Iron catalysts: A new family of catalysts for the hydrogenation of ketones?

SBC606 PROJECT SKILLS IN CHEMISTRY

Tasnia Kamal

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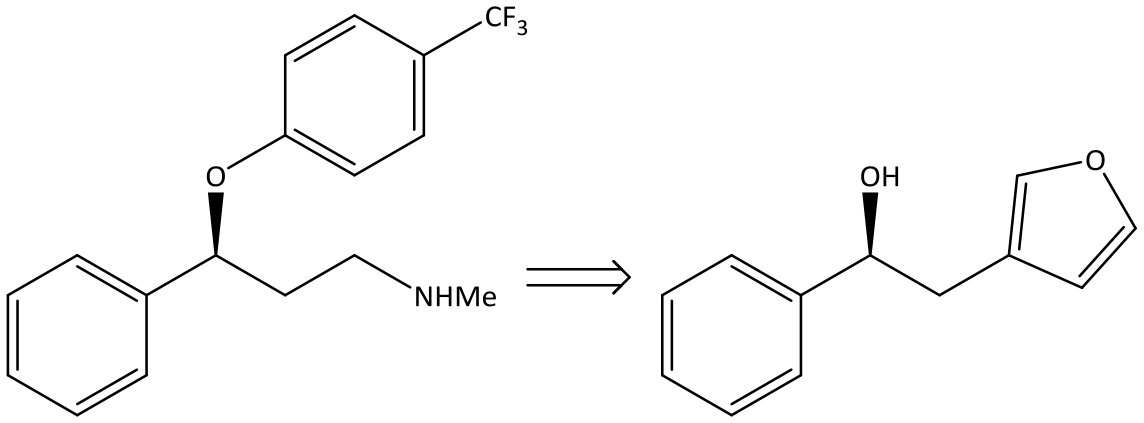
ABSTRACT

Chiral alcohols are in high demand in the pharmaceutical, fragrance, flavour, and agricultural industries. These chiral alcohols are typically derived from the hydrogenation of prochiral ketones, catalaysed by an organometallic complex. The previous catalysts used had ruthenium metal centres. These catalysts were very effective, but due to the scarcity an expensiveness of precious metals such as ruthenium – research has been done into iron alternatives for the catalysis of ketone hydrogenation. Not to mention, ruthenium is not environmentally friendly. Iron is attractive to use dues to it's high abundance, low cost, and environmental friendliness. Moreover, it has variable oxidation states, which make for an effective catalyst and also, iron hydrogenases are found in nature – this gives hope to develop highly active and enantioselective iron catalysts. This work aims to summarise the developments in iron catalysis for ketone hydrogenation thus far. The different classes of iron catalysts discussed are PNNP, PN(H)NP and PNP iron catalysts. There has been much research into PNNP and PN(H)NP iron catalysts, but PNP catalysts are a very much new area of research. The presence of nanoparticles being present during certain catalytic systems is also discussed. Overall, there are a few catalysts which could possible replace ruthenium catalysts and one PNP catalyst which shows promise but the area pf PNP iron catalysts just needs to be explored further.

1 INTRODUCTION

1.0 THE IMPORTANCE OF KETONE TO ALCOHOL CONVERSION

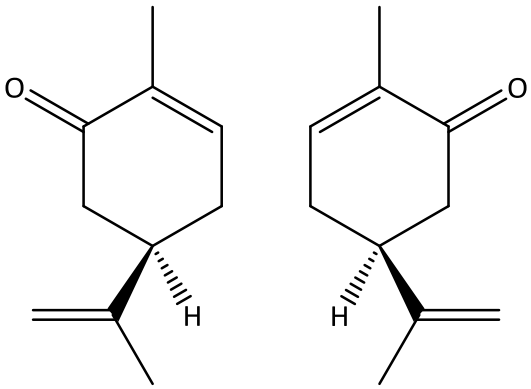
The hydrogenation of prochiral ketones to chiral alcohols is a field of research that has boomed in recent years. Enantiopure alcohols are in high demand in industries such as pharmaceuticals, perfumes and flavours [1] but also academically. [2] Chirality exists in many biological systems – for example many receptors in the human body are chiral and so they recognise only chiral molecules.[3] Thus intercepting biological pathways pharmaceutically, often requires enantiopure drugs. Chiral alcohols are needed as intermediates in the synthesis of many enantiomerically active pharmaceutical drugs. Dextromethorphan is an antitussive with no narcotic or analgesic properties. However, its enantiomer levomethorphan, whilst being antitussive is also an opioid narcotic and Class A drug.[4] This emphasises the importance of stereochemistry and how slight changes in structure can have major ramifications in pharmacological activity. Drugs such as, *(R)*-salbutamol, *(R)*-denopamine, *(R)*-tomoxetine, *(S)*-fluoxetine, and *(L)*-chlorprenaline are all synthesised from chiral alcohols and show the importance of enantioselectivity in ketone to alcohol reduction.



(*S*)-fluoxetine (*S*)-2-(furan-3-yl)-1-phenylethan-1-ol

Figure 1 Alcohol synthon of (S)-fluoxetine [4]

(S)-fluoxetine is synthesised from *(S)*-2-(furan-3-yl)-1-phenylethan-1-ol [5] (**Figure 1**). The withdrawing furanyl- group on *(S)*-2-(furan-3-yl)-1-phenylethan-1-ol signifies one of the current struggles to broaden the scope of recent catalysts for more functionalised ketones. A recent report on the impact of chiral technology worldwide [6] explains that about a third of global drugs sales are of enantiopure drugs. The report also predicts that the market for chiral technology altogether would reach 5.1 billion US dollars by 2017. Such a lucrative field requires much needed investment to research more efficient methods of procuring these enantiopure compounds.

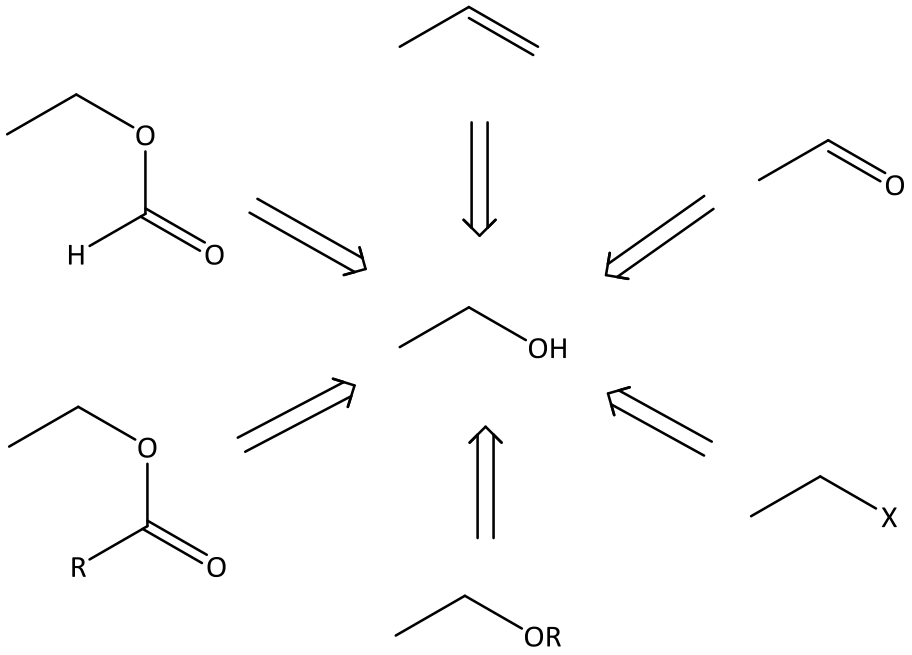


(R)-carvone *(S)*-carvone

Figure 2 Enantiomers of carvone [6]

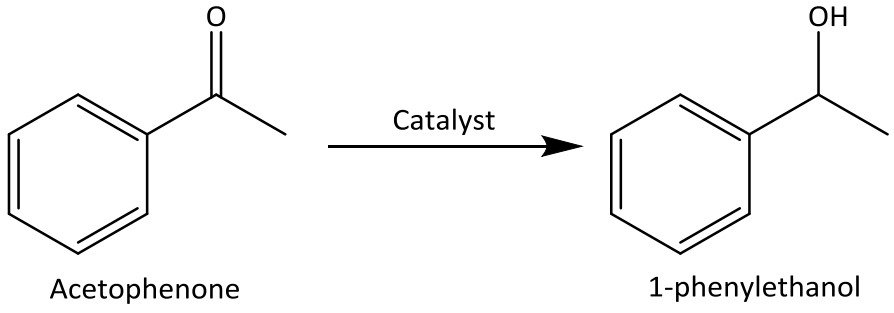
(R)-lavandulol is an example of a chiral alcohol used in the perfume industry. The corresponding *(S)*- enantiomer is only weakly fragrant, and as such, enantioselection is key. [7] Another example that emphasises the importance of enantioselection is that of carvone. *(R)*-carvone has a spearmint fragrance whereas *(S)*-carvone smells of caraway [8] (**Figure 2**).

Alcohols are very useful synthons for organic synthesis due to their facile transformation into a range of other functional groups as shown in **Scheme 1**. [9]



Scheme 1 A selection of alcohol transformations, where R = alkyl chain and X = nucleophilic group [10]

1-phenylethanol is an important compound in industry. As a fragrance, *(R)*-1-phenylethanol and *(S)*-1-phenylethanol both have distinct floral scents and *(S)*-1-phenylethanol is added to food as a scent additive. [11] *(R)*-1-phenylethanol is a preservative in ophthalmic drugs and may also decrease cholesterol levels by inhibiting the intestinal adsorption of cholesterol [12]. Both enantiomers of 1-phenylethanol are used to determine enantiomeric purity, and in the asymmetric opening of epoxides and cyclic anhydrides. [13] As 1-phenylethanol is derived from the hydrogenation of acetophenone, acetophenone is a good starting substrate for any new catalysts developed for hydrogenation reactions (**Scheme 2**).



Scheme 2 The hydrogenation of acetophenone to 1-phenylethanol [10]

The established route to obtain chiral alcohols is by means of the asymmetric transfer hydrogenation (ATH) of prochiral ketones using a catalyst.[14] These catalysts use metals such as Platinum, Iridium, Rhodium and Ruthenium – with high catalytic activity and enantioselectivity.[1] The most prominent of these catalysts is the Ru(II) based catalyst developed by Noyori and co-workers, [3][15] *trans*-[$Ru^{II}(H)_2$(*S*-xylbinap)(*S,S*-dpen)], which can convert acetophenone to *(R)*-phenylethanol with an *ee* of 99%.[16][17]

These noble metals make efficient and effective catalysts for the ATH of prochiral ketones. However, being precious metals, they are not very abundant and so they are expensive to use. Moreover, with growing pressure from governments on the chemical industry to go "green", the issue of these metals' toxicity becomes a serious issue. [1]

