Homogeneous Catalysis

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Sustainable Metal Catalysis with Iron: From Rust to a Rising Star?**

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Dedicated to Professor Wolfgang A. Herrmann on the occasion of his 60th birthday

coupling reactions · homogeneous catalysis · iron · oxidation · reduction

The development of sustainable, more efficient, and selective organic synthesis is one of the fundamental research goals in chemistry. In this respect, catalysis is a key technology, since approximately 80% of all chemical and pharmaceutical products on an industrial scale are made by catalysts—even more in the case of modern processes (ca. 90%). In particular, organometallic compounds have become an established synthetic tool for both fine and bulk chemicals and several hundreds of molecular, defined pre-catalysts are commercially available for chemists around the world. The reactivity and selectivity of the active catalyst are widely influenced by the choice of the central metal and by the design of surrounded ligands. During the last decades, manifold transition-metal catalysts especially based on precious metals such as palladium, rhodium, iridium, and ruthenium have been proven to be efficient for a large number of applications. However, the limited availability of these metals as well as their high price (Figure 1) and significant toxicity makes it desirable to search for more economical and environmentally friendly alternatives. A possible solution of this problem could be the increased use of catalysts based on first row transition metals, such as iron, copper, zinc, and manganese. Especially iron offers significant advantages compared with precious metals, since it is the second most abundant metal in the earth crust (4.7 wt%). Various iron salts and iron complexes are commercially accessible on a large scale or easy to synthesize. Furthermore, iron compounds are relatively nontoxic. In contrast to man-made precious-metal catalysts, iron takes part in various biological systems as essential key element, for example, in metalloproteins for the transport or metabolism of small molecules (oxygen, nitrogen, methane, etc.) and electron-transfer reactions (Figure 2). Thanks to the facile change of oxidation state and the distinct Lewis acid character, iron catalysts allow in principle a broad range of synthetic transformations, for example, additions, substitutions, cycloadditions, hydrogenations, reductions, oxidations,

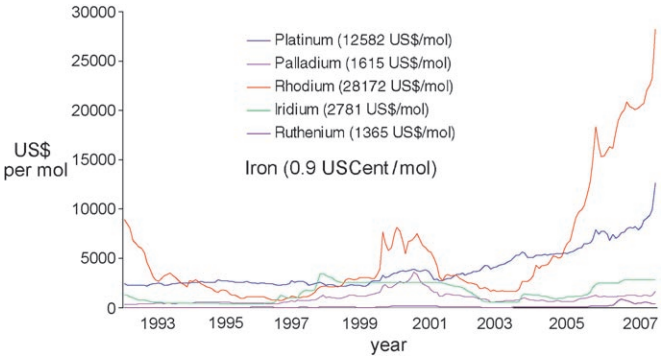

Figure 1. Market prices of transition metals.[2]

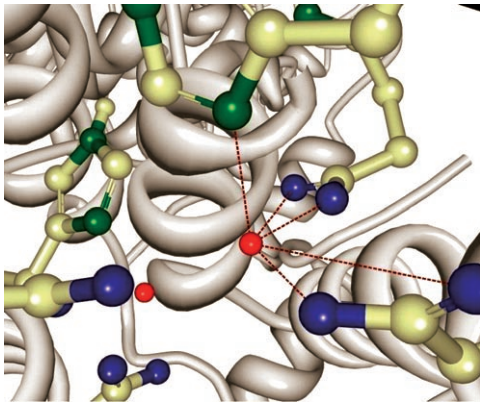

Figure 2. Example of a biological iron-based catalyst.[3] C white, Fe red, N green, O blue.

coupling reactions, isomerizations, rearrangements, and polymerizations. However, most of the known catalytic reactions with iron are either limited in scope or do not qualify for practical applications. In this respect the use of iron as catalyst is so far underdeveloped.

