J|A|C|S
ARTICLES
Published on Web 12/05/2002

Optically Active Iridium Imidazol-2-ylidene-oxazoline Complexes: Preparation and Use in Asymmetric Hydrogenation of Arylalkenes

Marc C. Perry, Xiuhua Cui, Mark T. Powell, Duen-Ren Hou, Joseph H. Reibenspies, and Kevin Burgess*

Contribution from the Chemistry Department, Texas A & M University, P.O. Box 30012, College Station, Texas 77842

Received August 14, 2002. Revised Manuscript Received September 27, 2002

Abstract: This work explores the potential of iridium complexes of the *N*-heterocyclic carbene oxazoline ligands **1** in asymmetric hydrogenations of arylalkenes. The accessible carbene precursors, imidazolium salts **2**, and robust iridium complexes **5** facilitated a discovery/optimization approach that featured preparation of a small library of iridium complexes, parallel hydrogenation reactions, and automated analysis. Three of the complexes (**5ab**, **5ad**, and **5dp**) and a similar rhodium complex (**6ap**) were studied by single-crystal X-ray diffraction techniques. This revealed molecular features of **6ap**, and presumably the corresponding iridium complex **5ap**, that the others do not have. In enantioselective hydrogenations of arylalkenes complex **5ap** was the best for many, but not all, substrates. The enantioselectivities and conversions observed were sensitive to minor changes to the catalyst and substrate structure. Ligands with aliphatic *N*-heterocyclic carbene substituents gave complexes that are inactive, and do not lose the 1,5-cyclooctadiene ligands under the hydrogenation conditions. Experiments to investigate this unexpected observation imply that it is of a steric, rather than an electronic, origin. Temperature and pressure effects on the conversions and enantioselectivities of these reactions had minimal effects for some alkenes, but profound effects for others. In one case, the enantioselectivities obtained at high-pressure/low-temperature conditions were opposite to those obtained under high-temperature/low-pressure conditions (−64% enantiomeric excess versus +89% enantiomeric excess); a transformation from one prevalent mechanism to another is inferred from this. The studies of pressure dependence revealed that many reactions proceeded with high conversions, and optimal enantioselectivities in approximately 2 h when only 1 bar of hydrogen was used. Deuterium-labeling experiments provide evidence for other types of competing mechanisms that lead to *D*-incorporation at positions that do not correspond to direct addition to the double bond.

Electron-rich carbenes have the potential to become the most interesting transition-metal ligands to emerge from the 1990s. Several factors have converged to bring this about. First, synthetic methods to prepare complexes of these ligands have improved. Early synthetic routes based on insertion of metals into the carbon−carbon double bonds of highly electron-rich alkenes[1−4] were inconvenient because the electron-rich alkenes are sensitive and not particularly accessible compounds. The discovery of carbenes that are stable at ambient temperatures[5−9] rapidly led to investigations of isolated carbenes with transition-metal compounds,[10] and interest in that area has expanded since.[9,11−13] In some cases, salts of small heterocycles can be converted directly to transition-metal carbene complexes providing an even more facile route to these materials.[14−16]

A second reason for the growing interest in transition-metal complexes of electron-rich carbenes is that they have several characteristics that make them valuable in catalysis. They tend to be air-stable materials in which the carbene ligands bind to the metal more strongly than electron-rich phosphines.[17] Their powerful σ-donating and weak π-accepting properties give metal

* Corresponding author. E-mail: burgess@tamu.edu.

(1) Hitchcock, P. B.; Lappert, M. F.; Terrenos, P.; Wainwright, K. P. *J. Chem. Soc., Chem. Commun.* **1980**, 1180−1181.
(2) Hitchcock, P. B.; Lappert, M. F.; Terrenos, P. *J. Organomet. Chem.* **1982**, *239*, C26−C30.
(3) Coleman, A. W.; Hitchcock, P. B.; Lappert, M. F.; Maskell, R. K.; Müller, J. H. *J. Organomet. Chem.* **1983**, *250*, C9−C14.
(4) Doyle, M. J.; Lappert, M. F.; Pye, P. L.; Terrenos, P. *J. Chem. Soc., Dalton Trans.* **1984**, 2355−2364.
(5) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361−363.
(6) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530−5534.
(7) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523−14534.
(8) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 725−728.
(9) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162−2187.
(10) Arduengo, A. J., III; Gamper, S. F.; Calabrese, J. C.; Davidson, F. *J. Am. Chem. Soc.* **1994**, *116*, 4391−4394.
(11) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Chem. Eur. J.* **1996**, *2*, 772−780.
(12) Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *600*, 12−22.
(13) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309.
(14) Öfele, J. *J. Organomet. Chem.* **1968**, *12*, 42−43.
(15) Wanzlick, V. H.-W.; Schönherr, H.-J. *Angew. Chem.* **1968**, *80*, 154.
(16) Herrmann, W. A.; Elison, M.; Fischer, J.; Kocher, C.; Artus, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371−2374.
(17) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370−2375.

10.1021/ja028142b CCC: $25.00 © 2003 American Chemical Society

centers that are electron-rich relative to the corresponding phosphine complexes.[18] Consequently, the carbene complexes tend to be highly active in oxidative addition reactions, but that activity can be tempered by sterically shielding the metal with umbrella-like aromatic substituents. For these reasons, complexes of electron-rich carbenes are proving to be robust and active catalysts for several different reactions[19−28] especially in alkene metathesis.[29]

Chiral modification of electron-rich carbene ligands is a logical progression in the field. Chiral, optically active, imidazolinylidines (alternatively called dihydroimidazolylidines) were first reported several decades ago[3] and several others have been reported more recently.[30−32] Chiral, unsaturated analogues of the imidazolinylidine ligands, that is, chiral imidazolylidines, have also been reported. Most of these are monodentate systems with chiral *N*-substituents,[33−35] or metalated derivatives[36] that might be expected to behave as a monodentate carbene complex in many catalytic reactions. A binaphthyl system[37] and the oxazoline-containing chelate[38] are the only robust, chiral, bidentate, unsaturated carbene complex types reported to date.

Despite these efforts to prepare optically active, electron-rich carbene complexes, there have been very few successful applications of these complexes in asymmetric catalysis. Before the work described here was submitted for communication,[39] the only asymmetric catalysis featuring *N*-heterocyclic carbene ligands involved an unspecified Heck reaction that gave enantiomeric excesses (ee's) of no more than 8%,[33] and hydrosilylation of an arylmethyl ketone with enantiomer excesses of 32% or less.[34] Since then, such ligands have been applied in an intramolecular cyclization reaction giving a product of 76% ee,[31] and in symmetry-breaking metathesis reactions that give excellent ee's in a limited number of reactions.[32,40]

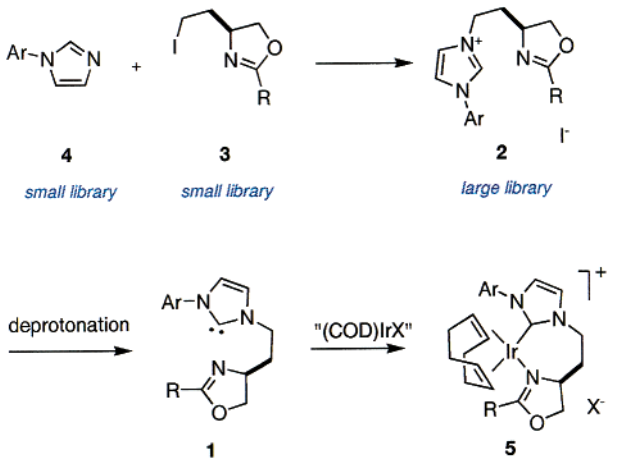


Figure 1. The concept of "reactions of libraries with libraries" applied to the carbene-oxazoline ligands **1**.

Our primary interest in catalysis is to demonstrate high-throughput methods can be used to accelerate catalyst discovery and optimization.[41−45] We believe that the slow step in such approaches is preparation of the catalyst library, rather than screening, so any advance that enables faster production of ligands with good molecular architectures for asymmetric catalysis is significant. Consequently, our thoughts settled on the new ligand design **1** (Figure 1). These are constrained, bidentate systems that seemed suitable for asymmetric catalysis. Moreover, they could be accessible via the imidazolium salts **2** obtained from the oxazoline electrophiles **3** and the imidazoles **4**; a relatively large library of ligand precursors **2** therefore could be generated from two very small libraries of synthetic constituents. This is a case in which reactions of libraries with libraries[46−49] could allow the production of a much bigger collection of compounds. For instance, if 20 imidazoles **4** were reacted with 5 oxazolines **3,** then 100 different ligand precursors could be prepared. Practically, that approach would be facilitated by the characteristics of the products **2**; these salts might be purified simply by precipitation from apolar solvents, and, unlike phosphines, the imidazolium salts **2** are easily handled, robust, air-stable materials.