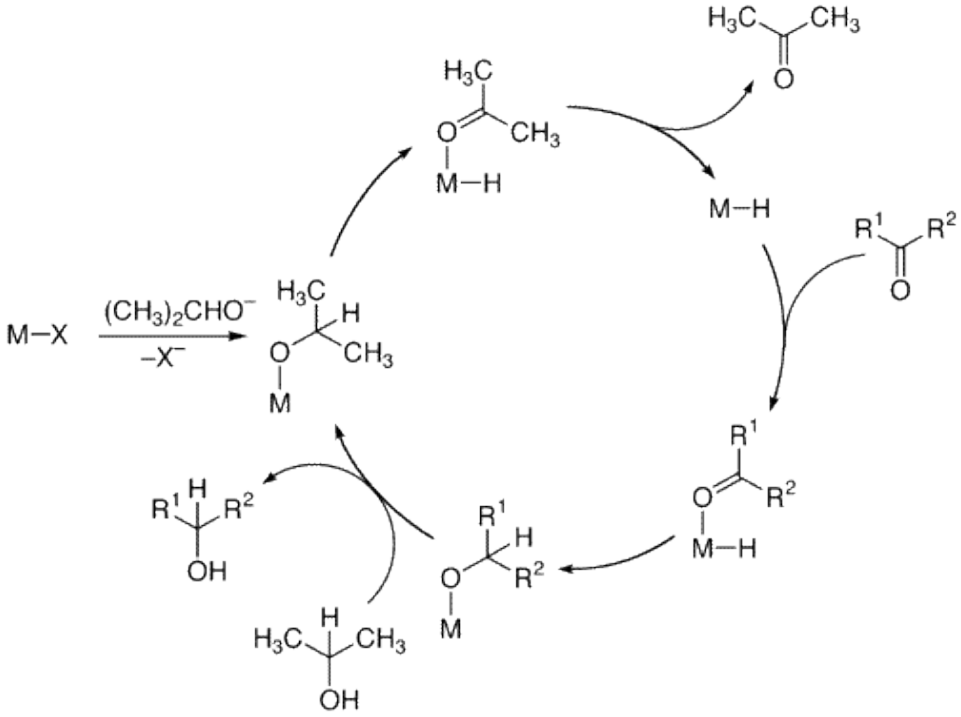
For these reasons, research is steering away from these noble metals and focusing on developing first row transition metal, and in particular iron, catalysts.[2] Nature frequently employs iron-based complexes as hydrogenases, [2][18] which further strengthens the growing interest in employing iron catalysts as a cheaper, non-toxic and more sustainable alternative to current ATH catalysts. [19] Another advantage of using iron catalysts is the variable oxidation state of iron and its Lewis acidity. [2]

As already mentioned, there has been a rapid increase in the development of such iron catalysts, but the constant challenge has been getting the activity and enantioselectivity up to the standards of the ruthenium predecessors. This work will aim to review the developments in iron catalysis for the ATH of ketones to enantiopure alcohols and find industrially viable catalysts. This will be done based on the catalytic activity and enantioselectivity, ligand types and conditions used and also the ease of synthesis of the catalysts. In many cases, studying the catalytic mechanism is key, as an understanding of the intermediates involved in the catalytic pathway will help expand the number of efficient catalysts available. [20]

1.1 PREVIOUS WORK ON RUTHENIUM CATALYSED ATH OF KETONES

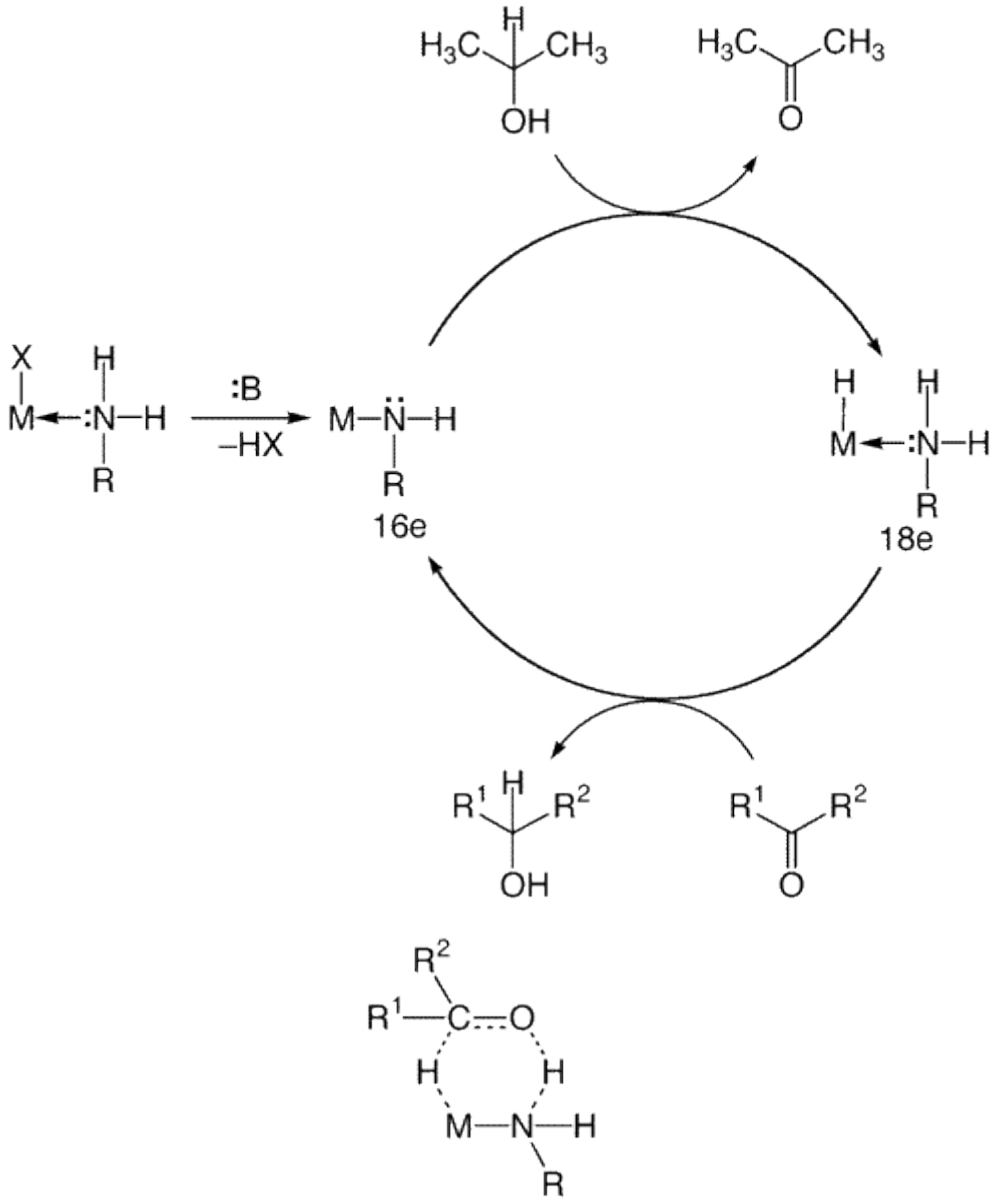
Metal-Ligand Bifunctional Catalysis [21] (MLBC) was a mechanism for the ATH of carbonyls first proposed by Noyori and co-workers using ruthenium based catalysts.

The conventional mechanism of ATH using a transition metal catalyst in 2001 was as shown in **Scheme 3**. This shows a stepwise mechanism involving ligation of the ketone to the catalyst metal centre. The role of the bases was thought to increase the concentration of the 2-propoxide ion.



Scheme 3 Conventional mechanism for ATH of prochiral ketones [21]

The majority of catalysts used for ATH at the time used aprotic neutral ligands. Noyori and co-workers looked into the use of protic neutral ligands such as alcohols and primary and secondary amine ligands. Complexing amines to the metal centre increases the acidity of the NH proton. The authors hypothesised an NH---O=C hydrogen bond in a transition state to expedite C=O hydrogenation.



Scheme 4 The MLBC mechanism put forward by Noyori and co-workers [21]

The MLBC mechanism put forward is shown in **Scheme 4** found via experimental and theoretical findings. The carbonyl does not ligate to the metal centre – thus carbonyl hydrogenation takes place in the outer coordination sphere of the metal hydride complex.

The hydrogen bonding stabilises the transition state shown in **Scheme 4** which Noyori and co-workers parallel with the Diels-Alder stereoselection where the stereochemistry depends on a secondary attractive interaction between sites that do not react with each other. The team thus came to the conclusion that enantioface discrimination is carried out by the chirality of the molecular surface of the catalyst – rather than by ligation of the ketone to the metal centre to form a template for ATH. This MLBC mechanism was subsequently confirmed by Iuliis and Morris in 2009. [22]

1.2 PREVIOUS WORK ON IRON CATALYSED ATH OF KETONES

In 1999, Knölker and co-workers [23] were the first to produce a bifunctional iron complex analogous to what is known as Shvo's catalyst (containing a Ru metal centre) which was synthesised by Shvo and co-workers in 1986. [24] In 2007, Casey and Guan [25] applied Knölker's catalyst **1**, **Figure 3**, to ketone ATH on the basis that they did extensive research into the application of their own Shvo analogue to ATH of ketones. Acetophenone hydrogenation by **1** was successful at room temperature in toluene-d^8 as shown in **Scheme 5**. However, acetophenone hydrogenation did not go to completion. Casey and Guan hypothesised that hydrogen transfer was reversible to account for this incomplete hydrogenation of acetophenone. The reaction was repeated with 2 equiv PPh_3 as a trapping agent. The function of this trapping agent was to capture the reactive intermediate **2**. Acetophenone was completely reduced to 1-phenylethanol within 4 h accompanied by the clean production of compound **3** where PPh_3 ligation occurred. The rates of reaction were taken between 10-25 ^{O}C and gave a highly negative entropy value ($\Delta S^{\ddagger}$) which supported the idea of a transition state of high order that brings together complex **1** and acetophenone for the transfer of hydrogen - this is in accordance with the ligand-metal bifunctional catalysis mechanism (See Section 2.1.0).

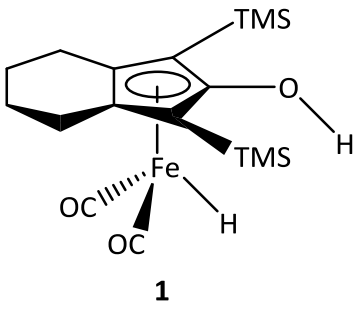


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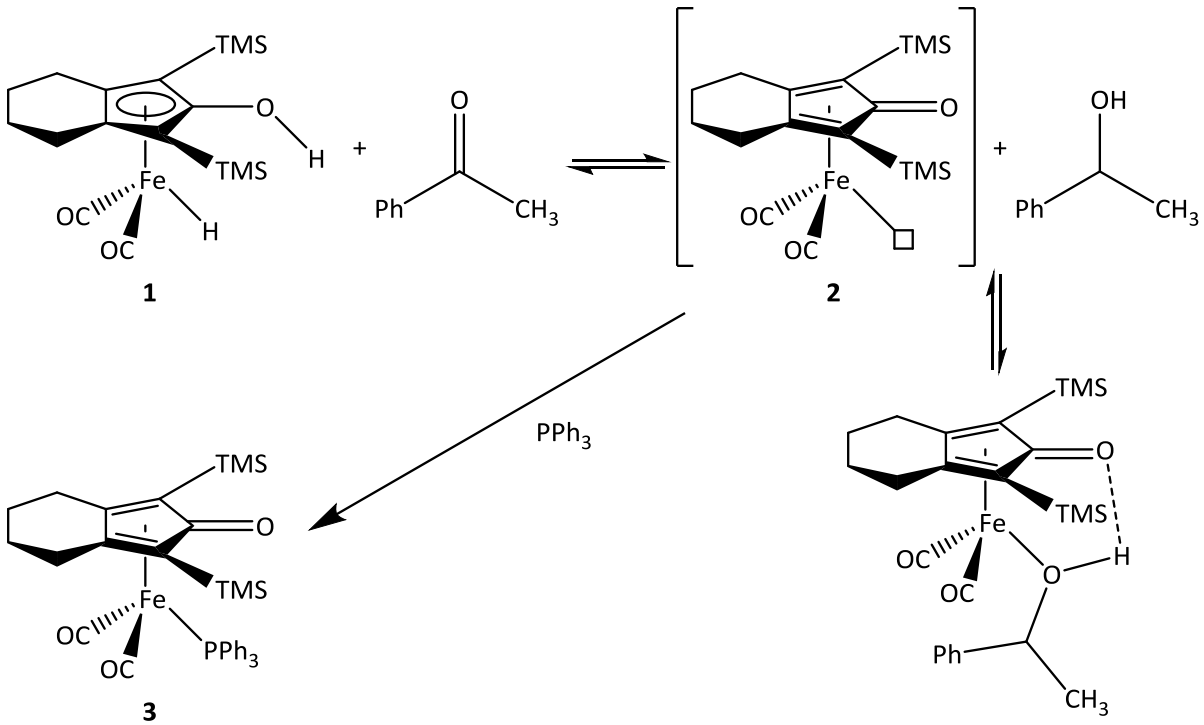
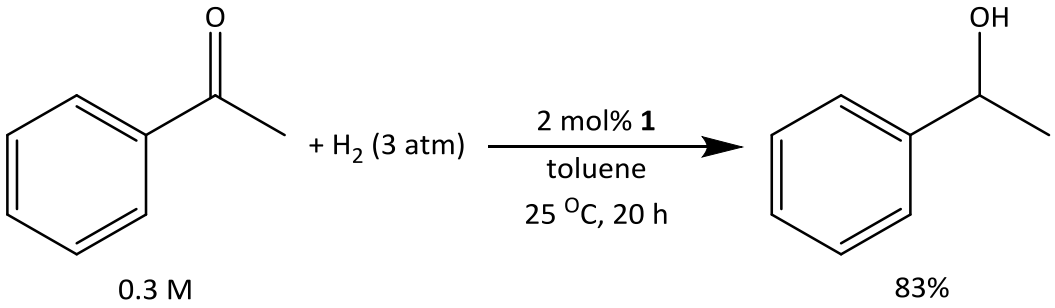
Figure 3 Knölker's catalyst [25]



