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Exploiting Metal–Ligand Bifunctional Reactions in the Design of Iron Asymmetric Hydrogenation Catalysts

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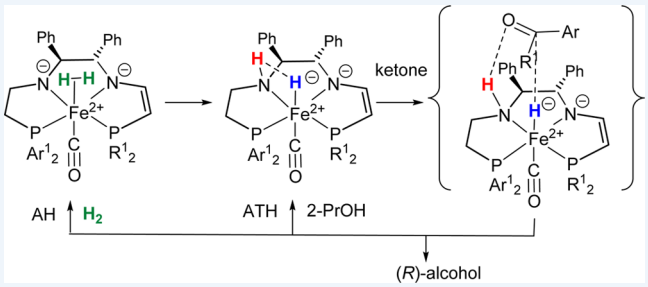
Robert H. Morris*

Department of Chemistry, University of Toronto, 80 Saint George Street, Toronto, Ontario M5S3H6, Canada

CONSPECTUS: This is an Account of our development of iron-based catalysts for the asymmetric transfer hydrogenation (ATH) and asymmetric pressure hydrogenation (AH) of ketones and imines. These chemical processes provide enantiopure alcohols and amines for use in the pharmaceutical, agrochemical, fragrance, and other fine chemical industries. Fundamental principles of bifunctional reactivity obtained by studies of ruthenium catalysts by Noyori's group and our own with tetradentate ligands with tertiary phosphine and secondary amine donor groups were applied to improve the performance of these first iron(II) catalysts. In particular the correct positioning of a bifunctional H–Fe–NH unit in an iron hydride amine complex leads to exceptional catalyst activity because of the low energy barrier of dihydrogen transfer to the polar bond of the substrate. In addition the ligand structure with this NH group along with an asymmetric array of aryl groups orients the incoming substrate by hydrogen-bonding, and steric interactions provide the hydrogenated product in high enantioselectivity for several classes of substrates. Enantiomerically pure diamines or diphenylphosphino-amine compounds are used as the source of the asymmetry in the tetradentate ligands formed by the condensation of the amines with dialkyl- or diaryl-phosphinoaldehydes, a synthesis that is templated by Fe(II). The commercially available *ortho*-diphenylphosphinobenzaldehyde was used in the initial studies, but then diaryl-phosphinoacetaldehydes were found to produce much more effective ligands for iron(II). Once the mechanism of catalysis became clearer, the iron-templated synthesis of (*S*,*S*)-$PAr_2CH_2CH_2NHCHPhCHPhNH_2$ ligand precursors was developed to specifically introduce a secondary amine in the precatalyst structures. The reaction of a precatalyst with strong base yields a key iron–amido complex that reacts with isopropanol (in ATH) or dihydrogen (in AH) to generate an iron hydride with the Fe–H bond parallel to the secondary amine N–H. In the AH reactions, the correct acidity of the intermediate iron–dihydrogen complex and correct basicity of the amide are important factors for the heterolytic splitting of the dihydrogen to generate the H–Fe–N–H unit; the acidity of dihydrogen complexes including those found in hydrogenases can be estimated by a simple additive ligand acidity constant method. The placement of the hydridic–protonic Fe–H···HN interaction in the asymmetric catalyst structure influences the enantioinduction. The sense of enantioinduction is predictable from the structure of the H–Fe–N–H-containing catalyst interacting with the ketone in the same way as related H–Ru–N–H-containing catalysts. The modular construction of the catalysts permits large variations in order to produce alcohol or amine products with enantiomeric excess in the 90–100% range in several cases.



INTRODUCTION

Bifunctional Asymmetric Hydrogenation and Transfer Hydrogenation

Asymmetric catalysts containing the bifunctional combination of a ruthenium(II)–hydride bond in parallel with a nitrogen–hydrogen bond of an amine ligand are potent reductants of ketones and imines.[1−3] The resulting enantioenriched alcohols and amines are of value to the pharmaceutical and fine chemical industries and to the synthetic organic chemist. This Account will describe how we applied this and other bifunctional design elements to create the first well-defined iron-based catalysts for the asymmetric hydrogenation (AH) and transfer hydrogenation (ATH) of these substrates. More thorough reviews of the methods for synthesizing these compounds can be found elsewhere.[4−7] There are significant benefits to using iron instead of ruthenium in catalytic processes that include a much lower cost, a much more abundant supply, and a lower toxicity as an impurity in products produced by iron catalysts.[8] While we and Gao's group[9] have focused on the asymmetric hydrogenation of polar bonds, Chirik's group has made significant advances in the asymmetric hydrogenation of olefins using catalysts based on cobalt and iron.[10−12] The bifunctional reactions and catalysts described here are a subset of the overall

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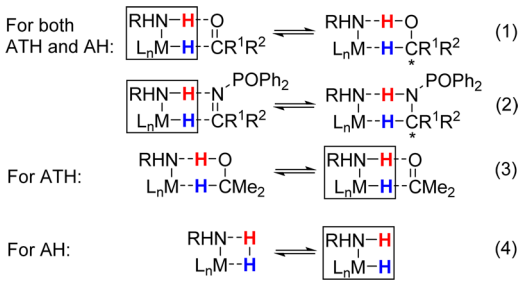
class of catalysts where there are sites of reaction at the metal and the ligand that allow cooperative action.[13−20]

