Towards the Industrial Implementation of Mn-based Catalyst for the Hydrogenation of Ketones and Carboxylic Esters

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Abstract: There is a constant pressure in industry to move away from platinum group metals (PGM) and achieve more environmentally friendly and sustainable production processes in the future. Recently developed Mn-based catalysts offer an interesting opportunity to complement established catalysts based on Ru. In this article, recent achievements in the field are highlighted and recent achievements in the collaboration of Solvias AG with the group of Prof. M. Clarke towards the implementation of these catalysts on industrial scale are outlined.

Keywords: Carbonyl group hydrogenation · Ferrocenyl-based ligands · Hydrogenation · Mn-based catalysts

Achim Link received his MSc in the Sparr Group at the University of Basel and was involved in launching the group's first research project. He remained for his PhD studies focusing on bifunctional organometallic reagents. A fellowship from the 'Camille & Henry Dreyfus' Foundation and an Early Postdoc Mobility fellowship from the 'Swiss Nat. Science Foundation' allowed him to join Prof. Buchwald at MIT investigating CuH-catalyzed reactions. In 2020, he joined Solvias as a project leader. In June 2022 Achim took over the lead of the catalysis team at Solvias and joined the steering committee of the business unit Products & Manufacturing Services.

Patrick Furer studied chemistry at the University of Applied Sciences Northwestern Switzerland. He began his professional career in the R&D department of Roche and subsequently worked for several years in start-up biotech and contract manufacturing organizations. In 2005, he joined the catalysis group of Solvias as head of the high throughput experimentation lab and in the role of project manager focusing on heterogeneous hydrogenation.

Matt Clarke is a Professor of Chemistry at the University of St Andrews. Matt completed a PhD in Organic Chemistry at the University of Bath, supervised by Prof. Jon Williams, post-doctoral research at St Andrews with Prof.'s Derek Woollins and David Cole-Hamilton, and a fixed term lectureship in Bristol (researching within Prof. Paul Pringles group). Matt started his own group in St Andrews in 2003, when they immediately began developing hydrogenation catalysts derived from bifunctional P,N,N ligands: eventually leading to the catalysts described here. Matt's group are interested in developing more efficient methods to synthesize industrial products using catalysis.

Marc-André Müller received his PhD from the University of Basel in the group of Prof. A. Pfaltz in the field of asymmetric hydrogenation. After a post-doctoral stay at the Max-Planck-Institute für Kohlenforschung with Prof. A. Fürstner, he started his industrial career at Dottikon ES where he was a chemist in the high-pressure lab. In 2015 he joined DSM as Laboratory Head in process research. Currently he is working as Head Operations Products leading the catalyst/ligand business and the fiberoptic products at Solvias.

Within the large variety of chemical reactions relevant for industrial production processes, hydrogenation reactions are among the most frequently used and most efficient transformations throughout the different industrial segments.[1] With its key features such as perfect atom economy, close to quantitative yields, mild reactions conditions, high selectivity, no aqueous work-ups and the large number of established catalysts, it is not surprising that a huge variety of industrial applications are known. Somewhat surprisingly the reduction of carbonyl compounds and in particular of carboxylic esters often still relies on stoichiometric metal-hydrides such as $NaBH_4$, $LiAlH_4$ and H-DIBAL. Nonetheless though more and more the synthesis of alcohols on scale is realized by transition metal-catalyzed hydrogenations mainly relying on Ru-based catalysts.[2-5] Using catalytic conditions, the formation of stochiometric amounts of waste and special work-up procedures can be avoided and the limited functional group tolerance can be overcome. Additionally, extremely harsh reaction conditions (up to 300 bar, >200°C) that have been reported for the catalytic hydrogenation of fatty esters are no longer required with this new generation of Ru-catalysts.[6]

The constant transformation of the chemical industry towards the implementation of more sustainable production processes is enabled by the use of non PGM-based catalysts. It is certainly an over-simplification to claim that the use of an earth-abundant metal catalyst is superior from a sustainability standpoint considering *e.g.* carbon footprint of a production process. Such parameters are much more difficult to elucidate and connected to many other factors like solvent, concentration, catalyst loading and many

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more. There are many examples of highly efficient applications of PGM catalysts, with recent examples like in the production of the novel fungicide Inpyrfluxam.[7-9] Nevertheless, by simply looking only at the metal itself comparing *e.g.* manganese-based with ruthenium-based catalysts, it becomes obvious that under similar reaction conditions more sustainable processes can be achieved. In addition for some processes, other reaction parameters can be either very similar to or in fact improved relative to PGM-based processes.