Scheme 5 Acetophenone hydrogenation with catalyst **1** [25]



Equation 1 Acetophenone direct reduction by catalyst **1** [25]

1 (2 mol%) catalysed the reduction of acetophenone in 20 hours at room temperature under 3 atm H_2 as shown in **Equation 1**. Catalyst **1** also exhibited impressive chemoselectivity and tolerance of functional groups. Isolated alkynes, alkenes, and epoxides and esters were not hydrogenated. For ketone substrates with isolated alkenes and alkynes, only the ketone C=O was reduced.

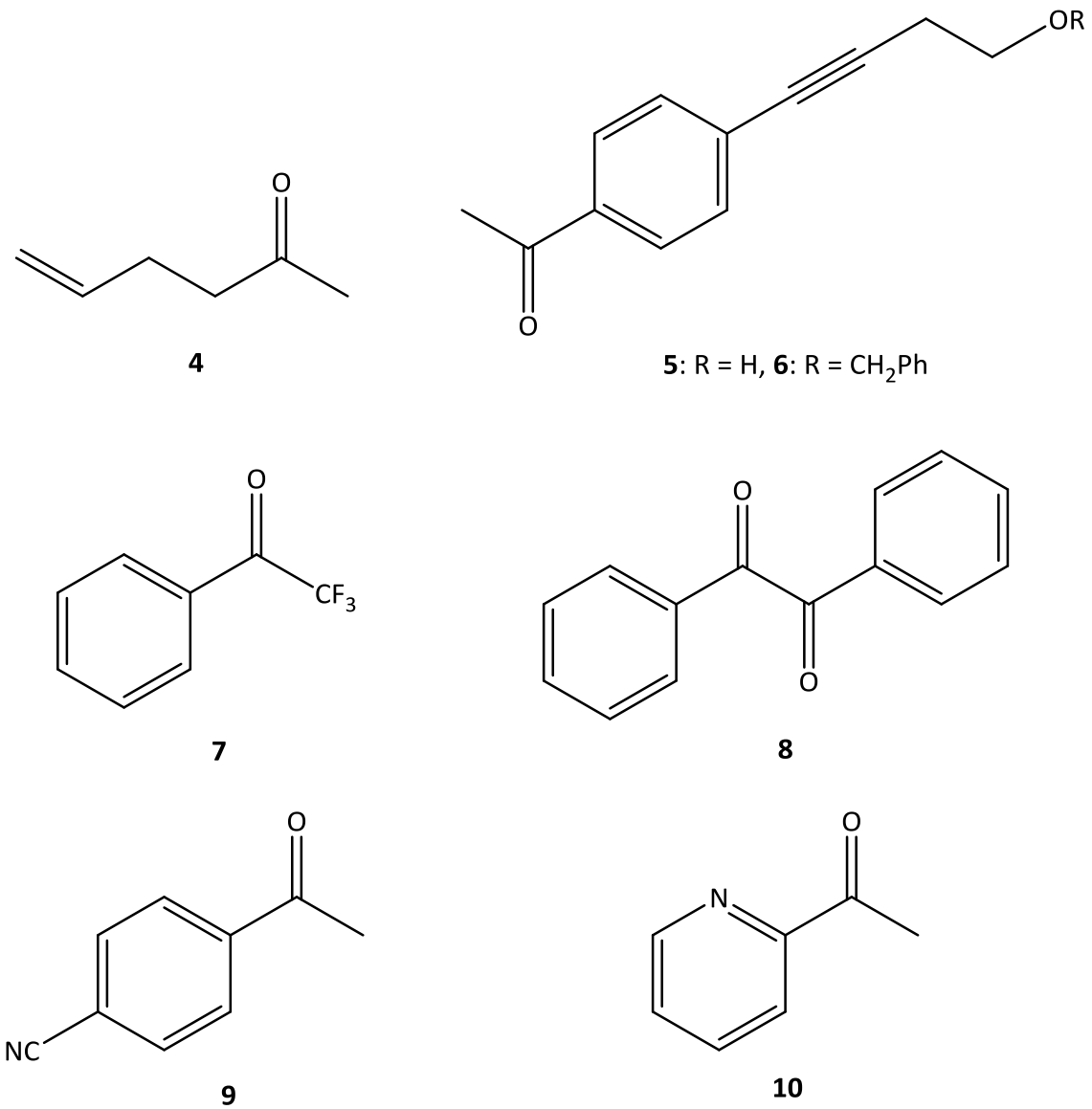
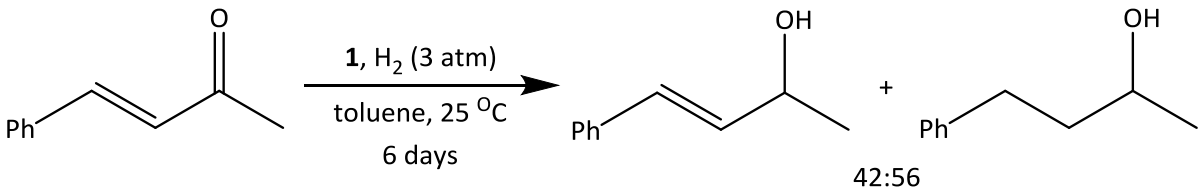


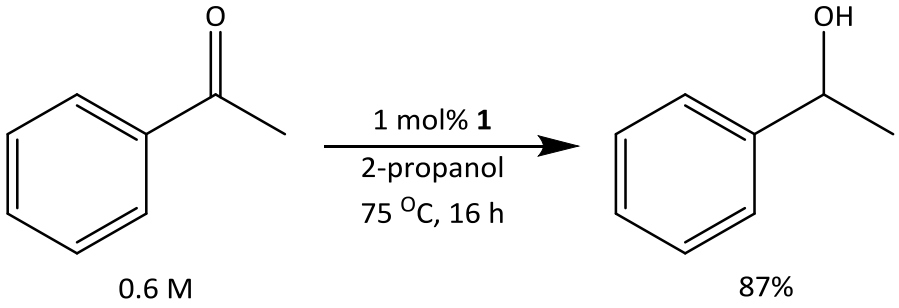
Figure 4 Substrates used with catalyst **1** [25]

Compounds **4**-**6**, **Figure 4**, were selectively hydrogenated at the ketone moiety. Ketones with electron-withdrawing groups (compounds **7** and **8** – **Figure 4**) were reduced much faster than other ketones which is probably due to the electron withdrawal increasingly stabilising the reaction intermediate/transition state. 4-acetylbenzonitrile, **9**, was not reduced, most likely due to the trapping of intermediate **2** by the nitrile functionality. The same trapping was expected with 2-acetyl pyridine (**10**) owing to the pyridine moiety - but such an inhibition of the catalytic reduction did not occur, in fact reduction was rapid (8 h). Reduction of α,β-unsaturated ketones did not purely result in carbonyl reduction due to partial reduction of the carbon-carbon double bond as shown in **Equation 2**. Catalyst **1** also catalysed the ATH of acetophenone with 2-propanol in 16 h as shown in **Equation 3**.

Knölker's catalyst, shown by Casey and Guan, was the first well-defined Fe catalyst for ketone hydrogenation under mild conditions (room temperature and 3 atm H_2) with attractive chemoselectivity.

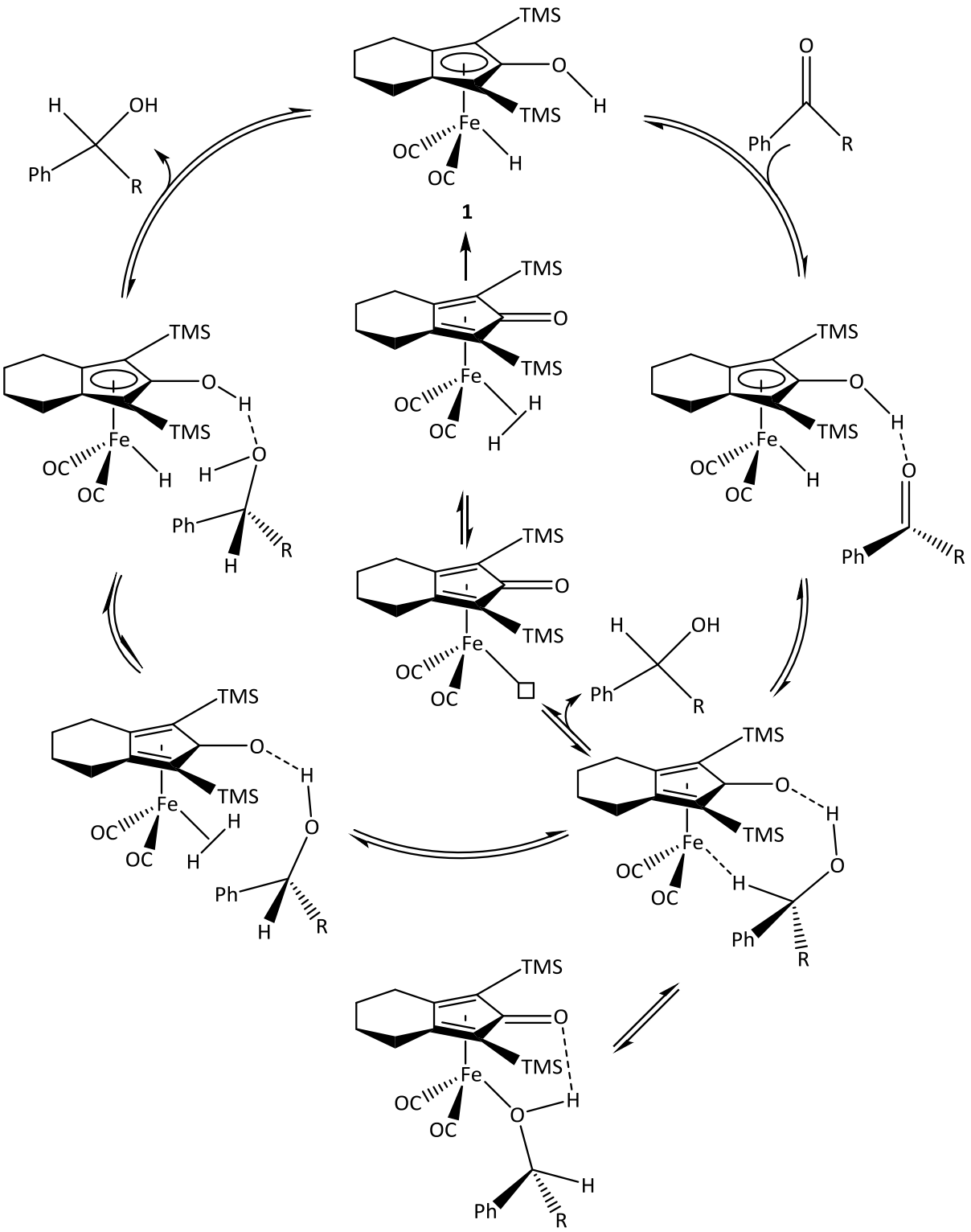


Equation 2 Mixture of products obtained in the hydrogenation of α,β-unsaturated ketones using catalyst **1** [25]



Equation 3 Transfer hydrogenation of acetophenone using catalyst **1** [25]

Zhang and co-workers [26] set out to determine in detail, the mechanism and as such the intermediates involved for the catalytic reduction reaction using Knölker's catalyst (**1**). The team confirmed through DFT studies of acetophenone reduction catalysed by **1** that hydrogen transfer occurs via a ligand-metal bifunctional mechanism (See Section 2.1.0). Hydrogen transfer is then followed by the heterolytic splitting of dihydrogen to replace the proton and hydride transferred from the catalyst. The proposed catalytic cycle is shown in **Scheme 6**. The team determined the rate determining step as the concerted proton-hydride transfer process and calculated the free energy for acetophenone hydrogenation as 18.97 kcal mol^{-1} which supports experimental values.