Bifunctional reactions (eqs 1 or 2 and 4) make up the simple catalytic cycle for the asymmetric hydrogenation (AH) of prochiral ketones catalyzed by Noyori's catalysts and our iron catalysts (Scheme 1). The bifunctional HM−N−H unit

Scheme 1. Bifunctional Reactions in the Asymmetric Hydrogenation (AH) and Asymmetric Transfer Hydrogenation (ATH) of Ketones and Imines



efficiently transfers a dihydrogen equivalent to the ketone (eq 1) or the imine (eq 2) in the outersphere. Typically the alcohols are produced in highest enantiomeric excess (ee) when they contain an aryl[21,22] or alkynyl (R^1)[23] and an alkyl group (R^2). While a variety of imines have been reduced, Scheme 1 shows *N*-diphenylphosphinoyl substituted imines that we[24] and Beller's group[25] have found to be reduced in high ee by our iron catalysts. The HM−N−H unit is regenerated in asymmetric transfer hydrogenation by the bifunctional dehydrogenation of an alcohol such as 2-propanol or formic acid (eq 3), or it is regenerated by the heterolytic splitting of dihydrogen across the metal−amide bond in asymmetric hydrogenation (eq 4).

RUTHENIUM(II)−LIGAND BIFUNCTIONAL CATALYSIS IN ATH AND AH

The cooperation of the metal−hydrogen and the amine nitrogen−hydrogen functions in the facile ATH of ketones and imines with 2-propanol or triethylammonium formate as the hydrogen source was a key discovery of the Noyori group.[26,27] They characterized both the ruthenium(II) hydride amine complex and the ruthenium(II) amide complex as intermediates in the hydrogen transfer process that produced alcohols enriched to greater than 90% ee (Scheme 2) and also amines with similarly high ee values. In a review of ruthenium hydride catalysts, we classified this bifunctional reaction as an outer sphere transfer of hydrogen with ligand assistance (OL).[2]

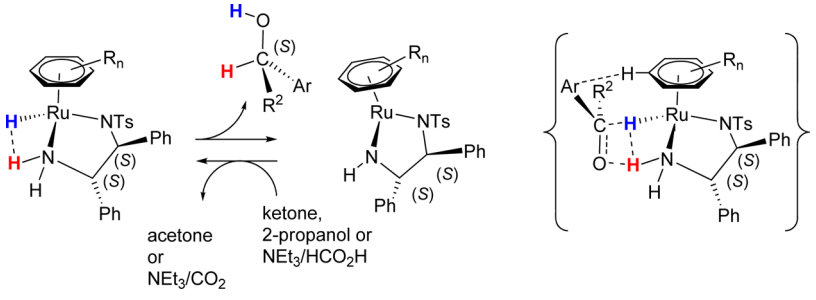
Three point binding of the aryl ketone at the Ru−H···C, N−H···O, and C^{arene}−H···aryl is thought to be the source of the enantioinduction.[28]

The structure of the hydride complex shown in Scheme 2 as determined by single crystal X-ray diffraction[26] caught our attention because of the short Ru−H···HN hydridic−protonic distance. We had been investigating the reactions of dihydrogen complexes with the H−H bond intact undergoing reversible heterolytic splitting to a thiolate sulfur[29] on the ligand or a pyridyl nitrogen on the ligand to give one of the first examples of a 1.8 Å hydridic−protonic bond[30] and wondered whether the same interactions would favor the heterolytic splitting of dihydrogen to the amide ligand.

The H−Ru−N−H motif was thought to be generated in asymmetric hydrogenation of ketones when Noyori's precatalysts of the type $RuCl_2$(diamine)(diphosphine) were activated with base in alcohol under pressures of dihydrogen. The Noyori group suspected the active forms to be of the type RuH(X)(diamine)$(PR_3)_2$ where X = H, OR, or another group.[22] Indeed we were able to identify the actual catalytic intermediates in the AH reaction (Scheme 3) as the *trans*-dihydride and not the alkoxide (or chloride).[31] It is important to have a low electronegativity atom *trans* to the hydride to make it sufficiently nucleophilic to attack the ketone in this OL reaction. In this case, the axial N−H group of the (*R*,*R*)-diamine is used to orient the substrate so that the (*S*)-alcohol is produced by this class of catalyst. A crystal structure determination clearly revealed the hydridic−protonic alignment. We also identified the ruthenium amide complex that was formed after the H^+/H^- was transferred to the ketone. The regeneration of the H−Ru−N−H motif by the heterolytic splitting of dihydrogen at ruthenium(II) had the highest energy barrier to the cycle.[32] The barrier can be reduced and the turn over frequency (TOF) increased when an alcohol molecule is present in the transition state structure to shuttle the proton from the dihydrogen to the amide nitrogen.[33,34] It should be kept in mind that acidic diamines such as *ortho*-diaminobenzene and aminonaphthalenes are ineffective ligands or even poisons to Noyori ruthenium catalysts in the presence of base because the aromatic ring stabilizes the resulting amide−ruthenium complex, rendering it insufficiently basic to heterolytically cleave dihydrogen.[35−37]