In the context of reducing ketones or carboxylic acid esters, Mn-based catalysts offer an interesting alternative to the established systems based on Ru. Mn is the third most abundant transition metal and overall, the 12th most abundant element in the earth crust with (0.095%) and therefore significantly more available than Ru (1×10^{-7}%).[10]Mn reveals a unique property with its large range of possible oxidation states from (-3 to +7), which allows the stabilization of many different transition states.

In the field of hydrogenation chemistry, the application of Mn-based catalysts for the hydrogenation of ketones dates back to 2016 by Beller and coworkers using a PNP-ligand with *i*Pr-residues on the phosphine (Fig. 1).[11] In their seminal publication the hydrogenation of various polar functional groups was described as well, *e.g.* nitriles or aldehydes. Other functional groups prone to hydrogenation like C-C double bonds, esters or heterocycles remained untouched. Soon afterwards, this methodology was extended to carboxylic ester reduction using a slightly modified PNP-ligand with ethyl-substituents on the phosphorus moiety containing two or three carbonyls coordinated.[12]

Since these first reports various catalysts were reported, and the number of Mn-based catalysts is continuously increasing. Still in 2016 new catalyst structures were published by Kempe and coworkers using a PNP-pincer type ligand based on a 1,3,5-tri-azine-moeity achieving the quantitative hydrogenation of various diaryl, aryl–alkyl, dialkyl, and cycloalkyl ketones with 0.1 mol% catalyst loadings.[13] Additionally, diverse functional groups are tolerated, including terminal olefins. Milstein and coworkers also reported in 2016 the application of a tridentate PNN-ligand including mechanistic insights based on NMR studies (Fig. 1).[14]

Since these first publications, various catalyst systems were reported for the hydrogenation of ketones and carboxylic esters. For example, a further catalyst for the hydrogenation of carboxylic esters was reported by Pidko and coworkers using a simple novel non-pincer-type Mn PN complex.[15] Catalyst loadings of only 0.2 mol% were enough to reach full conversion albeit under comparatively harsh conditions with 75 mol% of KO*t*Bu and 50 bar hydrogen pressure. Conducted DFT calculations revealed additional insight to the reaction mechanism, activation and resting state of the catalyst.[16]

The asymmetric hydrogenation of ketones is an often encountered quest in many industrial production processes. Most interestingly, several Mn-based chiral catalysts were reported in this context. Beller and coworkers reported in 2017 a catalyst that showed good enantioselectivity in the hydrogenation of aliphatic ketones.[17] Morris and coworkers used a PNP-ligand-based catalyst with two stereogenic centers in the ligand backbone.[18] Ding and coworkers applied an NNP-ligand-based catalyst containing the same phosphorous residue as used by the Beller group.[19,20] Clarke and coworkers published in 2017 a ferrocenyl-based catalyst that showed high enantioselectivities.[21] Zhong and coworkers[22,23] and Zhang and coworkers later reported the use of ferrocenyl-based ligands for this transformation (Fig. 2).[24]
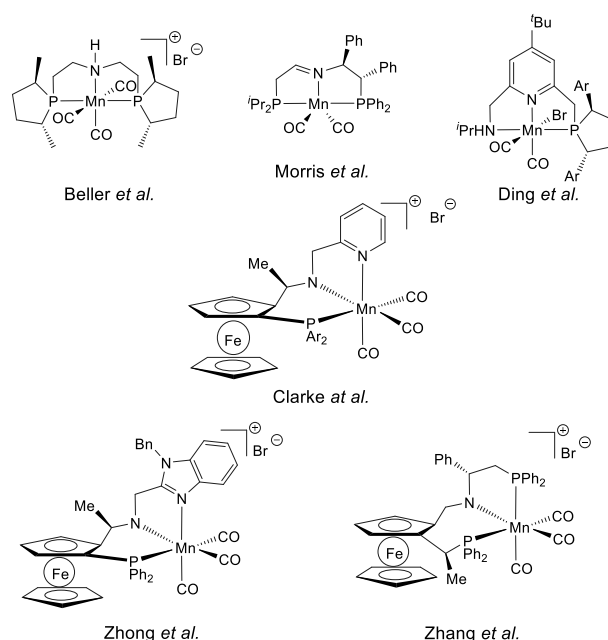