Asymmetric hydrogenations of alkenes that possess little or no coordinating functionality were identified as a worthy test application of the target ligand set. Substrate types suitable for asymmetric hydrogenations include trisubstituted and tetrasubstituted alkenes (Figure 2). If these substrates have large trans-orientated substituents, then desirable types of asymmetric catalyst topographies are easier to envisage (ligands that fill diagonally situated quadrants of space, e.g., C_2-symmetric ligands). However, there simply are not many homogeneous

(18) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678.
(19) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889−9890.
(20) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307−1309.
(21) Baratta, W.; Herrmann, W. A.; Rigo, P.; Schwarz, J. *J. Organomet. Chem.* **2000**, *593*−*4*, 489−493.
(22) Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Hermann, W. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602−1604.
(23) Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123−1127.
(24) Baratta, W.; Herrmann, W. A.; Kratzer, R. M.; Rigo, P. *Organometallics* **2000**, *19*, 3664−3669.
(25) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186−190.
(26) Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348−352.
(27) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93−96.
(28) Chen, C. A.; Ren, L.; Decken, A.; Crudden, C. M. *Organometallics* **2000**, *19*, 3459−3461.
(29) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.
(30) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.
(31) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402−3415.
(32) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem Soc.* **2002**, *124*, 4954−4955.
(33) Enders, D.; Gielen, H.; Raabe, G.; Runsink, J.; Teles, J. H. *Chem. Ber.* **1996**, *129*, 1483−1488.
(34) Herrmann, W. A.; Goossen, L. J.; Kocher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2805−2807.
(35) Herrmann, W. A.; Goossen, L. J.; Artus, G. R. J.; Kocher, C. *Organometallics* **1997**, *16*, 2472−2477.
(36) Enders, D.; Gielen, H.; Raabe, G.; Runsink, J.; Teles, J. H. *Chem. Ber.* **1997**, *130*, 1253−1260.
(37) Clyne, D. S.; Jin, J.; Genest, E.; Galluci, J. C.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 1125−1128.
(38) Herrmann, W. A.; Goossen, L. J.; Spiegler, M. *Organometallics* **1998**, *17*, 2162−2168.
(39) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878−8879.
(40) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225−3228.
(41) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220−222.
(42) Burgess, K.; Moye-Sherman, D.; Porte, A. M. In *Molecular Diversity and Combinatorial Chemistry*; Chaiken, I. M., Janda, K. D., Eds.; American Chemical Society: Washington, DC, 1996; pp 128−136.
(43) Burgess, K.; Porte, A. M. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 2, pp 69−82.
(44) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180−9187.
(45) Burgess, K.; Porte, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 2465−2469.
(46) Nielsen, J.; Jensen, F. R. *Tetrahedron Lett.* **1997**, *38*, 2011−2014.
(47) Baldino, C. M.; Casebier, D. S.; Caserta, J.; Slobodkin, G.; Tu, C.; Coffen, D. L. *Synlett* **1997**, 488−490.
(48) Neustadt, B. R.; Smith, E. M.; Nechuta, T.; Zhang, Y. *Tetrahedron Lett.* **1998**, *39*, 5317−5320.
(49) Boger, D. L.; Chai, W.; Jin, Q. *J. Am. Chem. Soc.* **1998**, *120*, 7220−7225.

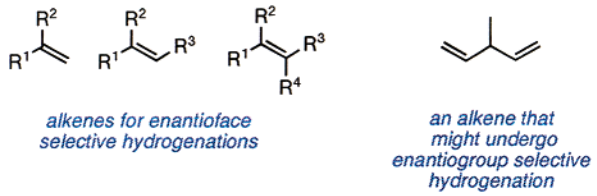
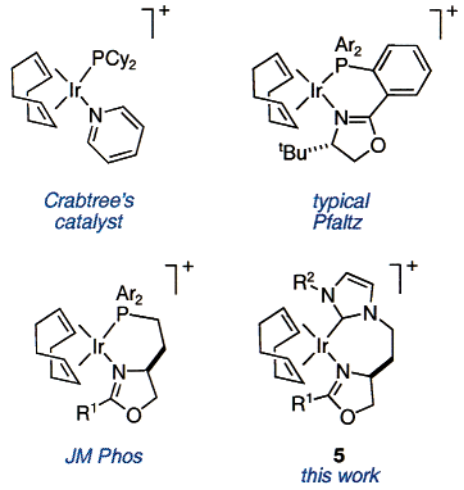


Figure 2. Types of prochiral alkenes.

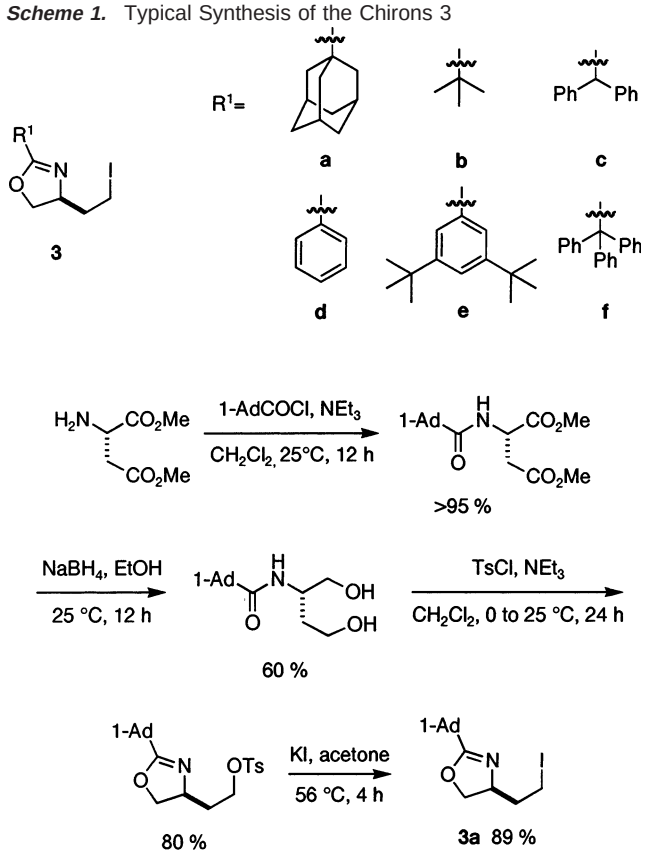
Chart 1. Asymmetric Variants of Crabtree's Catalyst



organometallic compounds known that will hydrogenate these more hindered substrates.

One class of homogeneous organometallic compounds that *will* hydrogenate tri- and tetrasubstituted alkenes are the cationic iridium complexes of the type [(1,5-cyclooctadiene; COD)Ir(py)(PR_3)]$^+$ including Crabtree's catalyst (Chart 1; R = cyclohexyl).[50] Pfaltz and co-workers recognized chiral phosphine-oxazoline ligands are similar to cis-disposed, monodentate, pyridine/phosphine ligand combinations.[51−59] Subsequently, they prepared several different types of *P*/*N*-ligands, complexed them with the "(COD)Ir" fragment, tested them as hydrogenation catalysts, and obtained some excellent enantioselectivities. The groups of Buchwald[60,61] and of Marks[62] have used titanocene, zirconocene, and cyclopentadienyl lanthanide complexes as hydrogenation catalysts for the same types of substrates. Excellent enantioselectivities have been obtained, but the catalysts are more difficult to prepare (highly air-sensitive) and harsher, less experimentally convenient conditions are required. Overall, some very important developments have occurred in the area of catalytic hydrogenations of aryl-substituted and unfunctionalized alkenes, but many challenges still remain.

Scheme 1. Typical Synthesis of the Chirons 3



These include increased enantioselectivities for a broader range of substrates, via reactions at lower H_2 pressures, and involving more accessible catalysts.

This work investigates similarities between Crabtree's catalyst, Pfaltz's phosphine-oxazoline complexes, some phosphine-oxazoline complexes prepared in these laboratories (JM Phos ligands),[63,64] and the iridium carbene-oxazoline complexes **5**. For this study, generation of a small library of complexes was ideal for two reasons. First, the ligands could be made easily, as outlined above. Second, iridium complexes of this type tend to be air-stable, and easily chromatographed if necessary, so a library of imidazolium-oxazolines **2** could potentially be transformed into the corresponding iridium complexes **5** without excessive effort.