Tetradentate P−N−N−P ligands with phosphorus and imine donors are readily prepared by the Schiff-base condensation of diamines with commercially available *ortho*-diphenylphosphinobenzaldehyde (Scheme 4).[38] Reduction of the imine groups produces bis-amine ligands P−NH−NH−P. Their ruthenium complexes $RuCl_2$(P−NH−NH−P) are highly active catalysts

Scheme 2. Mechanism of the ATH of Aryl Ketones Catalyzed by Noyori's Catalysts (Ts = $SO_2C_6H_4$-4-Me) and the Proposed Enantiodetermining Bifunctional Attack on the Ketone



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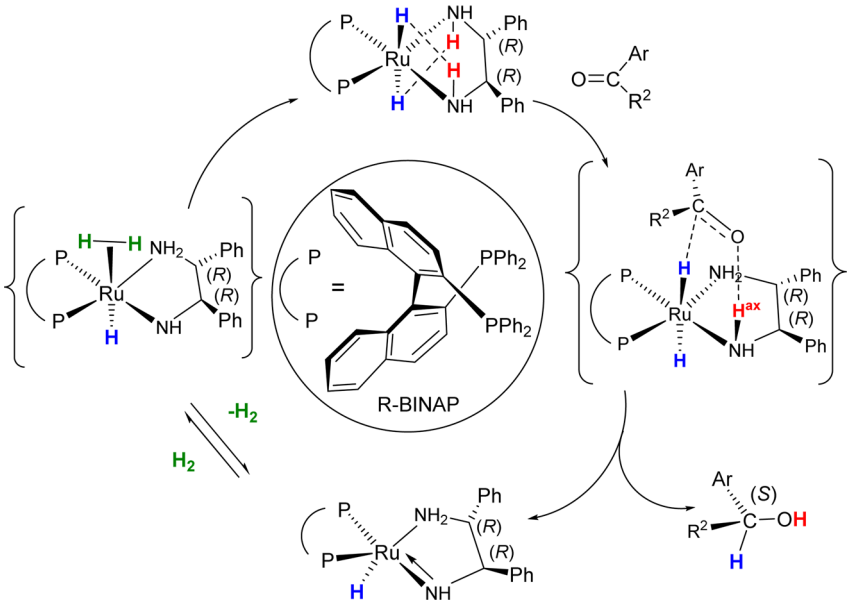
Scheme 3. Proposed Mechanism for AH Ketone Hydrogenation Catalyzed by Noyori-type Ru(II) Catalysts[31,32]



Scheme 4. Mechanism of Asymmetric Hydrogenation of Ketones Catalyzed by a Ruthenium Complex with a Tetradentate P−NH−NH−P Ligand Prepared from Commercially Available Components as Shown at Right

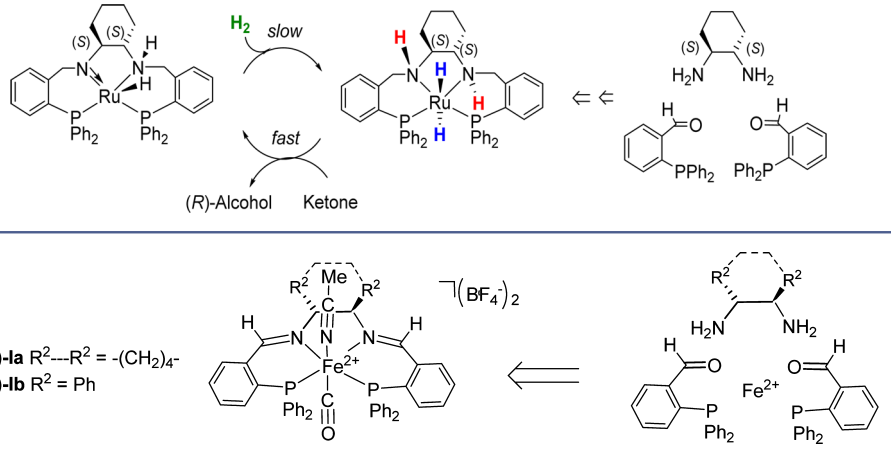


Figure 1. Examples of first generation ATH precatalysts that are prepared by the condensation of commercially available diamines and phosphine-aldehyde at iron(II).

for both AH and ATH of ketones when there is a strong base (KOH or KO^{t}Bu) in the 2-propanol solvent.[39,40] A study of the kinetics of acetophenone hydrogenation using the catalyst precursor complex *trans*-RuHCl(P−NH−NH−P) with KO^{t}Bu in benzene or 2-propanol (Scheme 4) revealed that the mechanism of catalysis is very similar to that of the diphosphine complexes (Scheme 3). The heterolytic splitting of dihydrogen is the turn over limiting step and the use of 2-propanol solvent significantly increases the rate of the reaction, presumably due to a proton shuttle effect (see below). The (*R*) alcohol is produced using the ligand derived from the (*S*,*S*)-diamine as in the diphosphine diamine system above.[40]

IRON(II)−LIGAND BIFUNCTIONAL CATALYSIS IN ASYMMETRIC TRANSFER HYDROGENATION

The high activity of ruthenium catalysts with tetradentate P−N−N−P ligands in the catalytic hydrogenation of ketones provided the impetus for investigating iron complexes with these ligands. Gao and co-workers had already found that adding such ligands to iron carbonyl clusters resulted in ATH activity.[41] Three well-defined classes of ATH catalysts were discovered in our lab, each significantly more active than the previous ones.

