Iron as a Powerful Catalysts for Transition Metal-Catalyzed Reactions

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ABSTRACT

Iron has received a significant amount of attention in the recent literature as a powerful catalyst for transition metal-catalyzed reactions. Due to its low cost, ready abundance, and low toxicity, iron is an ideal metal catalyst for large scale synthesis of fine chemicals. The development of iron-catalyzed processes, however, is still in its infancy. This review will provide a direct comparison between state-of-the-art transition metal-catalyzed reactions and recent efforts to employ iron as a catalyst for the equivalent transformations. Reactions of high synthetic impact including Kumada couplings, hydrogenative reductions, and dihydroxylations will be covered in this review.

Transition metal-catalyzed reactions are among the most powerful tools in organic synthesis. Extensive research effort has been invested in the development of palladium-, ruthenium-, rhodium-, iridium-, and even nickel-catalyzed reactions. Due, however, to the high cost and toxic nature of many of these metal catalysts, there has been a recent surge in reports of organic transformations catalyzed by cheaper and more environmentally friendly metals such as copper and iron. In particular, iron-catalyzed reactions have several practical advantages over the analogous palladium- or nickel-mediated reactions. The low cost and ample supply of iron salts coupled with their environmentally benign nature and lack of toxicity make them ideal for industrial scale synthesis of fine chemicals. Iron has recently received a significant amount of attention in the literature as a catalyst for allylic substitution reactions, epoxidation and C–H oxygenation reactions, hydrogenation of ketones, and cross-couplings of organic halides with organometallic reagents.

While iron is often considered a latecomer in the development of transition metal catalyzed reactions, the use of iron as a transition metal catalyst, in fact, precedes the use of palladium and other more common metals as catalysts. As early as 1941, iron was found to be an effective catalyst in the homocoupling of aryl Grignard reagents, and in the early 1950s iron was used as a catalyst for cross-coupling Grignard reagents with acid chlorides (Scheme 1). In the ensuing years, iron was set aside due to the control and predictability of palladium or ruthenium. Not until recently

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Several recent reviews have described the advances in iron catalysis and its potential as a powerful transition metal catalyst.2 However, no direct comparisons between most part to its advantages of low cost and low toxicity. has iron begun to receive much attention again, due in the most part to its advantages of low cost and low toxicity.

The purpose of this review is to provide such comparisons that will demonstrate the potential of iron to supplant the use of more expensive and potentially hazardous metal catalysts. The development of iron-catalyzed Kumada cross-coupling reactions, hydrogenative reductions, and dihydroxylation reactions has recently shown significant potential as useful transformations and thus will be the focus of further discussion.

Kumada coupling reaction. The Kumada coupling reaction was first reported in 1972 by Kumada and coworkers and involved a nickel-catalyzed coupling between an aryl Grignard reagent and a vinyl chloride.9 Later, palladium was also shown to affect the same reaction pathways. In these cases, coordinating phosphine18 and amine-bisphenolate19 ligands have allowed for highly efficient reactions (Scheme 4). The above results demonstrate that iron rivals the traditional palladium- and nickel-catalyzed Kumada coupling reactions in terms of reaction efficiency. Ligand

A significant advantage of this iron-catalyzed process is that it precludes the need for highly specialized and expensive ligands. Thus, under ligand-free conditions, alkyl magnesium bromide reagents react with aryl or alkyl halides at extremely low temperatures, tolerating such functional groups as esters, ketones and cyanides. Only when cross-coupling secondary alkyl halides with alkyl or aryl Grignard reagents has the use of stabilizing ligands proved necessary to prevent alternative reaction pathways. In these cases, coordinating phosphine18 and amine-bisphenolate19 ligands have allowed for highly efficient reactions (Scheme 4).

In addition to aryl-aryl bond formation, cross-couplings that generate new aryl-alkyl C–C bonds 12 as well as alkyl-alkyl C–C bonds 13 are also possible. For example, Kambe and coworkers recently reported the cross-coupling of non-activated alkyl halides and tosylates with alkyl magnesium bromide reagents (Scheme 2).

Kumada cross-coupling reactions with iron.

![Scheme 2. Kumada cross-couplings with Pd and Ni.](image)

16 Under certain conditions, Fe(0) and Fe(II) catalysts have also been proposed. See: (a) Fürstner, A.; Krause, H.; Lehmann, C. W. Angew. Chem., Int. Ed. 2006, 45, 440–444. (b) Cahiez, G.; Habiaik, V.; Duplais, C.; Moyeux, A. Angew. Chem. Int. Ed. 2007, 46, 4364–4366.
free reaction conditions and moderate functional group tolerance are often possible with iron-catalyzed Kumada couplings. These facts, in addition to the low cost and low environmental impact of iron salts should make iron the catalyst of choice for a wide range of cross-coupling reactions.