Fig. 2. Various manganese-based catalysts used for the asymmetric hydrogenation of ketones.[17-24]

New developments in the field are connected to the replacement of phosphine ligands by N-heterocyclic carbenes (NHCs) as reported by the groups of Pidko and Filonenko with a CNP ligand 2021.[25] These catalysts were extremely active and showed TONs of up to 200'000, being thermally robust at 120 °C. Later, in 2022, a CNC ligand was published by the same group.[26] Liu and coworkers reported in 2023 the use of a carbene-based NNC-ligand containing an imidazole moiety.[27] This catalyst was also used for the hydrogenation of carboxylic esters. Most recently the use of simple bis-carbene structures was reported by the group of Beller.[28] (Fig. 3). Using 1 mol% KHBEt₃ as additive, the hydrogenation of various carboxylic acid esters and ketones was achieved.

Recent reviews on the application of Mn-based catalysts for the hydrogenation of ketones and carboxylic esters cover different topics in the field.[29,30,31]

Among the catalysts previously discussed the one reported by Prof. Clarke from the University of St Andrews caught the attention of Solvias. This catalyst contains a ferrocene-based moiety well known from the Solvias product portfolio (Scheme 1).[32,33] Additionally, these new catalysts match very well with the concept of diversity since they are highly modular in regard to the
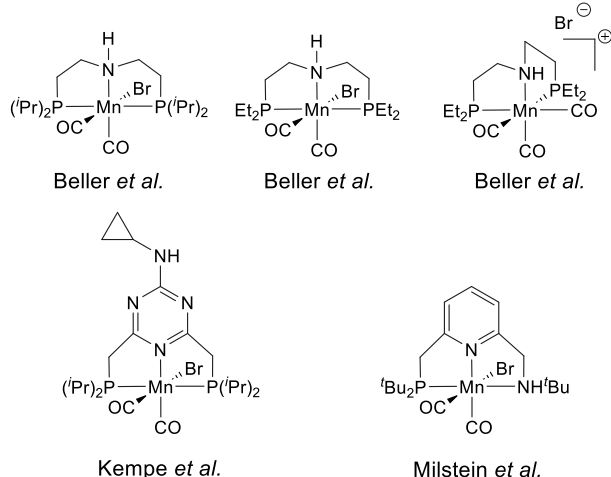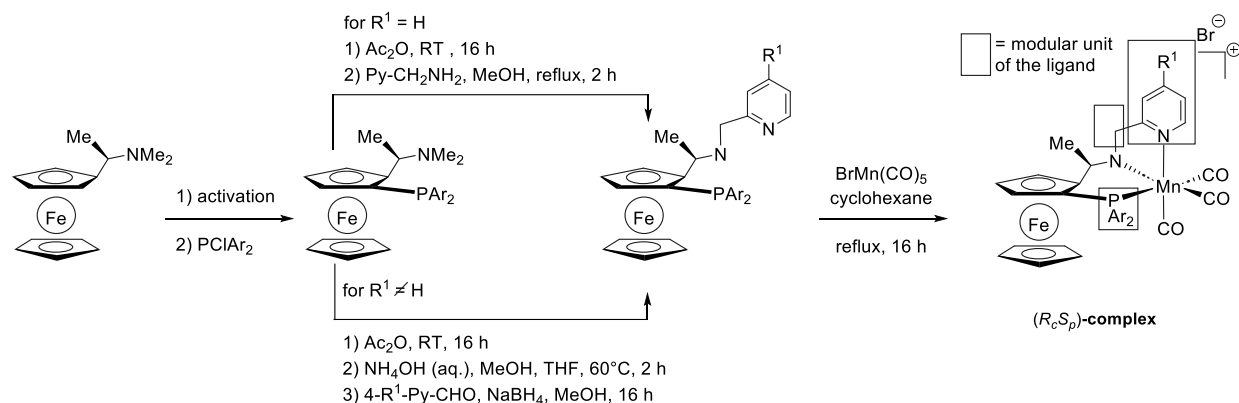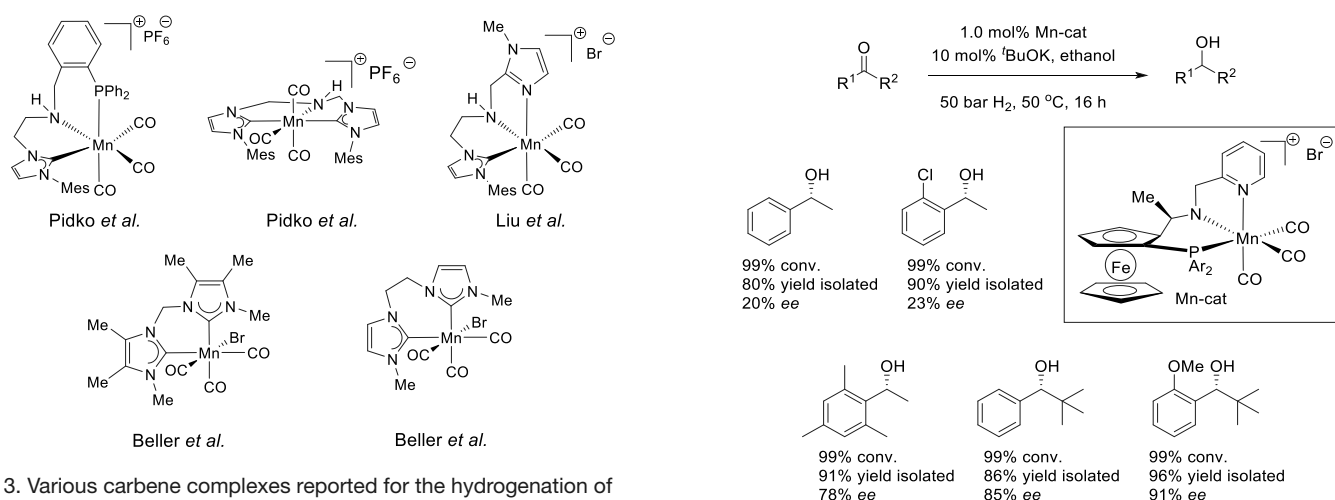