Scheme 6 Proposed mechanism of action of **1** by Zhang and co-workers [26]

Lu and co-workers [20] were not satisfied with the lack of investigation by Casey and Guan[25], and Zhang and co-workers[26] into other possible mechanisms of catalysis by Knölker's catalyst (**1**). With the aid of DFT calculations modelled using formaldehyde as the substrate, the team investigated 5 possible mechanisms of catalysis for **1**. Two inner-sphere mechanisms both had free energy barriers too high for the mechanisms to be kinetically feasible (both above 40 kcal mol^{-1}). Two outer-sphere mechanisms which required single proton and single hydride transfers had products that had a higher free energy than the reactants. The mechanism necessitating a single proton transfer had a free energy barrier above 40 kcal mol^{-1} indicating that this mechanism was not kinetically feasible. The mechanism necessitating a single hydride transfer had a free energy above 30 kcal mol^{-1} which indicated that this mechanism was possible but kinetically unfavourable. The third outer-sphere mechanism, shown in **Figure 5**, was the most likely mechanism of action for **1** with a free energy barrier of just above 10 kcal mol^{-1}. This involved the simultaneous transfer of hydride and proton to the substrate with no ligation of the substrate to the catalyst metal centre - hence an outer-sphere mechanism. When the system was modelled with acetophenone - the free energy barrier was increased to just above 20 kcal mol^{-1}, which is in accordance to experimental values. Lu and co-workers thus deduced that due to the concerted nature of the mechanism of **1**, the simultaneous increase in polarity of the CpO-H and Fe-H bonds could improve the activity of the catalyst (Cp = cyclopentadienyl). This increased polarity would promote proton and hydride dissociation from the catalyst towards the substrate. Moreover, increasing the polarity of the ketone C=O bond would increase the likelihood of hydrogenation taking place.

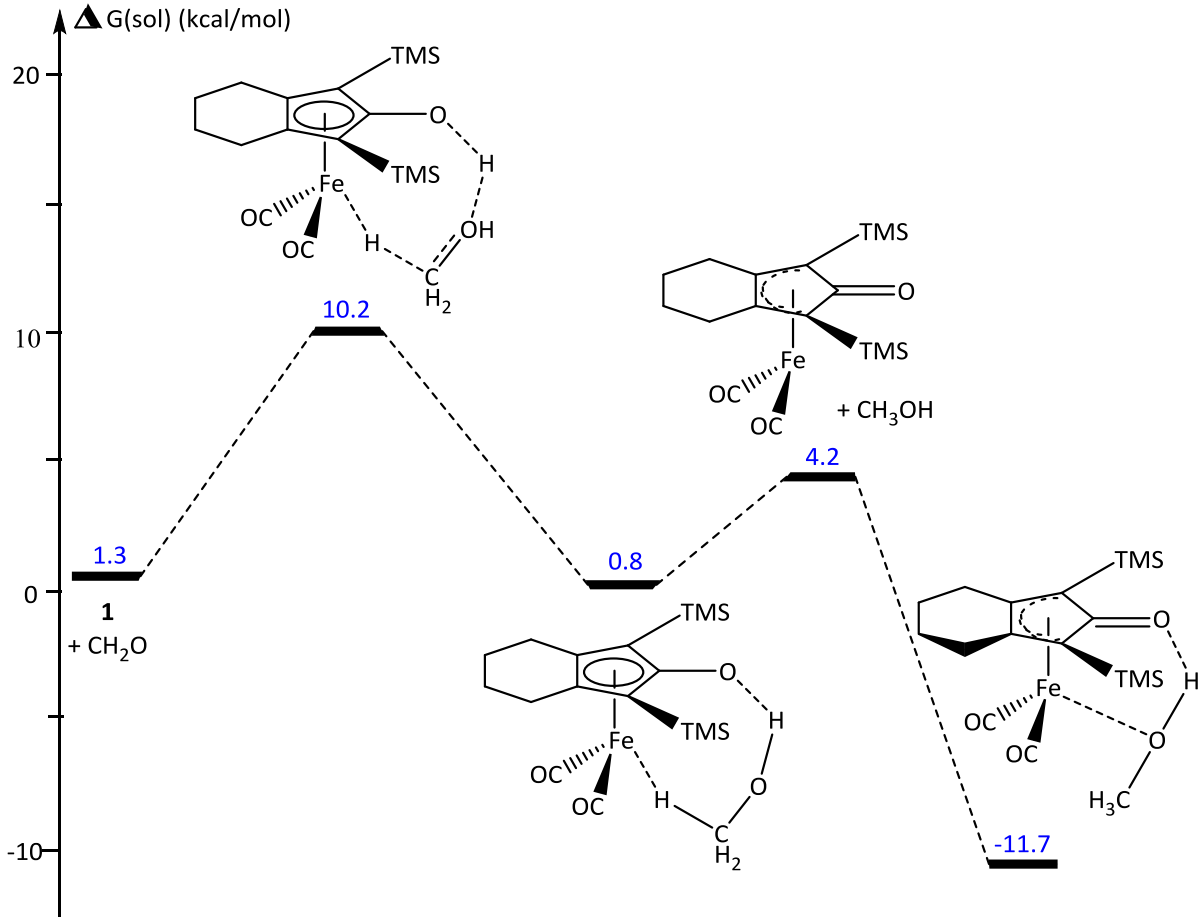


Figure 5 Outer-sphere mechanism 3: Concerted proton and hydride transfer using **1** where ΔG(sol) = solvation free energy, by Lu and co-workers [20]

2 LIGANDS USED

2.0 CYCLOPENTADIENYL-N-HETEROCYCLIC CARBENE

After the extensive work on **1**, Kandepi and co-workers [27] worked on a series of related cyclopentadienyl-N-heterocyclic carbene iron complexes of general formula (Cp^A-NHC)Fe(CO)X (where A is the substituent on the Cp ring) to be used for hydrogenation transfers. They investigated unsubstituted and substituted Cp rings. Their aim was to investigate the use of bidentate Cp-N-heterocylic carbene ligands as an alternative to monodentate ligands such as the functionalised Cp ligand in **1**. This was done in the hope that the bidentate ligand could better stabilise intermediate species that could not be stabilised through the use of monodentate ligands. The series of iron complexes synthesised and tested are shown in **Figure 6**.

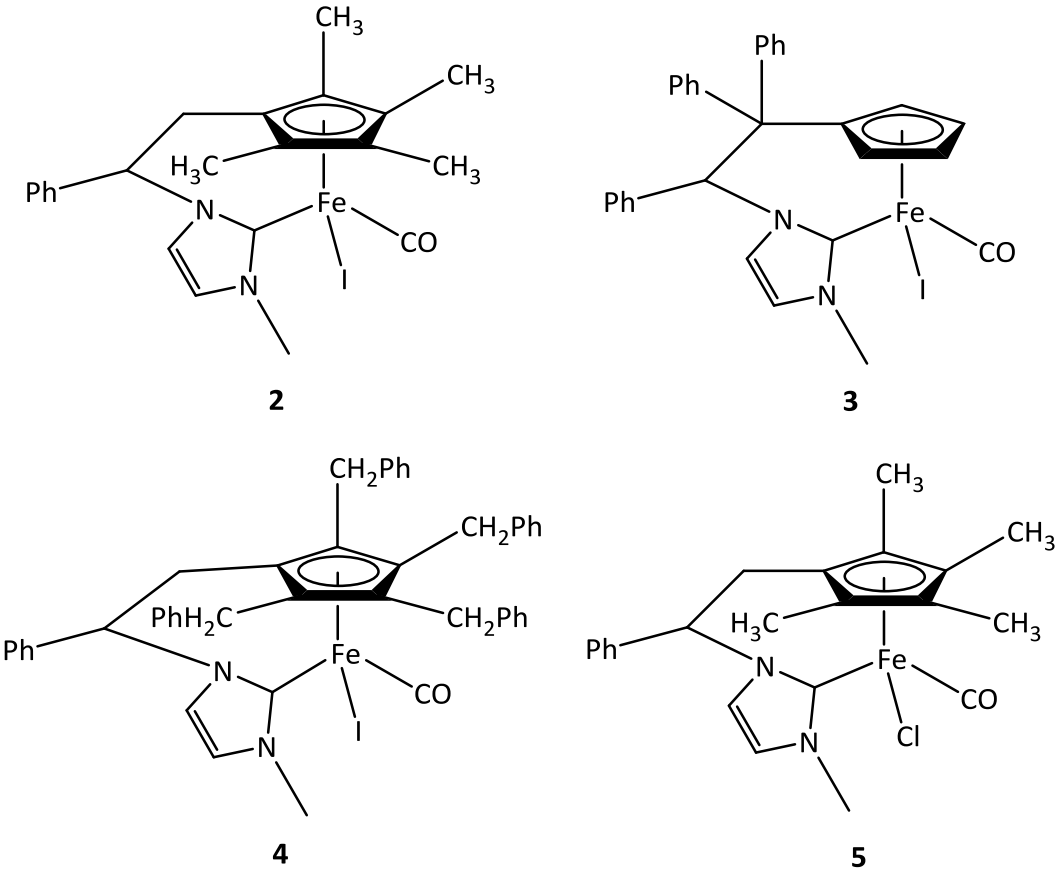
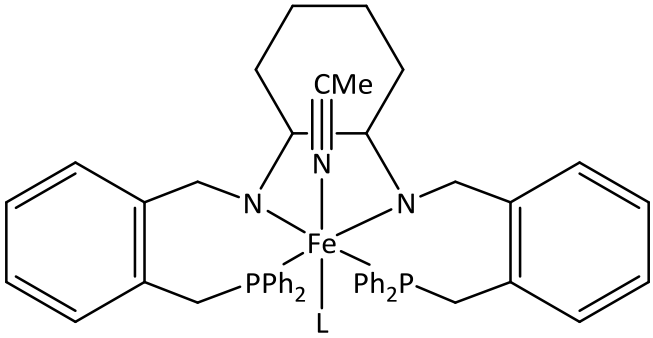


Figure 6 Complexes tested for catalytic activity by Kandepi and co-workers [27]

Kandepi and co-workers showed that iron complexes of the general formula (Cp^A_NHC)Fe(CO)I had attractive activity in ketone reduction using 2-propanol. The reactions using catalysts **2**, **3**, **4** and **5** were carried out at 80 ^{O}C, 2 mmol ketone and 1 mol% catalyst and all gave yields of at least 80% in 6 h. Interestingly, the most active catalyst **2** was also run at a lower catalyst loading of 0.5 mol% and still gave a yield of 75% in 6 h. This is the only case of the use of a bidentate-ligand-bearing iron complex and it indicated that iron complexes with ligands of higher denticity could make for efficient catalysts in ketone reduction reactions.

