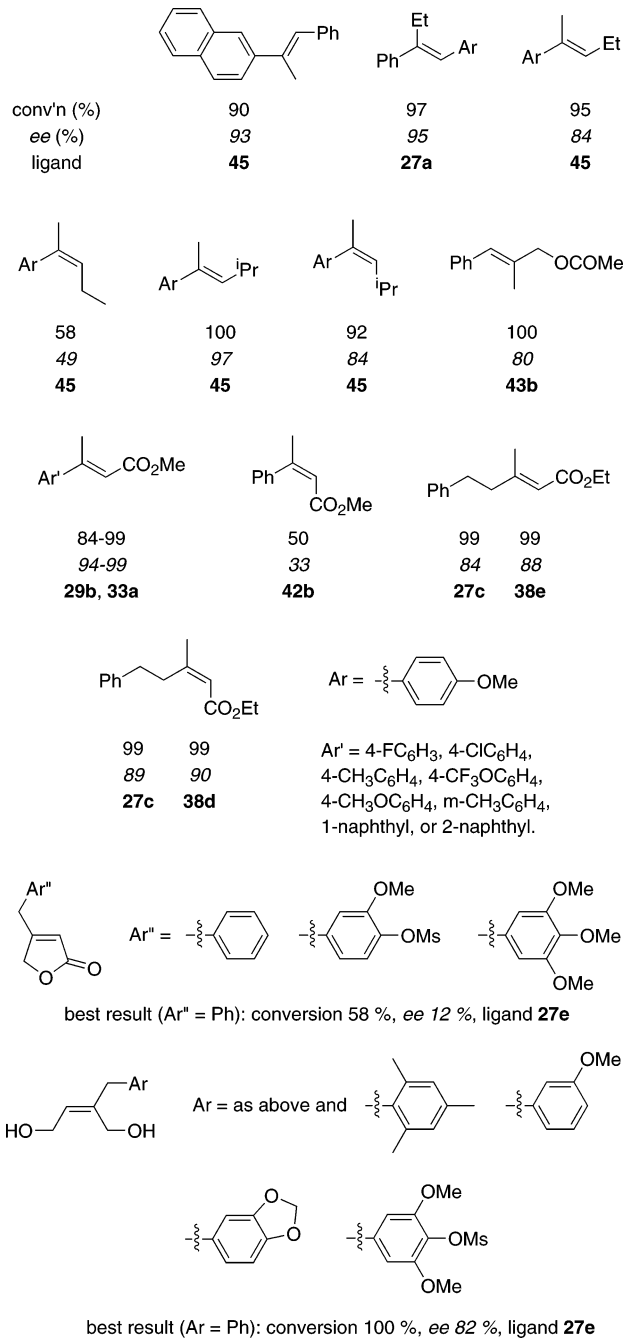
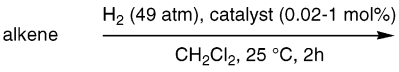
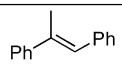
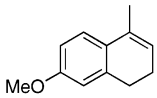
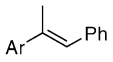
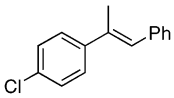
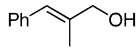
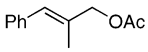
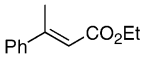
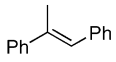
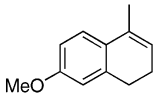
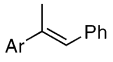
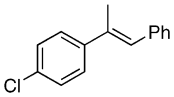
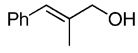
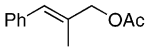
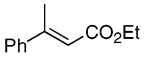


Figure 4. Less common substrates for Ir-mediated hydrogenations.[78] Reported hydrogenations of each of these substrates involve only one or two ligand types. Data in Roman type indicate conversion (%); data in italic type indicate ee (%).

Table 6. Hydrogenation of Trisubstituted Alkenes Using Iridium Catalysts[a,b]

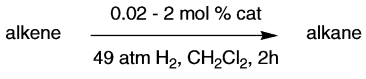


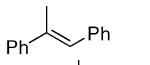
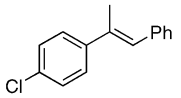
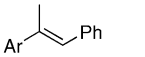
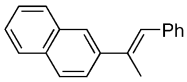
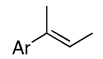
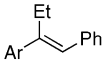
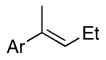
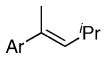
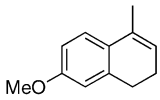
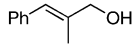
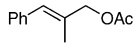
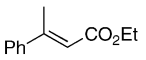
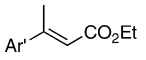
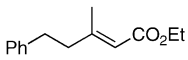
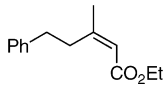
alkene	Ligand[c] (conversion %, *ee* %)									
	27	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
	**a** >99 *97*	**a** >99 *94*	**a** 99 *99*	**a** >99 *94*	**a** >99 *99*	99 *92*	**a** 100 *95*	**a** 99 *95*	**a** 100 *99*	**a** 99 *98*
	**a** 99 *81*	**b** >99 *90*	-	-	-	100 *76*	-	**a** 99 *93*	**b** 100 *75*	**b** 99 *91*
	**a** 97 *63*	**a** >99 *88*	-	-	-	100 *56*	-	**b** 70 *75*	**b** 100 *70*	**c** 99 *89*
	**a** 99 *72*	**a** >99 *91*	-	-	-	100 *64*	-	-	**a** 100 *92*	**a** 99 *95*
	**a** >99 *99*	-	**b, c** 99 *97*	-	-	99 *94*[d]	**a** 100 *91*	-	-	-
	**b** >99 *99*	-	-	-	-	-	**a** 100 *90*	-	-	-
	**a** 95 *96*	-	-	**b** >99 *94*	**b** >99 *94*	100 *94*	-	**c** 80 *67*	-	**a** 99 *97*
	**a** 99 *91*	-	-	-	-	-	-	**b** 53 *72*	-	-
	**a** 96 *84*	-	-	-	-	100 *88*	-	-	**a** 99 *92*	**a** 99 *94*

alkene	ligand (conversion %, *ee* %)									
	37	**38**	**39**[c,f]	**40**	**41**	**42**	**43**	**44**	**45**[g]	**46**
	**a-c** 100 *99*	**a** 59 *92*	99 *78*	**a** 93 *88*	**a** >99 *97*	**a-c** 99 *99*	**a, b** 100 *95*	**a** 99 *94*	100 *99*	28 *15*
	**a-c, e** 100 *99*	**b** 100 *91*	86 *37*	-	**b** >99 *87*	**b** 99 *96*	-	-	100 *97*	-
	**b** 100 *92*	**c** 100 *95*	-	-	**b** >99 *90*		-	-	100 *80*	-
	**d** 99 *87*	**a** 100 *86*	-	-	-	**b** 99 *94*	-	-	-	-
	-	**a** 60 *92*	>99 *90*	-	-	-	**b** 100 *95*	-	99 *97*	-
	-	**c** 52 *78*	92 *73*	-	-	-	-	-	-	-
	**a** 99 *92*	-	13 *77*	-	**c** 99 *96*	**b** 95 *98*	**b** 94 *69*	**a** 99 *70*	99 *93*	11 *4*
	-	-	-	-	-	**b** 99 *99*	-	-	-	-
	**f** >99 *96*	**b** 80 *92*	95 *72*	-	**d** >99 *95*	**b** 99 *93*	**b** 65 *58*	**a** 99 *65*	-	99 *38*

[a] Typical reaction conditions: 0.02−2.0 mol % catalyst, 49 atm H_2, CH_2Cl_2, 25 °C, 2 h. [b] Ar = 4-$MeOC_6H_4$. [c] Data in boldface type indicate catalyst number; data in lightface, Roman type indicate conversion (%); data in italic type indicate ee (%). [d] 20 atm H_2 at 0 °C. [e] 4 mol % catalyst, 98 atm. [f] Data here are from a later reference,[59] which seems to supersede the first.[60] [g] 1 atm H_2.

Table 7. Best Hydrogenation Results for Trisubstituted Aryl Alkenes



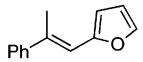
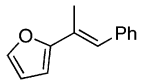
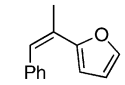
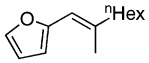
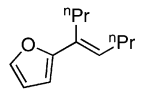
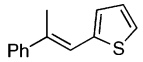
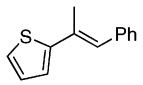
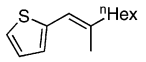
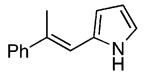
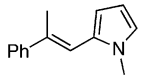
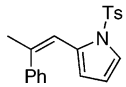
entry	alkene[a]	conv'n (%)	*ee* (%)	ligand
1		100	99	**29a**, **31a**, **35a**, **37a-c**, **42a-c**, **31**, **45**
2		99	99	**27b**
3		>99	99	**27b**
4		90	93	**45**
5		100	99	**37a-c**, **e**
6		97	95	**27a**
7		95	84	**45**
8[b]		100	97	**45**
9		58	49	**45**
10[b]		100	89	**45**
11		100	92	**37b**
12		99	95	**36a**
13		99	97	**36a**
14		99	99	**42b**
15		99	96	**37f**
16[c]		>99	95 to 99	**29b**, **33a**
17		99	88	**38e**
18		99	90	**38d**

[a] Ar = 4-MeOC$_6$H$_4$ [b] 1 atm H$_2$. [c] Ar′ = 4-FC$_6$H$_3$, 4-ClC$_6$H$_4$, 4-CH$_3$C$_6$H$_4$, 4-CF$_3$OC$_6$H$_4$, 4-CH$_3$OC$_6$H$_4$, 3-CH$_3$C$_6$H$_4$, 1-naphthyl, or 2-naphthyl.

alities are also more difficult, and they tend to require higher catalyst loadings.