The first complexes **(*R*,*R*)-1a** and **(*R*,*R*)-1b** (Figure 1) were conveniently prepared from the commercially available starting materials $[Fe(H_2O)_6](BF_4)_2$, *ortho*-diphenylphosphinobenzaldehyde, and 1,2-*trans*-(*R*,*R*)-diaminocyclohexane or 1,2-(*R*,*R*)-diphenylethylenediamine, respectively.[42−44] While these complexes have imine groups instead of the amine groups found to be important for the ruthenium complexes just discussed; we assumed that under the reducing conditions of the catalytic reactions the imine donors in the precatalyst would be reduced to amines. The formal charges drawn on the structures of the iron complexes shown here and below emphasize the fact that the iron remains in the formal Fe(II) oxidation state and is diamagnetic. Derivatives with other diamines were also prepared. The syntheses could be simplified by doing the

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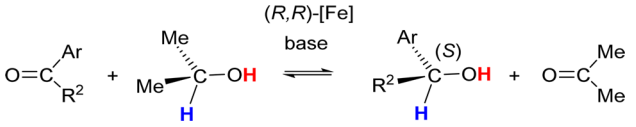
reaction in one flask and taking advantage of the template effect of the iron(II) to promote the formation of the P−N−N−P ligand. When these complexes (0.5 mol %) were dissolved with ketones in 2-propanol (2-PrOH) containing potassium *tert*-butoxide (KO^{t}Bu, 2 mol %) at 22 °C under Ar, they catalyzed the reduction of a variety of ketones to the enantioenriched alcohols with ee (*S*) up to 61% for (***R,R*)-1a** (Scheme 5, Ar = Ph, R^2 = Et) and 96% for (***R,R*)-1b** (Ar = Ph, R^2 = ^{t}Bu). We were surprised to learn that these complexes were converted to nanoparticles that appeared to be the catalytically active species.[45]

Scheme 5. Asymmetric Transfer Hydrogenation of Aryl ketones in 2-PrOH Catalyzed by (*R,R*)-Iron Complexes and Base (KO^{t}Bu, NaO^{t}Bu, or KOH)[a]



[a]The (*S,S*)-catalysts produce the opposite enantiomer.

The complexes of Figure 1 have flexible six-membered chelate rings that may allow ligand dissociation under reducing conditions, resulting in the formation of the nanoparticles. This is prevented by the use of new diaryl- and dialkyl-phosphinoacetaldehydes that condense with amines to form five-membered rings with the iron(II) (Figure 2).[46−49] The catalysts have a modular construction that allows a wide variation in structure; only a few of the variants are shown here.

Complexes **2a−2e** are listed in order of increasing activity for the transfer hydrogenation of acetophenone (Scheme 5, R^2 = Me, Ar = Ph) with **2a** requiring 50 min at a temperature of 50 °C and a catalyst loading of 0.2% and KO^{t}Bu of 1.6% to obtain an 80% conversion of 1-phenylethanol (57% ee (*R*)) while **2c−2e** required only 8 min at a temperature of 28 °C and a catalyst loading of 0.1% and KO^{t}Bu of 0.8% to obtain a 93% conversion to 1-phenylethanol (up to 90% ee (*R*) for **2c**); maximum turn over frequencies under these conditions reach 30 000 h^{-1}. Other substituents on phosphorus (Cy, ^{i}Pr, 2-MeC_6H_4, 4-$CF_3C_6H_4$, 3,5-$(CF_3)_2C_6H_3$) gave inactive complexes. Thus, there is a critical region of moderate substituent size (cone angle of approximately 140°) and moderate donor ability at phosphorus for high catalyst activity.[49]

Complex **(*S,S*)-2d** was found to catalyze the ATH of a variety of prochiral ketimines substituted at nitrogen with a diphenylphosphinoyl group (Scheme 1).[24] Amines were obtained at approximately 90% conversion with 95−99% ee (*R*) in 40−120 min when a catalyst loading of 1 mol % was used in 2-propanol at 30 °C (with 8 mol % KO^{t}Bu).

An investigation of the mechanism of these ATH reactions catalyzed by **(*S,S*)-2d** revealed that the ligand of the catalyst precursor was modified during an induction period before catalysis started (Scheme 6).[50] First the acidic methylene groups next to the PPh_2 groups are rapidly deprotonated by the excess strong base (KO^{t}Bu, NaO^{t}Bu, or KOH) needed to activate the catalyst. This produces an interesting bis-enamide complex, $Fe(CO)(PPh_2CH{=}CHNCHRCHRNCH{=}CHPPh_2)$; a related complex has been crystallographically characterized.[51] In a slow step, the addition of a proton and hydride from 2-propanol to one of the eneamide groups creates the active iron complex with the ligand hydrogenated on one side. The remarkable finding is that only one side of the ligand can be hydrogenated; when the other side is also reduced, the system becomes inactive.[50]

