Homogeneous Catalysis

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Iron-Catalyzed Hydrogenation of Esters to Alcohols

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*Dedicated to Professor Max Malacria on
the occasion of his 65th birthday*

The reduction of esters to alcohols is an important chemical transformation frequently used in industry and in academic research laboratories as well. The two classical protocols for reduction are based on the use of a stoichiometric amount of a hydride reagent and, alternatively, catalytic heterogeneous hydrogenation. The former method suffers from severe drawbacks such as the toxicity of the reagents and the generated waste. From an ecological point of view, the latter method is more promising as the reducing agent is molecular hydrogen. One excellent example is the large-scale reduction of fatty esters to give the corresponding alcohols, precursors for plasticizers and surfactants, in the presence of a copper chromite catalyst.[1] However, heterogeneous hydrogenation using metal oxide based catalysts is poorly chemoselective; high pressures and temperatures are often required. These harsh conditions are not compatible with other unsaturated functional groups (alkenes, alkynes, nitro functions). Homogeneous catalysis is an alternative as the reduction can be performed under milder conditions and the functional group tolerance is higher. Since the pioneering work by Grey and Pez,[2] tremendous improvements, concerning reaction conditions, selectivities, and catalytic efficiencies, have been described for the homogeneous hydrogenation of esters. Most of the catalytic systems reported up to now are based on ruthenium.[3] However, owing to environmental concerns, these noble metals should be replaced by Earth-abundant ones, such as iron. In this context, the groups lead by Milstein,[4] Guan and Fairweather,[5] and Beller[6] reported in 2014 the first examples of homogenous iron-based complexes as catalysts for the hydrogenation of esters under relatively mild conditions.

The three groups reported the use of structurally related iron complexes with $[Fe(H)_2(CO)]$ or $[Fe(H)(HBH_3)(CO)]$ fragments coordinated to a phosphorous/nitrogen-based tridentate pincer-type ligand (Figure 1), and it appeared that the nature of the PNP ligand has an important influence on the substrate scope.

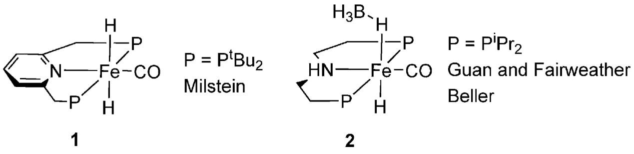

Figure 1. Iron complexes for the hydrogenation of esters.

Milstein and co-workers reported the hydrogenation of highly activated trifluoroacetate derivatives using PNP–iron complex **1** (PNP = 2,6-(di-*tert*-butylphosphinomethyl)pyridine) in the presence of a strong base (KH or potassium or sodium alkoxide).[4] Reactions were performed under moderate hydrogen pressure (usually 5 to 25 bars) at mild temperatures (40 °C) in the presence of 1 mol % of **1** and 5 mol % NaOMe in 1,4-dioxane. In related studies with ruthenium complexes[7] a cooperative effect between the PNP ligand and the metal was evoked. Again, ligand involvement was also proposed to activate molecular hydrogen. The proposed ligand dearomatization/aromatization process intrinsically requires only one equivalent of base relative to metal, but in this reduction a higher amount of base (up to 10 mol %) increased the catalytic activity and was thought to facilitate both the formation of the dearomatized intermediate and the removal of the acetal intermediate. Complex **1** displays some nice selectivity towards fluorinated aryl groups and ethers but also more interestingly towards nonpolarized and poorly substituted C=C bonds introduced on the ester moiety. Interestingly, the authors reported that further heating led to unexpected lower conversions, probably due to catalyst deactivation/degradation. Moreover, complex **1** appeared to be quite sensitive to steric hindrance of the ester moiety. Conversions dramatically decreased with an increase of the steric demand on the ester (isopropyl or methylcyclohexyl derivatives). Nevertheless, the interest in such a system is understandably quite limited due to the lack of conversion of slightly less activated difluoroacetate and less electron-demanding esters, such as acetate and benzoate derivatives.

