Asymmetric catalysis using iron complexes – 'Ruthenium Lite'?

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A review of recent developments in the use of iron catalysts for asymmetric transformations, including hydrogenations, transfer hydrogenation, hydrosilylation and oxidation reactions.

Introduction

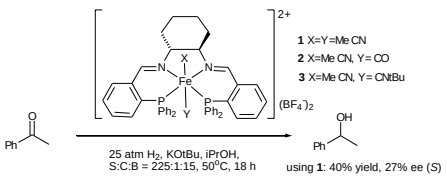
The role of iron in asymmetric catalysis.

In recent years, significant breakthroughs have been made in the development and applications of homogeneous iron-based catalysts to asymmetric transformations.[1-11] Several excellent reviews have been published which describe the key findings and many of the non asymmetric precedents for the catalysts in this review. Here the focus will be on recent developments in asymmetric reactions, although some non-asymmetric reactions will be discussed where they serve to place new findings into context.

The idea of using iron as a catalyst for chemical reactions is not a new one. The Haber process for ammonia production, dating back to 1909, depends on an iron catalyst,[12] and many enzymes, for example hydrogenases, contain iron at their active sites.[13] Compared to other transition metals, iron is significantly less developed as a homogeneous catalyst for organic reactions, particularly asymmetric processes. Yet sitting directly above its groupmates ruthenium and osmium, and close to its catalytically distinguished neighbours, iron appears to be ideally placed to form the basis of asymmetric catalysts. Given the far lower cost and greater abundance of iron over the more precious metals, it is clear that iron-derived complexes would provide a range of benefits if they could be made practical, stable, active and selective.

1) Reduction reactions of ketones and imines by pressure hydrogenation.

Several classes of homogeneous iron complexes have been reported to be active in the catalytic hydrogenation of alkenes,[1-11] of which the class reported by Chirik et al. are particularly well-established.[14] A key breakthrough in the development of iron catalysts for asymmetric ketone hydrogenation came in 2008[15] with the report by Morris et al. of complexes **1** and **2** formed between a simple iron(II) salt and a tetradentate diiminodiphosphine 'PNNP' ligand. These complexes, the design of which was inspired both by the well-established Ru(II)-based systems for asymmetric catalysis of ketone reduction,[16] and a closely-related iron complex for transfer hydrogenation (see next section),[17] could be formed by a number of methods, although perhaps most conveniently through the direct reaction of iron(II)chloride with the precursor ligand, followed by counterion and/or ligand exchange. An alternative, and highly effective method, which involved the iron-templated complex formation through the in situ condensation of the chiral diamine component with the precursor phosphinoaldehyde dimer.[18,19,20]



Scheme 1. Asymmetric hydrogenation of acetophenone using an iron-based catalyst.

Of the complexes tested, **1** proved to be an effective in the asymmetric hydrogenation of ketones (Scheme 1). At a relatively low loading of ca 0.45 mol% (S/C 225), which is typically used for many Ru(II)-based asymmetric catalytic systems, acetophenone was reduced in 40% conversion and 27% ee after 18h at 50°C (25 atm H_2). Although the enantioselectivity was modest, this represented a significant advance in iron-based asymmetric catalysis. Furthermore, several of the complexes proved to be active in asymmetric transfer hydrogenation and will be discussed in the next section. The related complex **2** was not an active hydrogenation catalyst.

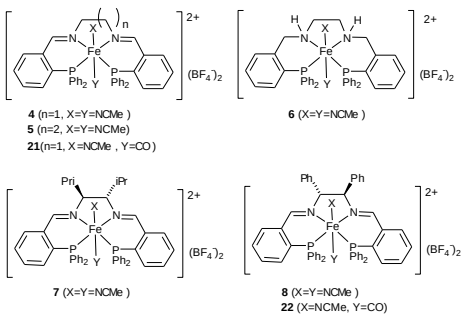


Figure 1. Bis(MeCN) complexes catalyse the hydrogenation of acetophenone.

Complexes **4 – 8** were also prepared, using the in situ templating method, and tested in ketone hydrogenation reactions.[21] The mechanism of the reduction reaction is not yet fully understood, however Morris has speculated that the imine group in the ligands may be reduced, in-situ, to give the saturated complexes, which act as the active catalyst

precursors.[21,22] Evidence for this came from the observation that complexes **4** and **6** give very similar conversions of ketones to hydrogenation products under the same conditions. Should this be the case, then the mechanism may resemble that commonly associated with the closely-related ruthenium complexes (Figure 2),[16] in which hydrogen is transferred to substrate through a concerted, 6-membered ring mechanism, the well-defined nature of which contributes to the high level of enantiocontrol in the reduction.

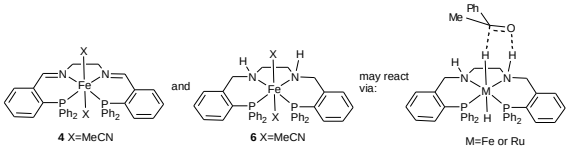


Figure 2. Complexes **4** and **6** catalyse the hydrogenation of acetophenone at similar rates, suggesting a similar mechanism.

The enantiomerically-pure complexes **7** and **8** were prepared and characterised by X-ray crystallography, which revealed that the substituents on the bridging ethylene group were axially positioned, possibly to avoid unfavourable steric clashes. This appears to be detrimental to activity, since only 3-4% ketone reduction was observed with these complexes after 18-24h reduction times under 25 bar hydrogen at 50°C (225/1 S/C), although **1** gave a product of 61% ee. Complexes lacking substituents on the bridging chains, were more active. Kinetic and molecular modelling studies indicated that dihydrogen splitting was likely to be the rate-determining step in the reactions with these catalysts. None of compounds **4** –**8** were reported to be active in transfer hydrogenation in isopropanol.

A closely related series of iron-based catalysts **9** were the subject of a recent density functional theory molecular modelling study.[23] A direct comparison was made between the (as yet unreported) iron complexes **9** and well-established Ru(II) catalysts **10**.[16] This concluded that the asymmetric hydrogenation of ketones with **9** and **10** should proceed through an essentially identical mechanism, with an equal opportunity for enantiocontrol in the process (Figure 3). This remains to be tested experimentally.

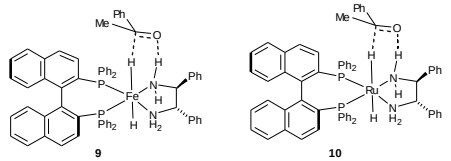


Figure 3. Theoretical iron and known ruthenium complexes believed to have similar mechanisms of action.[23]

Although a racemic process, a very significant breakthrough was reported in 2007 by Casey and Guan,[24,25,3] who found that the known[26,27] cyclopentadienyl iron hydride complex **11**, itself prepared from the iron tricarbonyl cyclone complex **12**, was effective at the catalysis of carbonyl and imine hydrogenation under relatively mild conditions (Figure 4). There are analogies in the speculated mechanism of the catalytic cycle to that of the reactions catalysed by the ruthenium-based Shvo catalyst **13**, which has also been extensively studied ~~by Casey et al.~~[28]

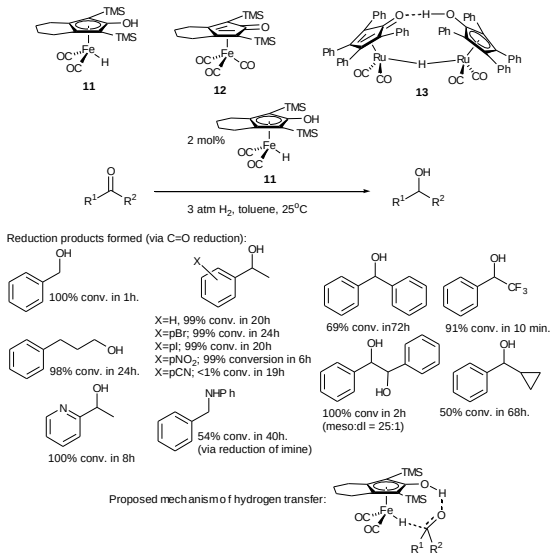


Figure 4. Hydrogenation of ketones catalysed by an iron cyclopentadiene complex.[26,27]

Using only 3 atmospheres of hydrogen, acetophenone reduction was achieved in 83% yield after 20h at 25°C (99% conversion). A wide range of ketones were reduced, and several other functional groups, including alkynes and cyclopropane rings in the substrate, tolerated. The reduction of an enone was complicated by reduction of both C=C and C=O bonds; a 42:56 mixture of the allylic alcohol:fully reduced products were isolated from PhCH=CHCOMe.