The catalysts from *C*,*N*-ligand **45** gave good results even when only one atmosphere of hydrogen was used (as opposed to 50 atm in most prior reports). This is a major advantage with respect to experimental convenience. However, it is clear that the dependence of enantioselection in these reactions on pressure and temperature is substrate-dependent. Enantioselectivities in hydrogenations of some substrates with these *C*,*N*-ligand-derived catalysts were observed to be pressure-/temperature-dependent, and

Table 8. Hydrogenation of Heteroaromatic Alkenes[a]

entry	alkene	conv'n (%)	*ee* (%)	ligand
1		>99	>99	**27c**, **37a**
2		>99	99	**37g**
3		>99	>99	**37a**
4		>99	84	**36a**
5		>99	80	**27a**
6		>99	>99	**37a**, **37g**
7		>99	>99	**27c**
8		>99	98	**36a**
9		>99	>99	**37g**
10		>99	>99	**37g**
11		81	91	**37f**

[a] Exact conditions not specified by authors.

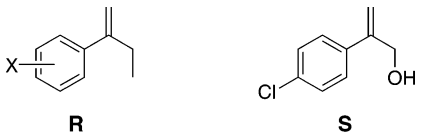
in some cases, the face selectivities could even be reversed by changing the reaction conditions.[75] Other substrates under the same conditions did not exhibit this behavior. More recently, the Pfaltz group have reinvestigated some of their hydrogenations using atmospheric pressures and found that the enantioselectivities can be enhanced in some cases.[79] Pressure dependence of enantioselectivities in these reactions could be due kinetic effects manifest from interconverting diastereomeric intermediates (Curtin−Hammett). However, there are other mechanistic possibilities, and it would be inappropriate to apply a Curtin−Hammett analysis when fundamental aspects of the mechanism are not understood.

Table 7 summarizes the best hydrogenation results for all the trisubstituted aryl alkenes studied. All these alkenes, *cis* or *trans*, were hydrogenated quantitatively and in most cases with excellent ee's if suitable catalysts and conditions are chosen.

The Pfaltz group recently summarized, in a review article, data from hydrogenations of trisubstituted alkenes with one aromatic heterocyclic substituent (Table 8).[60] These are interesting because of the applications of heterocycles in industry and because of the opportunities to modify the heterocyclic part, post-hydrogenation. Alkenes with furan, thiophene, and pyrrole were hydrogenated. Even though the catalytic activity of iridium complexes with *N*,*P*-

ligands can be diminished in the presence of coordinating groups (or solvents), all but one (entry 11) of the heterocyclic alkenes shown in Table 8 were hydrogenated at the alkene functionality with 100% conversion. Excellent ee's were obtained for alkenes with two trans aromatic substituents, (entries 1−3, 6−11), but the face selectivities were lower for alkenes with two aliphatic substituents (entries 4 and 5).

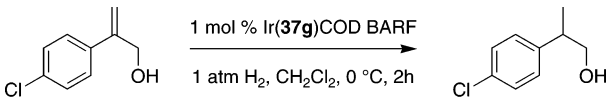
5.5. 1,1-Disubstituted Alkenes



R **S**

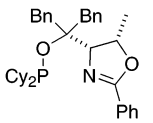
X = 4-MeO, 4-Me, 4-CF_3, 4-Cl, 4-Br, 3-Cl, 3-Br

The section above describes investigation of a reasonably diverse set of trisubstituted alkene substrates. For 1,1-disubstituted alkenes, the contrast is striking: only the 2-aryl-1-butenes, **R**, and the allylic alcohol, **S,** have been tested so far and then using just a few of the catalysts that are now available. 1,1-Disubstituted alkenes are less hindered than tri- or tetrasubstituted ones, so the conversions would be expected to be excellent, and they were. Enantioselectivities, however, vary from low to excellent depending on the catalyst. The most extensively studied substrate is the **R** structure with the 4-methoxygroup (Table 9). Catalysts with ligand **37g**, **42b**, and **45** give values close to or higher than 90%. The best ee is 97% with ligand **42b**.[57] It is also found that enantioface selectivities in this reaction change dramatically with H_2 concentration in solution. The ee's are usually higher at high temperature or low H_2 pressure or both, where the H_2 concentration in solution is low. In most cases, the optimal results are obtained at room temperature and atmospheric pressure. Results with the various substrate substitution patterns **R** using catalyst from ligand **37g** were similar (up to 94% ee), that is, the different substituents in the meta or para positions had relatively little influence on the enantioselectivities observed.[79]



>99 %, 88 % ee

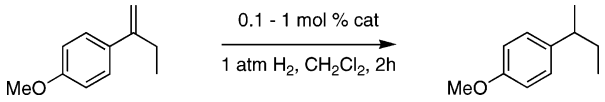
reaction 4



37g

An iridium catalyst from **37g** was found to give a good stereoselectivity in the hydrogenation of substrate **S** as shown in reaction 4.[79] This particular transformation proceeds with diminished enantioselectivities at high temperatures and pressures.

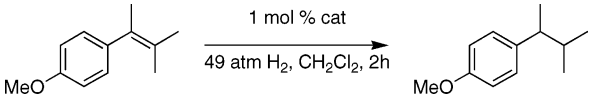
Table 9. Hydrogenation of 2-(4′-Methoxyphenyl)-1-butene



ligand	conversion (%)	ee (%)
27a	99	60
28c	99	54
32a	100	38
34b	99	44
37g	100	93
38d	99	70
42b[a]	99	97
45	100	89

[a] 49 atm H_2.

Table 10. Hydrogenation of 2-(4′-Methoxyphenyl)-3-methylbut-2-ene



ligand	conversion (%)	ee (%)
27d[a,b]	99	81
32a	52	4
41a	99	81
42a[a]	37	15

[a] 98 atm H_2. [b] 2 mol % catalyst.

5.6. Tetrasubstituted Alkenes

Asymmetric hydrogenations of some tetrasubstituted alkenes are interesting insofar as they can potentially generate two adjacent chiral centers in one step. Crabtree's catalysts hydrogenate tetrasubstituted alkenes (but, of course, without enantioface selectivity), so it would seem likely that iridium catalysts formed from some of the other chiral ligands described in this section might also mediate this reaction. Further, Buchwald's work in 1999[31] demonstrated chromatographic conditions to quantitate enantiomeric ratios for the reduction products derived from several tetrasubstituted alkenes. It is, therefore, surprising that Ir-mediated asymmetric hydrogenations of only one substrate in this class, 2-(4′-methoxyphenyl)-3-methylbut-2-ene, have been reported so far.

Table 10 summarizes the data collected for asymmetric hydrogenations of 2-(4′-methoxyphenyl)-3-methylbut-2-ene. Understandably, higher catalyst loadings and pressure and longer reaction times are required relative to reductions of less hindered systems. Catalysts from ligands **27d**[38,41] and **41a**[56] are notable insofar as they give full conversion and 81% ee. However, catalysts **32**[45] and **42**[57] only provide very low conversion and selectivity.

Conspicuously absent in the literature are descriptions of experiments in which 2-(4′-methoxyphenyl)-3-methylbut-2-ene has been *deuterated* using the chiral iridium catalysts. These may be significant omissions because the reactions could proceed via initial double bond migration then reduction; hence, the actual addition step may involve, at least to some degree, hydrogenation of a 1,1-disubstituted alkene

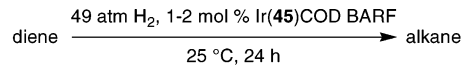
rather than a tetrasubstituted one. Indeed, such migration reactions are known for Ir catalysts with various alkene substrates.[47,74,75,80] Deuterium labeling studies would expose this eventuality. In fact, unpublished studies from our laboratory have shown that reduction of 2-(4′-methoxyphenyl)-3-methylbut-2-ene using the iridium catalyst derived from ligand **27e** gives significant incorporation of deuterium at carbons that were not sp^2 hybridized in the substrate. This contrasts with Buchwald's Zr-based catalysts (Table 5) that reduce tetrasubstituted alkenes with incorporation of deuterium only at the sp^2 hybridized carbon atoms.

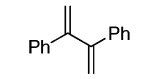
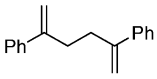
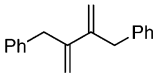
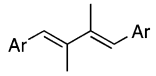
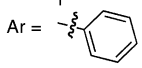
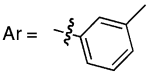
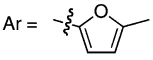
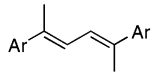
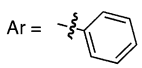
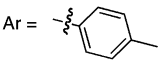
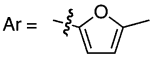
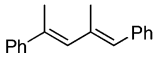
5.7. Dienes

Throughout the whole area of asymmetric hydrogenations of alkenes, functionalized or otherwise, reductions of dienes have attracted very little attention. Prior to our work, studies on only two substrates had been reported: ruthenium mediated hydrogenations of 2,3-disubstituted-1,3-butadienes where the substituents were either two phosphine oxide groups[81] or carboxylic acids.[82] Even non-asymmetric hydrogenations of dienes with homogeneous catalysts have not been studied very extensively.[83−85]

Asymmetric hydrogenations of dienes and polyenes is an ongoing interest of our research group; this class of reactions has the potential to generate multiple chiral centers with control of enantio- and diastereoselectivities. Our published work in the area so far has featured aryl-substituted dienes using an iridium catalyst formed from the *C*,*N*-ligand **45**.[86,87] There was no particular reason to use this catalyst except that it was developed in house; it seems highly likely that some catalysts containing *C*,*N*-ligands would give comparable results. The diene substrates studied can be divided into four types as indicated in Table 11. The first, type 1 dienes with 1,1-disubstituted double bonds, were hydrogenated with low enantio- and diastereoselectivities. This is unsurprising since 1,1-disubstituted monoenes are difficult substrates for enantioselective reactions. 1,4-Diaryl-2,3-dimethylbutadienes, type 2, gave quantitative conversions but, for the substrates with benzenoid (i.e., nonheterocyclic) substituents, only around 70% yields of the products. The remaining 30% of the material was converted to a tetrasubstituted monoene byproduct in a half-reduction/double-bond migration process. Hydrogenation of the furan-substituted type 2 system, however, was not complicated in the same way. All three substrates of this class are marginally selective for the *ent*- over the *meso*-products, and these formed in excellent enantioselectivities. Type 3 substrates, 2,5-diaryl-hexa-2,4-dienes, were the best-behaved substrates in the series. The benzenoid systems gave high diastereoselectivities, and the optically active products are formed in high ee's. However the diene with two furan groups is again anomalous; in this case, both aspects of the stereoselectivity are low for this substrate. Only one other diene was studied (type 4); the diastereoselectivity is moderate, and enantioselectivity for the major diastereomer is excellent.