In 2004, an excellent review article by Bolm et al. summarized the achievements in iron catalysis until that time.[1] Since then, a number of impressive examples demonstrated the increased potential of iron catalysts in the field of reduction, oxidation, and coupling chemistry, which are the most promising reactions for industrial purposes. Herein, we wish to emphasize selected results and raise the question whether iron will be a new star in the catalysis tool box?

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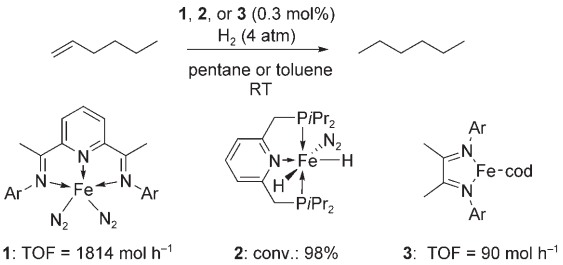
Starting with reductions, the group of Chirik has shown elegantly the use of low-valent iron complexes in the hydrogenation of various C–C double and triple bonds.[4] Catalyst precursors are synthesized by reduction of the corresponding dihalogen complexes with sodium amalgam under an atmosphere of dinitrogen. In the presence of comparatively low catalyst loadings (0.3 mol% iron), simple nonfunctionalized olefins such as 1-hexene or cyclohexene are hydrogenated with high turnover frequencies (TOF) under mild reaction conditions. Even under preferentially solvent-free conditions, similar activity is observed. The scope of the catalyst system was demonstrated in the hydrogenation of various simple olefins enclosing geminal, internal, and trisubstituted olefins. Notably, when comparing activity of catalyst **1** (1814 mol h^{-1}; Scheme 1) with standard heterogeneous and homogenous

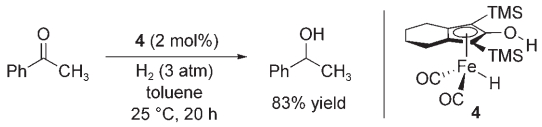


Scheme 1. Hydrogenation of olefins according to Chirik et al. Ar = 2,6-(iPr)$_2$C$_6$H$_3$.

catalysts, for example, Pd/C (TOF = 366 mol h^{-1}), [RhCl(PPh$_3$)$_3$] (10 mol h^{-1}), or [Ir(cod)(PCy$_3$)(py)]PF$_6$ (75 mol h^{-1}; cod = 1,5-cyclooctadiene; Cy = cyclohexyl; py = pyridine), in the hydrogenation of 1-hexene, a significantly higher value is observed with the iron catalyst. The tolerance of functional groups (ester, amide, hydroxy, amino, etc.) is of major importance for synthetic applications. Unfortunately, only a diminished activity is observed for dimethyl itaconate as substrate. Clearly, further improvements are needed. However, the functional group tolerance in other reduction reactions (see below) makes it likely that this goal might be achieved in the near future.

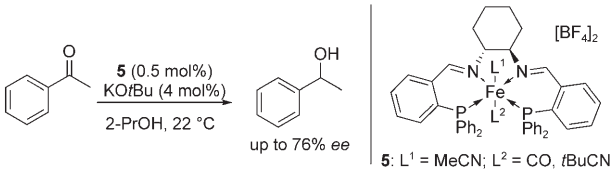
In addition to hydrogenation of C=C bonds, the reduction of C=O bonds is one of the industrially relevant reactions that was demonstrated to proceed in the presence of iron complexes by Casey and co-workers.[5] Catalyst **4**, which is somewhat related to the well studied ruthenium-based Shvo's catalyst, hydrogenated acetophenone smoothly in good activity (Scheme 2). A detailed study indicated similar behavior of catalyst **4** to Shvo's catalyst, since contribution of the hydroxy group for transferring the proton to the substrate is assumed. Furthermore, the catalyst showed high activity in the hydrogenation of several ketones, aldehydes, diketones, and imines.