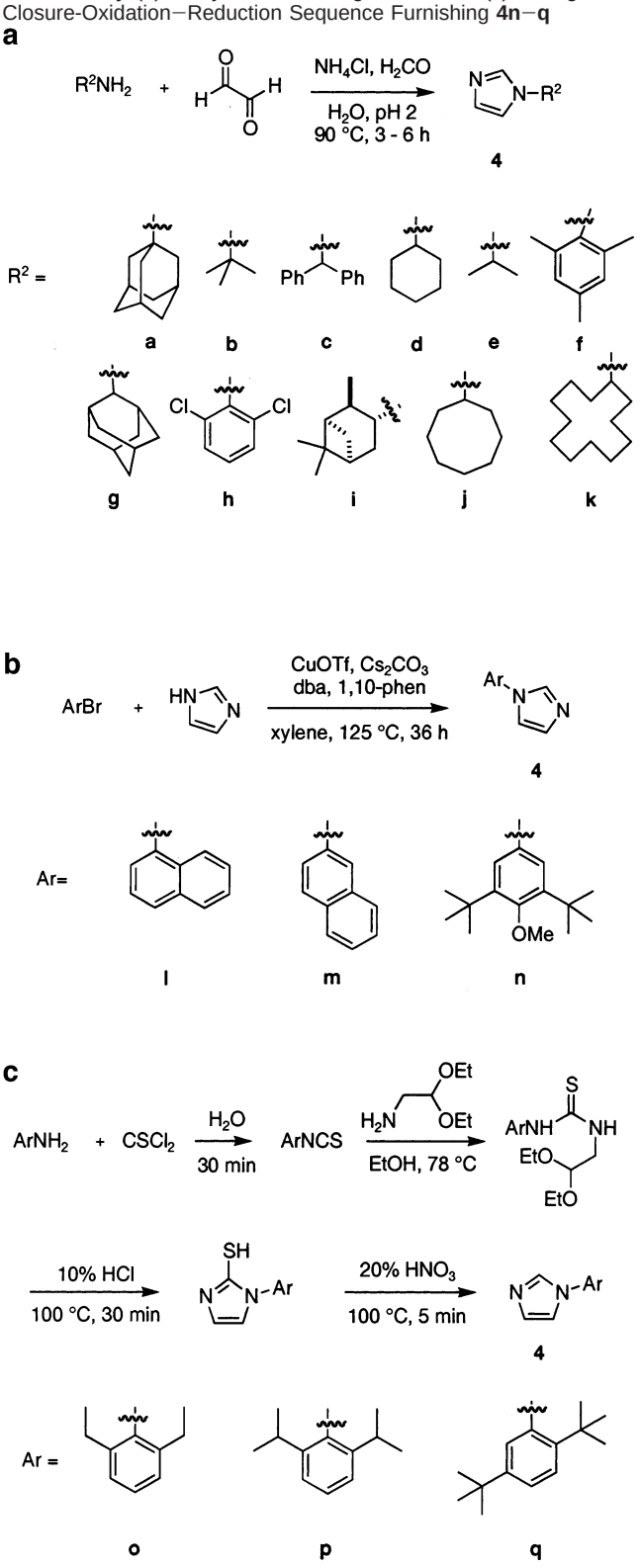
Results and Discussion

1. Preparation of the Oxazoline Electrophiles 3. Three syntheses of these chirons were developed in studies focused on the preparation of JM Phos ligands.[63,64] They each have different advantages and drawbacks regarding efficiency, scale-up, and scope for divergence. One of the most efficient is shown in Scheme 1, for oxazoline **3a**. This route and the other syntheses were used to prepare the iodides **3a**−**3f**.

2. Preparation of the Imidazoles 4. Scheme 2 summarizes the reported methods that were used to obtain the imidazoles **4a**−**4p**. The first synthesis (Scheme 2a) is a direct 1-pot condensation that works well for aliphatic amines.[65] Only a limited number of aromatic amines react well in these reactions;

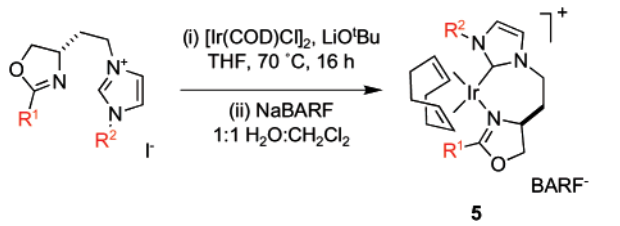
(50) Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331−337.
(51) Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F. M.; Kruger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887−892.
(52) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897−2899.
(53) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814−1816.
(54) Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Rosner, T.; Schnider, P.; Zimmermann, N. *Chirality* **2000**, *12*, 442−449.
(55) Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879−2888.
(56) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336−345.
(57) Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4445−4447.
(58) Cozzi, P. G.; Zimmermann, N.; Hilgraf, R.; Schaffner, S.; Pfaltz, A. *Adv. Synth. Catal.* **2001**, *343*, 450−454.
(59) Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, *344*, 40−44.
(60) Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569−12570.
(61) Troutman, M. V.; Appella, D. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4916−4917.
(62) Conticello, V. P.; Brard, L.; Giardello, M. A.; Tsuji, Y.; Sabat, M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 2761−2762.
(63) Hou, D.-R.; Burgess, K. *Org. Lett.* **1999**, *1*, 1745−1747.
(64) Hou, D.-R.; Reibenspies, J.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206−215.
(65) Gridnev, A. A.; Mihaltseva, I. M. *Synth. Commun.* **1994**, *24*, 1547−1555.

Scheme 2. Synthesis of the Imidazoles: (a) Direct Condensation to Give **4a**−**j**, (b) *N*-Arylation Affording **4k**−**m**, and (c) a Ring Closure-Oxidation−Reduction Sequence Furnishing **4n**−**q**



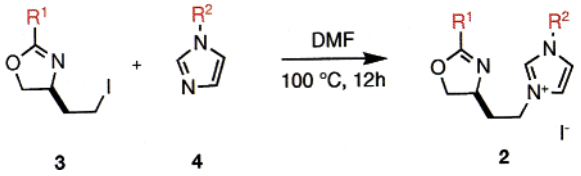
two such cases are shown (compounds **4f** and **4h**), but several that were tried did not work (e.g., R^2 = 3,5-$Me_2C_6H_3$, and 1-Nap). Scheme 2b shows another one-step route to the compounds. That approach works well for unhindered aromatic amines,[66] but scale-up is inconvenient because 1 equiv of 1,10-phenanthroline is used, and this basic heterocycle can be difficult to separate from the imidazole product; in fact, a column is always required. The last route that was used (Scheme 2c) involves multiple steps and is only applicable to aromatic amines.[67] This approach works well for scale-up purposes because no chromatographic separations are required.

Table 1. Carbene−Oxazoline Complexes Prepared



5	R^1	R^2	5	R^1	R^2
ab	1-Ad	^{t}Bu	**aq**	1-Ad	2,5-^{t}Bu$_2$C$_6$H$_3$
ac	1-Ad	$CHPh_2$	**ba**	^{t}Bu	1-Ad
ad	1-Ad	Cy	**bb**	^{t}Bu	^{t}Bu
af	1-Ad	2,4,6-$Me_3C_6H_2$	**bc**	^{t}Bu	$CHPh_2$
an	1-Ad	3,5-^{t}Bu$_2$-4-MeOC_6H_2	**bp**	^{t}Bu	2,6-^{i}Pr$_2$C$_6$H$_3$
ao	1-Ad	2,5-$Et_2C_6H_3$	**cp**	$CHPh_2$	2,6-^{i}Pr$_2$C$_6$H$_3$
ap	1-Ad	2,6-^{i}Pr$_2$C$_6$H$_3$	**dp**	Ph	2,6-^{i}Pr$_2$C$_6$H$_3$

3. Preparation of the Imidazolium Salts 2. The imidazolium salts **2** were prepared via S_N2 displacements of iodide from the electrophiles **3** by the imidazoles **4**. At the end of each reaction, the solvent was removed, and the residue was washed with diethyl ether, then dried under vacuum; the products were pure enough to use in the complex formation steps.