2.1 PNNP



6: L = CO, **7**: L = ^{t}BuNC

Figure 7 *(R, R)*-PNNP iron catalysts [28]

Sui-Seng and co-workers [28] were the first to synthesise iron precatalysts with a diiminodiphosphine (PNNP) tetradentate ligand such as complex **6** and **7** shown in **Figure 7**. This PNNP ligand is chiral and of *(R, R)* stereochemistry and converted ketones to *(S)*-alcohols. With a substrate: catalyst: base loading of 200:1:8, complex **6** reduced acetophenone at 22 ^{O}C in 0.4 h with a 95% conversion and ee of 33%. The conversion is comparable to ruthenium catalysts, but the selectivity is meagre. With a 200:1:8 loading, complex **7** reduced acetophenone at 22 ^{O}C in 2.6 h with a 34% conversion and ee of 76%. Although the conversion was much lower, the enantioselectivity increased - however, none of the reaction conditions or catalysts used could compare to the enantioselectivity of the ruthenium predecessors. More recent work by Chen and co-workers [29] included Density Functional Theory (DFT) calculations on related complexes which supported the supposition that the complexes developed by Sui-Seng and co-workers do in fact act as bifunctional catalysts.

This work was soon improved on by Morris and co-workers [30] who synthesised similar complexes which had a different N-N bridge (complexes **8** and **9** in **Figure 8**), with complex **10** having the corresponding PN(H)N(H)P. Complex **10** was found as two isomers, one with hydrogens on the same plane and one with hydrogens on opposing faces of the plane. Complexes **8** and **10** hydrogenated acetophenone in 18 h with conversions of 95% and 99% respectively. The similarity in activity of **8** and **10**, according to Morris in a later review [31], suggest that both complexes are converted to alike intermediates that contain hydride ligands and a diaminediphosphine tetradentate ligand. This imine to amine reduction would follow the mechanism of related ruthenium catalysts. [32]

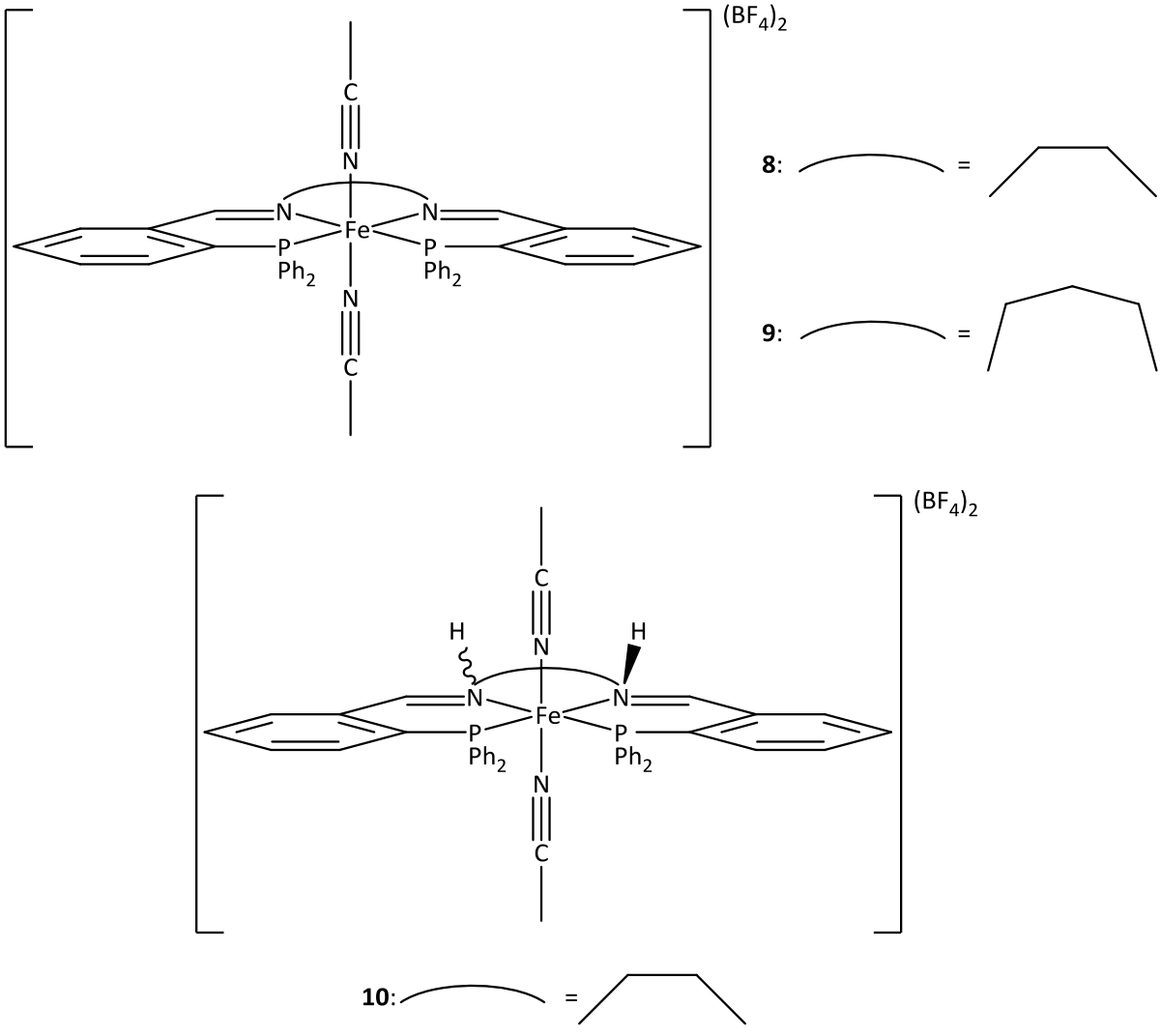
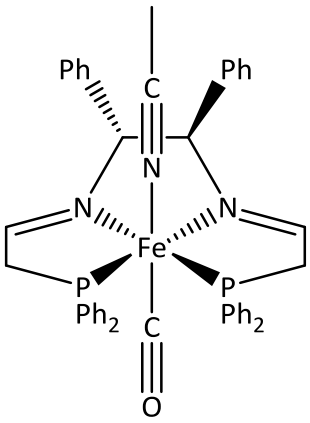


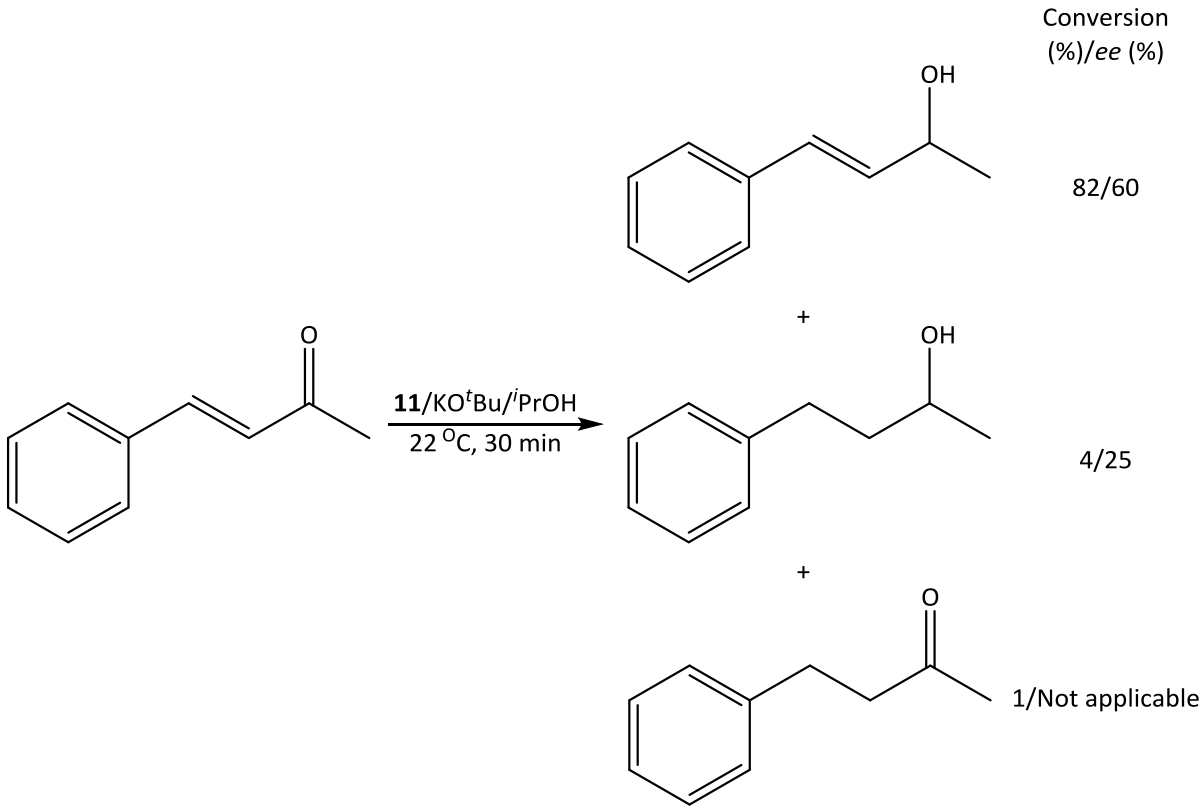
Figure 8 PNNP and PN(H)N(H)P ligand-bearing iron catalysts varying in N-N bridges [30]



11

Figure 9 Precatalyst developed by Milkhailine and co-workers [14]

Another variation on the N-N bridge was reported by Mikhailine and co-workers, [14] who used a -C(Ph)C(Ph)- bridge as shown in **Figure 9**. The team also simplified the N-P bridge, from a 5-membered bridge (developed by Sui-Seng and co-workers [28]) to a 4-membered bridge. Compared to the previous catalyst **6**, precatalyst **11** had much higher selectivity and activity. Complex **11** converted acetophenone to *(S)*-1-phenylethanol by transfer hydrogenation with an *ee* of 82% using either KO^{t}Bu, NaO^{t}Bu or KOH as the base. Changing the base used did not significantly change the *ee* obtained, but the conversion to product and turnover frequency (TOF) was best (90% and 3600 h^{-1} respectively) when KO^{t}Bu was used. The optimal catalyst:base ratio was found to be 1:8 and increasing the substrate loading increased the TOF. They also found that, as the reaction tends towards completion, the product became increasingly racemised. The team suggested that quenching the reaction, when the conversion an d *ee* are at their highest, would overcome this drawback. More sterically hindered ketones such as Ph-CO-Et and Ph-CO-(cyclo-C_4H_7) were hydrogenated with conversions of 90% and 95% respectively. However, the steric hindrance of -^{t}Bu was too demanding, as Ph-CO-^{t}Bu had a conversion of 35%, that too in 200 min. The team also showed that *para* substitution of the phenyl ring in acetophenone effects the TOF significantly, whereas *meta* substitution has little effect on the reaction. The reduction of *α,β*-unsaturated ketone *trans*-4-phenyl-3-buten-2-one proceeded with high chemoselectivity as shown in **Scheme 7**. This high chemoselectivity is probably due to the favouritism of the more polar C=O bond over the C=C bond. This fortifies the idea of an outer-sphere attack of a hydride-iron-nitrogen-proton moiety on the catalyst during the reaction mechanism . Thus, **11** was the first iron precatalyst to have viable enantioselectivity and activity as well as a respectable but improvable substrate scope.