Notably, molecular hydrogen can be used, but catalyst **4** also displayed activity in transfer hydrogenation reaction using 2-propanol as hydrogen source. Despite all advancements in hydrogenations and transfer hydrogenations, so far there exists only one example of a catalytic asymmetric hydrogenation with iron catalysts. Very recently Morris and



Scheme 2. Hydrogenation of ketones with iron catalyst **4**.

co-workers reported the first version of an enantioselective reduction of prochiral ketones in the presence of iron complexes containing tetradentate ligands (Scheme 3).[6]



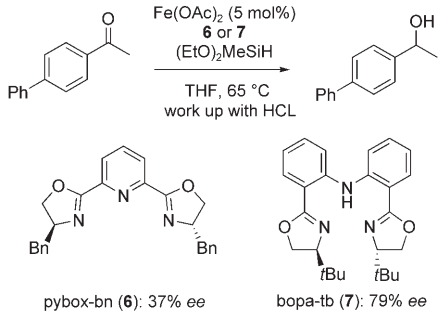
Scheme 3. Iron-catalyzed asymmetric transfer hydrogenation of ketones by Morris and co-workers.

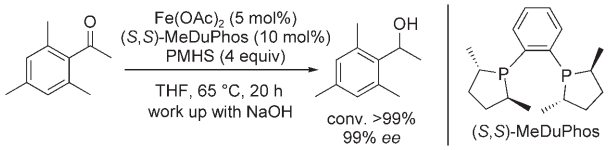
Enantioselectivities up to 76% *ee* were obtained using 2-propanol as hydrogen source. In addition, high catalyst activities (TOF up to 995 h^{-1}) were attained, which are competitive with ruthenium catalysts. These promising results indicate the potential of iron catalysts and will hopefully stimulate ongoing research in reduction chemistry.

A different strategy for the reduction of C=O bonds was shown by Nishiyama and Furuta.[7] They combined Fe(OAc)$_2$ with bi- and tridentate nitrogen-based ligands such as *N*,*N*,*N*′,*N*′-tetramethylethylendiamine (tmeda), bis(*tert*-butyl)bipyridine (bipy-tb), or bis(oxazolinyl)pyridine (pybox) to catalyze the asymmetric hydrosilylation of ketones to give the corresponding chiral alcohol after acidic cleavage of the silyl ether (Scheme 4). The reaction was carried out under mild conditions and gave yields of up to 95%. The best enantioselectivities were obtained in the presence of chiral tridentate nitrogen ligands. Hence, methyl 4-phenylphenylketone was reduced to methyl 4-phenylphenylalcohol in the presence of **7** with enantioselectivity up to 79% *ee*.

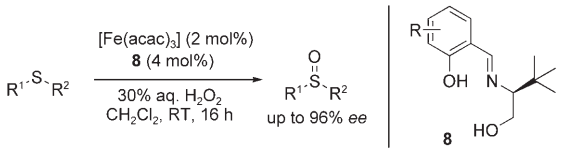
Most recent results revealed that it is possible to perform Fe-catalyzed hydrosilylations of acetophenones also in the presence of chiral phosphine ligands. In this case, enantioselectivities up to 99% *ee* were achieved in the presence of Fe/MeDuPhos complexes for sterically hindered substrates.[8]

Beside asymmetric reductions, transition-metal catalyzed oxidations play an important role in the synthesis of chiral building blocks. A general iron-catalyzed approach to chiral sulfoxides by oxidation of sulfides with inexpensive hydrogen peroxide has been developed by Bolm and co-workers (Scheme 5).[9] By using an in situ catalyst based on iron and chiral Schiff base ligands, several alkyl aryl sulfoxides were attained in enantioselectivities up to 90% *ee*.[9a] The simplicity of this procedure compared with established methods makes the process especially interesting. Later, the product yields as well as enantioselectivities (up to 96% *ee*) were improved by addition of catalytic amounts of carboxylic acids.[9b] Similar reactions were studied by Bryliakov et al. and Katsuki et al.