In a very detailed mechanistic study, Casey was able to obtain evidence which indicated that the hydrogen transfer reaction from **11** to ketones proceeded through a concerted transfer of both proton and hydride.[25] A later molecular modelling study also supported this.[29]

In a recent paper, Beller et al have described the combination of iron hydride complex **11** as the hydride donor in conjunction with the use of a chiral Bronstead acid (a cyclic phosphoric acid) to direct the asymmetric reduction of imines (Figure 5).[30] Following optimisation of the conditions it was found that a the cyclic phosphoric acid (*S*)-TRIP gave a product with the highest ee, of 94%. Iron complex **11** also gave a better result than alternative organometallic hydride transfer reagents, including the Shvo catalyst **13** and other iron complexes. In situ NMR studies indicated the formation of a 1:1 complex **14** between the TRIP and the iron hydride complex (along with generation of hydrogen). When PhC(=NPh)Me was added to a mixture of the same two reagents, the amine-containing complex **15** was also formed, along with **14**. Reaction with hydrogen gas led to full conversion to the amine product and hydride **11,** providing evidence for hydrogen transfer to the imine through a co-operative interaction with both the iron hydride and the phosphoric acid reagent.

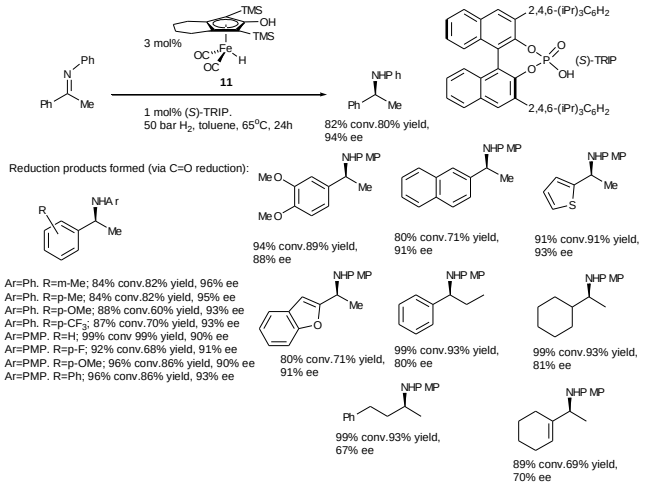
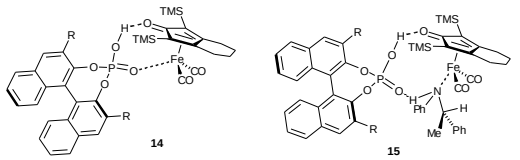
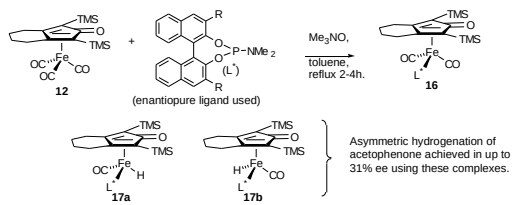


Figure 5. Asymmetric hydrogenation of ketone using an iron-based catalyst with a chiral phosphoric acid.[30]



An asymmetric version of the Knolker catalyst has recently been reported, and applied to asymmetric hydrogenation of ketones.[31] This was achieved by combining a homochiral phosphoramidite ligand with the tricarbonyl iron complex **12** (Scheme 2). The resulting chiral complex **16** was capable of catalysing acetophenone hydrogenation in up to 90% conversion and 31% ee. An observation of the hydrides formed by reaction of hydrogen with **16** revealed the formation of a mixture of diastereoisomeric hydrides **17a/b**. Although modest in terms of enantioselectivity, this represents the first use of an iron derivative of the Shvo catalyst in asymmetric ketone hydrogenation reactions.



Scheme 2. Iron(cyclone) catalysts for asymmetric hydrogenation of ketone by combining an iron complex with a chiral phosphorus ligand.[31]

2) Asymmetric transfer hydrogenation.

Organometallic complexes that can catalyse hydrogenation with hydrogen gas are also often capable of catalysing the closely related process of transfer hydrogenation. An early non-asymmetric precedent for this was reported in 1993 by Bianchini et al.[32] who used an iron complex of a tridentate phosphine ligand for the catalysis of hydrogen transfer between benzylideneacetone and cyclopentanol.

In a 2004 paper, Gao et al. reported the use of a complex formed in situ between ligands **18** and **19** with $(NHEt_3)[Fe_3H(CO)_{11}]$ for the asymmetric transfer hydrogenation of ketones.[17,33] Using S/C levels of ca 100, several examples of successful ketone reductions were achieved (Figure 6). The highest ees were observed for alkyl/aryl ketones in cases where there was a large alkyl group opposite the phenyl ring (up to 93% ee), although the conversions were not complete. An interesting speculation by the authors, through monitoring of the reaction with in situ IR spectroscopy, was that the triiron core of the complex remained intact throughout the catalytic process.

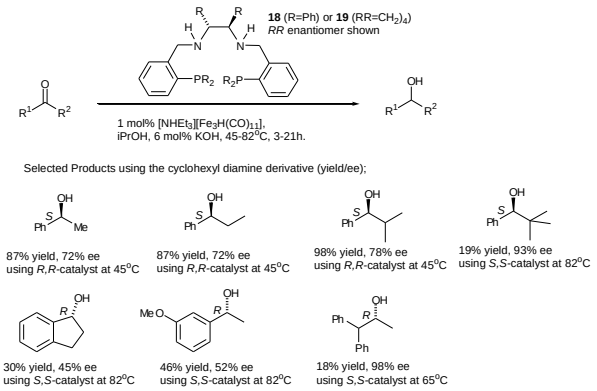


Figure 6. Asymmetric transfer hydrogenation of ketones using an iron complex of tetradentate PNNP ligands.[17]

The preformed and well-characterised Fe(II)/tetradentate 'PNNP' complex **2** described by Morris et al also works well in this application, as does the related complex **3**. In the earliest report,[15] hydrogen transfer from isopropanol to a series of substrates was successfully achieved using only 0.5 mol% of **2** (Figure 7). At 22°C, and in less than one hour, acetophenone was reduced in 95% conversion and 33% ee, with a preference for the *S* enantiomer. A number of ketones were tested, the highest ee, of 61% (*S*), being obtained using propiophenone as substrate, although at a slower rate (95% conversion in 3.6h). Interestingly, whilst the closely related complex **1** was an effective hydrogenation catalyst (see previous section), complex **2** was not.[15] The conversions were generally high; in most cases above 90% and in some cases 100%, whilst impressive turnover frequencies (TOF; moles product/mole catalyst/h) of up to 995 were observed. The highest ee for acetophenone, of 76% (*S*) was obtained using catalyst **3** although at a conversion of just 34% after 2.6h (TOF = 28 h^{-1}). The catalyst was also capable of tolerating a number of functional groups on the aromatic rings of the substrates, notable chlorine and methoxy. Benzaldehyde was reduced using 0.5 mol% of this catalyst in 94% conversion after 2.4h although cyclohexanone was not reduced.