Fig. 1. Collection of the first Mn-based catalysts reported in 2016 by several groups.[11–14]

Scheme 1. Synthesis of the ferrocenyl-based Mn-catalyst reported by Clarke *et al.*[21]

Fig. 3. Various carbene complexes reported for the hydrogenation of carbonyl functions.[25–28]

Scheme 2. First examples in the hydrogenation of ketones reported by the Clarke group (Ar = phenyl).

residues on the phosphine moiety, the linker between the N-donating function and the heteroaromatic residue with its electronic and steric parameters. Amongst others, with the available common intermediates from the Solvias library a quick access to new structures was realized.

All these units can be introduced starting from the known Ugi amine, achieving the synthesis of the catalysts in only 3 steps (Scheme 1).

These Mn-based catalysts were used to report the first enantioselective hydrogenation of ketones by manganese-based catalysts (Scheme 2). Enantioselectivities of up to 91 % were reached for sterically demanding ketones at rather mild reaction temperature of 50 °C. The hydrogenation of less sterically demanding substrates resulted in rather low enantiomeric excess using the current version of the catalyst at that time.

An additional feature of these catalysts is demonstrated in the hydrogenation of enantiomerically enriched α-chiral esters and lactones with close to no erosion of the chiral information of the stereogenic center in α-position. Additionally, various functional groups were tolerated.[34] The catalyst performance was showcased in the hydrogenation of (*R*)-(+)-Sclareolide to the corresponding diol, using K_2CO_3 as a base and only 0.1 mol% catalyst loading (Scheme 3). This transformation can be used for the synthesis of the well-known aroma compound Ambrox®.[35-37] Whilst the use of a chiral catalyst to conduct a transformation that is not enantioselective may initially sound inefficient, the short and efficient synthesis of these catalysts either in single enantiomer or racemic form, as well as the fact that they can be used using weaker and cheaper bases than most PGM ester reduction catalysts makes

them an attractive option. Later, it was found that ethanol can be used as the reductant for a transfer hydrogenation of esters that does not need high pressure equipment. A proof-of-concept example where a carboxylic acid was reduced by telescoping Steglich esterification conditions with the transfer hydrogenation was also communicated.[38]

Using the initial catalyst and conditions, several aspects were identified that would be desirable to improve upon. The catalyst had relatively low solubility in some desirable solvents such as ethanol and gave low selectivity for some sterically unhindered ketones. In addition, if possible, even higher reactivity would be desired and the acetophenone reductions were found to be zero order in substrate implying the hydrogen activation step might be improved. Collaboration between Solvias and St Andrews proved fruitful here, since Widegren and Clarke wanted to test a hypothesis that more electron-donating aromatic rings on phosphorous might lead to an improvement in reactivity. The precursors required to make a collection of ligands to examine were available at Solvias in significant quantities; after delivery of the precursors, a family of catalysts was easily made. Catalysts with 3,5-dimethyl-4-methoxy-phenyl groups in place of simple phenyl rings on phosphorus proved superior in every way. Remarkably, rates improved up to 4-fold, and solubility in ethanol improved more than expected, being five times more soluble and enabling catalyst solutions to be prepared and dispensed. In addition, the more economic reaction conditions using the weak base, potassium carbonate, enabled higher enantioselectivity in ketone hydrogenations that did not have bulky alkyl groups. For example, a
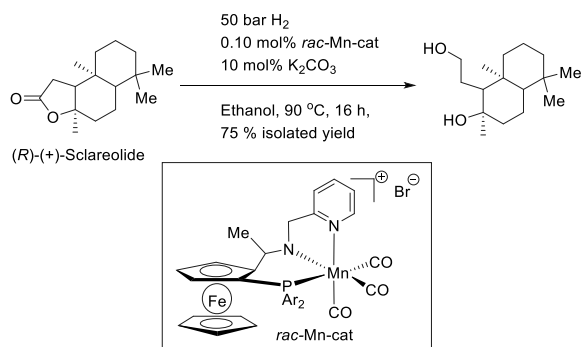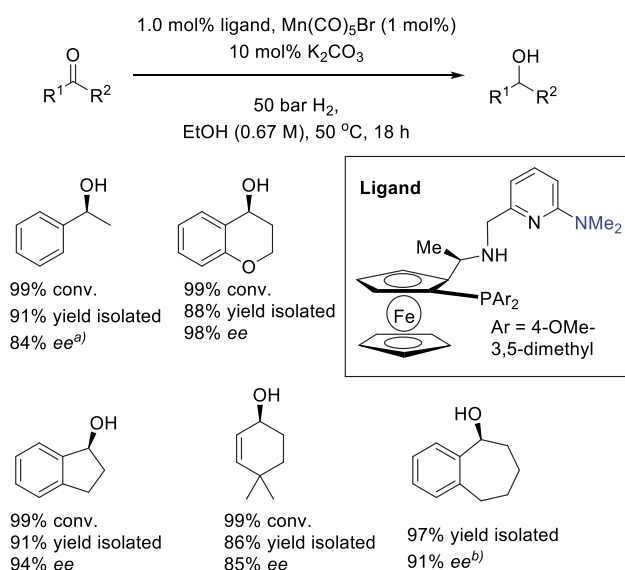
Scheme 3. Application of a ferrocenyl-based Mn complex in the hydrogenation of (R)-(+)-Sclareolide.

drug precursor was made by hydrogenation of 2,6-dichloro-3-fluoroacetophenone in 82% *ee*.[39] Around 35 substrates were shown to be reduced effectively, including some examples of transfer hydrogenation using isopropanol as the hydrogen source.