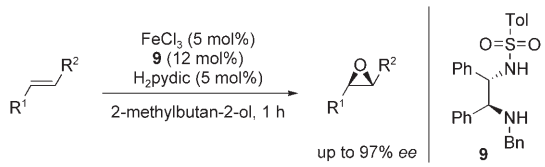
Scheme 4. Hydrosilylation of ketones with iron catalysts. Bn = benzyl; PMHS = poly(methylhydroxysilane).



Scheme 5. Enantioselective oxidation of sulfides with iron catalysts by Bolm and co-workers.

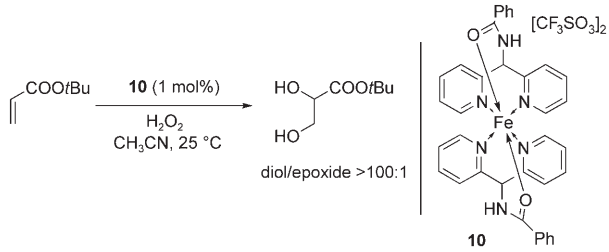
utilizing defined iron–salen complexes (salen = *N*,*N*′-bis(salicylidene)ethylenediamine anion) and iodosylbenzene or H_2O_2 as oxidant.[10] Recently, the group of Bolm reported also the oxidation of cycloalkanes and alkylarenes with catalytic amounts of iron salts.[11] Selective C–H oxidation occurred using ligand-free and mild reaction conditions; for example, ethyl benzene is converted into acetophenone and traces of phenylethanol. Again, the chemoselectivity of the reaction (towards the ketone) is improved by addition of carboxylic acids.

The potential of iron catalysts in the enantioselective epoxidation of olefins has been impressively demonstrated by Rose et al. When using a chiral binaphthyl-strapped iron porphyrin catalyst, excellent enantioselectivities (up to 97% *ee*) and activities (TON = 16000) are obtained in the epoxidation of a number of styrene-based substrates.[12] The application of the special porphyrin ligand led to the formation of a highly enantio-discriminating pocket. However, the necessity to use iodosylbenzene as oxidant makes the reaction less environmentally friendly since a large amount of waste is formed. A more economical and benign alternative was published last year, in which hydrogen peroxide is applied as oxidant (Scheme 6).[13] In the presence of a three-component catalyst system, consisting of $FeCl_3$, pyridine-2,6-dicarboxylic acid (H_2pydic), and a chiral diamine, 1,2-disubstituted aromatic olefines were epoxidized with enantiomeric excesses of up to 97% *ee*.



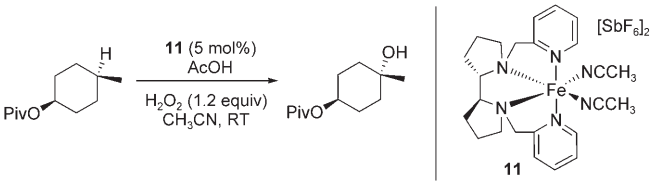
Scheme 6. Enantioselective epoxidation with an iron catalyst.

The crucial influence of the architecture of ligands on the outcome of oxidation reactions was demonstrated by Que and co-workers.[14] When using iron complexes containing bio-inspired N,N,O ligands, the *cis*-dihydroxylation process is favored over the typical epoxidation reaction (Scheme 7). Depending on the substrate, extraordinary selectivity (diol:epoxide > 100:1) was achieved under mild reaction conditions.



Scheme 7. Dihydroxylation with an iron catalyst according to Que and co-workers.

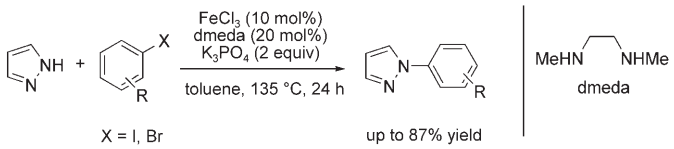
Beside the addition of oxygen to olefins, recently selective oxidation of non-activated sp^3 C–H bonds was realized elegantly by Chen and White.[15] By using straightforward iron catalysts, a variety of substrates were transformed into the corresponding alcohols, including highly functionalized examples under mild reaction conditions (Scheme 8). Notably, the usefulness of the presented iron catalyst was also demonstrated by applying this type of sustainable catalysis in the synthesis of a complex molecule.