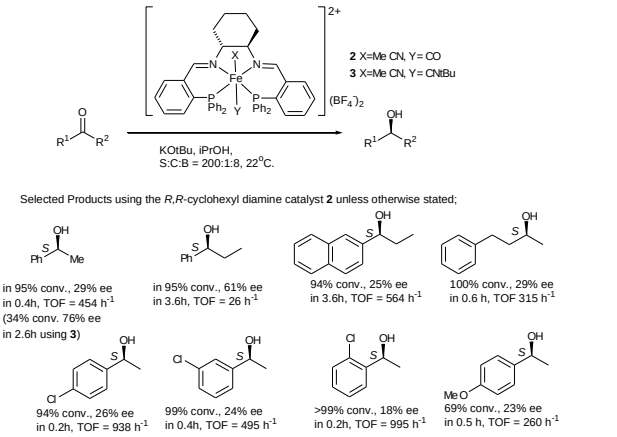
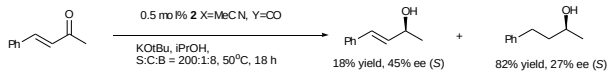


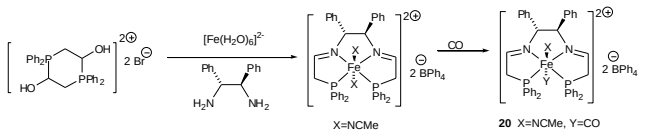
Figure 7. Asymmetric transfer hydrogenations of ketones using **2**.[15]

Catalyst **2** was also capable of the reduction of C=N bonds, with two examples reported. In the case of the benzaldehyde-derived imine PhCH=NPh, 100% conversion was achieved in 17h, however PhCMe=NPh, derived from acetophenone, was reduced in less than 5% conversion after the same reaction time. An attempt to reduce an enone was also undertaken. This is a challenging reaction, due to the dual functionality present in the substrate, and the obvious potential for reduction of alkene and ketone. In the event, a mixture of two products were formed, the better ee being observed for the unsaturated compound (Scheme 3).[15]



Scheme 3. Asymmetric transfer hydrogenation of an enone.

A further advance was made with the introduction of the modified catalyst **20**, derived from 1,2-diphenyl-1,2-diaminoethane and a shorter, non-aromatic, linker between the nitrogen and phosphorus atoms.[19] This complex could be assembled using an efficient metal-templated process in which the components formed the complex following their combination in a one pot process (Scheme 4).[18,20] The process greatly facilitates the synthesis of the complexes and is a method that has not to date been successfully applied to the equivalent ruthenium complexes.[22]



Scheme 4. Synthesis of iron-based transfer hydrogenation catalyst **20** by a metal-templated process.[19]

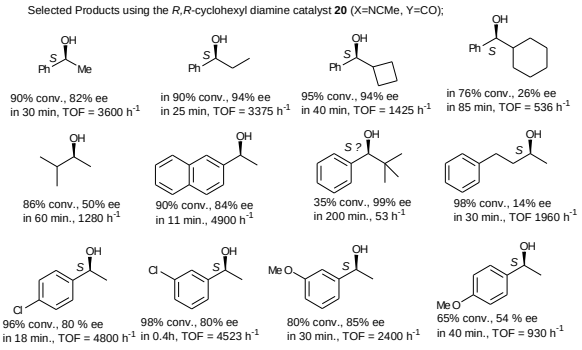


Figure 8. Asymmetric reduction products formed using complex **20** as a transfer hydrogenation catalyst.[19]

Complex **20** proved to be an excellent catalyst for ketone reduction using isopropanol as the reducing agent, not just with respect to activity but also enantioselectivity (Figure 8). TOFs of up to 4900 h^{-1} were reported for ketone reductions at S/C=1000, including highly-challenging substrates – notably the very hindered Ph/tBu ketone which was reduced in a remarkable 99% ee (35% conversion) at S/C of 200 and TOF of 53. With this catalyst, a higher selectivity of reduction of an unsaturated enone was recorded (Scheme 3), with an ee of 60% (82% conversion) but just 4% saturated alcohol formed. The use of an alkoxide base is essential, and electron-rich ketones were reduced more slowly, as would be expected.

In a detailed follow up report, Morris et al described further extensions to the study, using complexes (Figure 1) derived from ethanediamine (**21**), cyclohexyldiamine (**2**) and both enantiomers of 1,2-diphenylethanediamine (**22**) with a combination of CO and MeCN ligands (Figure 9).[34] Following the conversion revealed an initial period of constant rate until the conversion levelled off at the equilibrium point. As judged by the conversion in the first 10 minutes of the reduction, complex **2** was the most active catalyst, followed by **21** and then diphenyl-substituted **22** although the differences were small (72/62/57% conversion respectively). Because this is a reversible reaction, 100% conversion can only be achieved by removing the acetone from the reaction. By using vacuum to remove all of the solvents after the reaction had reached equilibrium, followed by addition of fresh isopropanol, almost full conversion (ca 99%) to reduction products was successfully achieved, without loss of enantioselectivity.[34]

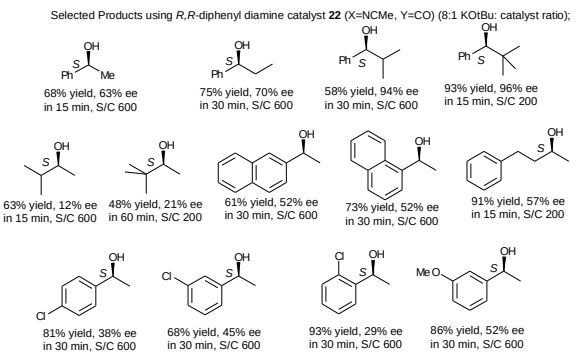


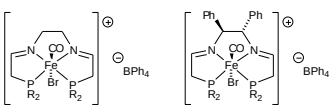
Figure 9. Asymmetric reduction products formed using complex **22** as a transfer hydrogenation catalyst.[34]

Complex **22**, although marginally less active than **2,** gave higher ees for certain substrates, e.g. 63% ee for 1-phenylethanol (Figure 9). The reduction of aromatic ketones containing bulky alkyl groups proceeded in particularly high enantioselectivity, particularly in the context of challenging nature of these substrates. It was also noted that racemisation of products occurred if the reaction was continued past the point when equilibrium was observed. For this reason, the best results are obtained by stopping the reaction after relatively short reaction times, as given in the Figures. Low activities were recorded for dialkyl ketone substrates.

At the time of writing this review, the full mechanistic details of the reaction had not been established. It was not clear, in the case of asymmetric *transfer* hydrogenation, whether the C=N bonds in the ligands were reduced to single bonds in the same way that they are speculated to be in the pressure hydrogenation reactions described earlier, with the subsequent mechanistic implications. The reaction is however a very practical one, with the iron catalysts exhibiting higher TOF values than have been measured for the more established ruthenium-based transfer hydrogenation catalysts. The iron catalysts are also tolerant to a number of functional groups in the substrate.

In a recent paper,[35] a series of complexes closely related to **20**, with bromide in place of MeCN and hence monocationic, and bearing a range of bridging diamines, including 1,2-diaminoethane, 1,2-diaminocyclohexyl, DPEN and 1,2-diamino-1,2-di(p(MeO)C_6H_4)ethane, were prepared and tested. These catalysts gave acetophenone reduction products of up to 82% ee and TOFs of ca 21,000 h^{-1} at 15-50% conversions but with very low catalyst loadings (S/C 6000/1). Added acetone retarded the rates of reactions, indicating that it competes for the active site of the catalyst, which may account for the reduction in rates at higher conversions. Catalyst deactivation was ruled out by an experiment in which further acetophenone was added, resulting in an increased rate of reduction.

In further extended studies, Morris *et al* described changes to the groups on the phosphorus atoms of the complexes **23-28**, which were prepared using the templated method, and characterised by X-ray crystallography.[36] As in the previous paper, iron-bromide complexes were prepared.

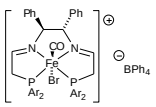


23 R= cC_6H_{11} **26** R= cC_6H_{11}
24 R= iPr **27** R= iPr
25 R= Et **28** R= Et

The complexes containing cyclohexyl and isopropyl groups were poor catalysts for transfer hydrogenation, possibly due to their bulky nature, however those with ethyl groups on P were active catalysts. A TOF as high as 4100 h^{-1} was measured for **28** for acetophenone reduction at 50°C. It was interesting to again note that a CO ligand is essential for transfer hydrogenation activity. The addition of base is required, although a number of hydroxide or alkoxide bases can be used. The observed ee using peaked at 55%, which is lower than for **20** (up to 82% ee), and racemisation was observed when extended reaction times were employed. Catalyst decomposition was also indicated by slower rates of reduction of further aliquots of acetophenone, whilst addition of fresh catalyst accelerated the reaction. The diphenyl-substituted **28** was more active than the unsubstituted **25**, indicating that these substituents have an important role, which may be steric (possibly helping to enforce a required conformation) or electronic in nature.