Table 11. Hydrogenation of Dienes



entry	diene	conv'n (%)	yield (%)	*ent:meso*	*ee* (%)
type 1					
1[a]		100	96	1.0:2.9	87
2[b]		100	100	2.1:1.0	86
3[b]		88	65	1.0:2.9	24
type 2					
4		100	69	1.3:1.0	98
5		100	67	1.3:1.0	97
6		100	96	1.8:1.0	99
type 3					
7		93	92	14:1.0	98
8		100	100	20:1.0	99
9		100	100	1.2:1.0	70
type 4					
10		100	>99	5.8:1	99

[a] 1 atm H_2. [b] 10 atm H_2.

5.8. Mechanistic Considerations for Asymmetric Ir-Mediated Hydrogenations

The mechanism of hydrogenation of alkenes by Wilkinson's catalyst, $RhCl(PPh_3)_3$,[14,15] is described in most textbooks on organometallic chemistry. Crabtree's catalysts have been known for almost as long (1976 vs 1966),[88] but their mechanism(s) of action is not known. We believe that Crabtree's catalyst is in some ways a more interesting system because it mediates hydrogenations of hindered, even tetrasubstituted, alkenes, whereas the Rh complex does not do this at a significant rate. The fact that contemporary research on asymmetric hydrogenations of largely unfunctionalized alkenes revolves around chiral analogues of iridium complexes more than rhodium-based ones makes lack of mechanistic information regarding the Ir-system even more conspicuous.

No proven active intermediates in the catalytic cycle for Ir-mediated hydrogenations of unfunctionalized alkenes have been observed, isolated, or characterized. Nevertheless, there are some experimental observations that can be made about the iridium-based systems that may eventually be reconciled with a mechanistic model, and some computer simulations that suggest the basis of the catalytic cycle.

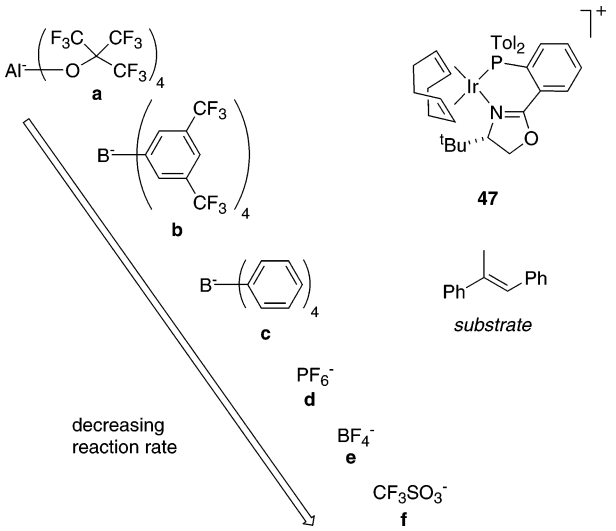


Figure 5. Qualitative summary of rate data for different counterions of catalyst **47** with *E*-1,2-diphenylpropene as shown.

Before the role of the iridium cation in these hydrogenations is discussed, it is timely to acknowledge the enigma of the BARF ($\{3,5\text{-}(CF_3)_2C_6H_3\}_4B^-$) counterion. This aspect of the story is very different from counterion effects observed in rhodium-mediated hydrogenations.[89] Crabtree's catalysts tend to be used as hexafluorophosphate salts; (COD)Ir(Py)-(Cy_3P) has not been prepared as the BARF salt, so the effects of that counterion on Crabtree's systems are still unknown. Unlike Crabtree's catalysts, BARF complexes of the asymmetric Ir-catalysts are more effective in the hydrogenation reactions.[38,41]

Recently, the Pfaltz group performed detailed kinetic analyses of some Ir-mediated hydrogenation reactions and determined some turnover numbers for complex **47** (Figure 5).[90] They found that aluminum-based anion **a** gave a higher optimal turnover frequency than the BARF anion **b**, but both were high, >5000 h^{-1}. Total turnover numbers of 2000−5000 were observed for catalysts **47a** and **47b**. Complexes with counterions **a**−**c** remained catalytically active after all the alkene was consumed, whereas salts of the others were not. Overall, the BARF salt **b** is preferred since it was shown to be less sensitive to water and to adventitious oxygen.

Kinetic studies of the hydrogenation of *E*-1,2-diphenylpropene using catalyst **47b** (BARF counterion)[90] (Figure 5) and the same catalyst but with a ligand containing PPh_2 not $PTol_2$ groups demonstrated that the reaction approximates a first-order dependence on hydrogen, implying dihydrogen is involved in the turnover-limiting step.[91] Note, however, that over-interpretation of the dependence of rate on dihydrogen pressure would be easy since rates of diffusion of dihydrogen across the gas−liquid interface[92−94] are critical for some combinations of substrates/vessels/stir-speeds/catalyst concentrations in these reactions. The rate dependence on the catalyst concentration was observed to be first-order at low catalysts concentrations. For catalyst **47b**, the reduction was essentially zero-order in *E*-1,2-diphenylpropene substrate, but became first-order in this alkene when the PF_6^- catalyst **47a** was used. The inference

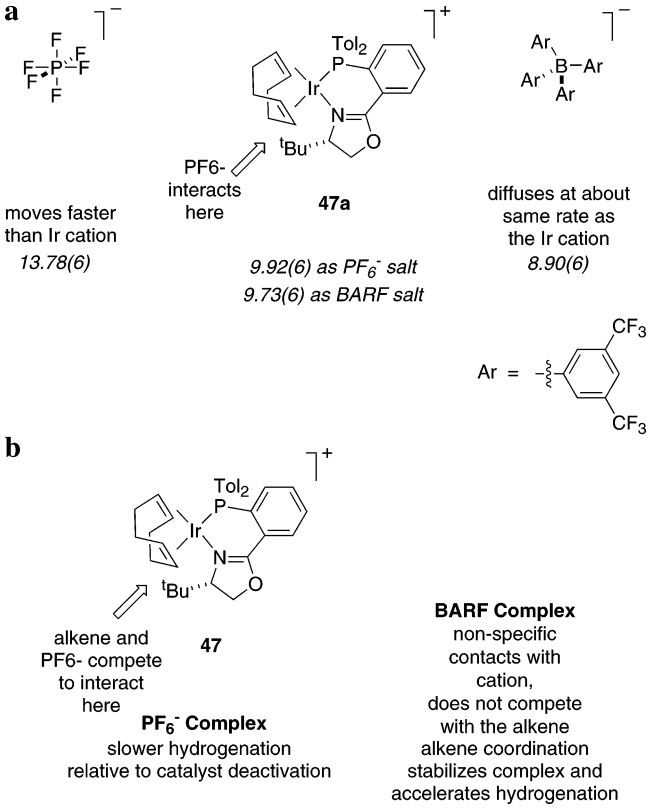


Figure 6. (a) Data from PGSE and ^{19}F HOSEY studies. The data in italic type are diffusion constants in units of 10^{-10} *D* (m^2 s^{-1}). Close contacts are deduced from the HOSEY studies. (b) Model to explain the role difference or reactivity and stability of the PF_6^- and BARF complexes.

of this fascinating observation is that the access of the alkene to the metal center is somehow impeded for the hexafluorophosphate salt relative to the BARF one.

The data described above are particularly interesting in light of an NMR study to contrast the BARF and PF_6^- salts of complex **47**.[95] Pulsed gradient spin−echo (PGSE) diffusion data (in CD_2Cl_2) were used to give an indication of ion pairing. Thus diffusion rates of a cation, for example, an iridium complex, can be followed via protons on that complex, and diffusion rates of the anion (BARF or PF_6^-) can be simultaneously tracked via ^{19}F nuclei. If the cation and anion move with similar rates, that is indicative of ion pairing. Figure 6 gives the data that were observed for the complex **47** as both a BARF and a PF_6^- complex. It also shows the diffusion rates measured for the anions in those complexes. The conclusion from these data is that the Ir cation moves at a similar rate to the BARF anion, indicative of ion pairing, while the PF_6^- is less closely associated with the cation. ^{19}F heteronuclear Overhauser effect spectroscopy (HOESY) was used in tandem with the PGSE experiments to gauge close contacts between Ir complexes and their counterions. The BARF ion showed generalized close contacts, while the *PF_6^- showed specific interactions with the oxazoline portion of the ligand*. The fact that PF_6^- interacts specifically with the oxazoline part of the ligand implies a preferred orientation; that is potentially significant because that is the calculated preferred orientation of approach of alkenes to the iridium center in these