Scheme 8. Iron-catalyzed oxidation of C–H bonds by Chen and White.

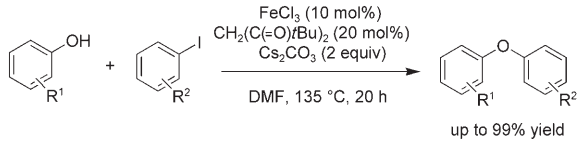
Although iron-based redox catalysts occur in many biological systems, and thus nature provides important inspiration for their design, similar catalysts for coupling processes are not known. Thus, it was common belief that the development of such artificial iron catalysts can not be based on nature's principles. In this regard, the recent report by the group of Bolm is important. In their seminal work, the

successful application of iron catalysts in N-arylation of aryl iodides and bromides is demonstrated generally (Scheme 9).[16] When using inexpensive $FeCl_3$ and bidentate nitrogen ligands (dimethylethylendiamine; dmeda) cross-coupling reactions of pyrazole proceeded with good yields and excellent selectivity.



Scheme 9. Iron-catalyzed N-arylation reactions.

The new iron-catalyzed method was further on extended to the coupling of amides, *N*-heterocycles, and sulfoximes.[16,17] However, so far the catalyst displayed limitations in the case of aromatic and aliphatic amines. Later, Bolm and co-workers also adopted their arylation protocol to an O-arylation, which is a challenging task.[18] After several optimization steps, a highly active and selective iron catalyst was developed which produces diaryl ethers from aryl iodides in excellent yield (Scheme 10). When using aryl bromides

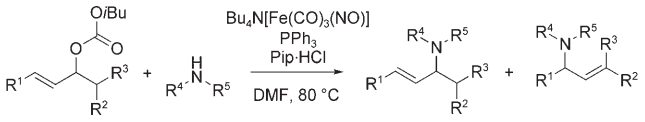


Scheme 10. O-arylation reactions with Bolm's iron catalyst.

instead of aryl iodides, longer reaction times are necessary to obtain reasonable product yields. Even the synthesis of aryl thioethers through S-arylation is possible in the presence of iron catalysts. By using the same catalyst as presented for the N-arylation reaction, excellent yield and selectivity were obtained for a variety of substrates.[19]

A different approach towards C–N bond formation was developed by Plietker.[20] Performing for the first time an allylic amination with iron-based catalyst, several allyl carbonates were treated with various amines to yield secondary or tertiary amines in good yields and selectivity. Notably, the stability of the catalyst was significantly improved by adding piperidinium chloride (Scheme 11).

In summary, a number of promising results applying iron as central metal in organometallic catalysts have appeared recently. We believe that this trend will continue. For important synthetic methods spanning from reductions to oxidations and to C–N and C–O coupling reactions, iron complexes are becoming a much more interesting and viable choice! Clearly, the reported catalyst systems are still far from immediate industrial applications. However, for the mid-term future we expect a significant increase in the use of "iron catalysis" in organic synthesis and finally also in "real" applications. The advantages of biomimetic or bio-inspired iron complexes in catalysis are obvious and convincing. One central research topic in the next few years should be the design of tailor-made ligands and the clarification of relationships between structure and action. Furthermore, the improvement of catalyst activity and productivity is challenging with respect to application. In this respect, the understanding of catalyst deactivation phenomena will be crucial. Finally, the development of more general enantioselective protocols will prove that it is possible to mimic nature with structurally more simple, sustainable catalysts.



Scheme 11. Allylic amination in the presence of an iron catalyst.

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