Scheme 7 Transfer hydrogenation of *trans*-4-phenyl-3-buten-2-one using **11** [14]

Meyer and co-workers [1] synthesised a series of iron precatalysts with a PNNP ligand. The N-P bridge was the same 5-membered bridge as developed by Sui-Seng and co-workers [26] but the N-N bridge was changed to create a family of complexes to trial as shown in **Figure 10**. The changes in steric hindrance on the N-N bridge between each complex had a minor effect on the catalytic activity. The only difference between complexes **14** and **15** are that **14** forms the *(R)*-alcohol and **15** forms the *(S)*-alcohol. Of the developed complexes, precatalysts **12**, **14** and **15** showed the most promise for both aromatic and non-aromatic ketones, although **12** was not enantioselective. Complex **15** catalysed the ATH of acetophenone to *(S)*-1- phenylethanol in 15 min with a conversion of 68% and *ee* of 63% (at 24 ^{O}C, 0.005 mmol catalyst, 0.04 mmol KO^{t}Bu base, in 6 mL ^{i}PrOH solvent with a substrate:catalyst:base loading of 600:1:8). Moreover, the team found that acetone (produced during the reaction) and propan-2-ol removal in vacuo increased the conversion to 99% and *ee* to 60% when catalyst **15** was used for acetophenone conversion. This was the first case where the conversion and enantioselectivity were both high - especially at such

mild conditions and relatively low loadings. Also, complex **15** dealt with substrates containing bulky substituents well.

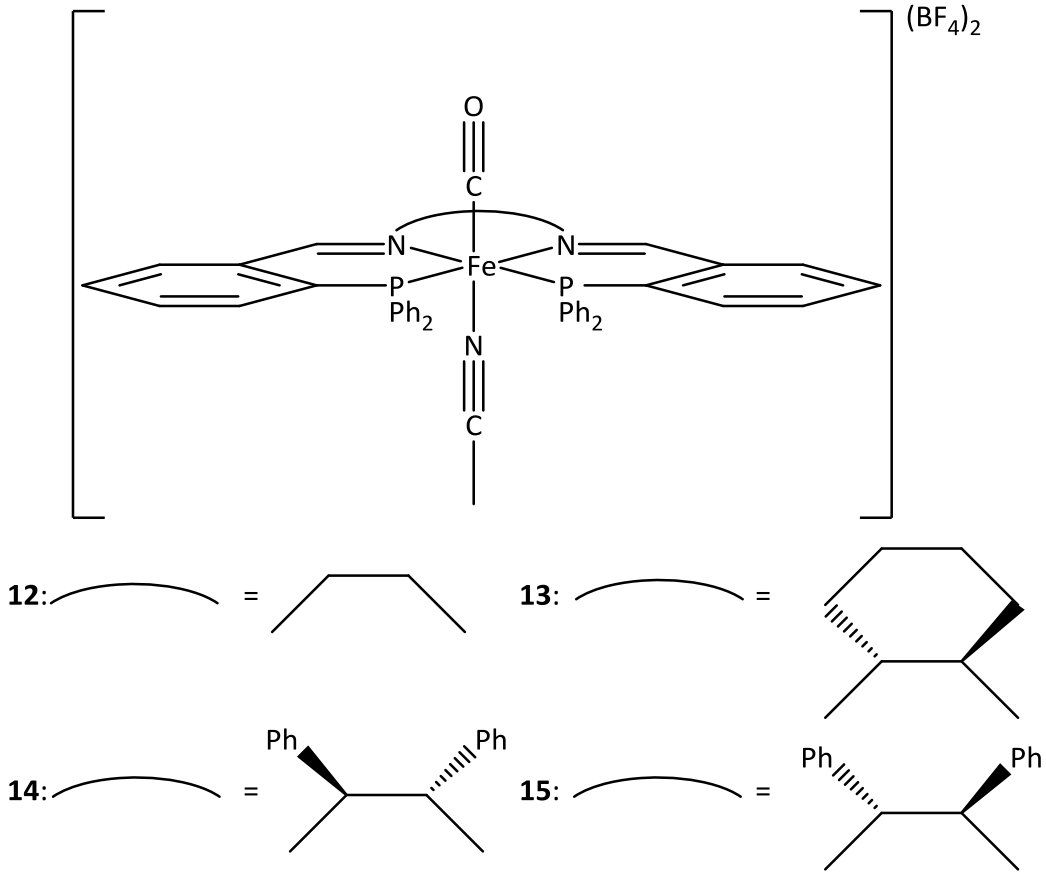


Figure 10 Catalysts developed by Meyer and co-workers where the N-N bridge is varied [1]

Mikhailine and Morris [2] studied the effect of changing the N-N backbone in PNNP-bearing Fe catalysts. The four complexes synthesised are shown in **Figure 11**. Complexes **11** and **17** had comparable activity and enantioselectivity (*ee* 82%) in the ATH of acetophenone, suggesting that the ligand *trans* to the carbonyl group has little effect on the reaction rate or enantioselectivity. The team showed that increasing the steric bulk on the N-N bridge increased the catalytic activity of the complex. These reactions were carried out at 28-30 ^{O}C in Argon, KO^{t}Bu base and a substrate:catalyst:base loading of 6000:1:8 - mild reaction conditions which make the system attractive for industrial use. The work by Milkhailine and Morris somewhat contradicts the work of Sui-Seng and co-workers [30] who found that N-N bridges of ethPNNP and prPNNP had good activity, whereas bridges of *(S,S)*-^{i}Pr-ethPNNP and *(R,R)*-Ph-ethPNNP (**Figure 12**) had much lower activity. This showed that larger N-N backbones do increase catalytic activity, but only up to a certain point, where steric bulk blocks access to the Fe metal centre.

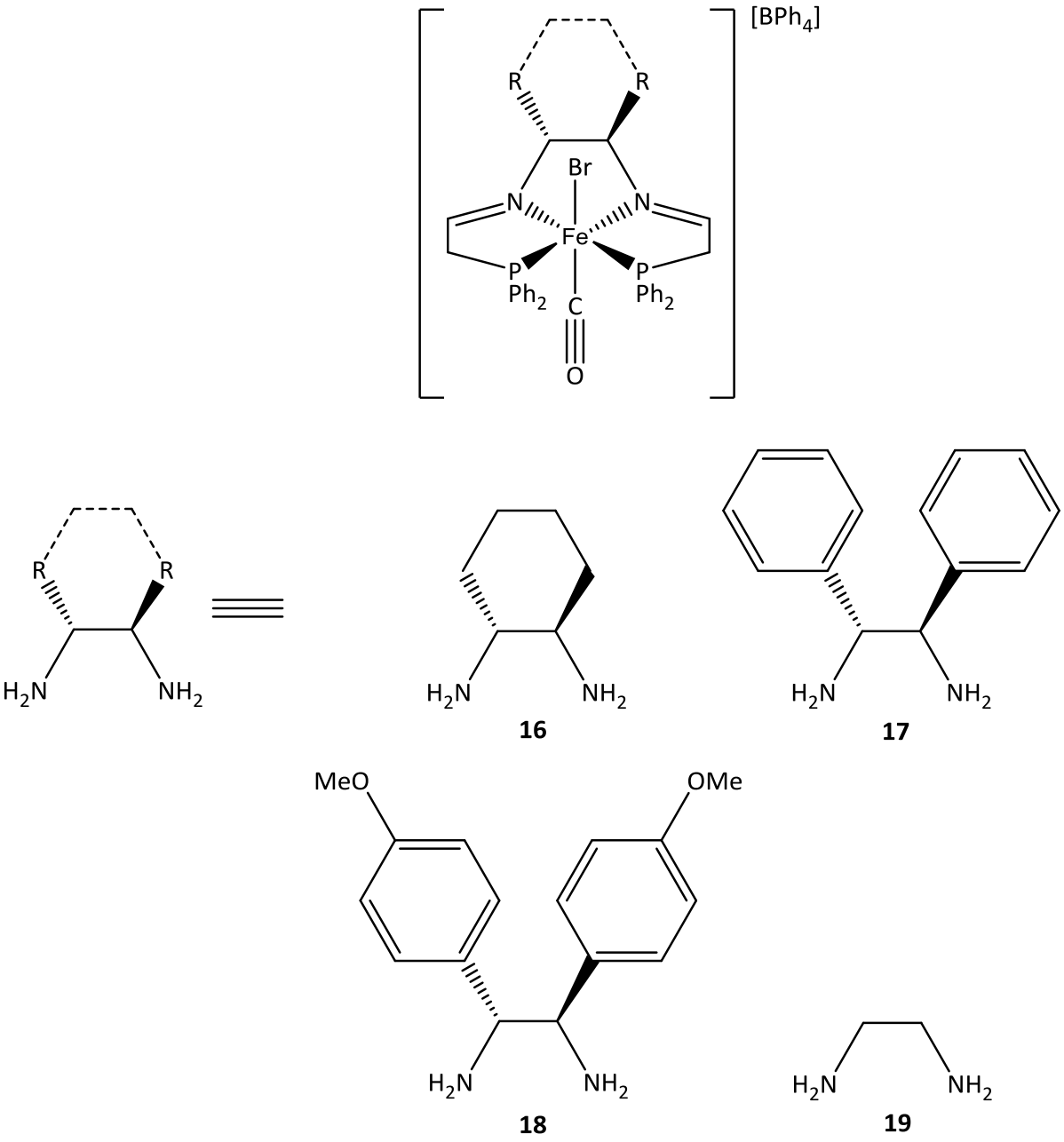


Figure 11 Varying N-N bridges tested by Mikhailine and Morris [2]

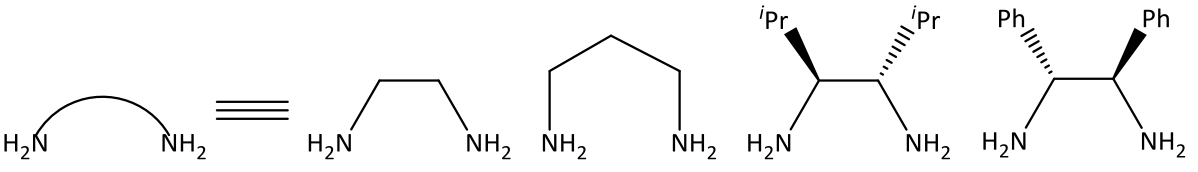
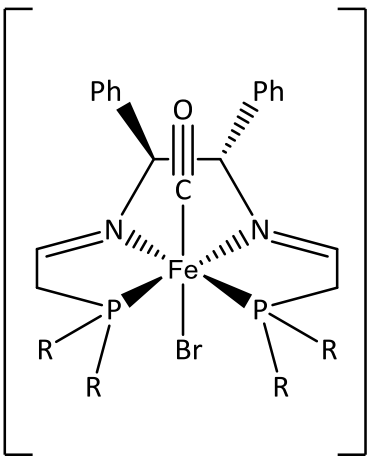


Figure 12 Varying N-N bridges by Sui-Seng and co-workers [30]



