Non-Precious-Metal Catalysts

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An Iron Catalyst for Ketone Hydrogenations under Mild Conditions**

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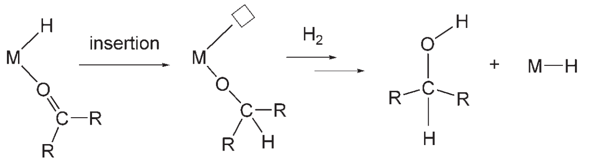
homogeneous catalysis · hydrides · hydrogenation · iron · proton transfer

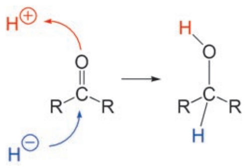
Homogeneous hydrogenations play a prominent role in the development of catalysis, and may be the most extensively studied type of homogeneously catalyzed reaction. Hydrogenations are required in a variety of lab-scale and industrial applications, being used in the synthesis of fine chemicals, as well as for compounds used in the pharmaceutical and agricultural fields. Despite decades of research and the resulting increased understanding of many of the details of how such reactions occur, unsolved problems remain, and new discoveries are propelling the field forward by addressing these challenges.

Traditional catalysts for ketone hydrogenation reactions are based on precious metals, and conventional mechanisms involve coordination of the ketone to the metal. A requisite step in the mechanism of most homogeneous hydrogenation catalysts based on noble metals is an insertion reaction. As shown in generalized form in Equation (1), insertion of a ketone into a M−H bond produces a metal alkoxide complex, where the open square represents a vacant coordination site on the metal. Reaction with H_2 produces the alcohol product and regenerates an M−H bond. Equation (1) shows only two of the key steps that are prevalent in conventional mechanisms; detailed mechanistic studies have revealed numerous variants of this type of mechanism.[1] In some cases the interaction of the metal complex with H_2 proceeds through a dihydrogen complex,[2] which is often not directly observed. While the traditional method for hydrogenations involves reaction with molecular H_2, transfer hydrogenations can also be carried out in which the hydrogen typically comes from isopropyl alcohol.[3]



(1)

Efforts to find catalysts that do not require noble metals ("Cheap Metals for Noble Tasks")[4] are appealing, as catalysts based on abundant, inexpensive metals would be much more economical to use on the large scale required for industrial reactions. Additional advantages may be less obvious—residual traces of metals such as iron or molybdenum will generally be less toxic and more environmentally acceptable than precious metals. Removing the requirement for precious metals may be accomplished by devising catalysts that operate by entirely different mechanisms. Ionic hydrogenations[4] involve the addition of a proton and a hydride to an unsaturated substrate, as shown in Scheme 1. The source of the H^- is a transition-metal hydride; extensive systematic studies by DuBois and co-workers showed that the thermodynamic hydricity (i.e., the hydride-donor ability) of metal hydrides can vary by more than 40 kcal mol^{-1},[5,6] and kinetic studies have identified trends in the rate of hydride transfer from metal hydrides.[7,8] The source of the proton in ionic hydrogenations can also be a metal hydride: a series of molybdenum and tungsten complexes have been reported for the catalytic ionic hydrogenation of ketones in which proton transfer from an acidic M−H bond is followed by hydride transfer from a hydridic M−H bond.[9] The proton donor can also be an O−H bond or an N−H bond. Many of the remarkably reactive ruthenium hydrogenation catalysts discovered by Noyori and co-workers involve proton transfer from N−H bonds and hydride transfer from Ru–H species, and are referred to as metal–ligand bifunctional catalysts.[10]



Scheme 1. Ionic hydrogenation of a ketone.

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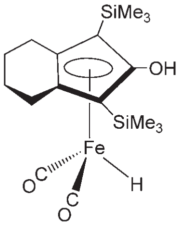

