Iron Catalysis

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Well-Defined Bifunctional Iron Catalysts for the Hydrogenation of Ketones: Iron, the New Ruthenium

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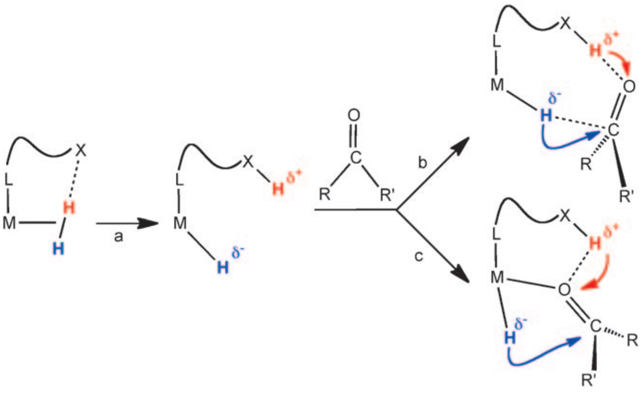
The catalytic reduction of polar multiple bonds—such as carbonyl functionalities—by molecular hydrogen plays a significant role in modern synthetic organic chemistry. The stereoselective hydrogenation of ketones to yield enantiomerically pure alcohols is a key step, in particular, in the synthesis of fine chemicals, perfumes, and pharmaceuticals. This reaction is excellently performed by using many transition-metal complexes containing noble metals such as ruthenium, rhodium, or iridium.[1] Ruthenium(II) complexes of the type *trans*-[$RuCl_2$(binap)(diamine)] (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) that are activated by base in isopropanol under 5–50 bar H_2 pressure are particularly effective catalyst systems. The (*R*)- or (*S*)-binap ligand is paired with a diamine of the correct enantiomeric configuration to achieve high enantioselectivity in the reduction of ketones.

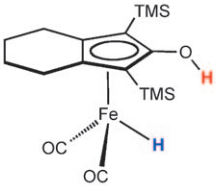
These catalyst systems have enzyme-like properties of outstanding productivity (reaching turnover numbers of 10^6) at a high turnover frequency near room temperature. Furthermore, they result in excellent enantioselectivity (exceeding 95 % *ee*).[2] Many of these hydrogenation reactions involve ligand–metal bifunctional catalysis (metal–ligand cooperation).[3] This means that the transition-metal complexes contain electronically coupled hydride ligands and acidic hydrogen atoms as a result of heterolytic dihydrogen cleavage (a), as shown in Scheme 1. These groups may subsequently be transferred to polar unsaturated substrates in an outer-sphere fashion (b) or by hydride migration (substrate insertion into the metal–H bond, (c)), both under mild conditions. This concept has changed the field of reduction chemistry dramatically in recent years.[4] However, the limited availability of precious metals, their high price, and their toxicity diminish their attractiveness for future use, and thus more economical and environmentally friendly alternatives need to be found.

In this respect, the preparation of well-defined iron-based catalysts of comparable activity would be desirable for the development of more sustainable reduction reactions. Iron is the most abundant transition metal in the Earth's crust, and is ubiquitous. Moreover, nature often uses iron-based catalysts such as hydrogenases for hydrogenations, which seem to proceed through bifunctional catalysis.[5] Accordingly, it is not surprising that the field of iron-catalyzed hydrogenation of polar multiple bonds is rapidly evolving.[6] Remarkable examples of well-defined hydrogenation catalysts have been reported recently, which will be elucidated in this Highlight.



Scheme 1. Key steps of the catalytic hydrogenation of ketones to alcohols with a bifunctional catalyst with acidic (red) and hydridic (blue) hydrogen atoms; (a)–(c) see text.

The first efficient iron catalyst for the reduction of ketones to alcohols was reported by Casey and Guan in 2007.[7] These authors used the well-defined bifunctional iron complex **1** (TMS = trimethylsilyl), prepared originally by Knölker et al. (analogous to the catalyst of Shvo et al.[8]).[9] Complex **1** catalyzes the hydrogenation of ketones under mild conditions with high chemo- and diastereoselectivity, as well as with TON = 50. Mechanistic details have recently been reported, based on DFT calculations, for this reaction.[10]



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In 2008 Morris and co-workers reported the use of several dicationic iron complexes of the types *trans*-[Fe(MeCN)$_2$(Z-P_2N_2)](BF_4)$_2$ (**2**) and *trans*-[Fe(MeCN)$_2$(eth-P_2(NH)$_2$)](BF_4)$_2$ (**3**) containing both achiral and chiral P_2N_2 ligands (Scheme 2) as precatalysts for the hydrogenation of acetophenone to 1-phenylethanol. Yields of up to 95 % and 99 %, respectively, were obtained after 18 h at