In a very recent paper, Morris disclosed that the requirement for the use of a base with complexes **23-28** could be avoided through pre-deprotonation of the complexes, which generates a neutral debrominated complex through deprotonation of the methylenes adjacent to the phosphorus atoms.[37] The resulting complexes are active without the need for added base during the hydrogenation reactions.

In very detailed follow up work on the highly active iron-bromide complexes,[38] a further series, **29-33** were prepared containing substituted aromatic rings on the phosphine units, together with a method for preparing the elusive electron-poor examples.[38] Of these, three were inactive however **29** proved to be the most active of this class of iron catalyst reported to date, with TOFs of up to 30,000 h^{-1}. Another, complex **31**, was found to be the most enantioselective for acetophenone reduction to date, producing 1-phenylethanol in up to 90% ee. The studies revealed a remarkably narrow set of electronic and steric parameters which had to be satisfied in order for the catalyst activity to be high.



29 Ar = p$(CH_3)C_6H_4$ high activity, up to 30,000 h^{-1} at 28°C.
30 Ar = o$(CH_3)C_6H_4$ inactive.
31 Ar = 3,5-$(CH_3)_2C_6H_3$ most selective complex - 90% ee for acetophenone.
32 Ar = p$(CF_3)C_6H_4$ inactive.
33 Ar = 3,5-$(CF_3)_2C_6H_3$ inactive.

Beller recently reported the reduction of diphenylphosphinyl ($P(O)Ph_2$)-protected imines using PNNP(imine) ligands in asymmetric transfer hydrogenation.[39] In this paper, a number of N and P- donor bidentate ligands were evaluated with the iron source $[Et_3N][HFe_3(CO)_{11}]$, revealing that ligand **19**, the precursor used for several of Morris's ligands, gave the best results (Figure 10). The use of diphenylphosphinyl imines was also important, to activate the C=N bond towards reduction. An N-tosyl imine was unreactive under the conditions tested.

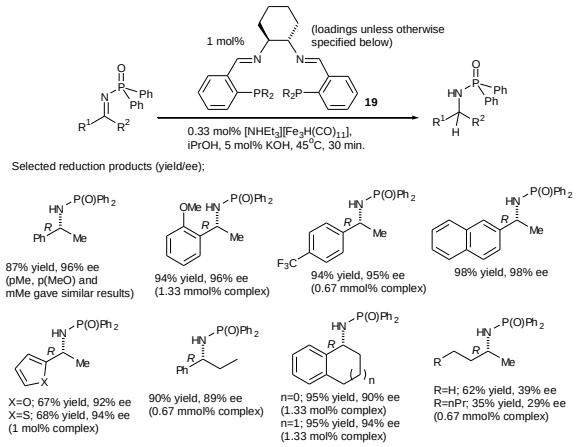
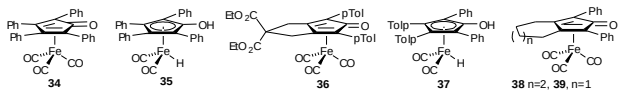


Figure 10. Asymmetric C=N bond reductions using a Fe/PNNP catalyst system.[39]

The resulting complex gave spectacular results (Figure 10). Base was required for the reaction to proceed, and the the catalyst loading could be dropped to as low as 0.17 mol% without loss of ee. The preformed catalyst **2** was also active, but gave a product of lower ee (91% ee for the first example in Figure 10). The reduction of a series of substrates was reported, with best results being achieved for acetophenone derivatives, and a good tolerance of functional groups being demonstrated. Heteroaromatic and cyclic substrates also worked well, however the yields and ees were lower for substrates derived from alkyl-substituted ketones.

The iron cyclone-derived catalyst **11** which was used by Casey for hydrogenation of C=O groups also reduces ketones under transfer hydrogenation conditions.[24] The use of 1 mol% of **11** (Fe hydride) in 2-propanol at 75°C for 16h resulted in 87% reduction of acetophenone ([acetophenone]=0.6M) to the alcohol. Other iron-cyclone complexes related to hydride **11**, and the precursor iron tricarbonyl cyclone have been reported and characterised. The complex (cyclopentadienone)$Fe(CO)_3$ [40] and (cyclopentadienyl)$HFe(CO)_2$ [41] have been described, as has the Fe equivalent of the tricarbonyl precursor to the Shvo dimer catalyst, i,e, complex **34**.[42]



Further recent studies on transfer hydrogenation with Fe-cyclone catalysts such as **34** have focussed on their use in oxidation reactions, i.e. Oppenauer-type reactions, rather than reductions. Williams[43] has used complex **34** in alcohol oxidation reactions with D6-acetone as the acceptor. The implication is that **34** (Fe Shvo) is converted to hydride **35** which is the true catalytic species. The addition of one equivalent of D_2O relative to catalyst improved the catalyst activity, presumably due to accelerated formation of Fe hydride **35**. The closely related complex **36** was much less effective in this application (<1% conversion with benzoquinone as a hydrogen acceptor).

More detailed studies were reported in 2010 by Guan et al,[44] who used hydride complex **11** to efficiently oxidise an extensive range of alcohols with acetone as acceptor (Figure 11). Diols could be cyclised to lactones and even a complex steroid alcohol could be oxidised, although a long-chain primary alcohol, a 1-trifluoromethyl alcohol and an α-hydroxy ketone resisted full oxidation. These authors also tested the 'Fe-Shvo' hydride complex **35** and closely related **37** and **38** in the reaction, however these were much less active than **11** (bisTMS). This low reactivity of the latter was attributed to the instability of their hydrides which could not be isolated and characterised. There was however evidence of the formation of diiron bridging complexes in attempted reactions with **37** and **38**, as evidenced by characteristic 1H NMR shifts for the iron hydride (ca δ -22- -23). In contrast, **11** exhibits an equivalent hydride shift at δ -13.05,[27] which is indicative of a stable monomeric species, presumed to be of higher reactivity in hydride transfers. The preference for monomer formation in the case of **11** is believed to be due to the high steric demand of the trimethylsilyl groups.

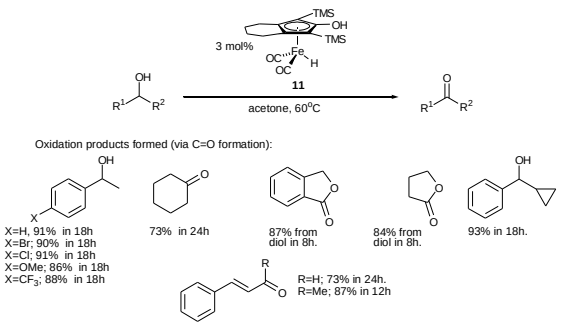


Figure 11. Oxidation of alcohols using an iron hydride complex **11**, via a hydrogen transfer reaction.

Funk et al.[45] have reported, in addition to **11**, the use of catalysts **38** and **39** in a similar catalytic oxidation process with acetone as acceptor, but with the addition of trimethylamine oxide as an initiator for the reaction. This is believed to react with a carbonyl group on the iron atom to release CO_2 and trimethylamine – evidence for which is provided by the observation that the use of a sealed vessel inhibits the catalysis due to an interaction of the trimethylamine with the unsaturated catalyst.

An alternative approach to the synthesis of asymmetric variants of iron cyclone catalysts was recently reported by our group.[46] Incorporation of chirality was assisted by a chiral centre in the backbone of the precursor to complexes **40a-c** and **41a-c**, which were formed as two enantiomerically pure, but separable, diastereosiomers (Scheme 5). A key intermediate were the ethers **42a-c**, formed from a common intermediate. Using these separated complexes, acetophenone reduction was achieved in up to 25% ee with formic acid/triethylamine as the reducing agent (Scheme 6).