**Hydrogenations.** The asymmetric hydrogenation of alkenes and polar bonds such as ketones and imines is a powerful strategy for generating chiral molecules. Indeed, an immense amount of research has been performed to generate efficient and selective hydrogenation reactions with ruthenium and iridium for use both in research laboratories and on the industrial scale. Asymmetric hydrogenation has been used as an effective alternative to other homogeneous catalysts. An important variable in catalyst choice for hydrogenations is turnover frequency (TOF) which gives an indication of the rate and catalyst loading needed. Chirik and coworkers have shown that iron complex 1 can perform hydrogenations of simple alkenes with turnover frequencies superior to many ruthenium- or iridium-catalyzed processes (Scheme 5). The system lacks the selectivity for the selective reduction of polar bonds. Two drawbacks to this reaction, however, include long reaction times and the fact that only ketones react efficiently with this catalytic system. Nevertheless, these early reports demonstrate the ability of iron catalysts to affect these important and widely used transformations.

Although asymmetric hydrogenations with iron have yet to appear in the literature, recent examples of asymmetric transfer hydrogenations and hydrosilations of ketones have established the ability of iron to affect such asymmetric reactions. The most recent results of Beller and coworkers demonstrate the ability of iron-phosphine complexes to perform highly selective reduction reactions. Utilizing sterically hindered aryl ketones, they were able to obtain excellent yields with almost absolute selectivity (Scheme 6). While this system is obviously limited by the constraints of the substrate, it provides a foundation for the development of highly selective iron-catalyzed reductions.

**Scheme 4.** Ligands for iron-catalyzed Kumada couplings.

**Scheme 5.** Iron-catalyzed hydrogenations.

**Scheme 6.** Asymmetric hydrogenation with iron.

In the field of asymmetric hydrogenation, iron has just begun to establish a presence. These early examples of iron-catalyzed hydrogenations and transfer hydrogenations bespeak the potential of iron to replace more expensive and hazardous metal catalysts as an efficient, cost effective and selective alternative. However, significant improvements in both reactivity and selectivity stems from the bifunctional nature of the catalyst as both a hydride and a proton donor, allowing for the selective reduction of polar bonds. Two drawbacks to this reaction, however, include long reaction times and the fact that only ketones react efficiently with this catalytic system. Nevertheless, these early reports demonstrate the ability of iron catalysts to affect these important and widely used transformations.

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selectivity are needed if iron is to become a viable alternative to existing hydrogenation protocols.

**Dihydroxylation of olefins.** The osmium-catalyzed dihydroxylation of olefins is an indispensable tool in organic synthesis for the generation of diol diacetates. With the advent of the AD-mix-α and β formulations, this process has become operationally simple and widely used for large-scale asymmetric dihydroxylation. The Sharpless asymmetric dihydroxylation is particularly useful due to the wide range of olefins that can be dihydroxylated with excellent enantioselectivity. These olefins include simple alkenes, skipped polyenes, styrenes, and allylic alcohols just to name a few. Osmium-catalyzed dihydroxylation are also amenable to large scale synthesis, as seen in a recent report by Sutin and coworkers where kilogram quantities of highly enantioenriched product was obtained (Scheme 7).

The major drawbacks of the Sharpless asymmetric dihydroxylation are the high cost and extreme toxicity of osmium salts. While catalyst loadings for this transformation are often below 1 mol%, large scale syntheses utilizing tons of grams of osmium salts are still problematic due to the toxicity of the waste generated. To address this issue, researchers have looked to other metal sources to affect this transformation, most notably to palladium. In a recent example, Dong and coworkers found that efficient diacetoxylation of olefins could be performed with as little as 2 mol% Pd(dppe) (Scheme 7). While this transformation provides a significant alternative to the osmium-catalyzed process, it still employs an expensive transition metal catalyst.

Iron has recently been reported to be an efficient catalyst for the dihydroxylation of olefins. Que and coworkers reported that biomimetic iron complexes inspired by the Rieske dioxygenase nonheme iron enzymes could perform efficient dihydroxylations with hydrogen peroxide as the terminal oxidant. While the corresponding epoxidation of the olefin was a major competing side reaction, Que has shown that the dihydroxylation can be favored by varying the structure of the catalyst (Scheme 8). It is important to note that these iron-catalyzed transformations proceed efficiently at very low catalyst loadings, and that costly organic oxidants such as NMO can be replaced with hydrogen peroxide. When employing a chiral polystyrene catalyst, high levels of enantioselectivity have also been obtained (Scheme 8). While high ee values are obtained with a variety of trans-disubstituted olefins, the generality of the reaction is limited as cis alkenes and alkenes bearing electron withdrawing groups react with only modest selectivity (up to 76% ee). These early results, however have shown that iron catalysts can provide an efficient and highly enantioselective alternative to the existing osmium-catalyzed methodologies.

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**Scheme 7.** Dihydroxylation reactions.

![Scheme 7](image)

**Scheme 8.** Iron-catalyzed dihydroxylation.

![Scheme 8](image)

**Conclusion.** While the field of transition metal-catalyzed reactions continues to produce new and important transformations, a growing body of research is focusing on replacing expensive transition metal catalysts with cheaper, more environmentally friendly and sustainable metals such as iron. The wealth of knowledge concerning reaction pathways that is available for transition metal-catalyzed reactions will continue to foster growth of well defined catalytic systems with iron. This review focuses on only three of the many important transition metal-catalyzed reactions and the ability of iron to affect these processes. The precedents described here suggests that iron will continue to appear as a viable alternative transition metal catalyst that is cost effective, nontoxic, and environmentally benign.

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