4. Preparation of the Iridium Complexes 5. Table 1 shows how the complexes **5** were prepared by using 1.5 equiv of *tert*-butoxide to deprotonate the imidazolium salt to give the corresponding carbene. In general, the complexes were air-stable and easily purified via flash chromatography. In some cases, especially where the substituents involved were bulky, the reaction was not clean, and the desired complex was not isolated (e.g., **5ep** where R^1 = 3,5-^{t}Bu$_2$C$_6$H$_3$; R^2 = 2,6-^{i}Pr$_2$C$_6$H$_3$). However, in most cases where a particular R^1 and R^2 combination does not appear in Table 1, we simply did not attempt to make it. This is because the screening process described below began as soon as the first batches of complexes were prepared, and continued as more were made, so we were able to focus our library of complexes in response to the data emerging from the screens.

5. Crystallographic Analyses of Illustrative Complexes. Three iridium complexes, **5ab**, **5ad**, **5dp**, and the rhodium complex **6ap** were analyzed via single-crystal X-ray diffraction (Supporting Information). The latter was made because we were unable to obtain X-ray crystals of the complex that later emerged as the most enantioselective in many reactions, **5ap**. The coordination spheres of the Ir atoms in **5ab** and **5ad** and of the

(66) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657−2660.
(67) Johnson, A. L.; Kauer, J. C.; Hsarma, D. C.; Dorfman, R. I. *J. Med. Chem.* **1969**, *12*, 1024−1028.

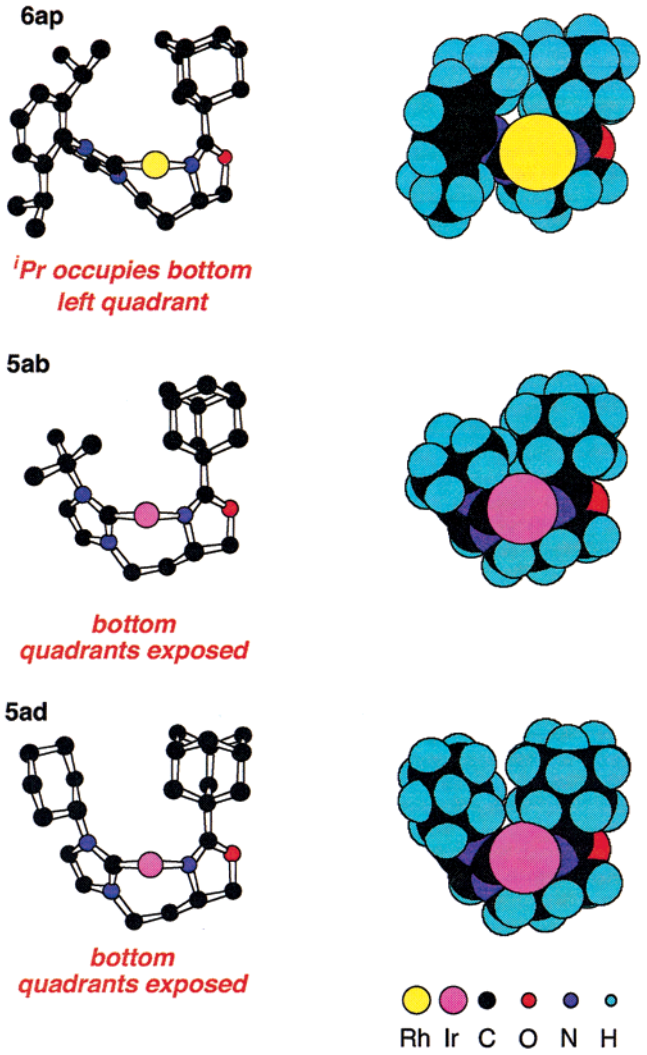


Figure 3. Comparison of structures **5ab**, **5ad**, and **6ap**, side-on with COD ligand omitted ($BARF^-$ counterion not shown).

Rh atom in **6ap** can be described as *pseudo*-square planar. The chiral ligands in the complexes exist as U-shaped entities in which the imidazolylidine and oxazoline substituents are projected above the metal square plane (Figure 3). For complexes **5ab** and **5ad** the imidazolylidine substituent, i.e., the *tert*-butyl group of **5ab** and the cyclohexyl of **5ad**, only fill space above the metal. The corresponding group for **6ap**, 2,6-$^{i}Pr_2C_6H_3$, is larger, it interacts more with the oxazoline substituent (1-Ad), and projects into an area in front of, below, and to the left of the Rh-square plane (when viewed in the orientation indicated in Figure 3). This fundamental difference between the complex with the 2,6-$^{i}Pr_2C_6H_3$-substituent and the rest, may, by inference, provide an insight into the unique reactivity of corresponding iridium complex **5ap** (vide infra).

6. Enantioselective Hydrogenations with Complexes 5. (a) Effects Of Catalyst Structure. Figure 4a summarizes yield and enantioselectivity data that were obtained in the early screens with some representative complexes **5** in which the *N*-heterocyclic carbene ligand substituent (R^2) was always 2,6-di-*iso*-propylphenyl, but the oxazoline substituent R^1 was varied. Both the yield and enantioselectivity of the catalyst were highly dependent on R^1. Unsatisfactory chemical and optical yields

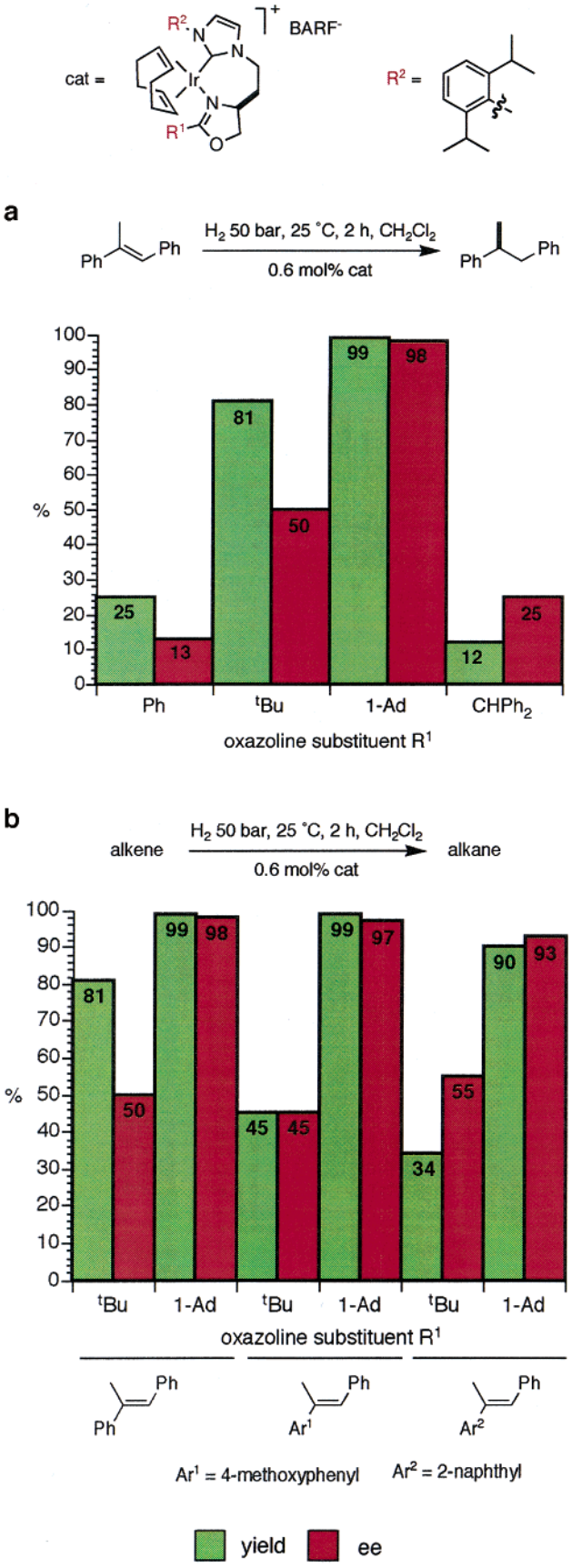


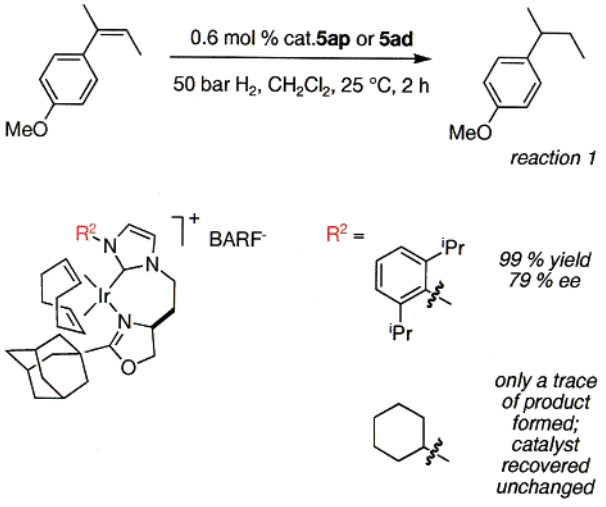
Figure 4. Yield and enantioselectivity data for asymmetric hydrogenations (a) using catalysts with four different oxazoline substituents; and (b) using catalyst **5bp** and **5ap** to compare R^1 = ^{t}Bu and 1-Ad for three different alkenes.

were obtained for R^1 = Ph, ^{t}Bu, and $CHPh_2$, but both the results were excellent for R^1 = 1-Ad (i.e., 1-adamantyl, complex **5ap**).