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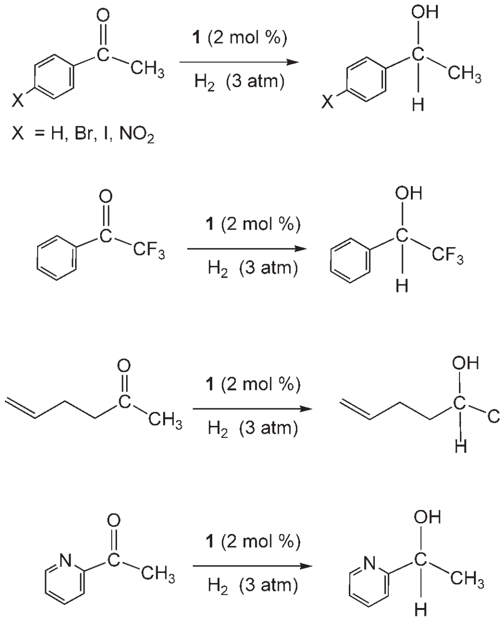
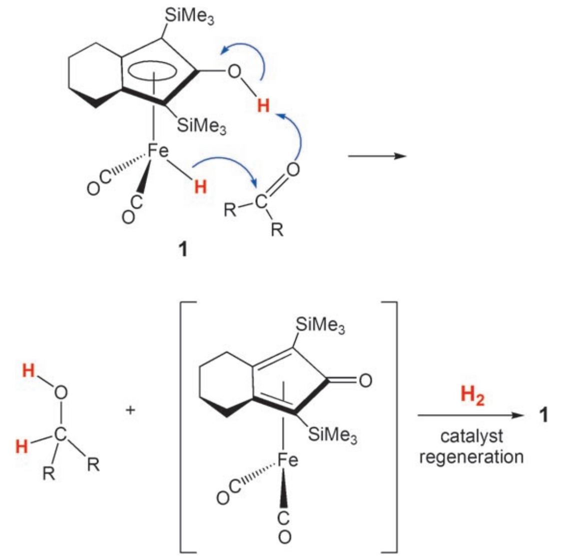
Casey and Guan have recently developed an iron catalyst (**1**) that efficiently hydrogenates ketones under mild conditions (25 °C, 3 atm H_2).[11] Some of the ketones that are efficiently hydrogenated to alcohols using **1** as a catalyst are shown in Scheme 2. When monitored by NMR spectroscopy, these hydrogenations proceed in essentially 100 % yield; yields of isolated products are also high (generally > 83 %). Most of these reactions proceed to completion in less than 1 day at room temperature. Only ketone hydrogenations are shown in Scheme 2, but the iron catalyst hydrogenates aldehydes at an even faster rate, with a 90 % yield of PhCH$_2$OH being isolated after a reaction time of one hour for the catalytic hydrogenation of benzaldehyde. Ketones with electron-withdrawing groups are hydrogenated quickly; hydrogenation of Ph(C=O)CF$_3$ was complete in 10 minutes at room temperature. Excellent chemoselectivity was observed with this catalyst: the C=O hydrogenation proceeded in the presence of isolated C=C bonds, and the reaction is not suppressed by the basic site of a pyridyl substituent. Functional groups tolerated by this catalyst include nitro groups, benzyl ethers, aryl carbon–halogen bonds, and cyclopropyl rings. Unsaturated functionalities that were not hydrogenated by this iron catalyst included C≡C bonds, epoxides, and the C=O bond of esters.



Scheme 2. Examples of ketones catalytically hydrogenated by **1**.

How does the iron catalyst by Casey and Guan accomplish the hydrogenation of C=O bonds under such mild conditions, without needing a precious metal? Not only the metal, but the ligands are different from those normally used in hydrogenation catalysts. A key aspect of the success of this system is that hydrogen can be delivered by an ionic hydrogenation mechanism. Rather than requiring coordination of the ketone substrate to the metal as in a traditional mechanism [Eq. (1)], the hydrogen is delivered in the form of H^+ and H^- to the ketone substrate (Scheme 3). Ionic hydrogenation catalysts are particularly well-suited for the hydrogenation of polar bonds, such as the C=O bond of ketones. Proton transfer from the O−H group, coupled with hydride transfer from the Fe−H group, accomplishes the overall addition of H_2 to the C=O bond. The iron intermediate (shown bracketed in Scheme 3) that results after H^+/H^- transfer has a substituted η^4-cyclopentadieneone ligand, such that the iron center is a 16-electron coordinatively unsaturated species. Regeneration of the catalyst must accomplish the heterolytic cleavage of H_2 to produce O−H and Fe−H bonds, possibly through an unobserved η^2-H_2 dihydrogen complex.

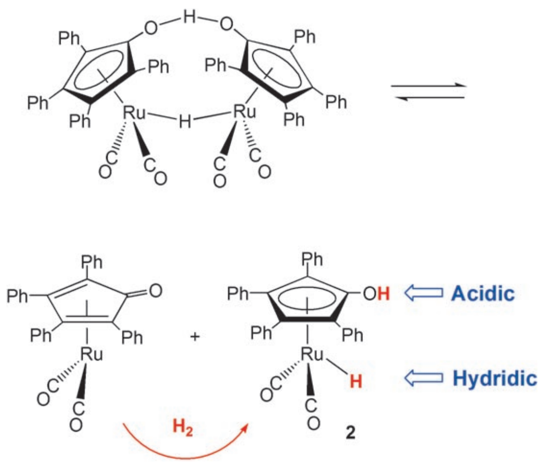


Scheme 3. Proposed mechanism for hydrogenation of a ketone by **1**.

Casey and Guan reported mechanistic studies that provided further information about the proposed mechanism. When the catalytic reaction was monitored by infrared spectroscopy, the only species observed was **1**, indicating that hydrogen transfer is the turnover-limiting step in the catalytic cycle. The rate of hydrogenation of acetophenone was first-order in **1** and first-order in acetophenone, and was independent of hydrogen pressure.

The iron complex **1** is related to ruthenium complexes that have been studied in detail. In the mid-1980s, Shvo and coworkers reported that a bimetallic ruthenium complex (Scheme 4) served as a catalyst precursor for the hydrogenation of C=O and C=C bonds.[12] The two metals were joined by both a bridging hydride as well as an O−H−O bridge, as shown in Scheme 4. The catalytic ketone hydrogenations were carried out at 145 °C, under an initial H_2 pressure of 500 psi.