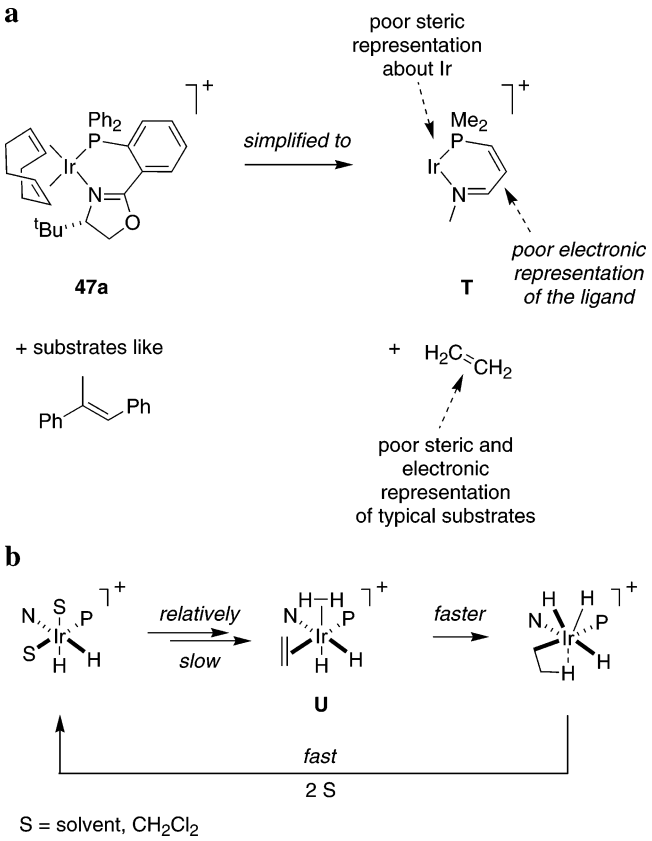


Figure 7. (a) Simplification in the original DFT calculations for the mechanism(s) of chiral Ir-mediated hydrogenations. (b) Overall conclusions from those simulations.

reactions (vide infra). Thus, in conclusion, the PGSE data shows that the PF_6^- anion is less strongly associated with the metal than the $BARF^-$ but the interactions it does have are more specific.

There have been two concerted attempts to elucidate the mechanism(s) of asymmetric Ir-mediated hydrogenations of largely unfunctionalized alkenes via theoretical methods. The first was by Brandt et al. using primarily the B3LYP method.[91] This method is a hybrid of density functional theory (DFT) and Hartree−Fock approaches and, because of this, cannot use density-fitting basis sets. Inaccessibility of density-fitting basis sets makes the method computationally expensive and extremely slow for large molecules with heavy atoms such as the complex **47b**, for instance. Consequently, Brandt and co-workers were forced to make gross simplification of the catalyst structure to entity **T**; otherwise the calculations would have been intolerably slow at today's state-of-the-art computational speeds. These simplifications compromised the ligand shape and steric environment about the metal and the electronic complexion of the ligand because the N and P centers are more directly conjugated in the ligand (Figure 7a).

The calculations described above led to a model in which, after the COD is hydrogenated and dissociated from the metal center, the vacant sites formed are occupied by two hydride ligands and two solvent molecules. This is consistent with experimental data for oxidative additions of dihydrogen to Ir(1+) complexes: they tend to be fast, even at low temperatures.[96] Computer simulated displacement of the solvent molecules with dihydrogen and alkene leads to a key Ir(3+) intermediate **U** with the alkene ligand trans-oriented to the worse π-acceptor of the *N*,*P*-ligand, the phosphine, and the hydride opposite to the oxazoline, the better π-acceptor. They then calculated that intermediate **U** undergoes migratory insertion of the alkene into the hydride ligand *with concomitant cleavage of the dihydride giving the Ir(5+) oxidation state*. The simulation indicates that the catalytic cycle closed by rapid and irreversible reductive elimination of the alkane. Enantioselectivity would then be determined by a combination of two factors: the face selectivity of the alkene complexation and the relative rates of the migratory insertion step (Figure 7b).

These observations could be thought of as calculations inspired by good chemical logic and vice versa. For instance, several stereoisomers of intermediate **U** were also evaluated, and several of them had ground-state energies and transition-state energies that were similar for intermediate **U** and its migratory insertion process. These differences would tend to be within the margin of error of the calculations, especially if the approximations regarding the ligand and substrate are factored in. Consequently, the calculations alone do not definitively point to the mechanism indicated in Figure 7b.

Brandt's calculations and conclusions were mostly in agreement with the second theoretical study by Hall and co-workers.[97] Importantly, B3LYP was only used as a validation method in this work. Most of the calculations were performed using a pure DFT method, PBE, for which density-fitting functions *can* be used; hence the method is several times faster than B3LYP. Further, the accuracy of the calculation is comparable, and indeed, model Ir-mediated hydrogenations simulated using PBE and using B3LYP agreed closely. Enabled by this faster technique, Hall et al. applied it to the *C*,*N*-complex **48** (from the carbene ligand **45**) using real substrates and the actual ligand structure. They excluded many mechanistic possibilities and the pathway shown in Figure 8 emerged.

There are important similarities between the mechanisms shown in Figures 7 and 8. In the latter, the enantioface selectivity converges on the formation and reactivity of an intermediate **U′**. Like intermediate **U** in the Brandt mechanism, that intermediate aligns the alkene opposite the worst π-acceptor, here the carbene, and the hydride opposite the oxazolidine. However, unlike in the first simulations, the calculated energies required to reach the transitions states en route to the migratory insertion product in Figure 8 were on the order of 15.5−17.6 kcal mol^{-1} (depending on the alkene); these are realistic values considering that these reactions are fast at room temperature. In Figure 7, the corresponding free energy changes are only ca. 7 kcal mol^{-1}. Further, Hall et al. calculated pathways for favored and disfavored enantioface selection for three different alkenes; they successfully predicted the correct sense of the inductions, and the calculated $\Delta\Delta G$ values closely corresponded to the experimentally determined enantioselectivities.

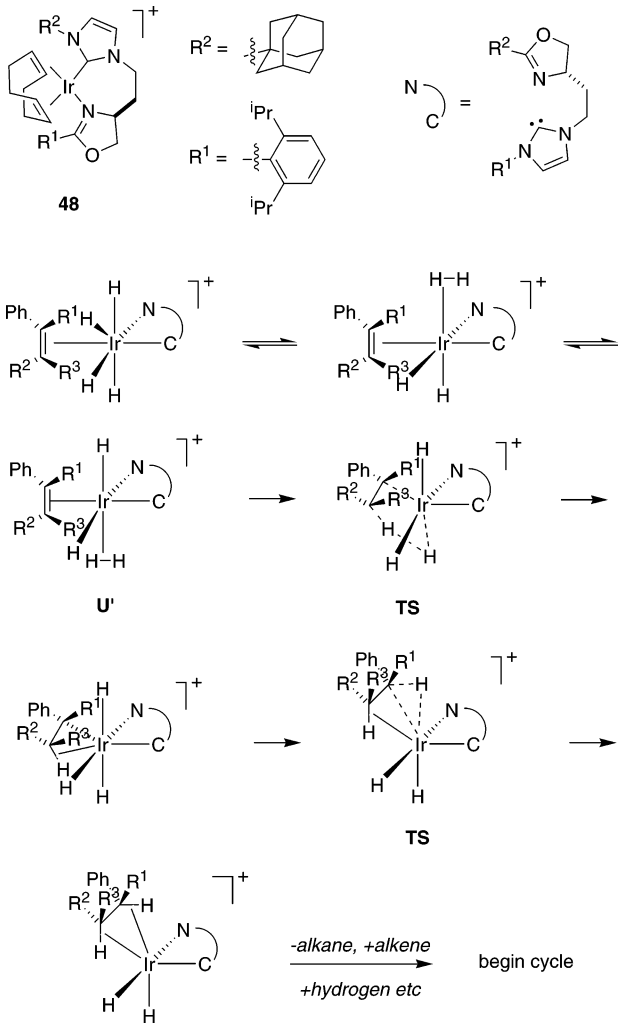


Figure 8. Simulated asymmetric hydrogenation by complex **48** (**TS** = transition state).

There are some significant differences between Hall's and Brandt's simulations. First, solvent molecules play no significant role in the Hall model, but it is easy to envisage how solvents more coordinating than dichloromethane might get involved. Second, there is a fast equilibrium between the hydrides and dihydrogen (see **U′**) through an iridium tetrahydride in the Hall mechanism. This is important because it allows facile redistribution of coordinating groups prior to the migratory insertion step and also involves an iridium(5+) intermediate. Both the Brandt and Hall mechanisms invoke Ir(5+)/Ir(3+) oxidation states, but only the Hall pathway has the alkene reacting metathetically with a dihydrogen ligand, in preference to a hydride.

The calculations by Hall et al. provide a credible working model for enantioselective hydrogenations via catalyst **48**. The catalyst is a delicately balanced system in which the alkene is driven trans to the carbene part where it interacts primarily with the oxazoline adamantyl substituent. Simultaneously, hydrogen is directed to enter near the 2,6-di-isopropylphenyl carbene substituent by the trans effect of the oxazoline ligand. These electronic factors dominate, but they are reinforced by steric effects that ultimately define the enantioface selectivities given these directions of approach (Figure 9). Refinements

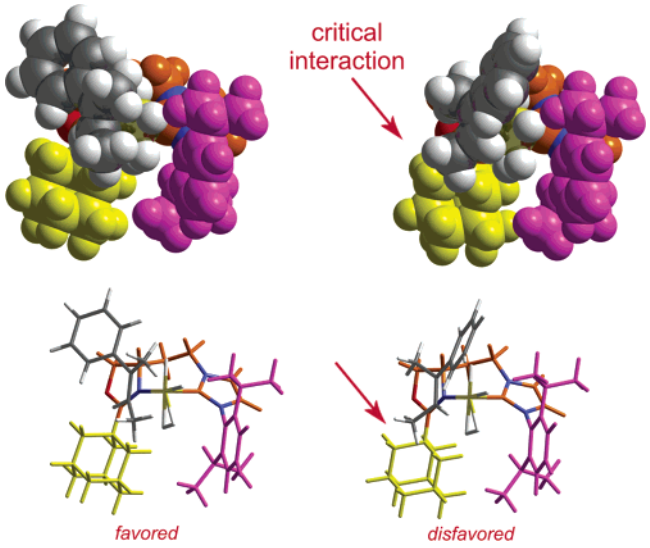


Figure 9. Space filling and stick models for diastereomeric intermediates **U′** where the alkene is *E*-2-phenylbut-2-ene coordinated via the most favorable enantioface and the disfavored one.