The contrast between the catalysts where R^1 is *tert*-butyl (**5bp**) and 1-adamantyl (**5ap**) in these initial screens was remarkable, so further experiments were undertaken to probe if the trends observed also apply to asymmetric hydrogenations of other substrates (Figure 4b). In direct comparisons for three different alkenes, the 1-admantyl complex **5ap** gave superior chemical and optical yields to the *tert*-butyl complex **5bp**. These observations show slight topographical differences in the ligand that can dramatically affect the performance of the catalyst.

The imidazolylidine substituent (R^2) can also have dramatic effects on the results obtained for a given substrate. Figure 5 shows data that illustrate this. Catalysts **5ao** and **5ap** are structurally similar, differing only slightly in the *N*-heterocyclic carbene substituent, but **5ao** is marginally more effective for one of the substrates shown and **5ap** gives better data for the other.

A surprising observation was made when the screen was expanded to include other variations of the heterocyclic carbene portion (R^2) while retaining the 1-adamantyl R^1 substituent. Hydrogenation of the 4-methoxyphenyl-substituted alkene shown in reaction 1 with catalyst **5ap** (R^2 = 2,6-^{i}Pr$_2$C$_6$H$_4$) gave good conversion and high ee as expected. However, a similar catalyst **5ad** that has R^2 = cyclohexyl (Cy) gave almost no detectable conversion. Moreover, in the latter case, the catalyst was recovered unchanged at the end of the reaction; the COD ligand had not been removed. This was confirmed in an experiment in which the two complexes were maintained under 1 atm of H_2 in $CDCl_3$ for 3 h; catalyst **5ap** was transformed into a mixture of products whereas **5ad** was unchanged. Lack of reactivity of 1,4-cyclooctadiene complexes is not surprising because this type of phenomenon has been reported several times before in the literature,[68,69] but the contrast between catalysts **5ap** and **5ad** is remarkable. Other experiments (data not shown) indicated complexes **5ab** and **5ad** were unreactive as catalysts in similar reactions; both have aliphatic R^2 substituents on the *N*-heterocyclic carbene.



Two dicarbonyl derivatives **7** and **8** were made to investigate possible electronic differences at the iridium center caused by

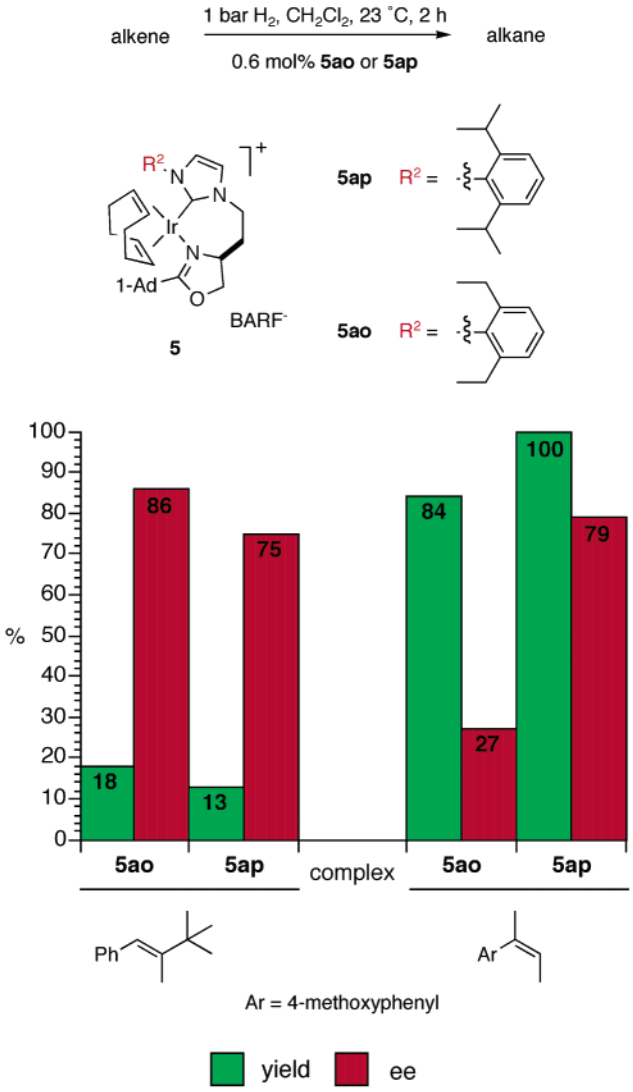
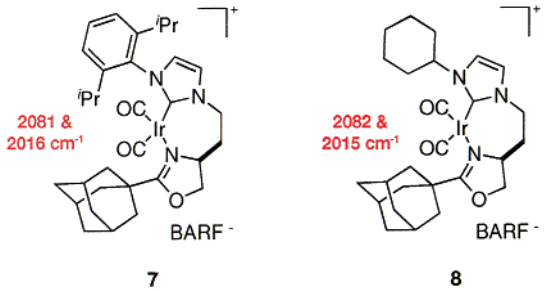


Figure 5. A comparison to illustrate the effects of minor changes to the imidazolylidine substituent R^2, that is, for **5ao** (R^2 = 2,6-Et$_2$C$_6$H$_3$) and **5ap** (R^2 = 2,6-^{i}Pr$_2$C$_6$H$_3$).

the *N*-heterocyclic carbene substituent. There was, however, no significant difference in the metal carbonyl IR stretches for the two complexes. Apparently, the reactivity differences observed in reaction 1 most probably have steric origins.



(b) Some Effects of Changing the Alkene Substrate. As a result of the data described above and other studies (Supporting Information), the subsequent work focused on complex **5ap** (R^1 = 1-Ad, R^2 = 2,6-^{i}Pr$_2$C$_6$H$_3$). Figure 6 shows chemical and optical yields for hydrogenations of six alkenes having methyl, ethyl, and *iso*-propyl substituents in cis- and trans-orientations

(68) Drexler, H.-J.; Baumann, W.; Spannenberg, A.; Fischer, C.; Heller, D. *J. Organomet. Chem.* **2001**, *621*, 89−102.
(69) Borner, A.; Heller, D. *Tetrahedron Lett.* **2001**, *42*, 223−225.

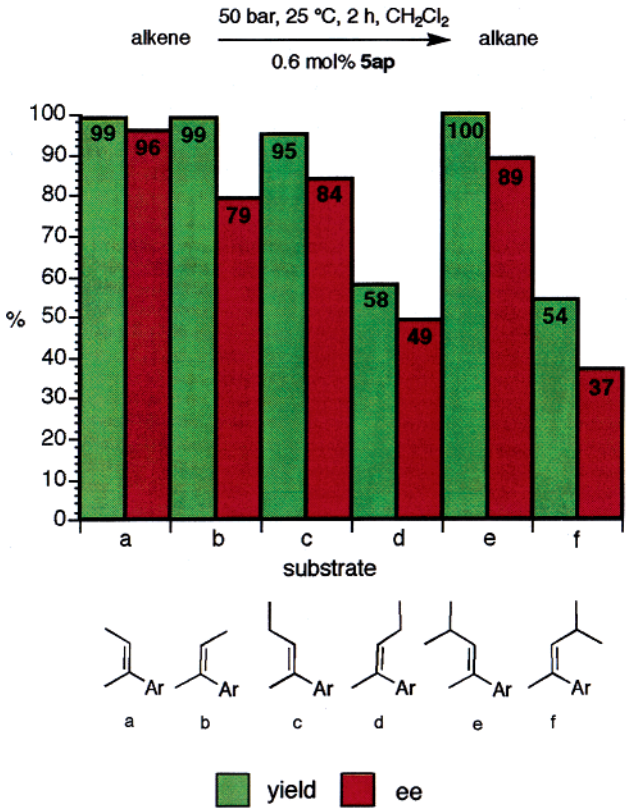


Figure 6. Yield and enantioselectivity data for hydrogenation of 2-(4-methoxyphenyl)-alkenes (Ar = 4-$MeOC_6H_4$) using catalyst **5ap**.

relative to the aryl substituent. In general, *E*-alkenes produced better results than their cis-isomers.