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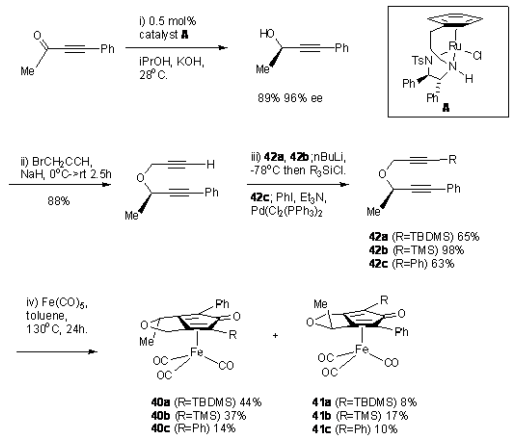
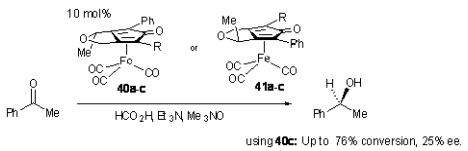


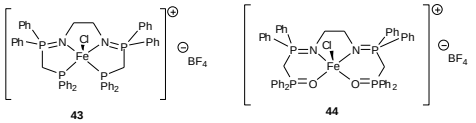
Scheme 5. Synthesis of enantiomerically-enriched iron cyclone catalysts for asymmetric ketone reduction.



Scheme 6. Asymmetric reduction of acetophenone using complexes **40/41a-c.**

In a non-asymmetric variant which preceded asymmetric variants with the DuPHOS, Beller et al reported the application of an $Fe_3(CO)_{12}$ system with terpy ligands to the transfer hydrogen from isopropanol to ketones.[47] Moderate conversions but good selectivities were observed. Effects of base and added phosphines were decribed in some detail. Described as a biomimetic transfer hydrogenation, the reduction of 2-alkoxy and 2-aryloxy ketones by iron-catalysed transfer hydrogenation was also reported by Beller.[48] A very wide range of substrates were reduced using a porphyrin –iron complex formed in situ. In many cases, full conversions were observed.

A range of complexes containing ligands with P=N bonds, of which **43** and **44** are representative examples, and representing an interesting variation on the traditional 'PNNP' tetradentate ligand were introduced by Le Floch et al.[49] Although not asymmetric, their modular nature and derivation from 1,2-diamines opens possibilities for future asymmetric versions. Complex **43**, formed with an Fe(II) salt, was characterised by X-ray crystallography and bears some resemblance to the Morris systems described earlier. Using just 0.1 mol% of catalyst, the reduction of acetophenone was achieved in isopropanol in conversions of up to 91% after 6-8 hours at 82°C. Complex **43** reduced acetophenone in 75% in 8h and complex **44** in 89% conversion in 6h. Hydrogenation with hydrogen gas was also investigated using these catalysts, however conversions of <10% was observed after 20h at 60°C. Although racemic, the high activities of these compounds renders them promising candidates for future research work.



An unusual yet highly active and enantioselective complex, **45** (the most selective of 5 similar structures), was introduced by Reiser *et al*. [50] This consisted of a 2:1 complex of a bis-isonitrile ligand with $FeCl_2$ in which each ligand formed an 12-membered heterocyclic ring. Asymmetric transfer hydrogenation of ketones was achieved in up to 84% ee, including the successful reductions of some challenging ketones (Figure 12). An unexpected switch in enantioselectivity was observed for some of the heterocyclic substrates relative to the acetophenone derivatives. On the basis of IR studies of the reaction in situ, and the non-observation of a Fe-H peak in the 1H-NMR spectrum, the authors proposed a Meerwein-Porndorf-Verley-type reaction mechanism, with participation of the isonitrile ligand, for this class of catalyst. These results offer extraordinary promise for the future development of iron reagents for asymmetric catalysis.

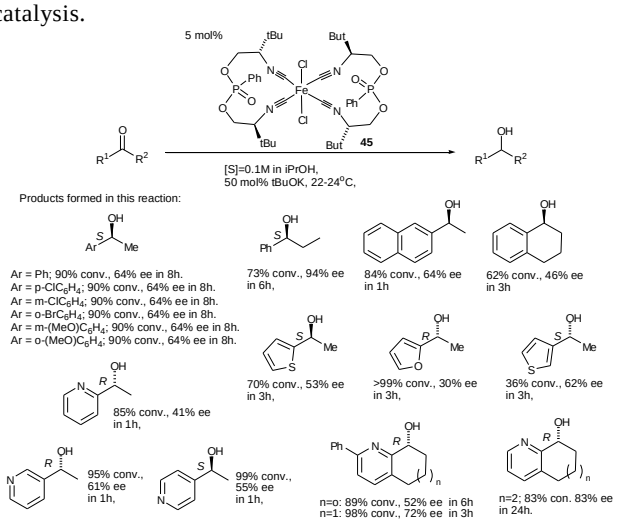


Figure 12. Asymmetric ketone reduction using an iron complex containing a tetra(isonitrile) ligand.

3) Hydrosilylation.

Asymmetric hydrosilylation represents an alternative method for the generation of enantiomerically enriched alcohols from ketones. Catalytic iron-catalysed hydrosilylation has been achieved using a number of catalysts,[51] with examples dating from 1990. Nishiyama has published a number of findings in this area. In early work the catalysis of ketone hydrosilylation with iron complexes of bis(oxazolinyl)pyridine ligands was disclosed, including a number of asymmetric applications (Figure 13). [52]

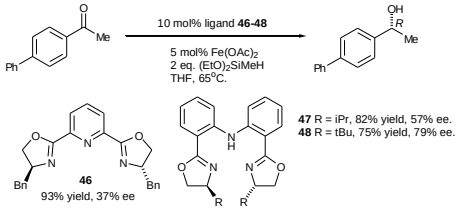


Figure 13. Asymmetric hydrosilylation of ketones using bis(oxazoline) complexes of iron.

In further extended studies on the more promising N-bridged bisoxazoline ligands **47**/**48**, the derivative **49** derived from the diphenylmethyl-substituted amino alcohol ('Bopa-*dpm*') proved to be the most enantioselective when used in conjunction with iron diacetate.[53] Products of up to 88% ee were formed with conversions as high as 99% in many cases (Figure 14). The suggested mechanism involves the formation of a metal hydride and transfer of the hydrogen atom to the ketone substrate via a complex with the ketone co-ordinated to the iron.

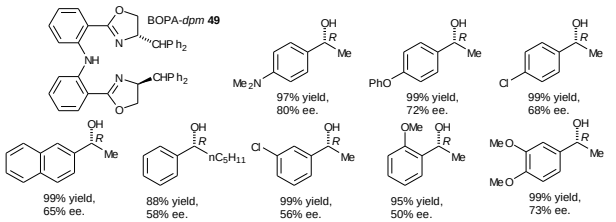


Figure 14. Asymmetric reduction of ketones by $Fe(OAc)_2$/BPA-dpm complexes.

In recent work, Nishiyama *et a.l* reported that the addition of zinc metal to the preformed iron/bisoxazoline complexes had a remarkable effect – the sense of enantioselectivity reversed from *R* to *S*, whilst the level of ee and conversion remained high (Figure 15).[54] At present the reasons for the switch are not clear, but it remains a remarkable, and highly synthetically useful, effect. The majority of substrates were acetophenone derivatives, although the best results in terms of ee were obtained for fused-ring ketone substates. PhCOcPr was reduced in *S* configuration with both catalyst combinations, albeit in low ee, as was $PhCH_2CH_2COMe$.

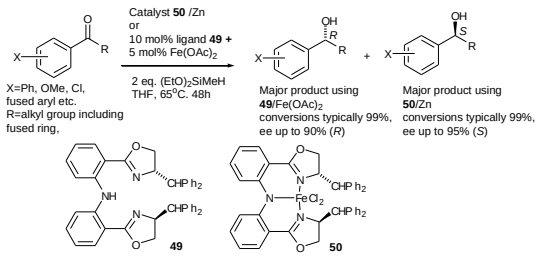


Figure 15. Switch of enantioselectivity upon addition of zinc to an iron-catalysed asymmetric hydrosilylation.