of the Brandt model point to similar conclusions.[57]

Conclusions from the theoretical papers described above are inconsistent with some conclusions drawn from mass spectrometry experiments. Specifically, Chen et al. have studied catalytically active samples of complex **49** with styrene in an apparatus designed to maintain a hydrogen pressure in the process of electrospray MS.[98] They made a few experimental observations that related directly to the mechanism: (i) ions corresponding to the molecular masses of Ir(**27e**)(styrene)$^+$, (H_2)Ir(**27e**)(styrene)$^+$, and $(H_2)_2$-Ir(**27e**)(styrene)$^+$ are observed in catalytically active solutions; (ii) the (H_2)Ir(**27e**)$^+$ species can be bombarded with ethylbenzene in the electrospray process to give an ion corresponding to Ir(**27e**)(ethylbenzene)$^+$; (iii) bombardment of Ir(**27e**)(ethylbenzene)$^+$ with argon causes rapid loss of hydrogen to give the ion corresponding to Ir(**27e**)(styrene)$^+$; and, importantly, (iv) when the ion corresponding to mass Ir(**27e**)-(styrene)$^+$ was bombarded with D_2 gas *only products corresponding to incorporation of one and of two, but not of three, deuteriums were observed*, that is, Ir-(**27e**)(styrene)$^+$-D_1 and Ir(**27e**)(styrene)$^+$-D_2. Based on these data, Chen et al. proposed the Ir(+1)/Ir(3+) mechanism shown in Figure 10.

Chen et al. exclude the types of Ir(3+)/Ir(5+) mechanisms inferred in the theoretical studies on the basis of the fourth observation listed above. They argue that the bombardment of the ion corresponding to Ir(**27e**)(styrene)$^+$ with D_2 would have produced species corresponding to $(D_2)_2$Ir(**27e**)-(styrene)$^+$ under the conditions used. This is reasonable based on the data given, especially since ions equivalent to $(H_2)_2$Ir(**27e**)(styrene)$^+$ were observed in the catalytic reaction. However, they conclude that "...given the reversibility of the elementary steps in the gas phase reaction, even a transient Ir(5+) intermediate with three chemically equivalent deuterides (and an alkyl group with one deuterium atom) would produce at least partial incorporation

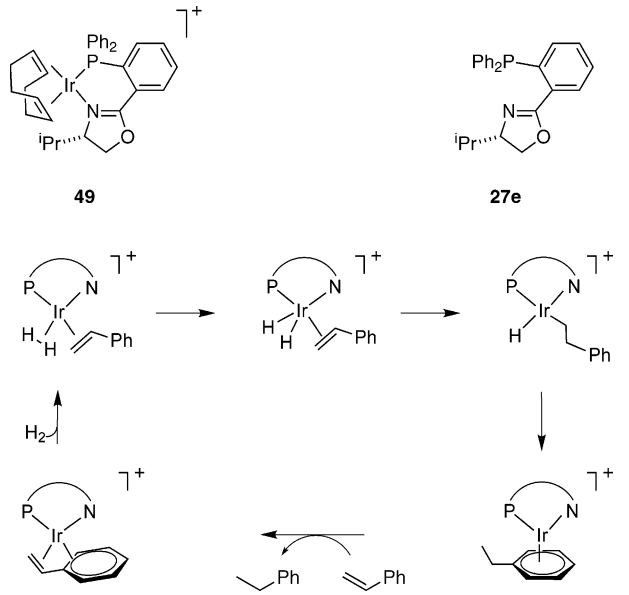


Figure 10. Chen's postulate for the mechanism of Ir-mediated hydrogenations, based on MS studies.

of more than two deuterium atoms into the styrene substrate."

Despite these assertions, the deuterium labeling studies may not provide evidence to support the Ir(1+)/Ir(3+) mechanism shown in Figure 10 over the Ir(3+)/Ir(5+) pathway. The reversibility of all the steps depicted in the Ir(1+)/Ir(3+) mechanism shown in Figure 10 could also lead to formation of trideuteride species, whereas if the formation of Ir(**27e**)(ethylbenzene)$^+$ were irreversible then perhaps only two deuterium atoms (maximum) would be incorporated via an Ir(3+)/Ir(5+) pathway. It is possible that mono- and di- but not tri-deuteration may arise from a pathway that is not directly relevant to the actual mechanism. Even if the Ir(1+)/Ir(3+) pathway is actually valid for the MS experiments, the relevance of these gas-phase experiments with a terminal, unhindered alkene to the solution phase systems with hindered prochiral alkenes is a matter of conjecture.

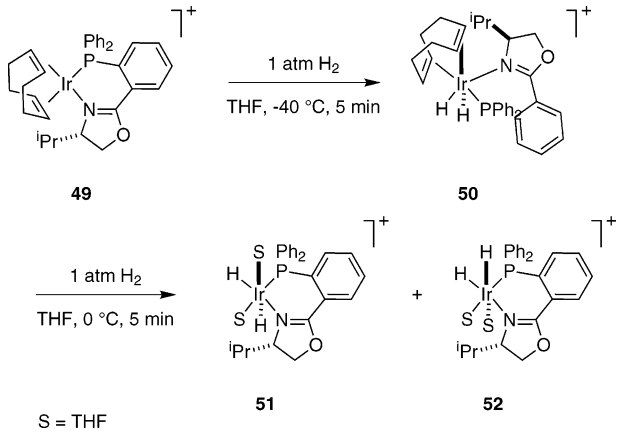
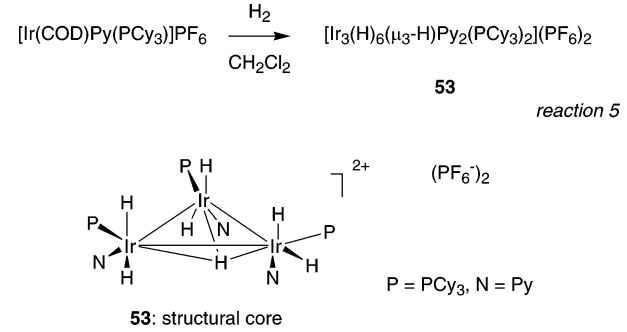
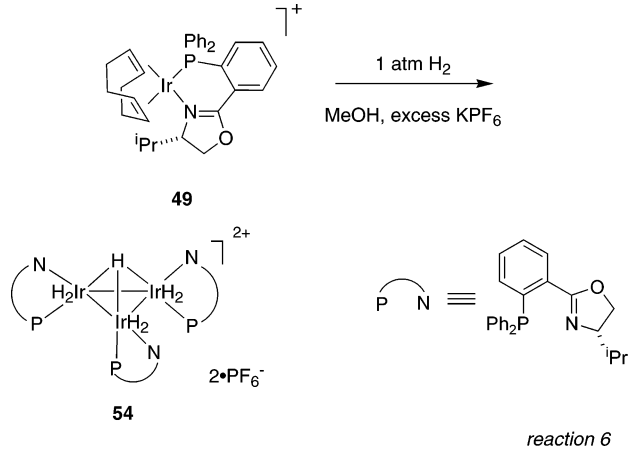


Figure 11. On the stereochemistry of addition of H_2 to chiral phosphine oxazoline complexes.

Whatever the mechanism(s) of the Ir-mediated hydrogenation reactions, early removal of the COD ligands in the mechanistic pathway is inevitable. Over 25 years ago, Crabtree had observed addition of dihydrogen to his $\{Ir(COD)L^1L^2\}^+$ systems to give $\{(H_2)Ir(COD)L^1L^2\}^+$ species.[99] The same addition reactions were recently investigated for the chiral iridium complexes **49** (Figure 11).[100] In CD_2Cl_2, the solvent used for the hydrogenation reactions, a complex mixture of hydrido complexes formed that could not be analyzed. However, in the THF-D_8, the situation is much clearer. After 5 min at −40 °C, only one of the four possible diastereomeric oxidative additions products was observed, that is, complex **50**. On warming to 0 °C, the COD ligand was lost as cyclooctane, and two of the four possible diastereomeric, disolvated complexes were formed, that is, **51** and **52**. It was concluded that these result from a combination of steric and electronic preferences. The assignments of the stereochemistries of these complexes were supported by DFT calculations to elucidate the relative energies of the stereoisomeric forms.



Crabtree had observed formation of triiridium hydride clusters, for example, **53** (reaction 5), concomitant with loss of activity of his catalysts in hydrogenation reactions,[10] and degradation products have subsequently been crystallographically characterized.[101,102] Similarly, for chiral complex **49**, trimeric iridium-hydride clusters **54** have also been isolated and crystallographically characterized (reaction 6).[103] Formation of **54** is much



slower for catalysts with BARF as the counterion than for PF_6^-. These results are significant because the trimeric iridium hydride clusters are not active as hydrogenation catalysts, so the rate of their formation is probably related to the overall number of turnovers obtained for these reactions.