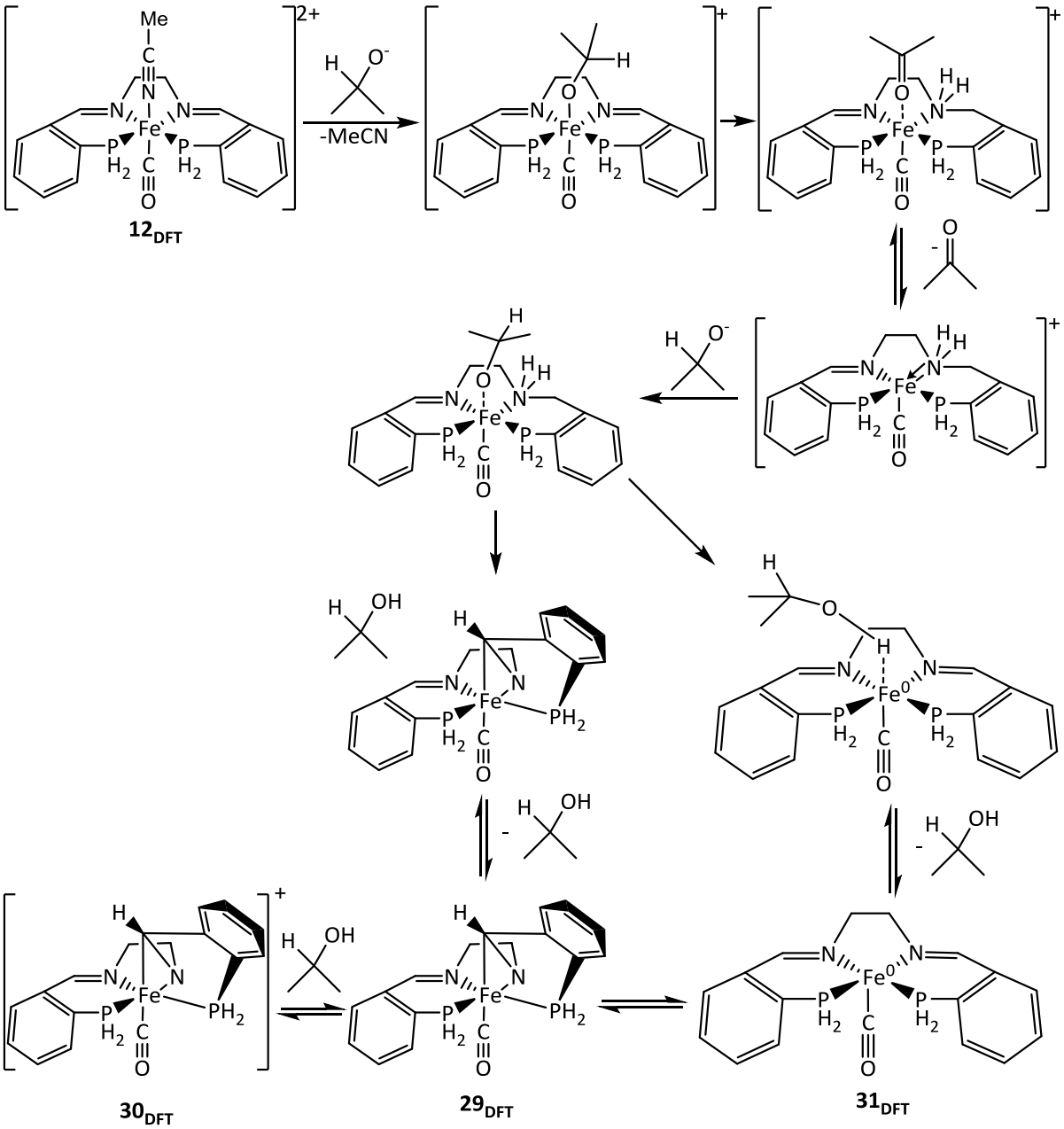
20: R = *para*-$CH_3C_6H_4$
21: R = *ortho*-$CH_3C_6H_4$
22: R = 3,5-$(CH_3)_2C_6H_3$
23: R = *para*-$CF_3C_6H_4$
24: R = 3,5-$(CF_3)_2C_6H_3$
25: R = Ph
26: R = Et
27: R = ^{i}Pr
28: R = Cy

Figure 13 Varying substituents on the phosphorus atoms of the PNNP ligand [33]

In 2011 Sues, Lough and Morris [33] later investigated the effect of changing the substituents on the phosphorus atoms along the PNNP ligand as shown in **Figure 13**. The only active catalysts were **20** and **22**. **20** became the most active Fe catalyst and **22** became the most enantioselective Fe catalyst by 2011. **20** reduced acetophenone to *(R)*-1-phenylethanol with a TOF of 30 000 h^{-1} and *ee* 84%. **22** reduced acetophenone to *(R)*-1-phenylethanol with a TOF of 26 000 h^{-1} and *ee* 90%. By any measure, both catalysts would be industrially viable alternatives to previous ruthenium catalysts. However, although the reactions proceeded under 28 ^{O}C, in ^{i}PrOH solvent, and KO^{t}Bu base - the substrate:catalyst:base loading was 1000:1:8. Thus a much higher substrate loading is needed compared to old ruthenium catalysts to achieve similar activity and enantioselectivity.

Using the complex **12**, Prokopchuk and co-workers [34] did extensive research into the species present during the hydrogenation of acetophenone through NMR, IR and DFT methods. NMR observations during catalysis showed oxidised free PNNP ligand as well as an iron complex that the team thought to be a neutral ferraaziridinido complex (complex **29**). IR data revealed that two electron-rich Fe species with CO stretches less than 1900 cm^{-1} are formed during catalysis. This is because peak absorptions below 1900 cm^{-1} are characteristic of iron (0) compounds or bridging C=O ligands. [35][36] Reacting the starting precatalyst **12** with NaO^{i}Pr in benzene produced complex **30** which was thought to be an intermediate in the catalytic process. **30** does not have any catalytic activity on acetophenone without base present - the NMR of **30** did not match the NMR of the transfer hydrogenation mixture thus **30** is not the active species in catalysis. The X-ray diffraction of **30** indicated a distorted ligand geometry. **30** was reacted with KO^{t}Bu base in the presence of ^{i}PrOH to deprotonate the ferraaziridine N atom to afford complex **29**. Complex **29** could not be purified, thus crude **29** was evaluated by NMR and subsequently matched the NMR of the transfer

hydrogenation mixture. **29** was also unsuccessful in acetophenone reduction. This indicates that **29** is an intermediate in the catalytic process, but is not the active species in the catalysis. **29** was also found to have a distorted geometry like **30** - an intriguing "ligand folding". [34] DFT studies were used to propose the most thermodynamically viable mechanism (**Scheme 8**) for the production of **29** and **30** which are produced during catalysis. DFT was also used to proposed a structure for the formation of an Fe(0) species (**31(31$_{DFT}$)**) to account for the IR results obtained. The only downfall is that the complexes were simplified to keep the cost of DFT calculations down - thus the mechanisms proposed are good estimations - but not accurate for the real catalytic system. The team consequently hypothesised the facile deprotonation of **30** to **29** and **31** - the products of which account for the two C=O stretches below 1900 cm^{-1} observed in the transfer hydrogenation mixture. The team also mention that more recent work [37] by part of the team proved the existence of Fe(0) nanoparticles "...coated with chiral ligand" [34] present in this catalytic system (See Section 3). The team were also pleased to give experimental data to support the idea that ligand folding due to a distorted ligand geometry is feasible.



Scheme 8 The proposed mechanisms for formation of **30**$_{DFT}$, **29**$_{DFT}$ and **31**$_{DFT}$ [34]

2.1.0 CATALYTIC MECHANISM OF PNNP-BEARING COMPLEXES

Chen and co-workers [29] computed a reaction coordinate diagram showing the relative energy of transition states and intermediates in the catalytic ketone ATH as shown in **Figure 14**.