Cleavage of the bimetallic complex under these conditions produces an 18-electron complex (**2**, with a Ru−H and an O−H bond) that carries out the hydrogenations, together with the unsaturated 16-electron intermediate having a



Scheme 4. Conversion of Shvo's complex to an active catalyst by reaction with H_2.

substituted η^4-cyclopentadieneone ligand. Addition of H_2 converts the unsaturated intermediate into the 18-electron complex which is capable of delivering hydrogen (shown at the lower part of Scheme 4).

Casey and co-workers found that an analogue of the mononuclear ruthenium complex **2** (in which two phenyl substituents were replaced by tolyl) smoothly hydrogenates aldehydes or ketones.[13,14] Kinetics of the hydrogenation of benzaldehyde were carried out at temperatures as low as −49 °C; benzaldehyde is hydrogenated 75–300 times faster than acetophenone.[14] Thus the delivery of H_2 from this complex is facile, with the much higher temperatures used under catalytic conditions being required to regenerate the active mononuclear catalyst from the bimetallic complex, which is the resting state of the catalytic reaction. Casey's[13,15] and Bäckvall's[16] groups have conducted detailed mechanistic studies on how these Shvo catalysts operate in the hydrogenation of ketones, hydrogenation of imines, dehydrogenation of alcohols, and related reactions. In contrast to the outer-sphere mechanism that does not involve substrate coordination, Bäckvall proposed an alternate mechanism involving coordination of the substrate to the metal, together with ring slippage of the substituted cyclopentadienyl ring.

The exceptionally mild conditions under which iron catalyst **1** hydrogenates C=O bonds are even more surprising considering the comparison with the more well-studied ruthenium complexes. An especially attractive feature is the ability of the mononuclear iron complex **1** to be regenerated directly from H_2, and avoid the formation of a bimetallic complex. Both the mononuclear ruthenium and iron complexes deliver H_2 under mild conditions, but the higher temperature required for the ruthenium catalyst is due to the much higher barriers faced in converting it into the active mononuclear form with Ru−H and O−H bonds. The $SiMe_3$ groups flanking the OH group in the iron complex appear to provide sufficient steric bulk to suppress dimer formation, compared to the Ph substituents in the ruthenium complex (Scheme 4). The iron complex **1** was previously synthesized by Knölker and co-workers,[17] so Casey and Guan used this known complex in their initial studies. It is not clear that the six-membered ring annulated to the substituted cyclopentadienide ring in the iron complex **1** is actually required for the catalytic activity, but its presence was necessary in Knölker's synthetic procedure.

This discovery of an iron catalyst that functions under mild conditions is an excellent example of progress in seeking catalysts that do not require noble metals. The earlier work on the ruthenium analogues shows that mechanistic studies can be very useful in providing guidance on the features needed for successful catalyst design, particularly for catalysts that operate by unconventional mechanisms. One question posed for study by Casey is whether asymmetric versions of this complex can be synthesized that would lead to enantioselective hydrogenation catalysts. Future research on this class of complexes will also need to more fully explore questions about how to avoid formation of the bimetallic complex that leads to slower catalysis. Is the difference that arises from the $SiMe_3$ groups on the iron complex as against the aryl groups on the ruthenium complexes only a steric effect? Or are electronic effects also responsible for some of the enhanced rate of reaction of the iron complex over the ruthenium analogue? The substituents ($SiMe_3$, Ph, etc.) on the substituted cyclopentadienyl ring will have an influence on the acidity of the OH group, which is a key factor influencing the reactivity of this type of catalyst. Those same substituents will also have some effect on the hydricity of the M−H bond. The hydride donating ability will also be dependent on the metal. The kinetics of hydride transfer from $[(C_5Me_5)Ru(CO)_2H]$ are faster than those from $[(C_5Me_5)Fe(CO)_2H]$.[8] Thermodynamic hydricities were also shown by DuBois to be higher for second-row transition metals than for first-row transition metals, in examples comparing $[HM(diphosphine)_2]^+$, where the second-row palladium hydrides have higher hydricity than the first-row nickel hydrides.[5] Yet Casey and Guan's work shows that an iron complex can have catalytic activity that exceeds that of similar ruthenium complexes.

Substantial cost savings can be obtained from using inexpensive metals compared to precious metals, though specialized ligands may be expensive to synthesize, even when the metal is cheap. Along with these new results on catalytic hydrogenation of C=O bonds, homogeneous iron catalysts for hydrogenation of C=C bonds have been reported,[18] apparently proceeding through conventional insertion mechanisms. Whether by an ionic or a traditional insertion mechanism, finding cheap metals to replace precious metals can be accomplished. Mechanistic studies have been very useful in the rational design of new types of catalysts, and are expected to continue to guide the development of new catalysts based on inexpensive metals.

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