Catalysis proceeds much like the ruthenium systems above where the bifunctional Fe-amide group receives a proton and hydride equivalent from the 2-propanol solvent and then in a reverse reaction transfers it to the ketone substrate with the same enantioinduction as the ruthenium system of Scheme 3, the (*S,S*)-catalyst producing the (*R*)-alcohol. Molecular models indicate that acetophenone approaches the iron hydride catalyst so that the oxygen is hydrogen-bonding to the N−H group, and the phenyl group of the ketone lies over the flat eneamide part of the complex, producing the (*R*)-alcohol in the same way as is shown for the ruthenium complex in Scheme 3. Density functional theory calculations reveal that the transfer of the hydride and then the proton to the ketone occurs in a stepwise fashion, with the first being rate-limiting.[52]

Once the mechanism shown in Scheme 6 became clear, the next step was the direct synthesis of an unsymmetrical ligand system that would take all of the iron complex rapidly into the catalytic cycle. This was achieved by first synthesizing an enantiopure ligand of the type (*S,S*)- or (*R,R*)-$PAr^1{}_2CH_2CH_2NHCHPhCHPhNH_2$ and then condensing it with dialkyl- or diaryl-phosphinoacetaldehydes at iron(II) (Figure 3).[6,53−55] Only one isomer is generated with the general structure assigned on the basis of a single crystal X-ray diffraction determination of **(*S,S*)-3d**.

The reaction of these precatalysts with excess base rapidly produces the catalytically active unsymmetrical amide-eneamide complex as a mixture of two interconverting isomers; Scheme 6 (above) shows the formation of the major isomer, presumably by movement of the carbonyl from one side to the other in the five coordinate complex. This amide(eneamide) complex was generated independently and reacted with 2-propanol in order to completely characterize the iron hydride complex of Scheme 6.[53] The presence of the bifunctional H−Fe−N−H unit was signaled in the ^{1}H NMR spectrum as a doublet of doublets at −2.25 ppm for the Fe−H and a multiplet at 4.01 ppm for the N−H. There is a strong nuclear Overhauser effect between

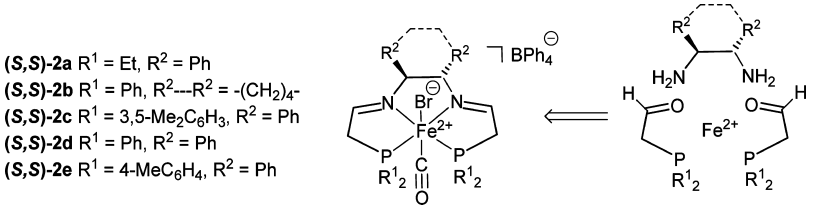


Figure 2. Examples of second generation "FeATHer" precatalysts that are prepared by the condensation of an enantiopure diamine and dialkyl- or diaryl-phosphinoacetaldehydes at iron(II).

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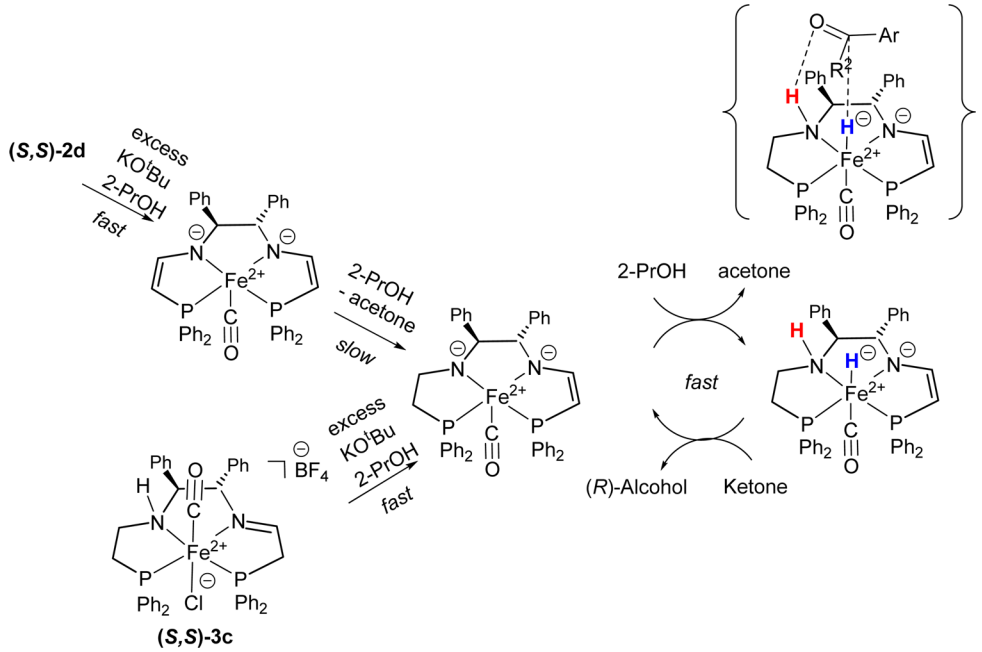
Scheme 6. Proposed Mechanism of the ATH of Ketones Starting Slowly from the Bis(imine) Precatalyst (*S,S*)-2d, or Quickly from the Amine(imine) Precatalyst (*S,S*)-3c by Reaction with Excess Base in 2-PrOH