Independently, Guan and Fairweather, and Beller reported the use of an iron pincer complex bearing a bis(diisopropylphosphinoethyl)amine) ligand, which was previously described by Gusev for the homogeneous osmium-catalyzed hydrogenation of esters.[8] With this ligand, Guan and Fairweather reported that the corresponding [(PNP)Fe(H)(Br)(CO)] precursor was slightly active in the presence of KO*t*Bu. But more importantly, both research groups noticed that the

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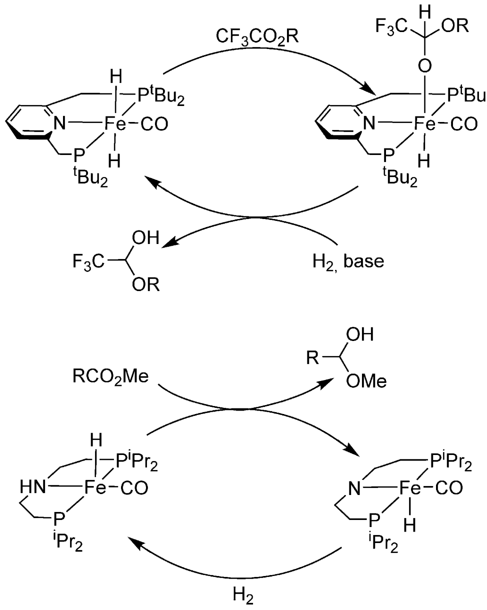
corresponding [(PNP)Fe(H)(HBH_3)(CO)] complex **2** did not require the addition of base to efficiently effect the hydrogenation of esters; added base was even detrimental for the catalytic activity. Then, when the pyridine fragment in the ligand was replaced with an amine, the reaction conditions could be modified (reaction could be performed at higher temperature than with the Milstein system) and higher catalytic activities could be obtained for a broader scope of substrates.

Neither group was able to decrease catalyst loading (1–3 mol%), and Guan and Fairweather clearly noticed rapid reaction shutdown probably due to catalyst decomposition. But improved conversions could be achieved under milder conditions. This catalytic system could be used for the efficient hydrogenation of a large variety of esters with a loading of 1 mol%, even in the case of non-activated purely aliphatic derivatives. THF or toluene was usually used as solvent; however, Guan and Fairweather reported some transformations of potential industrial interest and hydrogenated a mixture of C_{10}–C_{16} fatty esters under neat conditions. Concerning the selectivity, hydrogenation reactions using pincer complex **2** also appeared to be quite tolerant towards various functional groups. As a matter of fact, ester hydrogenation was efficiently performed with benzoates having ether or halide substituents, as well as with nitrogen-, oxygen-, or sulfur-based heterocyclic esters as described by Beller. Nevertheless, an aromatic nitrile functional group was reduced to a primary amine. Moreover, the electron density on the aromatic ring of benzoate derivatives clearly affects the catalytic efficiency. Electron-poor aromatic esters were more efficiently reduced than electron-rich ones. Both research groups noticed that α,β-unsaturated esters were hydrogenated to the fully saturated alcohols. However, Beller observed also that nonpolarized 1,2-disubstituted alkenes remained unchanged in these conditions, reminiscent of Milstein's catalyst selectivity. Finally, Beller reported the use of complex **2** as a catalyst for the chemoselective hydrogenation of a methyl ester in the presence of not only an olefin but also more sterically hindered acetate and carbamate groups, and secondary and tertiary amides, as exemplified by the hydrogenation of a challenging and pharmaceutically relevant dodecapeptide.

Beller and Milstein performed DFT calculations to propose a reasonable reduction pathway. Both groups stated that the first step was a direct transfer of the hydride from the metal center to the carbonyl moiety, without prior coordination to the metal, and also that formation of the hemiacetal was the rate-determining step. But, whereas Milstein suggested the release of the hemiacetal by base-assisted dearomatization of the pyridine ring (following an inner-sphere-type mechanism), Beller proposed a simultaneous proton transfer from the NH moiety by an outer-sphere mechanism,[9] leading to the formation of an iron amido complex along with the free hemiacetal (Scheme 1). This simultaneous proton transfer was supported by both theoretical and experimental studies. Then, after dissociation of the acetal into alcohol and aldehyde in solution, the latter is readily hydrogenated into alcohol.



Scheme 1. Proposed mechanisms by Milstein[4] and Beller.[6]

The reports by Milstein, Guan and Fairweather, and Beller clearly pave a new route for the homogeneous hydrogenation of esters to alcohols. They clearly demonstrate the potential of cheap, abundant, and biocompatible iron metal to perform such a major transformation under relatively mild conditions. These complexes showed quite good functional group tolerance and were also applied in transformations of industrial interest. But, up to now, due to the moderate catalytic activities and the price of the ligand, the replacement of the most active ruthenium complexes by iron catalysts for industrial applications is not topical. Tuning of the ligand structure should be a future research area not only to improve the catalytic efficiency but also to decrease the ligand cost.

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