(c) Temperature and Pressure Effects. The next step in this study was to investigate temperature and pressure effects. Figure 7a shows the effects of temperature in the hydrogenations of three isomeric cis-, trans-, and 1,1-disubstituted alkenes. The cis- and trans-alkenes show almost no temperature dependence, but there is a remarkable enantioselectivity variation for the 1,1-disubstituted alkene. These experiments show that the variation of enantioselectivities with temperature is substrate dependent, and that it is impossible to generalize on the effects of temperature for a range of substrate classes.

Figure 7b shows the pressure effects on the hydrogenation of six different alkenes. Three of these substrates show no significant yield or enantioselectivity variations with pressure. For both isomers of 2-(4′-methoxyphenyl)-4-methylpent-2-ene, the enantioselectivities of the hydrogenation reactions varied with pressure, and ee/pressure correlations were observed for the 1,1-disubstituted alkene (the same substrate that showed interesting ee/temperature dependence in Figure 7a). Because enantioselective hydrogenations of 1,1-disubstituted alkenes are generally difficult, a set of experiments were undertaken to optimize the enantioselectivity of hydrogenation of this substrate *in favor of either enantiomer*. Two aspects of the data obtained in those experiments (Figure 8) are notable. First, the enantioselectivity, and presumably the prevailing mechanism, switches abruptly on varying the conditions between −15 °C, 85 bar and 25 °C, 1 bar. High concentrations of hydrogen in solution (low temperature and high H_2 pressure) favor formation of the (*S*)-enantiomer, whereas the (*R*)-antipode is preferred when the concentration of hydrogen in solution is low. Second, the

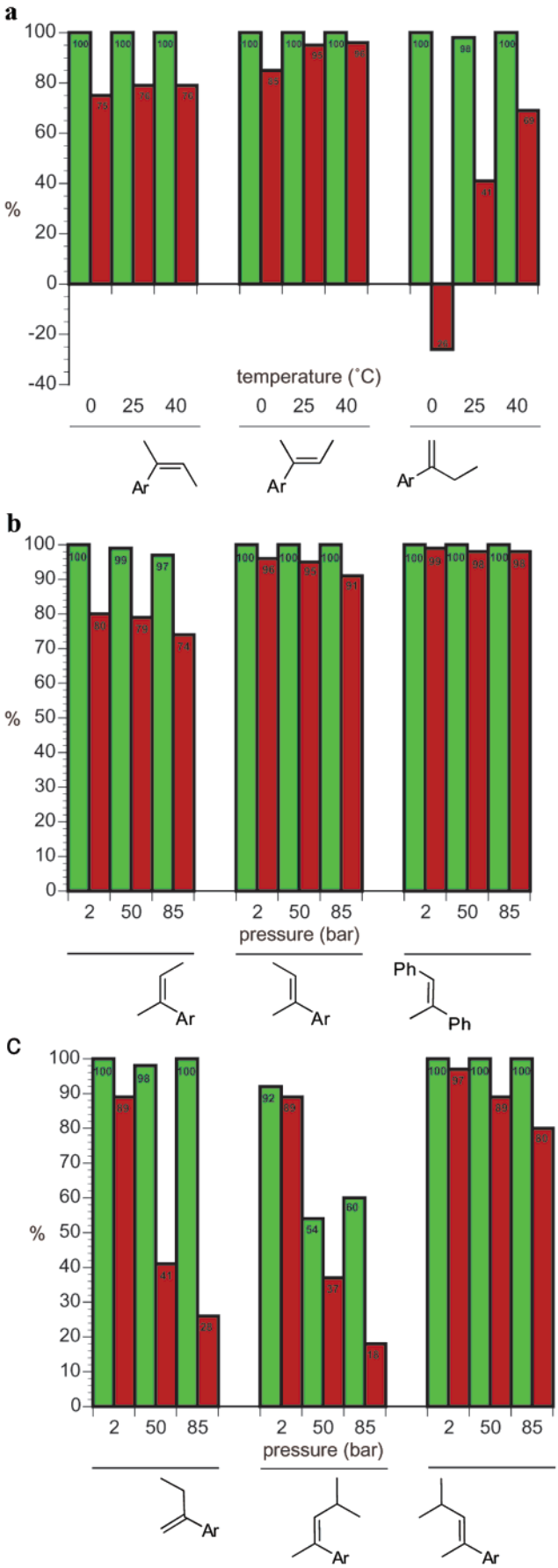


Figure 7. (a) Temperature effects in hydrogenations of three isomeric alkenes and (b) pressure effects in hydrogenations of five alkenes (throughout Ar = $MeOC_6H_4$).

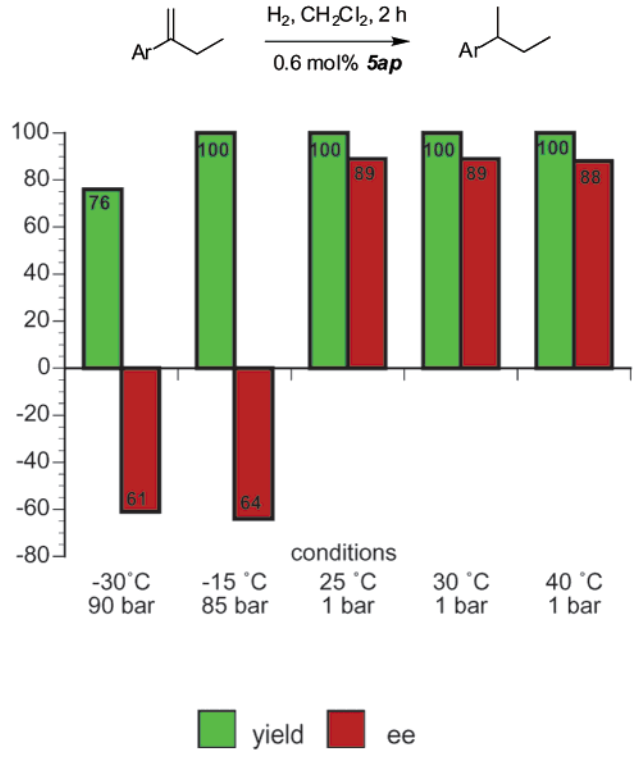
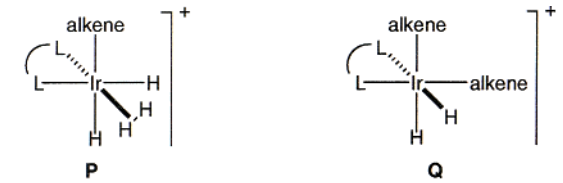


Figure 8. Optimization of enantioselectivity of hydrogenation of one substrate based on the temperature and pressure effects outlined in Figure 7, parts a and b. Throughout Ar = 4-MeOC$_6$H$_4$.

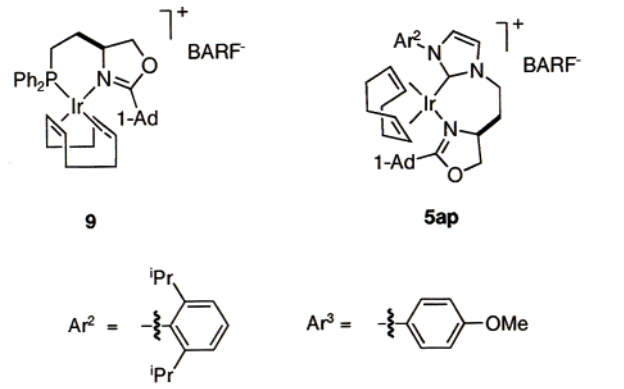
variation of enantioselectivity observed is much greater than Pfaltz and co-workers reported for the same substrate using their catalysts (e.g., 62% ee at 50 bar and 85% ee at 1 bar).[59]

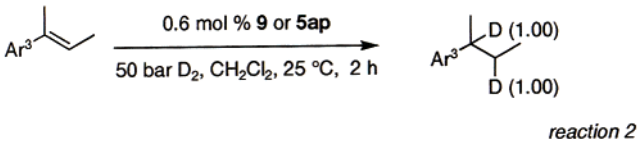
Pronounced variation of enantioselectivities with hydrogen concentration in solution is indicative of two (or even more) different mechanisms that happen to give opposite enantiomers; one pathway predominates at low [H_2] (high temperature and low pressure) and the other dominates at high [H_2]. The variation of enantioselectivities between the extremes is surprising, especially because several other substrates do not exhibit this behavior.