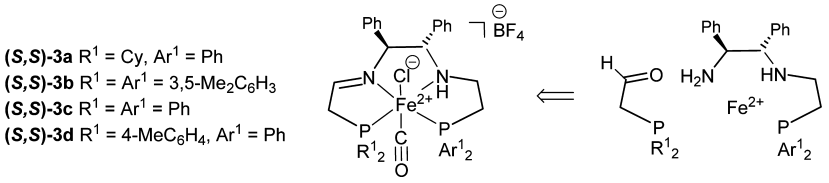


Figure 3. Examples of third generation "FeATHer" precatalysts (*S,S*)-**3a–d** that are prepared by the condensation of enantiopure P–NH–NH_2 and dialkyl- or diaryl-phosphinoacetaldehydes at iron(II).

these two hydrogens proving that they are aligned by a hydridic–protonic interaction.

The precatalyst activation is very efficient and the catalyst system is exceedingly active for the ATH of a variety of prochiral ketones and certain ketimines. The activity of the catalyst systems for the ATH of acetophenone increases as listed in Figure 3 from (*S,S*)-**3a** to (*S,S*)-**3d**. At catalyst loadings of 0.02 mol % and base loadings of 0.16% in 2-PrOH at 30 °C, a TOF of up to 150 s^{-1} was achieved. The effect of catalyst structure on the enantioselectivity is still being explored, but certain precatalysts provide the alcohol in higher ee, depending on the ketone structure; examples are shown in Figure 4. The conversions of these equilibrium reductions can be increased where necessary by evaporating the solvent and adding fresh 2-PrOH and catalyst to push the reaction to completion.

When the ATH of ketones approaches equilibrium, the catalyst system sometimes decomposes or changes to a system that starts to racemize the product alcohol. One side reaction that we have observed is the loss of chirality in the diamine part of the ligand structure by a slow dehydrogenation reaction.[56]

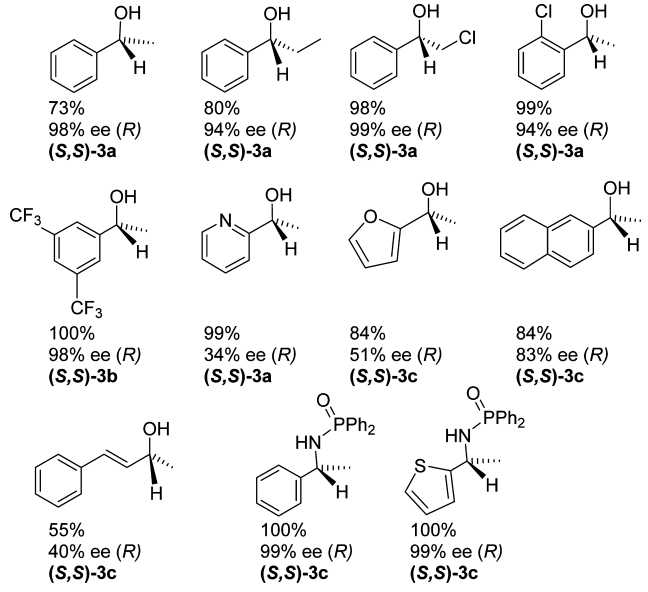


Figure 4. Representative conversions and ee of the alcohols and amines obtained using the best ketone/precatalyst or imine/precatalyst combination, respectively.

IRON(II)–LIGAND BIFUNCTIONAL CATALYSIS IN ASYMMETRIC HYDROGENATION

Large scale industrial hydrogenations utilize hydrogen gas. The development of hydrogenation catalysts based on abundant metal continues to be an area of great interest. The heterolytic splitting of dihydrogen at a bifunctional iron(II)–amide bond by analogy to the ruthenium system of Scheme 3 is a very promising route to generate iron hydride reductants of polar bonds. We attempted to prepare bidentate diphosphine

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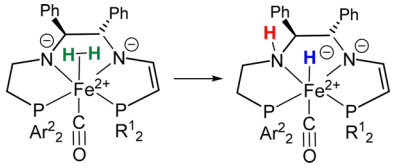
diamine complexes of iron(II) by analogy to those of ruthenium(II) without success. DFT calculations had suggested that such complexes should be suitable as ketone hydrogenation catalysts.[44,57] The iron complexes *trans*-[Fe(MeCN)$_2$(P−N−N−P)](BF$_4$)$_2$ with tetradentate ligands shown in Figure 1[42,44] and *trans*-[Fe(CO)(Cl)(P−N−NH−P)]BF$_4$ ((*S,S*)-**3b−d**)[54] have so far proven to be only moderately active with poor enantioselectivity. For example complexes (*S,S*)-**3c** and (*S,S*)-**3d** at 1.0 mol % in THF with 2 mol % KO^{t}Bu catalyze the hydrogenation (at 50 °C, 20 atm) of acetophenone to racemic 1-phenylethanol with a TOF 50% conversion of approximately 40 and 80 h^{-1}, respectively. Complex (*S,S*)-**3b** provides the alcohol in 35% ee at a TOF of 18 h^{-1} under similar conditions; the best result to date is for the substrate α-tetralone, which was hydrogenated to 70% ee (*R*). The (*R*)-configuration is consistent with the bifunctional H−Fe−NH attack on the ketone by the hydride shown in Scheme 6 that is also responsible for the ATH of ketones. The hydride complex is regenerated by the heterolytic splitting of dihydrogen at the bifunctional iron-amide as shown in Scheme 7, and this turnover limiting energy barrier was found