Recently published DFT calculations on the catalytic cycle lead to the development of the modified ligand, which enabled the higher enantioselectivities in the hydrogenation of ketones (Scheme 4).[40] The ligand used contains an additional dimethyl-amino substituent in the 2-postion of the pyridine ring. Compared to the previously published results a significant improvement of the enantiomeric excess was achieved with results of up to 98% *ee*.

After the successful hydrogenation of ketones and carboxylic esters a further broadening of the substrate scope was demonstrated by achieving good enantiomeric ratios and full conversion in the hydrogenation of substituted *in situ* synthesized imines (Scheme 5). Similar reaction conditions as in the hydrogenation of the carboxylic esters were applied, and both activated isolated imines or relatively deactivated (*e.g.* phenyl, 4-methoxyphenyl) nitrogen substituents could be used. A qualitative analysis of the sustainability credentials of this reaction relative to several alternative approaches showed this compares favorably over several parameters (catalyst, step-count, imine synthesis conditions, solvent choice, and base choice).[41]

In the meanwhile, these catalysts were also applied by others. State-of-the-art results with up to >99% *ee* can be achieved in the asymmetric hydrophosphination of alkenes.[42] Recently, further interesting applications in hydrophosphination have been achieved with these catalysts (Scheme 5).[43]

The exchange between Solvias and the group of Prof. M. Clarke started in 2017 shortly after the initial publication describing these chiral Mn-catalysts for the first time. As already stated, the hydrogenation of ketones and carboxylic esters is an important field for chemical production processes and the access to efficient cost-attractive and sustainable catalysts is of upmost importance. Since this field was also considered as a natural extension of the product and service portfolio, it was clear right from the beginning that Solvias wanted to support this interesting journey by providing the enantiomerically pure starting materials to help to accelerate the development of these catalysts. Further discussions on new catalyst structures and industrially relevant substrates, also resulted in an internship of a PhD student, who was able to perform reactions at Solvias laboratories. Solvias also provided access to its high-throughput-screening platform located in Basel.
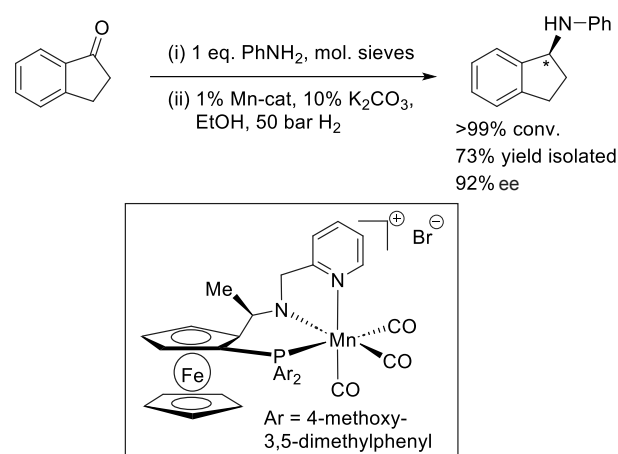
Scheme 5. An example of a highly enantioselective imine hydrogenation catalyzed by one of the catalysts. Imines could either be isolated or made *in situ* immediately before reaction.

Scheme 4. Improved enantioselectivity achieved by ligand modification guided by DFT calculations; a) isolated catalyst was used; b) 1.5 mol% of ligand and metal precursor was used.

The transfer from the demonstration of the feasibility in small scale to an industrial application is not trivial. Solvias is now working in close partnership with Prof. Clarke's group to make this new and innovative technology available to customers. Most important is the commercial availability of the catalyst from the initial mg and g quantities for R&D trials up to multi-kg to feed pilot and manufacturing applications. To accelerate this journey and provide availability of this interesting catalysts to the market, an exclusive license agreement was filed between Solvias and St. Andrews for the hydrogenation of esters and ketones.[44,45] Currently, Solvias is launching the product supply by developing the scale up of these catalysts. In order to foster and further broaden their application, the Solvias experts also offer service programs on the development of chemocatalyzed reactions supported by a sophisticated high throughput screening platform and the most diverse library.

Overall, this collaboration is looking forward to further develop these catalysts together with the group of Prof. M. Clarke towards their first application in a large scale and contribute to create more sustainable and environmentally friendly processes in the future.[39]

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