In related work, iron-complexes **51** derived from 'phebox' ligands (i.e. which contain a direct C-Fe bond) were isolated and applied to ketone hydrosilylation, furnishing products in up to 66% ee in the best case.[55] Iron complexes derived from pybox ligands or box ligands have also been reported to be effective in this application.[56] Using as low as 0.3 mol% **52** or **53**, ketones could be reduced in ca 99% conversion and 54% and 42% ee respectively. Pybox and box-derived iron complexes with alternative substituents to iPr were also prepared and tested, as were a range of other ketones. Although the conversions were excellent, the ees remained moderate-low (generally below ca 54% for tetralone) although one exception was the reduction of hindered 2,4,6-trimethylacetophenone, which gave a product of 90% ee in 17% conversion using the Box/Fe complex (Figure 16).[56]

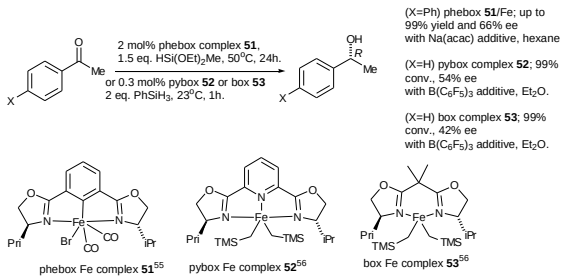


Figure 16. Comparison of Fe Phebox and Pybox ligands in asymmetric hydrosilylation.

An alternative approach to hydrosilylation was taken by Beller, who employed a series of chiral diphosphines in the asymmetric reduction of ketones with iron salts.[57] The best results were obtained with DuPHOS ligands, which gave products with full conversions and ees of up to 77% in initial tests with acetophenone. These results could be improved upon optimisation of the silyl reagent and in some cases high ees of up to 99% were obtained (Figure 17). Notably, the highest selectivities were obtained with particularly hindered acetophenone derivatives bearing ortho-substituents on the aromatic ring. The very challenging 2-methylbenzophenone was reduced in 51% ee, which hints at possible future improvements for this class of substrate. A number of dialkyl substrates were also investigated using the method and promising results were obtained, for example reduction of acetylcyclohexane gave a product of 45% ee (57% yield) and 1-acetylcyclohexene was reduced in 79% ee (68% yield).

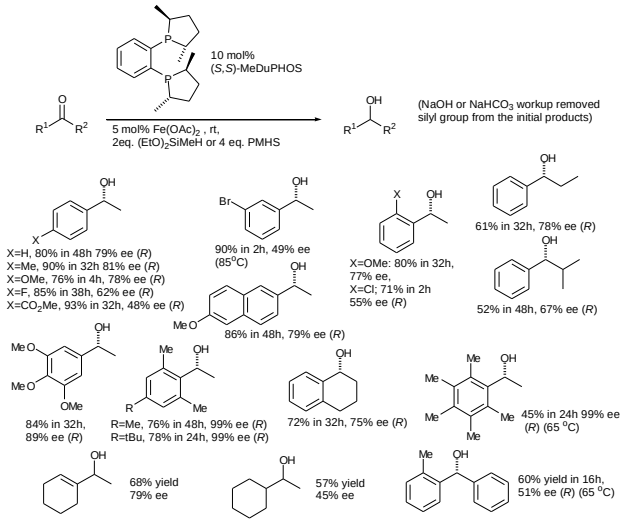


Figure 17. Use of an iron/diphosphine catalyst for asymmetric hydrosilylation of ketones.

The reaction of 1,2-dicyanobenzene with 2-aminopyridines provides a means for the formation of a library of catalysts of which **54** represents a structurally characteristic member.[58] Complexation with iron generates a complex (structure inferred from analogous Cu complex) which acts as an efficient catalyst for ketone hydrosilylation, giving products in up to 93% ee at the lower temperature tested (Figure 18). The analogous Co complexes were used in asymmetric cyclopropanation reactions.

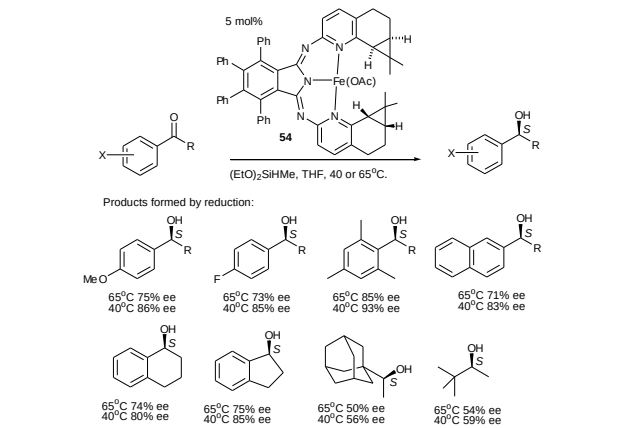


Figure 18. Use of Iron complexes of bis(pyridylamino)isoindoles in ketone hydrosilylation.

4) Oxidation reactions of alkenes.

The earliest report of the use of modified iron-porphyrin complexes for the asymmetic epoxidation of alkenes was reported by Collman and Rose et al in 1999.[59] Using a biaryl-strapped chiral directing group, epoxides of >90% ee were formed, generally in yields in excess of 73% using as little as 0.1 mol% catalyst. Styrene itself was epoxidised in up to 83% ee, and the method was versatile enough to be extended to a series of structurally-similar substrates with similar selectivities. Cis-alkenes were gave products of lower ee, typically 49-55%, than the terminal alkenes. The developments in this area of chiral strapped porphyrins,[60] not only of iron but also containing Mn and Ru, has recently been summarised in a detailed review.[61]

In other early work, Jacobsen described the use of combinatorial methods to discover an optimised catalyst for iron-catalysed epoxidation of tran-β-methylstyrene.[62] Following a process of split-mix bead functionalisation and testing with a range of metals, several $FeCl_2$ complexes **55** and **56** emerged as sucessful in the epoxidation reaction using aqueous hydrogen peroxide (Figure 19). Enantiomeric excesses, however, were low at only 15-20% in the best cases.

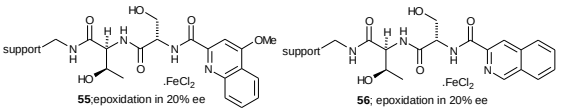


Figure 19. Catalysts for trans-β-methylstyrene epoxidation identified using library screening.

An example of an asymmetric epoxidation with 2 mol% of a $Fe(dcm)_3$ complex and O_2 gave products of 48-92% ee.[63] The aldehyde was added to act as a reducing agent. Without this addition, oxidative cleavage of the allene double bond was observed (Figure 20).

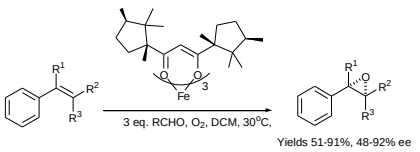


Figure 20. An iron complex of a chiral acetoacetate used in asymmetric epoxidation.

Beller has reported extensively on the development of iron catalysts for the oxidation of alkenes.[64] and has recently published details of an asymmetric system which employs hydrogen peroxide and a simple catalyst comprising of an iron complex of a monotosylated 1,2-diphenylethane-1,2-diamine derivative (Figure 21).[65,66]

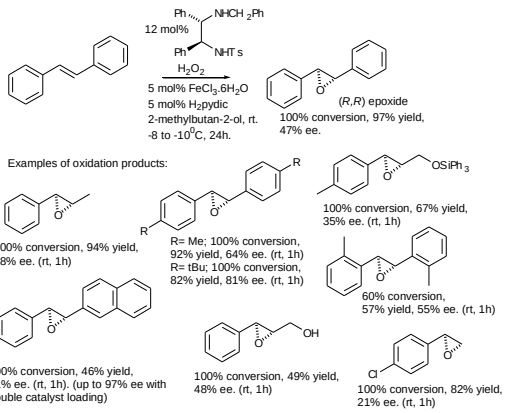


Figure 21. Enantioselective epoxidation reactions using a monotosylated diamine.