Scheme 7. Postulated Rate-Limiting Heterolytic Splitting of Dihydrogen at the Bifunctional Iron-Amide in the Hydrogenation of Acetophenone Catalyzed by Complexes (*S,S*)-3b−d Activated by 2 equiv of KO^{t}Bu in THF[54]



experimentally to be 20 kcal/mol. DFT calculations designed to probe the possible mechanism of acetophenone hydrogenation catalyzed by a simplified model of (*S,S*)-**3c** in THF provided a barrier to hydrogen splitting of 18 kcal/mol, greater than the 13 kcal/mol barrier for the bifunctional hydride and proton transfers to the ketone.[54] The barrier to H$_2$ splitting to the eneamide nitrogen is calculated to be much higher, and this explains the need for the more basic amide nitrogen in the amide(eneamide) form of the catalyst. On the other hand, the eneamide part of the ligand in the hydride complex neutralizes the overall charge, making the hydride sufficiently nucleophilic to attack the weakly electrophilic ketone. Cationic hydrides are usually not nucleophilic enough.[58]

Iron complexes of the type Fe(P−N−P)(CO)(X)(Y), X = H, Y = Br, BH$_4$, are active for the hydrogenation of ketones and imines and a variety of dehydrogenation processes.[59−65] We have recently reported the first enantiomerically pure complexes of this type.[66] They are prepared by the condensation of dialkylphosphinoacetaldehydes with enantiopure P−NH$_2$ compounds templated by FeBr$_2$ as indicated schematically in Figure 5 for the PCy$_2$-containing complex (*S,S*)-**4**.

This precatalyst can be used to generate *in situ* preparations of catalyst solutions for the AH of ketones and imines. The activation step involves reaction first with LiAlH$_4$ in THF to reduce the imine to the required N−H containing P−NH−P′ ligand and then treatment with *t*-amyl alcohol to remove the aluminum salts. Hydrogenations of ketones are conducted using 0.1 mol % iron and 1 mol % KO^{t}Bu in THF at 50 °C and

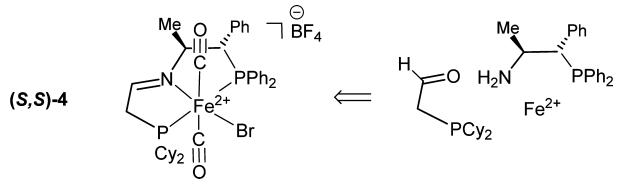


Figure 5. An example of AH precatalyst (*S,S*)-**4**, which is prepared by the condensation of enantiopure P−NH$_2$ and dicyclohexylphosphinoacetaldehyde at iron(II).

20 atm H$_2$ and are complete within 0.5 to 4 h (TOF up to 1980 h^{-1}). Some results of ketone reductions are shown in Figure 6.

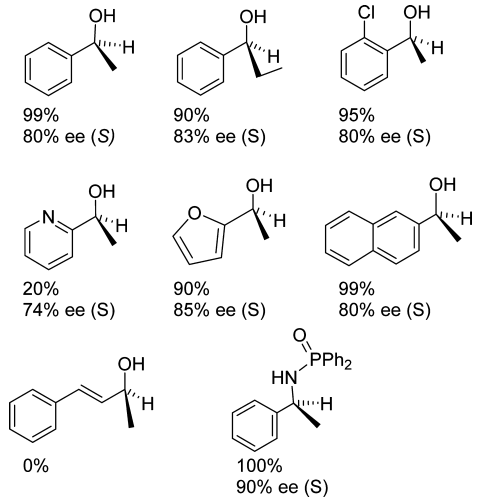


Figure 6. AH of substrates catalyzed by an *in situ* generated catalyst derived from (*S,S*)-**4**.[66]

The enantioselectivity is good, and in the case of 2-acetylfuran, better, than the ATH catalysts with tetradentate ligands while the sense of enantioinduction is opposite to those of the ATH catalysts. A catalyst loading of 1 and 10 mol % KO^{t}Bu in THF, with other conditions the same as above, was required to completely reduce *N*-(diphenylphosphonyl)-propiophenoneimine to the amine at 90% ee (*S*). The characterization of the hydride complexes involved in catalysis will be reported shortly. This first catalyst system is an excellent starting point for further catalyst development.