The enantioselectivity changes noted above imply the prevailing mechanism varies with the amount of hydrogen in solution, that is, [H_2] impacts the first irreversible step that sets the enantioface selection. Oxidative addition of hydrogen across iridium tends to occur at lower temperatures than similar transformations for rhodium complexes.[50,70,71] However, it is conceivable that at higher temperatures and low H_2 pressures oxidative addition of H_2 is slow enough to directly impact the enantiofacial selectivity of the reaction, whereas at high [H_2] another step in the mechanism is critical. Another explanation for the temperature and pressure effects is that the types of intermediates that might be involved are **P** and **Q** below, that is, two alkenes might be coordinated to the metal in the intermediate that precedes the enantioface-determining step in the process, particularly under low [H_2] conditions. Crabtree has discussed the possibility that two alkenes are coordinated in hydrogenations involving his catalysts.[72]

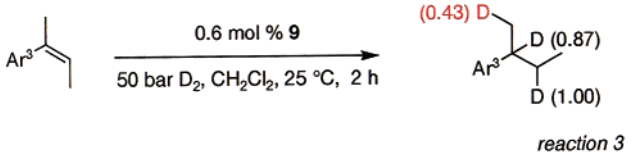


Most of the prior work on enantioselective, iridium-mediated hydrogenations has featured reactions performed at 50 bar, and relatively little emphasis was placed on the effects of using lesser pressures. The data shown in Figure 7 show that the reactions

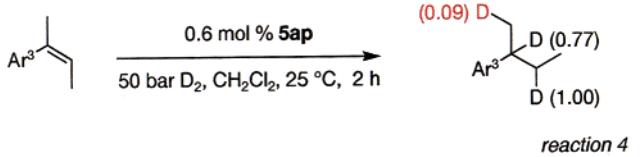




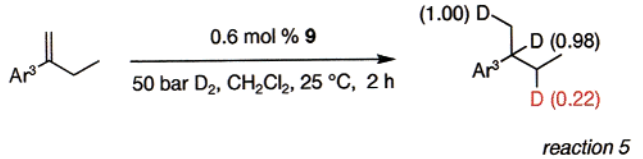
reaction 2



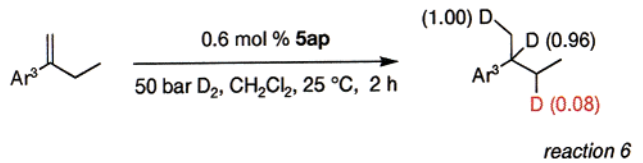
reaction 3



reaction 4

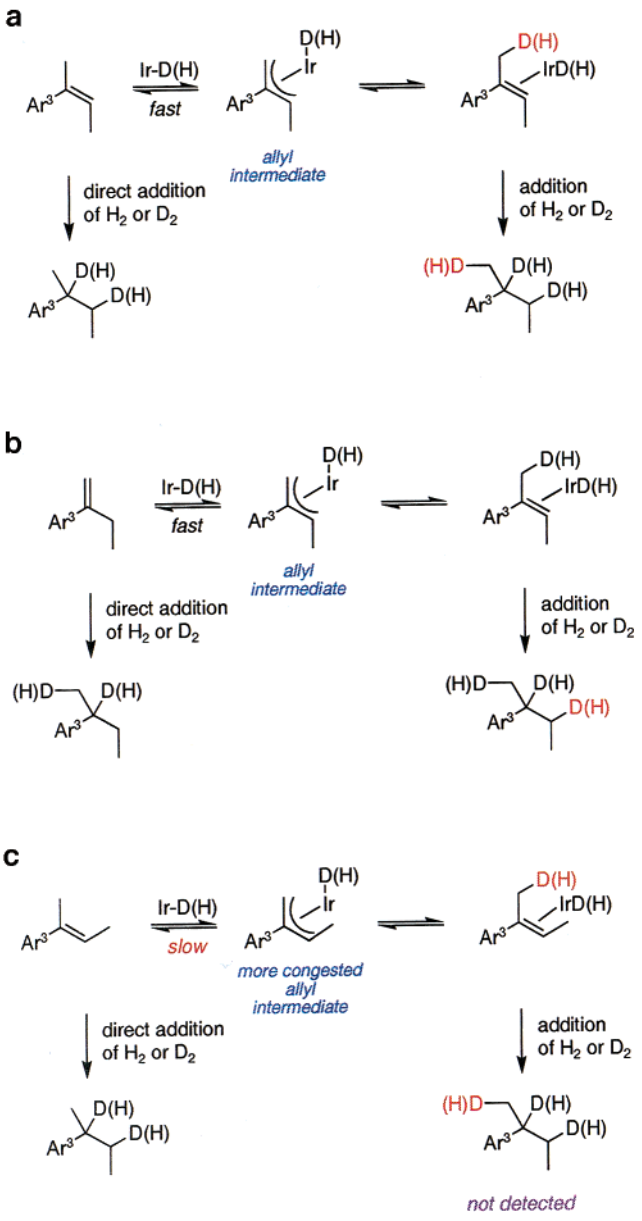


reaction 5



reaction 6

Scheme 3. A Possible Mechanism To Account for "Unexpected" Deuterium Incorporation Illustrated for Isomeric *Z*- and 1,1-Disubstituted Alkenes That Do Give Anomalous Incorporation, and an *E*-alkene That Does Not



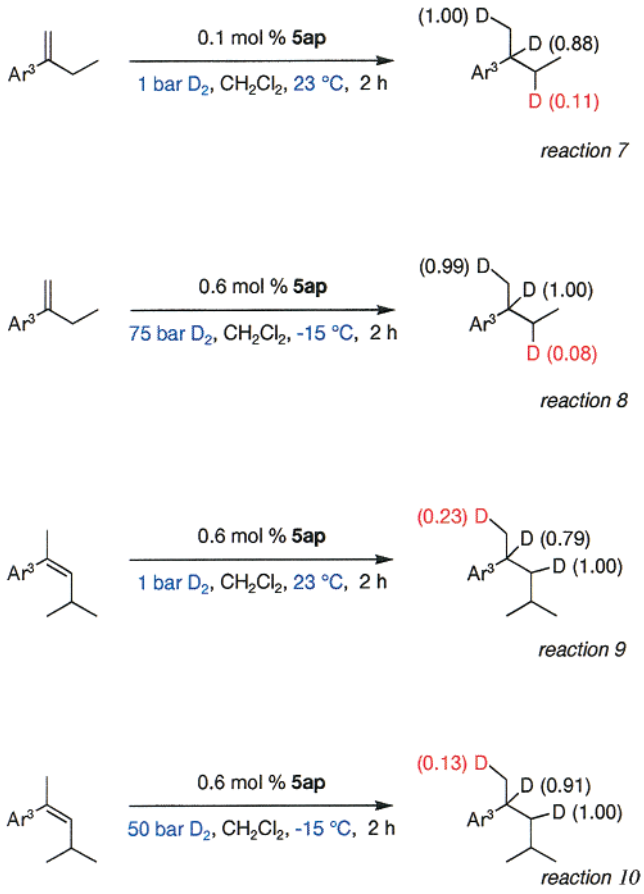
tend to proceed to completion with optimal ee's when only one atmosphere of hydrogen is used. This is important with respect to experimental convenience and scale-up issues.

(d) Deuterium Labeling Studies. In labeling experiments, incorporation of deuterium at positions that do not correspond to direct addition to the double bond are indicative of competing mechanisms. Reaction 2 illustrates a case where only direct addition is observed (values quoted relative to the maximum, set at 1.00, with the results of indirect addition shown in red), but evidence for indirect incorporation pathways was obtained for several other substrates. Mass spectra data indicate that when deuterium scrambling is observed, more than two deuteriums can be incorporated into the product.

Scheme 3 shows a possible mechanism for the incorporation of deuterium at unexpected positions as indicated. It is based on similar mechanisms proposed by Brown and co-workers for similar reactions of Crabtree's catalyst.[73] This is not the only possibility, but formation of allyl intermediates neatly explains why deuteration of the isomeric alkenes shown in Scheme 3a,b gives deuterium incorporation at anomalous positions. We propose that the third isomeric alkene shown in Scheme 3c does not give anomalous incorporation because a more congested allyl intermediate would be involved.