Typically using 12 mol% of the optimal N-benzylated

TsDPEN ligand, epoxidation could be achieved of stilbene in up to 47% ee. A low temperature was required for optimal enantioselectivity. Of a selection of alkenes screened, the substrate with a 2-naphthyl group was oxidised in the highest ee – which could be raised to 97% through the use of additional catalyst. In detailed follow-up studies,[66] a comparison of TsDPEN derivatives was made, and the effect of catalyst loading was studied; above 12 mol% ligand gave little improvement to the yield and a reduction in ee was observed.

Detailed mechanistic studies revealed that several iron complexes form within the mixture, several of which were identified by ESIMS. The reaction also appears to proceed via a radical intermediate with secondary kinetic isotope effects suggesting the oxygen atom transfer took place through an unsymmetrical transition state in a stepwise manner.

Following early work by Jacobsen[67] on non-asymmetric pyridine-containing ligands for use in iron-based epoxidation catalysts, other researchers have investigated more rigid bipyridyl ligand systems (Figure 22).[68,69] Ménage et al used bipyridine **57** to construct a catalytically-active diiron complex which was effective in the epoxidation of a range of alkenes in up to 63% ee (for *trans*-β-methylcinnamate; 35% yield).[68] *Trans*-Chalcone was epoxidised in 66% yield and 56% ee using only 0.2 mol% of catalyst with peracetic acid as the oxidant. The majority of alkenes were oxidised in rather low ee (max 28%) however. Kwong et al prepared a very well-defined catalyst **58**, which contained two iron centres, and characterised this by ESI-MS.[69] The application to alkene epoxidation gave mixed results however, with ees not exceeding 43% (for styrene, formed in 95% yield) when 2 mol% catalyst was employed with aqueous hydrogen peroxide as the oxidant..

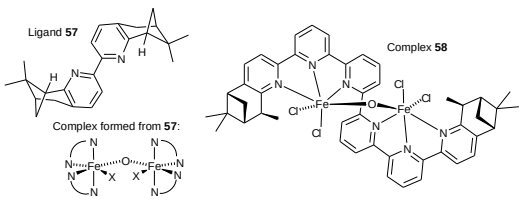


Figure 22. Bipyridine ligands for alkene epoxidation.

An asymmetric epoxidation of β,β-disubstituted enones has been achieved by using an iron-catalysed approach. In this process, the combination of a chiral bipyridine derivative complexed to $Fe(OTf)_2$ directs the reaction of peracid with enones with ees of up to 91% in preliminary studies (Figure 23)[70]

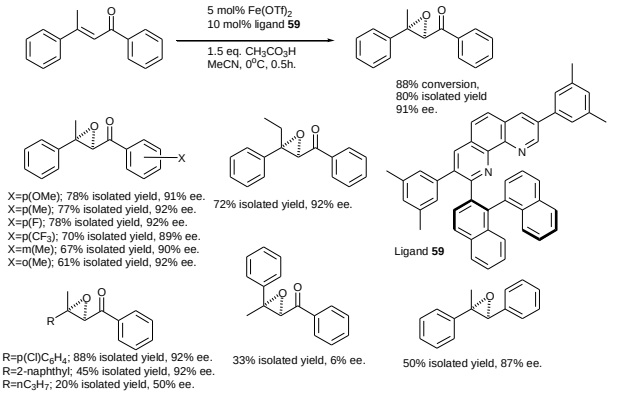


Figure 23. Enantioselective epoxidation of enones.

In this process, the formation of a very hindered 2:1 complex between the ligand and the iron(II) was isolated and characterised by X-ray crystallography. This creates a bulky catalyst with a well-defined chiral environment, however the means by which asymmetric induction is achieved still remains unclear and is the subject of ongoing investigations. Intriguingly, even a non-activated alkene could be epoxidised; *trans*-α-methylstilbene was converted to the epoxide in 50% yield and 87% ee.

Following on from a series of papers related to non-chiral alkene oxidation using biomimetic iron/amine complexes,[71] Que et al reported in 2008 the use of a series of C2-symmetric tetradonor ligands containing a combination of pyridyl and tertiary amine donors.[72] A difference with this system, however, was the preference for diol products over epoxides. Of the series of five ligands tested, in combination with Fe(II), complex **60** gave the best result for *cis*-dihydroxylation of *trans*-2-heptene (Figure 24).

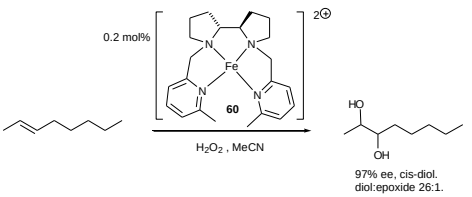


Figure 24. Enantioselective alkene epoxidation using a mixed pyridyl/tertiary amine ligand.

An X-ray crystallographic structure solution on complex **60** confirmed a C2-symmetric environment around the metal, created by the tetradentate ligand. A good result (96% ee, diol:epoxide 13:1) was achieved with trans-4-octene, whilst 1-octene was dihydroxylated in 76% ee with a 64:1 diol:epoxide ratio. Ethyl trans-crotonate gave a diol of 78% ee, and dimethyl fumarate a diol of just 23% ee, indicating the loss of enantioselectivity related to electron-withdrawing groups on the substrate. Other terminal alkenes which were tested included allyl chloride (70% ee) and tert-butyl acrylate (68% ee).

5) Other asymmetric reactions catalysed by iron complexes.

The conversion of sulfides to enantiomerically-enriched sulfoxides was reported by Inoue in 1992, using a C2-strapped porphyrin as a P-450 model catalyst. Turnover numbers of up to 178 were achieved, and the best enantioselectivity was 71%. Although this represents an excellent result, the preparation of the catalysts required the use of chiral HPLC to separate the enantiomers, which represents a limitation on its practical applicability, particularly on a larger scale.[73] Bolm later reported on the use of a structurally-simple catalyst series typified by **61** which catalysed the formation of sulfoxides in up to 90% ee, albeit in low-moderate yields.[74] This was improved in later work through the use of a lithium carboxylate additive to furnish a versatile and selective system.[75]

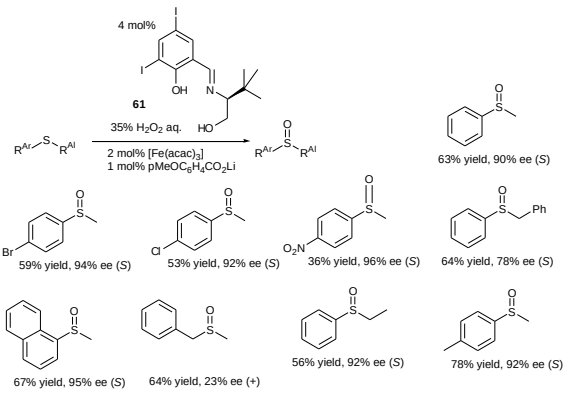
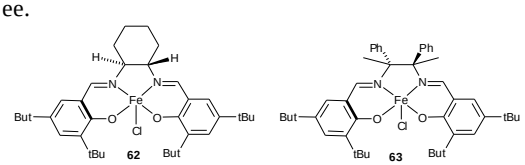


Figure 25. Bolm's asymmetric sulfoxidation catalyst.

The use of iron(salen) complexes for the catalysis of asymmetric sulfoxide formation was reported by Bryliakov and Talsi in 2004.[76] Complexes **62** and **63** both worked effectively in the applications, converting alkyl/aryl sulfides in almost quantitative conversion, high (up to 99% sulfoxide formed in preference to other products) selectivity and up to 62% ee.



An enantioselective sulfide oxidation catalyst has also been reported by Katsuki et al, who have optimised the structure through introduction of additional bulky groups.[77] Using 2 mol% of iron/salan complex **64**, selective oxidation could be achieved in 96% ee with limited over oxidation (Figure 26). The method was applicable to a range of sulfide substrates including those containing alkyl substituents, frequently with enantiomeric excesses of over 90%.