HETEROLYTIC SPLITTING OF DIHYDROGEN AND CATALYTIC ACTIVITY

Improvements on this design of the iron AH catalysts will focus on lowering the barrier to the hydrogen splitting step. A possible approach is to make the dihydrogen ligand in the intermediate iron dihydrogen complex more acidic. The low acidity of the uncharged dihydrogen intermediates Ru(H$_2$)H(NHCHRCHRNH$_2$)(diphosphine) of Scheme 3 and the Fe(H$_2$) intermediate in Scheme 7 is an important consideration. The amide nitrogen has to be sufficiently basic to deprotonate the dihydrogen. This is why acidic diamines such as those with amines attached directly to aromatic rings make inactive complexes[46,51] and why amino-substituted aromatics in the ligand are catalyst poisons in ruthenium chemistry.[36]

The first known iron dihydrogen complex *trans*-[Fe(H$_2$)H(PPh$_2$CH$_2$CH$_2$PPh$_2$)$_2$]BF$_4$ readily undergoes reversible deprotonation with triethylamine (Scheme 8) so that its pK_a^{THF} is close to that of triethylammonium (pK_a^{THF} 12).[67] Thus, the iron

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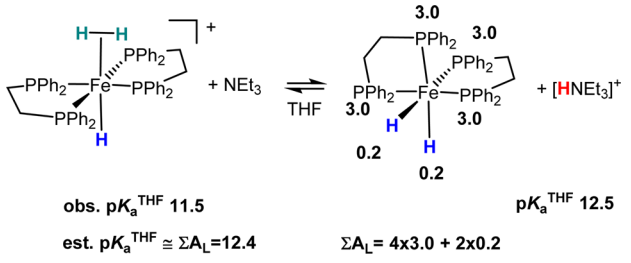
Scheme 8. Heterolytic Splitting of Dihydrogen at Iron(II)



cation decreased the pK_a^{THF} of dihydrogen from about 60 for free dihydrogen dissolved in THF, to approximately 12 for the coordinated dihydrogen in the iron complex.

Recently we proposed that the acidity of such metal complexes can be predicted by simply adding acidity constants for each class of ligand in the conjugate base form and correcting for the charge.[68] For the case of the acidic dihydrogen complex $[Fe(H_2)H(PPh_2CH_2CH_2PPh_2)_2](BPh_4)$ of Scheme 8, the conjugate base form is the neutral dihydride complex $FeH_2(PPh_2CH_2CH_2PPh_2)_2$. The acidity constant is 0.2 for each hydride in a metal complex and 3.0 for each diarylalkylphosphine donor (each PPh_2CH_2 donor), giving a total sum of 12.4 for the estimated pK_a of the dihydrogen complex.[68] This is in accord with the observed equilibrium with $[HNEt_3]BPh_4$, which has a pK_a^{THF} of 12.5.[69] While phosphorus and nitrogen donor ligands give a positive contribution to the pK_a of metal hydrides, carbonyl (−3) and cyanide (approx. −11) ligands have negative contributions. Thus, the carbonyl complex *trans*-$[Fe(H_2)(CO)(PEt_2CH_2CH_2PEt_2)_2](BF_4)_4$ and cyanide complex *trans*-$[Fe(H_2)(CN)(PEt_2CH_2CH_2PEt_2)_2](BF_4)$ and hydrogen isocyanide complex *trans*-$[Fe(H_2)(CNH)(PEt_2CH_2CH_2PEt_2)_2](BF_4)_2$ are very acidic.[70−72] This could explain why nature's hydrogenase enzymes have carbonyl and cyanide ligands on iron: to increase the acidity of the iron dihydrogen complexes close to the pH of the protein environment, approximately 7.[70,73,74] The carbonyl ligand also plays this role in our iron catalysts as well as keeping the complexes stabilized in the low spin Fe(II) d^6 octahedral configuration.

CONCLUSIONS

We have had success in applying lessons learned from ruthenium bifunctional hydrogenation catalysis to the field of iron in catalysis. We have already found good iron catalysts for the ATH hydrogenation of ketones and imines ("FeATHer" catalysts) that are competitive with precious metal counterparts. The relatively rapid progress was aided by experimental and computational investigations that elucidated the structure and bifunctional reactions of the catalytically active hydride and amide species and by the modular construction of the catalysts that allowed many new variants to be readily synthesized. This process is underway to improve our first AH iron catalysts with tridentate P−NH−P′ ligands. Our improved knowledge of the acidity of dihydrogen complexes will also assist in this endeavor. The use of homogeneous catalysts based on abundant metals like iron in place of precious metals is a burgeoning field with much promise. There is certainly a need for cheap effective catalysts for other processes, especially involving CO_2 and H_2 utilization to achieve a sustainable, benign energy economy.

AUTHOR INFORMATION

Corresponding Author

*E-mail: rmorris@chem.utoronto.ca.

Notes

The authors declare no competing financial interest.

Biography

Prof. Robert H. Morris was born in Ottawa in 1952. He received his Ph.D. from the University of British Columbia in 1978 and held a NATO postdoctoral position at the AFRC Unit of Nitrogen Fixation, Sussex, U.K., and an NSERC postdoctoral position at the Pennsylvania State University before accepting a position of Assistant Professor at the University of Toronto in 1980. He is currently Professor of Chemistry and a Fellow of the Royal Society of Canada and of the Chemical Institute of Canada. He served as Acting Chair and then Chair of the Chemistry Department from 2008 to 2013. His research interests include organometallic chemistry and catalysis, particularly involving the iron group elements.

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