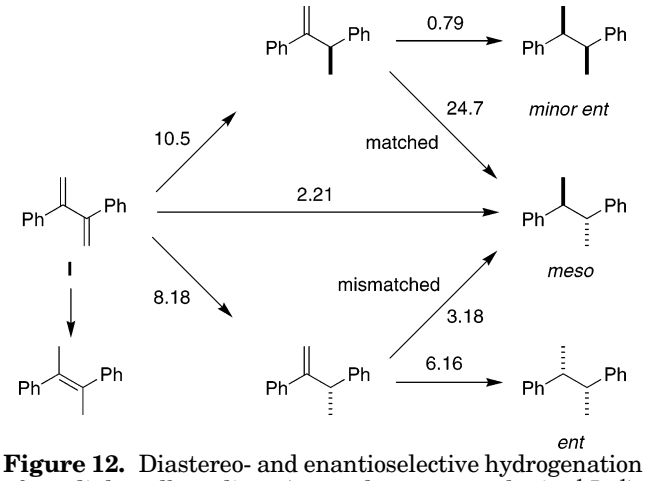
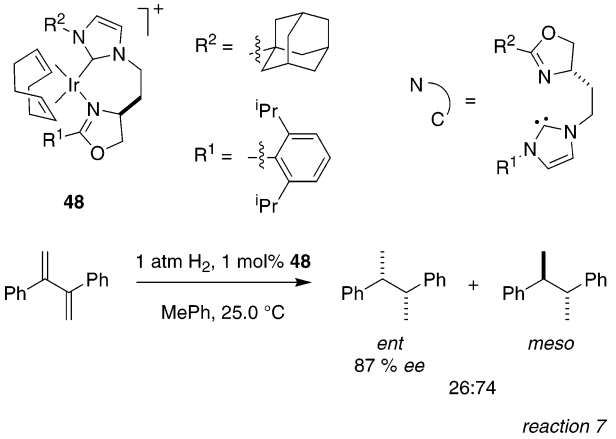


Figure 12. Diastereo- and enantioselective hydrogenation of 2,3-diphenylbutadiene (rates shown are mol min^{-1} L^{-1}).

Ultimately, it may be unwise to make too many generalizations about the mechanism of asymmetric iridium-mediated hydrogenations because they are bound to be somewhat substrate-dependent. This is obviously true for dienes, where the reaction could proceed via several pathways, many of which include half-reduction products. The particular case of hydrogenation of 2,3-diphenylbutadiene using catalyst **48** (reaction 7) has been studied in some depth.[86]



Reduction of this substrate occurs predominantly in a stepwise fashion, through monoene intermediates. There is a relatively short induction period, which is believed to correspond to reduction of COD to form the active catalyst. NMR experiments indicate that generation of active catalysts in the induction period requires both hydrogen and alkene to be present. Like hydrogenations of monoenes, the first step, diene to monoene, is zero-order in alkene and first-order in catalyst. The reaction also apparently approximates to first-order in hydrogen pressure, though gas−liquid diffusion effects become significant under conditions that favor rapid consumption of the dihydrogen dissolved in the solution, that is, high catalyst concentrations, slow stir speeds, and vessels with low surface area/volume ratios. The relative reaction rates for conditions that are close to but not yet at a point where gas−liquid diffusion effects have a significant effect are shown in Figure 12. The first phase of the hydrogenation (diene to monoene) is slower and less enantioselective than the second one.

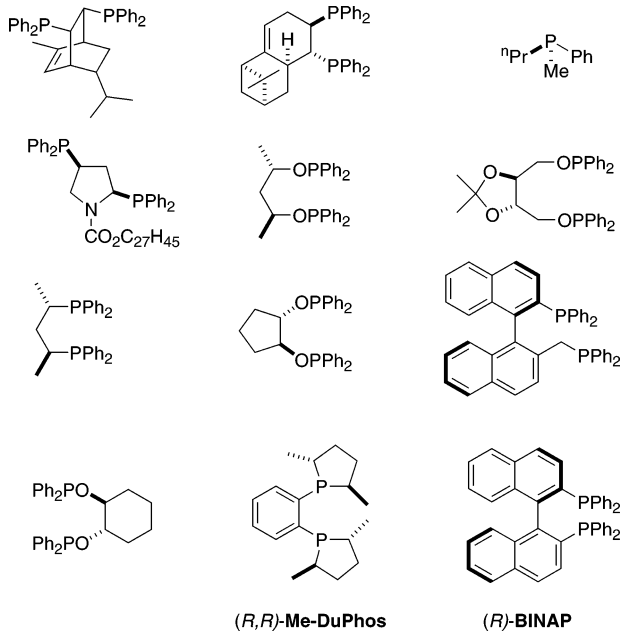


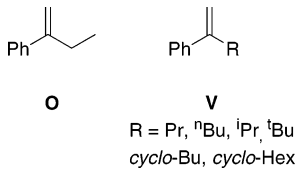
Figure 13. Chiral phosphine ligands used on rhodium or ruthenium for largely unfunctionalized alkenes.

A matched/mismatched[104] catalyst−substrate relationship is established in the second phase of the reaction (monoene to alkane). The major product is the *meso* alkane, and the major chiral product is formed in enantiomeric excesses of around 90%.

6. Rhodium- and Ruthenium-Based Catalysts

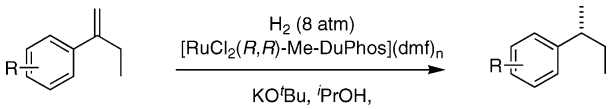
6.1. Reductions of Alkenes with Only Aryl Substituents

1,1-Disubstituted alkenes are not particularly hindered, so it is to be expected that even ones without coordinating groups could be hydrogenated using catalysts from rhodium and ruthenium. This is true, but the literature cited in this section indicates that only a small number of different substrates of this type have been studied, and no highly enantioselective method has emerged for asymmetric hydrogenations of largely unfunctionalized alkenes.



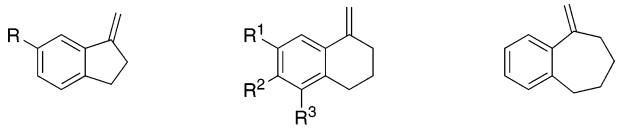
Various chiral phosphines on rhodium have been investigated as catalysts for the hydrogenation of 1,1-substituted alkenes. Figure 13 shows some of the phosphines that have been used on rhodium to hydrogenate styrene derivatives. This research originates from several groups over a period of more than 35 years, but the results are mostly disappointing.[105−113] Almost all these studies have been restricted to 2-phenyl-1-butene **O** as the sole {largely unfunctionalized} substrate, with two exceptions. Inagaki and co-workers investigated several derivatives **V**,[114] and the maximum enantioselectivity observed was for R = ^{n}Pr (77% ee). The second excep-

Table 12. Hydrogenation of 1,1-Disubstituted Alkenes Using $RuCl_2\{(R,R)$-Me-DuPhos$\}(dmf)_n/KO^tBu$ in 2-Propanol



R	S/C	conversion (%)	yield (%)	ee (%)
H	200	100	92	86
p-CH_3	330	87	83	87
p-Cl	1380	94	88	85
p-Br	660	100	89	83
m-Cl	520	87	81	89
m-Br	520	100	89	86
o-Br	390	33		69

tion is work by Takaya et al. in which they explored **O**, **V**, and the cyclic systems **W**−**Y** (R = ^{i}Pr, ^{t}Bu) using BINAP/$\{Rh(COD)X\}_2$ combinations.[115] Their best results were for **W** (100% conversion, 66% ee) and **X** (R^1,R^2,R^3 = H; only 44% conversion but 79−82% ee).[115] Chiral cyclopentadienyl rhodium derivatives of the type $\{Rh(C_5R^1{}_4R^2)Cl_2\}_2$ (R^1 = H, R^2 = neomenthyl and R^1 = Me, R^2 = menthyl) were also explored; these are active hydrogenation catalysts in the presence of triethylamine, but gave less than 13% ee for the enantioselective reduction of 2-phenyl-1-butene **O**.



W
R = H, OMe

X
R^1,R^2,R^3 = H,H,H; MeO,H,H; H,MeO,H; and, H,H,MeO

Y

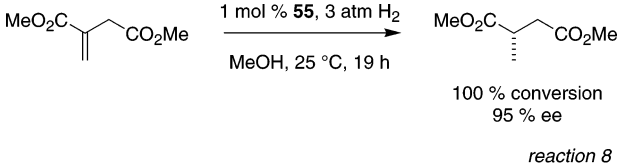
There has been comparatively little work on ruthenium catalysts for hydrogenations of 1,1-disubstituted alkenes. Alkene isomerization occurred when BINAP-based catalysts were used with several ruthenium salts, hence reducing the value of these reactions. The best data obtained were for substrate **W** (98% selectivity for the hydrogenation product and 78% ee) and **X** (R^1,R^2,R^3 = H; only 89/11 selectivity hydrogenation/isomerization, 66% ee). The second ruthenium catalyst reported for this task was from $RuCl_2((R,R)$-Me-DuPhos$)(dmf)_n/KO^tBu$ in 2-propanol.[116] Several 1,1-disubstituted 2-aryl-but-1-enes were tested, as summarized in Table 12. Under mild conditions, ee's higher than 80% are obtained for all meta- and para-substituted aryl alkenes: the highest, 89%, is close to the best results obtained with Ir catalysts. Ortho-substituted alkenes were less reactive than other isomers, presumably due to steric effects. Some of the reactions were not run to complete conversion, but, on the other hand, low catalyst loadings were used. The Me-DuPhos, KO^tBu, and 2-propanol combination was special; some other phosphines and alcohols tested gave inferior chemical or enantioselectivities. The reaction was observed to be much slower and less enantioselective in the absence of KO^tBu.

No practical homogeneous Rh- or Ru-based systems have been reported for asymmetric hydrogenations of tri- or tetrasubstituted alkenes that have only alkyl or aryl substituents. To the best of our knowledge, only one group has documented such transformations, and the times required were long and the enantioselectivities were poor.[106]

6.2. More Functionalized Alkenes

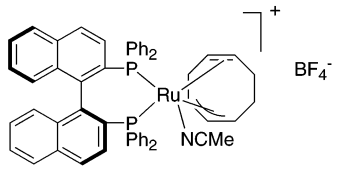
We began this review by describing how the interpretation of the term "unfunctionalized alkene" would vary from person to person. We end it by attempting to draw a boundary between the types of substrates that are definitely encompassed by this term and those that are not; consequently, beyond here, this article is not intended to be comprehensive. It is appropriate that this issue should arise in the section on rhodium and ruthenium complexes, because catalysts from these two metals clearly dominate the asymmetric hydrogenations of *functionalized* alkenes.