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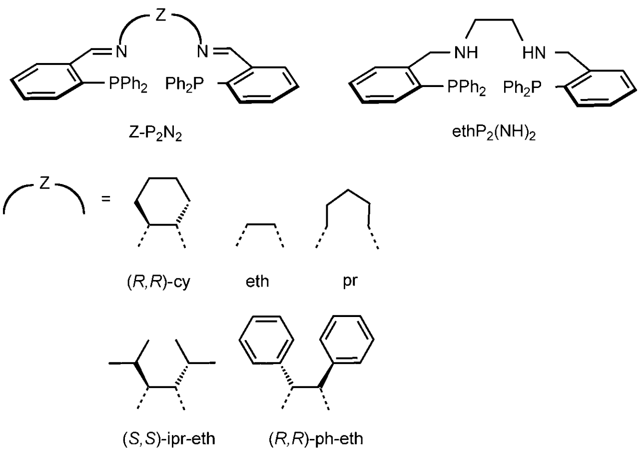
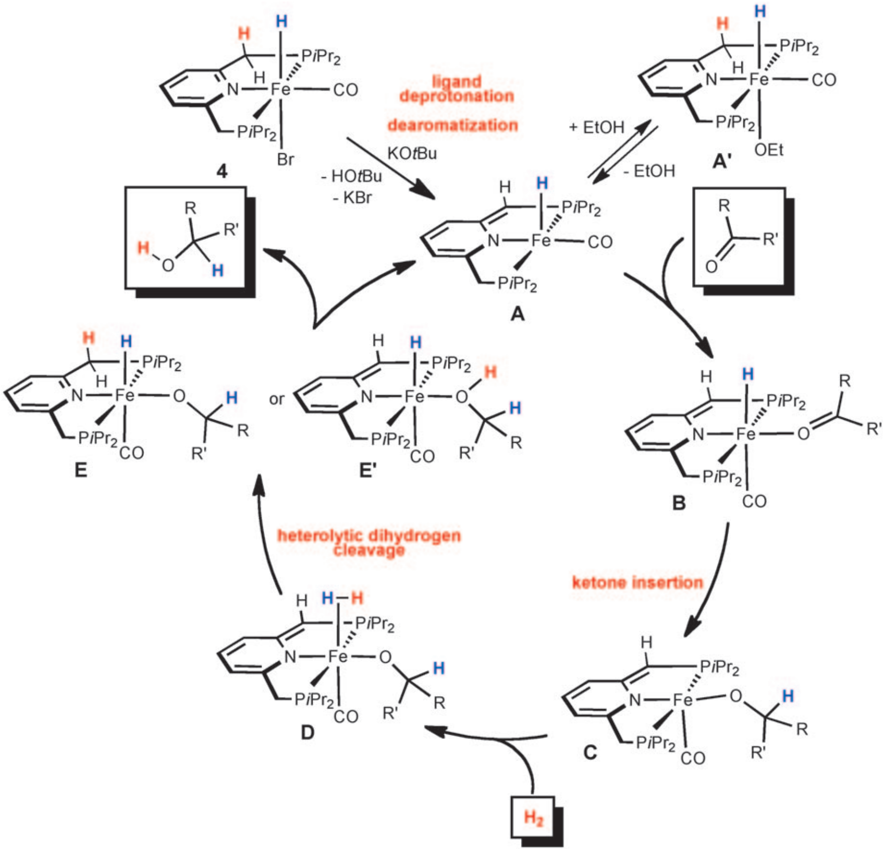


Scheme 2. Examples of tetradentate P_2N_2 ligands.

50 °C and 25 bar hydrogen pressure.[11] The fact that both the imine and amine ligands provided catalysts of comparable activity suggests that both complexes are converted into a similar intermediate with a H-Fe-N-H pattern that permits outer-sphere hydrogenation. DFT calculations on related complexes support the assumption that these complexes are acting as bifunctional catalysts.[12] It is also important to note that Morris and co-workers achieved for the first time an enantioselective hydrogenation, although the conversion and enantioselectivity were modest (40 % conversion, 27 % *ee*).

More recently, Milstein and co-workers were able to synthesize a novel monohydride iron(II) pincer complex of the type [Fe(Br)(CO)(H)(PNP-*i*Pr)] (**4**).[13] Complex **4** is the most efficient well-defined bifunctional iron catalyst reported to date for the hydrogenation of ketones to alcohols. The reaction takes place under very mild conditions, with turnover numbers of up to 1880 when using 4.0 bar hydrogen pressure at ambient temperature (26–28 °C). Preliminary studies showed that this reaction is facilitated in alcoholic solvents, with ethanol giving the highest activity. No hydrogenation was observed in THF or neat acetophenone. NMR spectroscopic studies on stoichiometric reactions performed to gain insight into the mechanism of this catalytic process revealed that the reaction indeed proceeds through dearomatized intermediates. A mechanistic rationale is shown in Scheme 3. The catalytically active species is formed after the addition of KO*t*Bu to a solution of **4** in ethanol, which yields the pentacoordinated deprotonated and dearomatized $16e^-$ species [Fe(CO)(H)(PNP^H-*i*Pr)] (**A**). Since ethanol is crucial for the catalytic performance, intermediate **A** might be stabilized by reversible addition of ethanol to afford the aromatic complex **A′**. Coordination of the ketone to **A** followed by its insertion into the iron–hydride bond affords the $16e^-$ alkoxide complex **C**. This intermediate readily adds H_2 to form **D**. Heterolytic cleavage of the coordinated H_2 ligand may yield the aromatic hydrido alkoxide complex **E**. An alternative scenario may be the heterolytic cleavage of H_2 assisted by the adjacent alkoxide ligand to form intermediate **E′**, which