Comparison of the data from reactions 3−6 shows that the carbene complex **5ap** gives less of these competing processes than the phosphine oxazoline **9**, at least in the reactions explored to date. This is significant because the enantioselectivities are easier to control for reactions that have fewer competing mechanistic pathways.

Reactions 7−10 explore a different issue related to the two substrates that were previously found to undergo profound variations of enantioselectivities with hydrogen pressure in the hydrogenation process, probably because of a change in the predominant mechanism of the hydrogenation process on varying the conditions between high H_2 pressure/low temperature and low H_2 pressure/high temperature. If the competing pathways in Figures 7 and 8 were the dominant "second mechanism" then near-complete double-bond migration before hydrogenation would be expected under some conditions. The data show that for both substrates this is not so: there is marginally *less* deuterium scrambling under high-H_2-pressure/low-temperature conditions (compare reactions 7 and 8, and 9 and 10); hence, there is no evidence for complete double-bond



(70) Kimmich, B. F. M.; Somsook, E.; Landis, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 10115−10125.
(71) Crabtree, R. H.; Uriarte, R. J. *Inorg. Chem.* **1983**, *22*, 4152−4154.

shift before the reduction step, that is, double-bond migration does not correlate with the mechanistic change inferred from the temperature/pressure effects shown in Figure 6.

Conclusions

N-Heterocyclic carbene ligands are useful in asymmetric hydrogenation processes. Their complexes are reasonably stable and easy to prepare from robust imidazolium salts, which in turn are conveniently accessible by combining libraries of oxazoline electrophiles and imidazole nucleophiles. Many of the reactions performed with the carbene complexes can be run at room temperature and 1 bar of hydrogen; hence, the reactions are experimentally convenient, whereas the same reactions using *P*-oxazoline-based catalysts generally have been performed using 50 bar of hydrogen.

When this study was initiated, there was no guiding concept for how the ligands should be designed. None of the proposed ligand structures were C_2-symmetric, nor do they have PAr_2 aryl groups to provide edge-face arrangements about the metal.[74] To be effective, ligands **1** had to provide asymmetric environments for catalysis in other ways. It would have been very difficult to predict ideal combinations of the ligand R^1 and R^2 groups required for this, especially because the mechanistic uncertainties preclude reliable predictions via modeling. Efficient routes to a small library of catalysts and parallel screening methods were therefore valuable for this project.

The structural data that have now been obtained (Figure 3) hint at the desirable molecular characteristics of ligand **1ap** relative to two others (**1ab** and **1ad**). Figure 9a shows this ligand in complex **6ap**. In this graphic, the area of space around the metal center in complex **6ap** is divided into eight regions on the basis of the C−Rh−N plane, so the Rh−C and Rh−N bonds make angles of approximately 45° with the *x* and *z* axes. The quadrants of space may then be labeled NW, NE, SW, SE, front and back. In **6ap** the 2,6-$^{i}Pr_2C_6H_3$ imidazolylidine substituent penetrates into the front NW quadrant, and a little into the front SW quadrant. Ligand **1ab** in the corresponding iridium complex, where $R^2 = {}^{t}Bu$, has less steric influence on events in the front quadrants around the metal (Figure 9b).

This analysis does not imply that *all* carbene oxazoline ligands should be modeled on ligand **1ap** because, as illustrated in Figure 4c, optimal results will be obtained by modifying the ligand to match specific substrates. However, it is likely that the steric presence of the ligand in the octants of space around the metal where substrate binds will tend to be critical.

The mechanisms of hydrogenation of alkenes with the catalysts presented here, those for Pfaltz' complexes, and even the achiral systems developed by Crabtree more than 25 year ago, are unknown. The work described here illustrates factors that complicate mechanistic work in this area. For instance, temperature and pressure effects are such that, for some substrates, but not others, different mechanisms prevail according to the conditions. Scrambling of deuterium labels demonstrate that minor competing pathways are also operative. Nevertheless, high enantioselectivities were obtained here for several substrates.

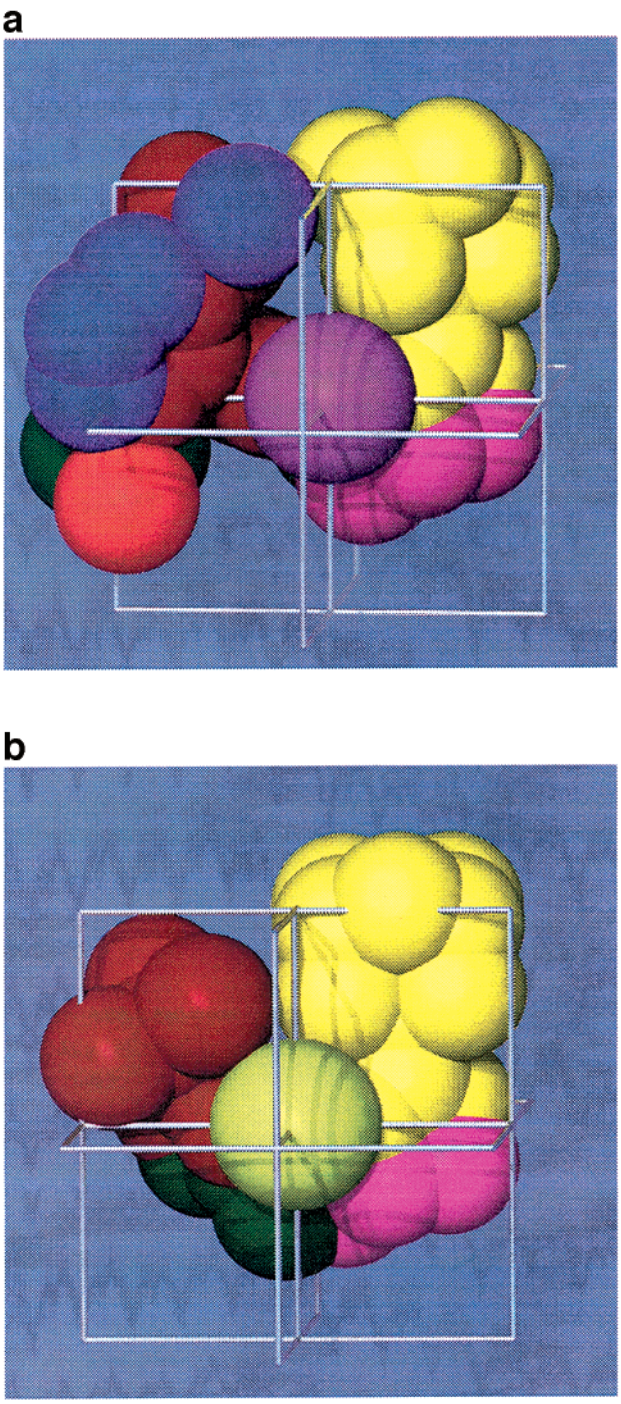


Figure 9. Octants of space around the metal in (a) **6ap** and (b) **5ab**.

Carbene oxazoline ligands are potentially useful for other types of asymmetric catalysis, including other hydrogenations, some oxidative processes, allylations, Heck and related couplings, hydroformylations, and hydrosilylations. Efforts are underway in these laboratories to explore those reactions. Approaches based on syntheses of small libraries of catalysts coupled with parallel screening and automated analyses are likely to lead to some interesting discoveries. In general, this strategy aligned with structural and mechanistic work to focus the library syntheses, is likely to prove the most efficient way to discover and optimize catalysts for many diverse reaction types.

(72) Crabtree, R. H.; Demou, P. C.; Eden, D.; Mihelcic, J. M.; Parnell, C. A.; Quirk, J. M.; Morris, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 6994−7001.
(73) Brown, J. M.; Derome, A. E.; Hughes, G. D.; Monaghan, P. K. *Aust. J. Chem.* **1992**, *45*, 143−153.
(74) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2108−2110.

Acknowledgment. Financial support for this work was provided by The Robert Welch Foundation and Johnson Matthey plc. We thank Dr. Thomas A. Colacot (JM) and Dr. Shane Stichy (TAMU/LBMS-Applications Laboratory) for help and advice, and Jing Liu for preparation of imidazole **4q**.

Supporting Information Available: Comparison of enantioselectivities with some relevant literature values, experimental procedures for the preparations of the ligands, complexes, and hydrogenation/deuteration procedures, discussion of assignments of absolute configuration and tabulated details of these (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA028142B