Alkenes that have only an ester functional group are somewhat functionalized, and in some cases, the orientation of the ester group clearly is favorable for high enantiofacial selectivities in reduction, presumably driven by coordination. A good example of this is the particular case of enol acetates, for which there has been much recent interest, and many good methods have emerged (for illustrative examples, see some of the work from Neil Boaz[117] and the Xumu Zhang,[118,119] Manfred Reetz,[120] and Albert Chan[121] groups). However, asymmetric hydrogenation may be more difficult when the alkene is arranged differently relative to the ester functionality, as the following examples illustrate.



100 % conversion
95 % ee

reaction 8



55

Enantioselective reduction of α,β-unsaturated esters is not a solved problem, though there are some promising results. Attempted reduction of methyl tiglate gave only recovered starting material under the same conditions that were used very successfully to reduce tiglic acid.[122] Conversely, another ruthenium BINAP system, **55**, has been used to reduce methyl itaconate with high enantiofacial selectivities as indicated in reaction 8.[123]

Figure 14 shows some lactones, diketene, enol ethers, and anhydrides that have been reduced

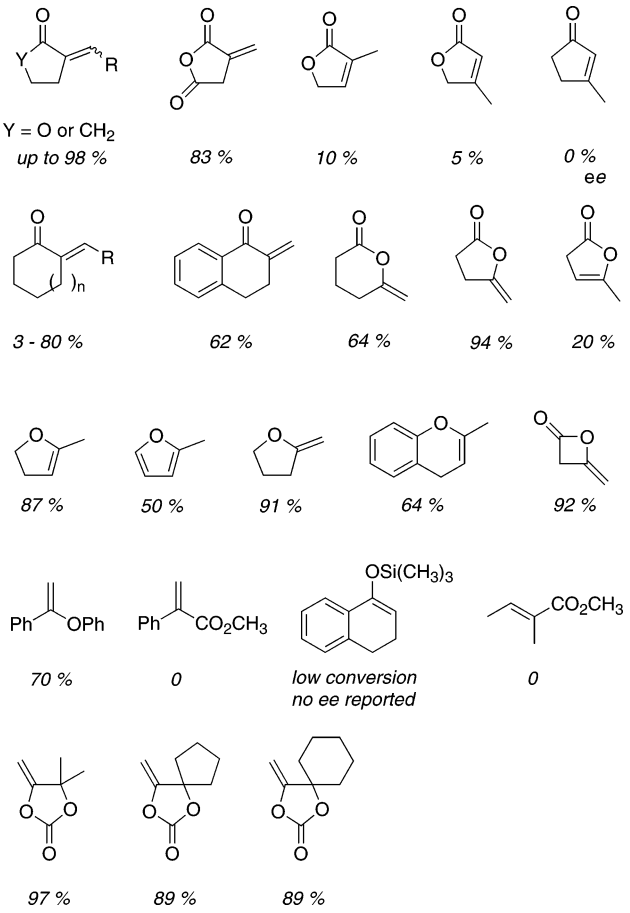


Figure 14. Some lactones, unsaturated ketones, anhydrides, enol ethers, esters, and enol carbonates that have been reduced using Ru-BINAP catalysts.

with Ru-BINAP based systems; it also shows the enantioselectivities that were obtained.[124] This chart also includes data, published by different authors,[125] for the reduction of three vinyl carbonates. A series of 2-pyrones and enones has also been hydrogenated with Rh-DuPHOS[126−128] and Ru-BINAP catalysts.[129] The results for these more functionalized substrates were good.

Overall, the data shown in Figure 14 indicate a high degree of enantiomeric excess variability with substrate type. This is undesirable for those wishing to apply the techniques to their substrate of interest: practitioners like generality and simplicity.

6.3. Allylic Alcohols[130,131]

Probably the best known example of asymmetric hydrogenations of allylic alcohols is the reduction of geraniol and nerol by Ru-based BINAP[132] catalysts such as **56**.[133−135] The reaction is notable for the high enantiomeric excesses obtained and the low substrate-to-catalyst ratios used. It proceeds with negligible reduction of the nonallylic double bond; hence the allylic alcohol functionality clearly plays an important role. For the homoallylic alcohol **Z**, the enantio-

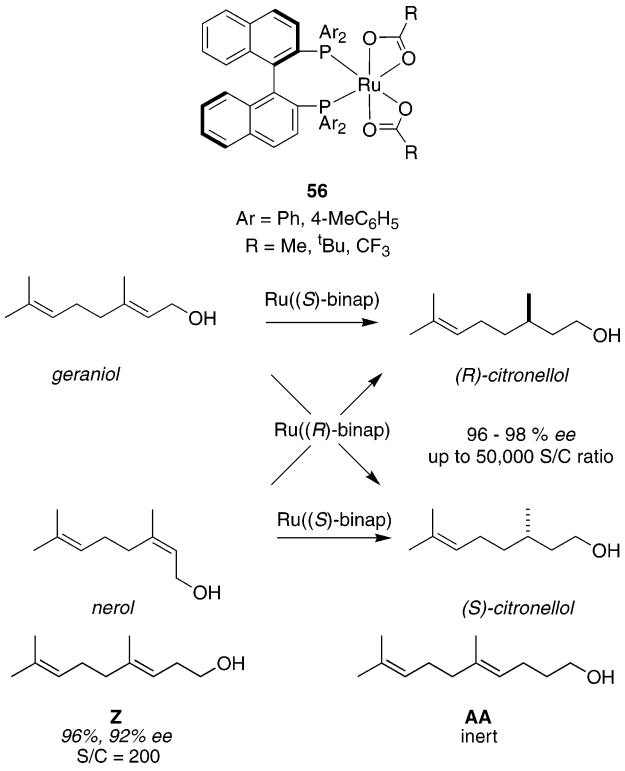
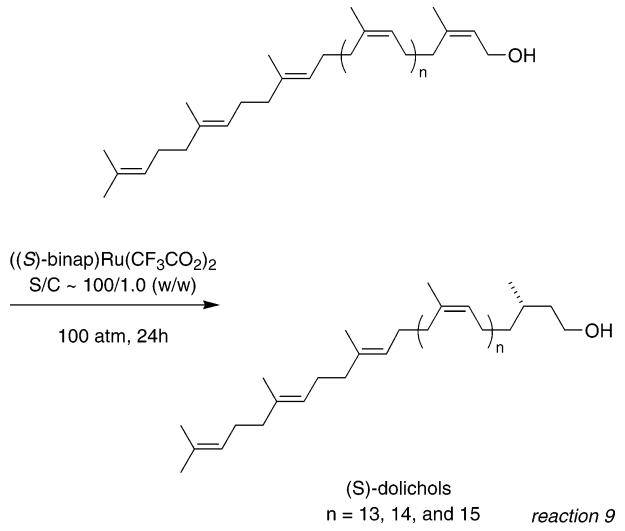


Figure 15. Noyori's reduction of geraniol and derivatives.

facial selectivity is high, but the homologue **AA** is inert (Figure 15). Reduction products from geraniol and close analogues have been used to prepare natural products.[136−139]



Ru-BINAP catalysts seem particularly well suited for prenol type substrates, and polyprenols have been reduced as in reaction 9. The stereochemistry of the chiral center produced was used to infer the *Z*-double bond geometry of the allylic alcohol double bond, such is the reliability of the sense of the facial selectivity in these reactions.[140]

Ru-BINAP catalysts can be used for catalyst-controlled diastereoselective reactions. For instan-

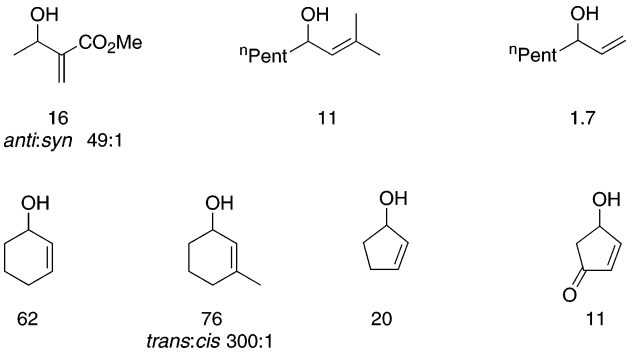
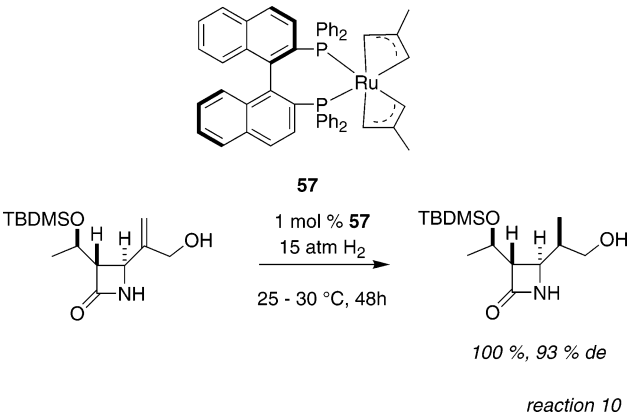


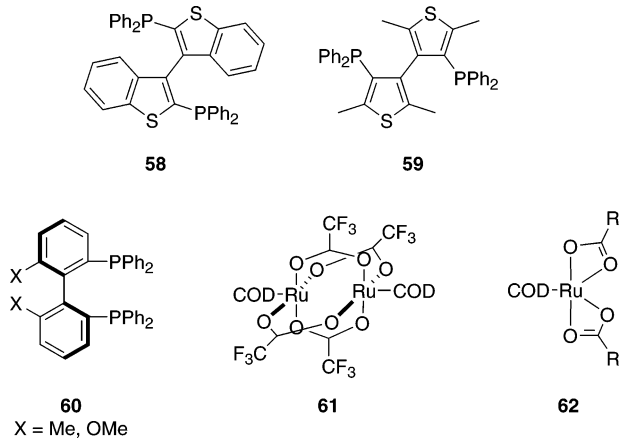
Figure 16. Relative rates of reduction of enantiomeric forms of alcohols by catalyst **56** (Ar = Ph, R = Me).