Scheme 3. Proposed catalytic cycle for the hydrogenation of ketones to alcohols catalyzed by [Fe(Br)(CO)(H)(PNP-*i*Pr)] (**4**).

contains an alcohol ligand. This step would not require protonation of the PNP^H ligand. The catalytic cycle is closed upon elimination of the product alcohol, thereby regenerating the starting species **A**.

In conclusion, we have described the pioneering studies carried out by Casey, Morris, and Milstein, who for the first time used iron as the metal in well-defined catalysts for the hydrogenation of ketones. In all these cases, strong-field tri- and tetradentate ligands (and sometimes also CO ligands) are required to apparently maintain the iron in a low spin state. Nature utilizes strong-field carbonyl (and cyanide) ligands in hydrogenases. These results are remarkable and important for the development of more environmentally friendly and sustainable reactions in the near future. Despite still being in its infancy, these examples have demonstrated its great potential and will stimulate ongoing research in reduction chemistry. A major task will be to design efficient chiral versions of these processes.

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[1] a) H. U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103–151; b) F. Naud, F. Spindler, C. J. Rueggeberg, A. T. Schmidt, H. U. Blaser, *Org. Process Res. Dev.* **2007**, *11*, 519–523.

[2] a) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73; b) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108–2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022.

[3] a) R. H. Crabtree, *New J. Chem.* **2011**, *35*, 18–23; b) H. Grützmacher, *Angew. Chem.* **2008**, *120*, 1838–1842; *Angew. Chem. Int. Ed.* **2008**, *47*, 1814–1818; c) J. I. van der Vlugt, J. N. H. Reek, *Angew. Chem.* **2009**, *121*, 8990–9004; *Angew. Chem. Int. Ed.* **2009**, *48*, 8832–8846.

[4] R. M. Bullock, *Chem. Eur. J.* **2004**, *10*, 2366–2374.

[5] a) J. A. Wright, P. J. Turrell, C. J. Pickett, *Organometallics* **2010**, *29*, 6146–6156; b) C. Tard, C. J. Pickett, *Chem. Rev.* **2009**, *109*, 2245–2274.

[6] a) R. H. Morris, *Chem. Soc. Rev.* **2009**, *38*, 2282–2291; b) S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 3363–3367; *Angew. Chem. Int. Ed.* **2008**, *47*, 3317–3321; c) S. Gaillard, J.-L. Renaud, *ChemSusChem* **2008**, *1*, 505–509; d) C. Bolm, J. Legros, J. Le Paith, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254; e) S. Enthaler, B. Hagemann, G. Erre, K. Junge, M. Beller, *Chem. Asian J.* **2006**, *1*, 598–604.

[7] a) C. P. Casey, H. Guan, *J. Am. Chem. Soc.* **2007**, *129*, 5816–5817; b) C. P. Casey, H. Guan, *J. Am. Chem. Soc.* **2009**, *131*, 2499–2507.

[8] Y. Shvo, D. Czarkie, Y. Rahamim, D. F. Chodosh, *J. Am. Chem. Soc.* **1986**, *108*, 7400–7402.

[9] H. J. Knölker, E. Baum, H. Goesmann, R. Klauss, *Angew. Chem.* **1999**, *111*, 2196–2199; *Angew. Chem. Int. Ed.* **1999**, *38*, 2064–2066.

[10] H. Zhang, D. Chen, Y. Zhang, G. Zhang, J. Liu, *Dalton Trans.* **2010**, *39*, 1972–1978.

[11] a) C. Sui-Seng, F. Freutel, A. J. Lough, R. H. Morris, *Angew. Chem.* **2008**, *120*, 954–957; *Angew. Chem. Int. Ed.* **2008**, *47*, 940–943; b) C. Sui-Seng, F. N. Haque, A. Hadzovic, A.-M. Pütz, V. Reuss, N. Meyer, A. J. Lough, M. Zimmer-De Iuliis, R. H. Morris, *Inorg. Chem.* **2009**, *48*, 735–743.

[12] H.-Y. T. Chen, D. Di Tommaso, G. Hogarth, C. R. A. Catlow, *Dalton Trans.* **2011**, *40*, 402–412.

[13] R. Langer, G. Leitus, Y. Ben-David, D. Milstein, *Angew. Chem.* **2011**, *123*, 2168–2172; *Angew. Chem. Int. Ed.* **2011**, *50*, 2120–2124.