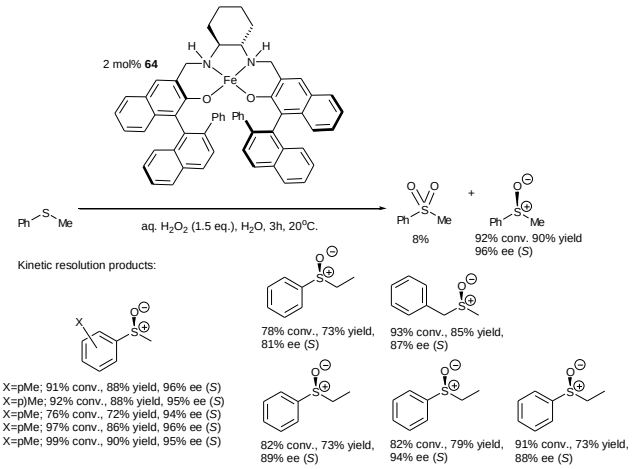


Figure 26. Asymmetric oxidation of sulfides using an Fe(Salan) complex.

Katsuki also recently reported the use of iron(salan) complexes for aerobic oxidative kinetic resolution of secondary alcohols (Figure 27).[78] An important feature was that the catalyst required the addition of a molecule of naphthoxide in order for it to exhibit the desired properties; running the reaction in the presence of 1-naphthol was sufficient to achieve this modification. Using 3 mol% of catalyst **65**, a range of alcohols were oxidised with a very high level of kinetic resolution (K_{rel} up to 39).[78]

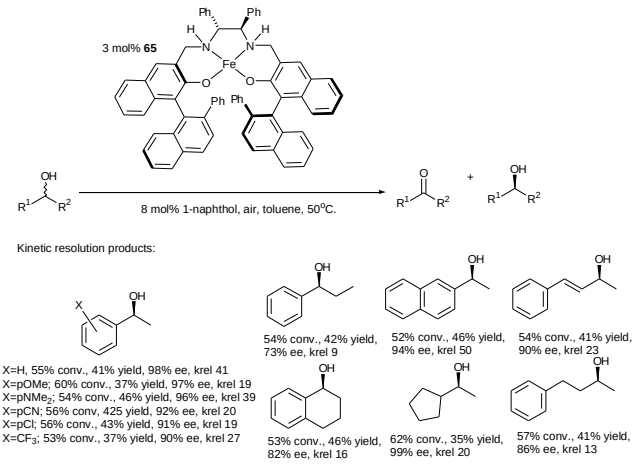


Figure 27. Kinetic resolution of alcohols using an Fe(Salan) complex.

In a further application of the ubiquitous iron-Salan complexes, the coupling of 2-naphthols can also be promoted in ees ranging from 87-95%.[79,80] In this process, both homocoupling[126] and cross-coupling[79] can be achieved using 4 mol% of the Fe/Salan complexes previously discussed (Figure 28). A radical cation mechanism was proposed for this transformation.

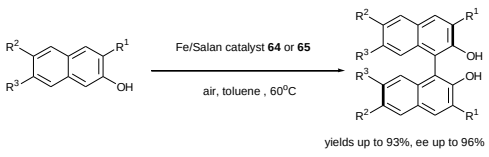


Figure 28. Asymmetric biaryl coupling catalysed by an Fe(Salan) complex.

An unusual reaction for the formation of asymmetric centres by C-O bond formation is illustrated in Figure 29. In this process, enantiomerically pure iron/bisoxazoline complex **66** promotes the decomposition of a diazoester followed by enantioselective trapping to give an enantiomerically-enriched α-alkoxy ester in up to 99% ee.[81] Even water could be used as a reagent, leading directly to the formation of alcohols in up to 95% ee. In this proces, the iron complexes were more efficient than those based on other metals, including Cu, Co, Ni, Au, Ag, Rh and Ru.

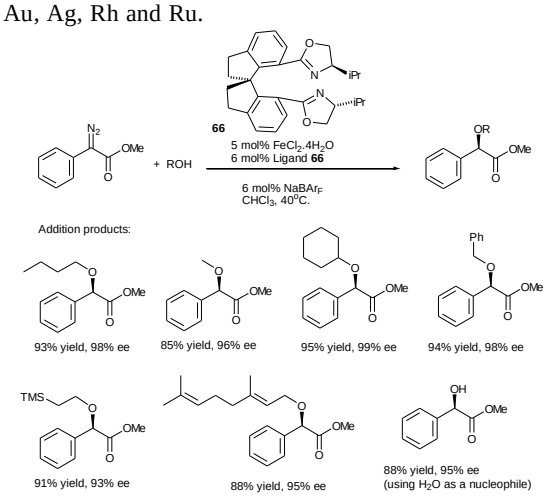


Figure 29. Asymmetric C-O bond formation using an iron/bis(oxazoline) complex.

The combination of iron(II) with a pybox ligand has been demonstrated to be capable of the control of the addition of thiols to crotonyl-substituted oxazolines in ees of up to 90%, the best result being achieved with $Fe(BF_4)_2$ as the metal source, at -20°C (Figure 30).[82] The method proved to be reasonably versatile, although with the exception of benzylthiol, the thiols were almost exclusively aromatic derivatives.

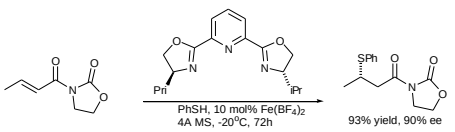


Figure 30. Asymmetric conjugate addition of thiols to E-3-crotonyloxazolidin-2-one.

Another interesting reaction was is the asymmetric carbozincation of cyclopropene derivatives, which can be asymmetrically catalysed through the use of a combination of iron trichloride and pTol-BINAP (Figure 31).[83]

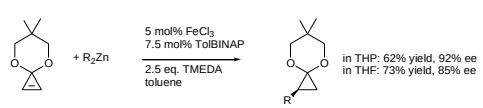


Figure 31. Asymmetric carbozincation of a cyclopropene.

Several examples of asymmetric Diels-Alder reactions catalysed by iron complexes have been reported.[84] The use of the dibenzofurandiyl bis-oxazoline **67** has been reported to give a particularly impressive result (Figure 32).[84a]

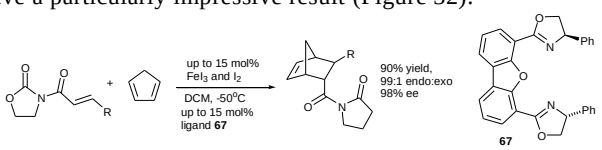


Figure 32. Asymmetric Diels-Alder reactions catalysed by an iron complex.

The iron complex **68**, containing a C2-symmetric phosphorus-donor ligand, is highly effective at the control of asymmetric Diels-Alder reactions between αβ-unsaturated aldehydes and dienes. In several cases, highly enantioselective cycloadditions were achieved (Figure 33).[85]

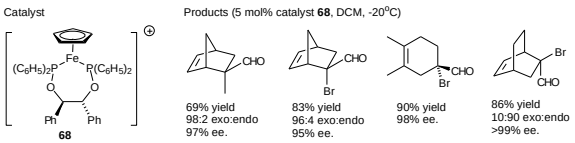


Figure 33. An iron-based asymmetric catalyst for Diels-Alder reactions and a selection of products formed.

The reaction of methylvinyl ketone with α-ketoesters have been promoted by asymmetric iron complexes of a range of homochiral ligands, although with modest enantioselectivities (18% or less).[86] Menthol-derived imine/pyridine ligands, complexed to iron(II) form a complex which can catalyse the dimerisation of butadiene to give a six-membered ring product of up to 63% ee, although the eight-membered ring was the major product[87] Isoprene and 1,3-pentadiene can be coupled to form an eight membered product in up to 61% ee using a menthyl-functionalised dimine ligand complexed to Fe(II).[88]

Conclusions.

In conclusion, iron-catalysed asymmetric homogeneous reactions have recently enjoyed a period of dramatic development and widespread application to synthesis. Whilst this review has primarily served to highlight the diversity of iron-catalysed asymmetric reactions which currently exist, an opportunity has also been taken to highlight areas of recent resaerch in non-asymmetric catalysis, which may have promise for future development. In addition to those presented herein, reference is made to a further series of non-asymmetric catalytic applications of iron complexes in synthetic transformations,[89] C-C bond formation,[90] polymerisations,[91] regioselective hydroxylations[92] and hydrogenation.[93]

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Notes and references

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