ce, the β-lactam derivative shown in reaction 10 is reduced with high conversion.[141] This transformation demonstrates that Ru-BINAP catalysts are tolerant of other functionality in the molecule.[142]

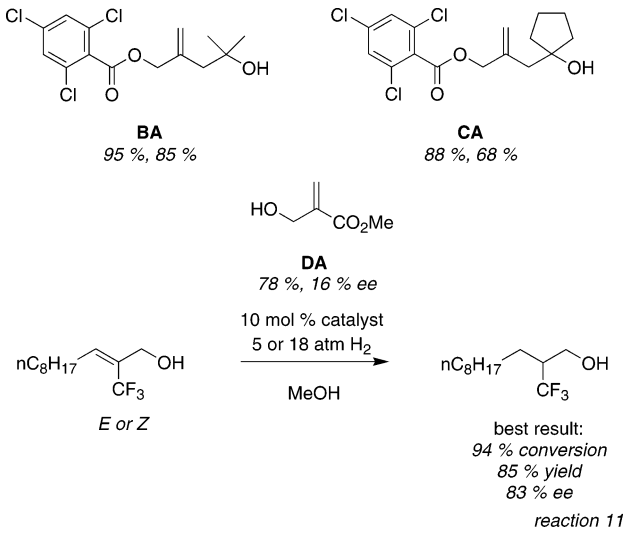


Kinetic resolutions of chiral allylic alcohols tend to proceed with relative rates of reaction of the enantiomers over 10:1, and this is usually efficient enough for a practical kinetic resolution (Figure 16). [142] A useful building block in prostaglandin synthesis is formed from the reduction of 4-hydroxy-2-cyclopentenone.

Several BINAP-derivatives and other atropisomeric phosphine ligands have been used in Ru-based reductions of allylic alcohols,[143−145] for example, **58**[146] and **59**.[147] In other cases the source of ruthenium has also been varied,[145,148] as in use of ligand **60** with complexes **61** and **62**.[149]



Despite the ligand/metal complex modifications, there are still distinct limitations of these Ru-based asymmetric reductions of allylic alcohols. For instance, it was necessary to make and test a series of different ester derivatives to obtain the relatively modest enantioselectivities shown for substrates **BA** and **CA**.[150] The data obtained in a different study on the ester-functionalized alkene **DA** were also poor.[143] Similarly, the optimal data shown for the 2-trifluoromethyl allylic alcohols in reaction 8 are less than ideal.[151] Ruthenium-based asymmetric hydrogenations of allylic alcohols do not have the generality of the corresponding reactions of ketones. Nevertheless, they tend to be the best methodology available and are usually superior to rhodium-based methods.[152,153] In fact, "directed" diastereoselective hydrogenations[154] of allylic alcohols using Rh- and Ir-based diphosphine catalysts were investigated intensively about 2 decades ago, but the results with chiral ligands to increase face selectivities were not encouraging.[155−157]



At least two challenges must be overcome to increase the generality of Ru-mediated hydrogenations. The first is to prepare catalysts, presumably a series of different ones, that will deliver hydrogen enantioselectively to allylic alcohols with diverse substitution patterns. This is difficult given the variability in this type of substrate. The second challenge is to suppress competing double bond migration reactions. Blackmond et al. discovered that geraniol (but not nerol) isomerized in the presence of Ru−BINAP catalysts, and presumably under the hydrogenation conditions.[92,94,158] The two isomers of geraniol are hydrogenated with opposite face selectivities, so this process is detrimental to the enantioselectivity of the process (Figure 17).

7. Conclusions

Only a few homogeneous catalysts, even including achiral ones, will mediate reductions of tri- and tetrasubstituted alkenes. Ones that will catalyze reduction of 1,1-disubstituted alkenes are comparatively numerous, but it is intrinsically harder to design chiral catalysts that will do so face-selectively

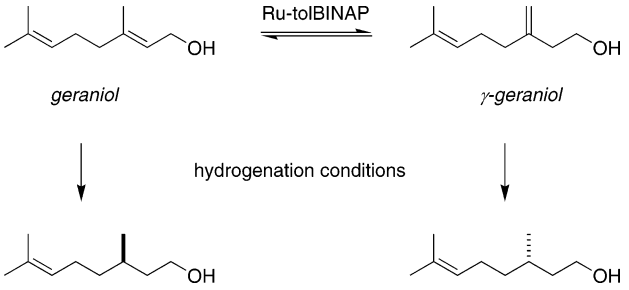


Figure 17. Competitive isomerization of allylic alcohols can occur under the conditions of Ru-BINAP mediated hydrogenations and lead to diminished enantioselectivities.

for this type of substrate. Overall, there are very few unexplored leads for the development of chiral catalysts for asymmetric reductions of largely unfunctionalized alkenes.

Outstanding among achiral catalysts for reductions of hindered alkenes is Crabtree's catalyst **2**. This has gained a level of acceptance as a reagent for organic chemistry; hence it has been used in some diverse synthetic applications[159−171] but perhaps less frequently than might be expected.

The chiral catalysts that have been used extensively to perform asymmetric reductions of largely unfunctionalized alkenes can be classified as metallocene- (mostly titanium, zirconium, and lanthanide complexes), iridium-, and rhodium/ruthenium-based. In the following several paragraphs, we shall talk about each of these in turn.

Several chiral titanocene and zirconocene catalysts have been made and tested in asymmetric hydrogenations of largely unfunctionalized alkenes (e.g., **11**−**22**). Only a few alkenes (typically three, **O**−**Q**) were tested, most gave relatively poor results, and the enantiomeric excesses were determined by polarimetry. The exception is Buchwald's work with the Brintzinger-type systems **21** for which a range of substrates were explored (Tables 4 and 5), and good, reliable enantiomeric excesses were obtained. Buchwald's zirconium catalyst is presently the best for asymmetric reductions of tetrasubstituted alkenes. Disadvantages of these catalysts are their air-sensitivities and their requirements for high catalyst loadings and, in many cases, for relatively high pressures. Lanthanide metallocenes were studied in great detail by Marks et al. This work is a mechanistic *tour de force,* but only a few substrates were studied. These are essentially 1,1-disubstituted alkenes: we infer that more hindered alkenes are not substrates from published work on similar achiral complexes. However, there is no obvious difference between Ti/Zr-based metallocenes and Ln-derived systems that implies lack of reactivity toward hindered alkenes is intrinsic to lanthanides. More likely, the ligand types so far found to form stable complexes of the lanthanides also preclude reactions with larger alkenes. The lanthanide systems are also extremely air-sensitive. Overall, less than 20 alkenes have been reported as substrates for the metallocene-based catalysts, and these alkenes tend to be structurally similar.

Pfaltz has led the search for chiral iridium catalysts for asymmetric hydrogenations of largely unfunctionalized alkenes. The first ligand type explored was the phosphine oxazoline systems **27**, but ligand development in this area has burgeoned to include many modifications (e.g., **28**−**44**) and even an effective *N*-heterocyclic carbene oxazoline ligand, **45**. Nevertheless, the number of monoene substrates that have been tested is not large (Tables 6−10, and Figure 4); they include many structurally similar trisubstituted styrene and stilbene derivatives, only a few 1,1-disubstituted alkenes, and one tetrasubstituted one. Investigation of dienes as substrates (Table 11) is adding a new dimension to the area.

Mechanistic features of iridium-mediated hydrogenations have not been proven, though DFT (and similar) calculations on this system have been particularly enlightening. This evidence, and some experimental observations, point to rapid oxidative addition of hydrogen to the catalyst precursors, removal of the COD group, and then reduction of the alkene via an Ir(3+)/Ir(5+) cycle. However, some mass spectrometric data have been interpreted to support an Ir(1+)/Ir(3+). The field awaits some definitive experiment that would clearly eliminate one of the two possibilities.

For alkene substrates with little or no coordinating functionalities, rhodium- and ruthenium-based catalysts have only been moderately successful for a few 1,1-disubstituted alkenes. The levels of induction obtained, however, would be unacceptable for most practical applications (Table 12). Ruthenium-BINAP systems (e.g., **56**), in particular, are more useful as the degree of coordinating functionality increases. Thus, some enones, unsaturated lactones, enol ethers, and similar molecules can be hydrogenated with moderately good enantiomeric excesses (Figure 14), though still not at "practical levels" in most cases. Noyori's BINAP system is considerably more effective with allylic alcohols. However, the reaction is not flawless: it is vulnerable to complications caused by double bond migration, and the number of allylic alcohols that have been reduced with good enantiomeric excesses is probably less than ten. In fact, iridium-based systems are competitive with the Ru-BINAP ones in terms of enantiomeric excesses, for allylic alcohols and α,β-unsaturated esters. The ruthenium systems, however, are superior for these substrates with respect to turnover numbers. For alkenes that are more functionalized than allylic alcohols, of course, rhodium- and ruthenium-based BINAP catalysts, and similar systems, give superb results.

Overall, this area is at an intriguing stage of development. The focus seems to be settling on iridium-based catalysts, but there is certainly a need for alternatives. More effort has been placed on ligand development for iridium systems, particularly *N*,*P*-ligands, than on investigations of substrate scope. Consequently, simple "test alkene" substrates have been explored extensively. It will be interesting to see whether the field can move beyond this and asymmetric hydrogenations of alkenes develop into a useful and widely applied synthetic method.

8. Acknowledgment

Financial support for this work was provided by The National Science Foundation (Grant CHE-0456449) and The Robert Welch Foundation (Grant A1121).

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CR0500131