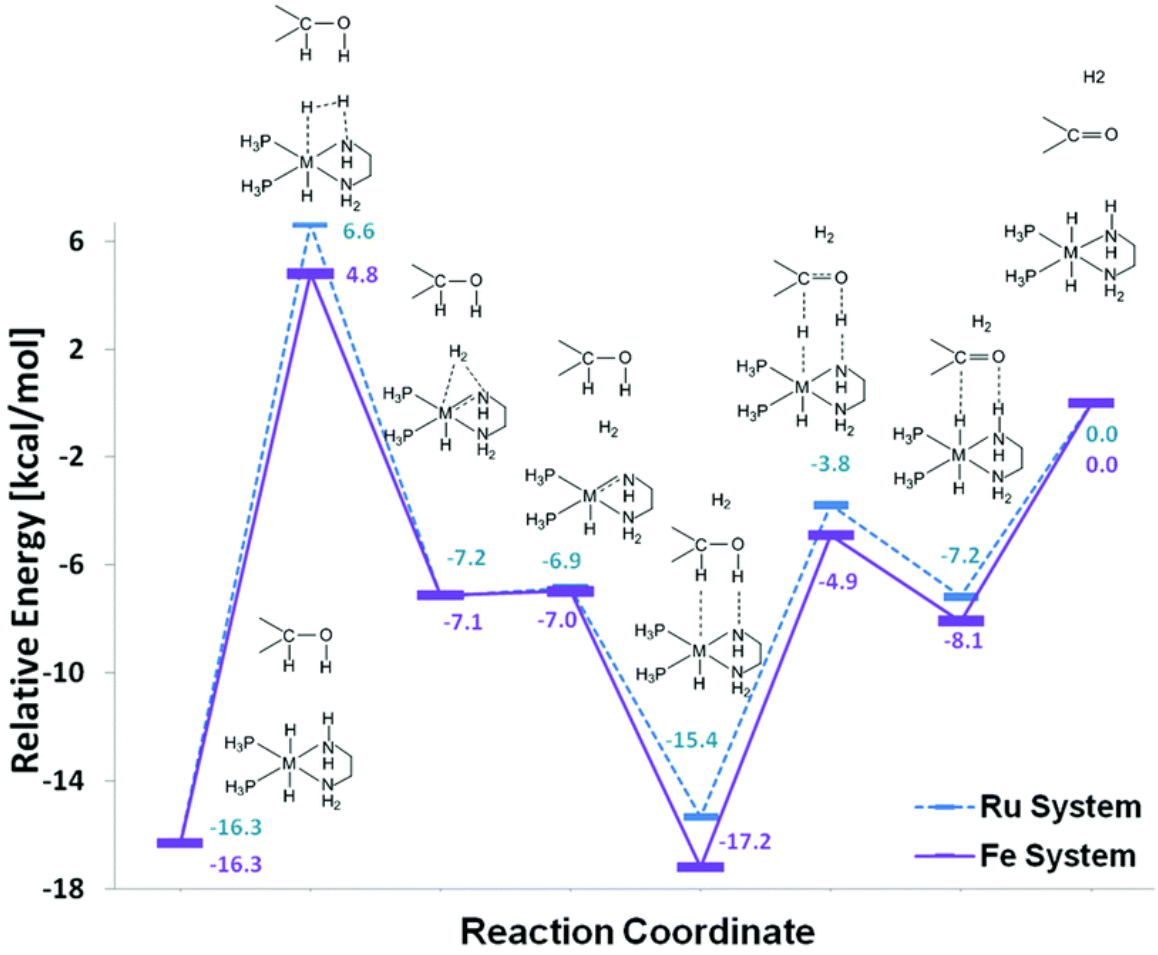


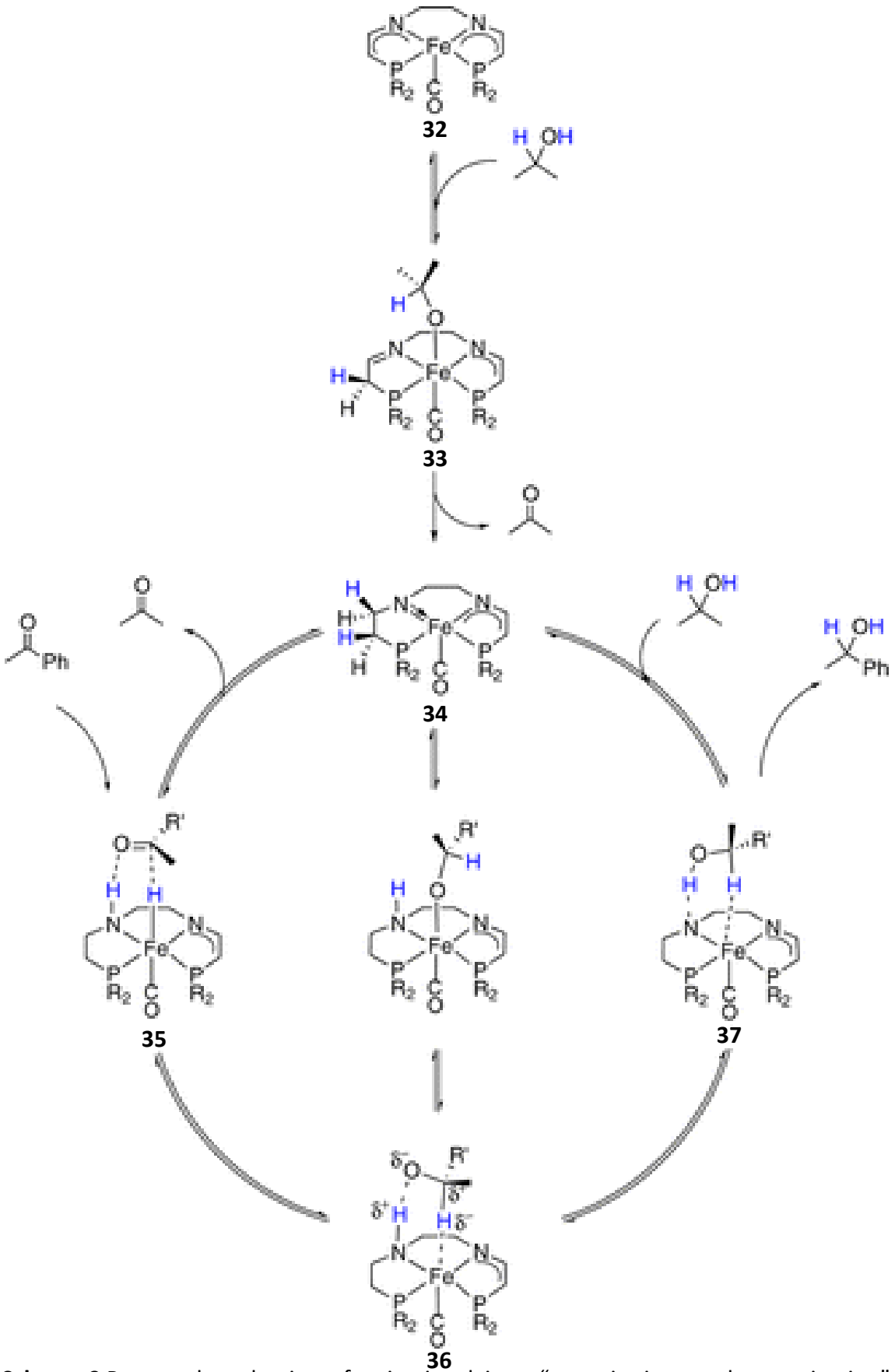
Figure 14 reaction coordinate diagram comparing Re and Fe catalytic systems [29]

This reaction coordinate diagram compares the very successful $[Ru^{II}(H)_2(diphosphine)(diamine)]$ complex (*ee* of 99%)[16][17] with the $[Fe^{II}(H)_2(diphosphine)(diamine)]$ complex. Both reaction profiles followed the same pattern with very similar energies at each energy peak and trough. From this the team concluded that not only could Fe based complexes follow the same MLBC mechanism as the corresponding Ru complexes, but also that the Fe compound studied could have comparable activity to the Ru analogue.

The origin for this high enantioselectivity is the correction of the ketone orientation prior to the actual hydrogen transfer process taking place. This work gave real promise in the search for cheaper and greener alternatives to current Ru catalysts.

Even the work by Sui-Seng and co-workers [29] which looked at iron complexes that had catalytic activity without the presence of NH functionality was recently revised by Zuo and co-workers [38]. The latter team noted that a partially saturated PN(H)NP ligand (See Section 2.2) made for a more reactive iron catalyst precursor than the corresponding iron complex with a PNNP ligand.

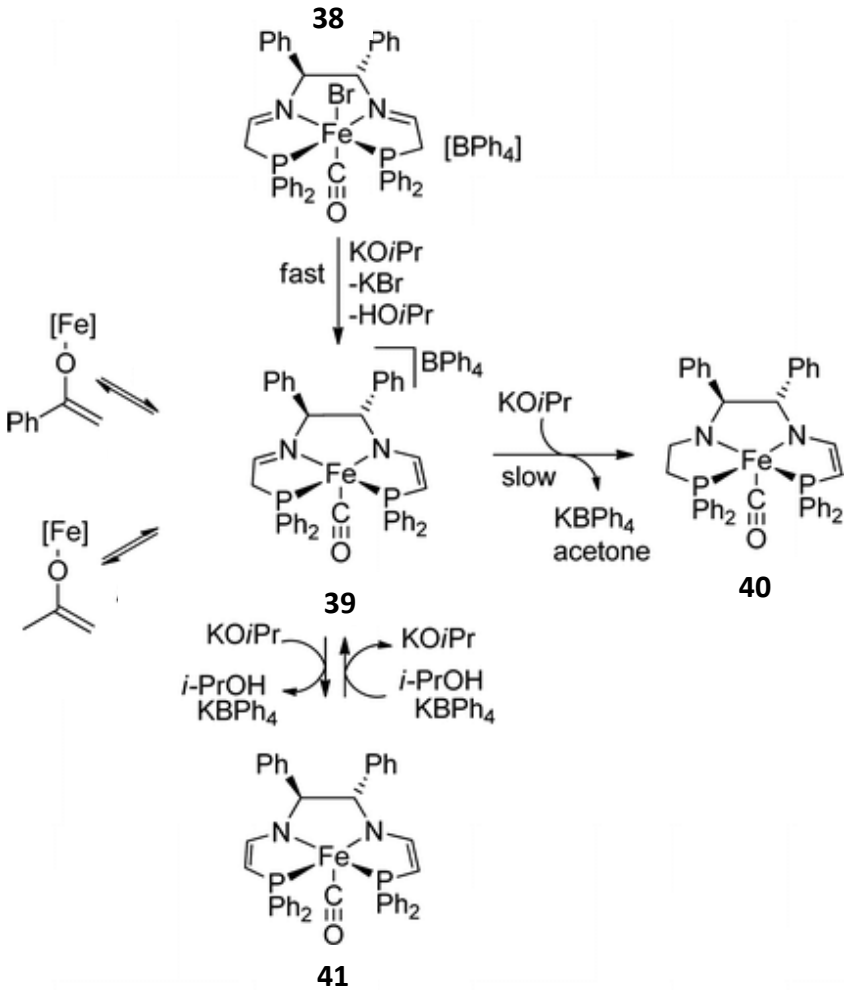
Not long after, Prokopchuk and Morris [39] described the mechanism of the PNNP-bearing compound **32** after activation. This arose from the team's DFT calculations (R = H) where compound **32** is activated by ^{i}PrOH to yield the amido-eneamido complex **33**. The amido N and Fe centre of **33** are then protonated and hydridated respectively to form the active catalytic species **34**. This concludes the “stepwise inner-sphere activation”. Now the substrate can bind by hydrogen bond to the FeH and amido NH as shown in **35**. Then the “stepwise outer-sphere catalysis” can occur in much the same way as described before in MLBC. However, the H^-/H^+ transfer is not concerted. First, the Fe hydride is transferred to the carbonyl carbon (**36**). This is then followed by the transfer of the nitrogen proton to the carbonyl oxygen (**37**). Finally, the formed alcohol dissociated from the complex, reforming complex **34** and thus completing the catalytic cycle. This shows that the activity of the catalyst would be increased if the complex already had the NH and FeH moieties - hence PN(H)N(H)P ligands would make for a more active catalyst than PNNP ligands as the extra activation step by isopropanol would not be required.



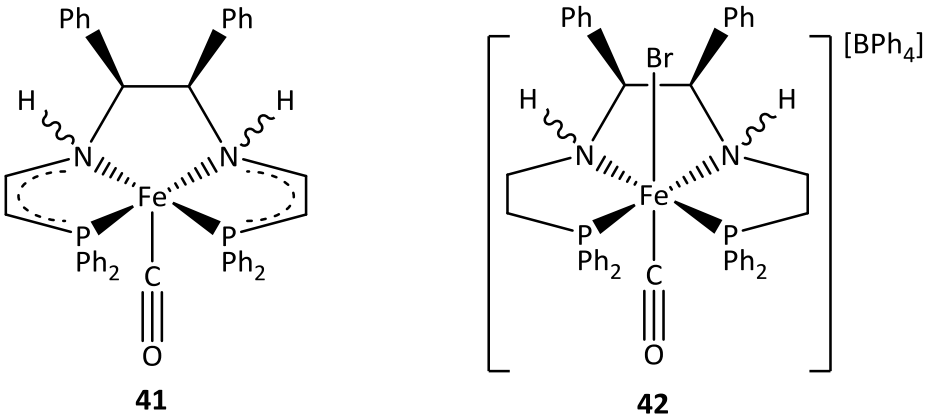
Scheme 9 Proposed mechanism of action involving a "stepwise inner-sphere activation" and "stepwise outer-sphere catalysis" [39]

2.2 PN(H)NP

A review by Clapham and co-workers [40] showed that iron complexes with PN(H)N(H)P ligands had much higher activity than PNNP ligands. Prompted by this, Milkhailine and co-workers [41] studied the mechanism of action of the precatalyst 38. They presented evidence that when **38** is reacted with base, one imine group is reduced in the PNNP backbone to give complex **40** via **39** (**Scheme 10**). Complexes **41** and **42** (**Figure 15**) which have PN(H)N(H)P backbones are not as active as **40**. The team thus concluded that catalysts with a partially reduced PNNP ligand gave the highest activity. Although the team found it hard to isolate **40** due to it's high reactivity, **40** is thought to have an amido-eneamido backbone as when it is oxidised to give **43** (**Scheme 11**), **43** was found to have a PN(H)NP backbone. **43** was found to reduced acetophenone to *(R)*-1-phenylethanol at 25% conversion with a TOF of 55,000 h^{-1} and *ee* 82% under mild conditions - making it much more active than precatalyst **38**. Therefore this work shows that catalysts with P(N)HNP ligands are much more active than those with PNNP or PN(H)N(H)P ligands.

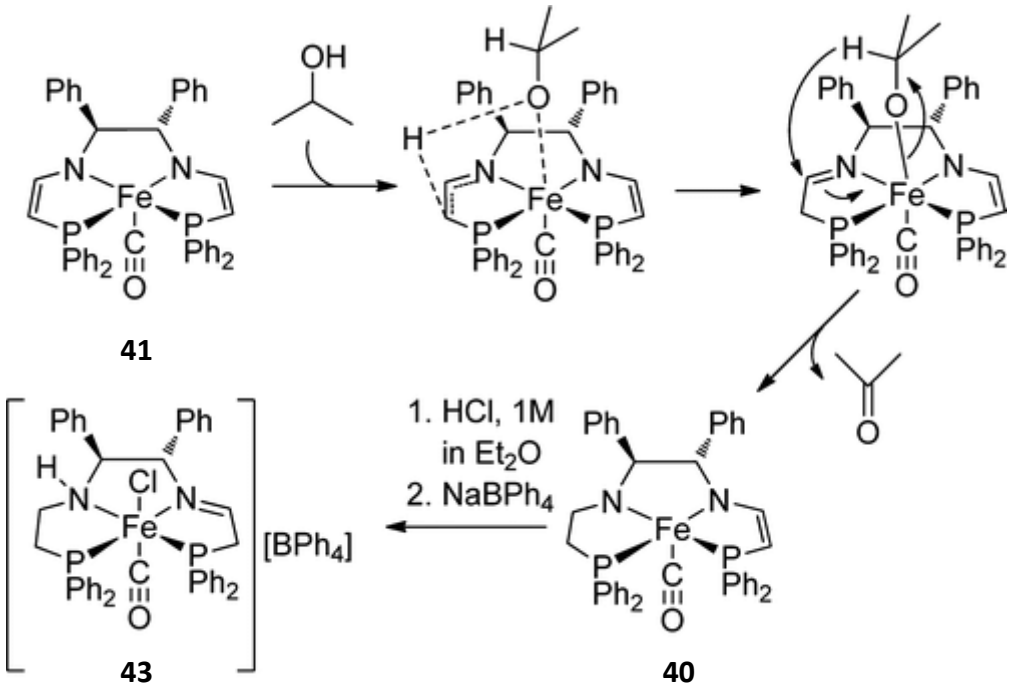


Scheme 10 Mechanism of activation proposed by Mikhailine and co-workers [41]



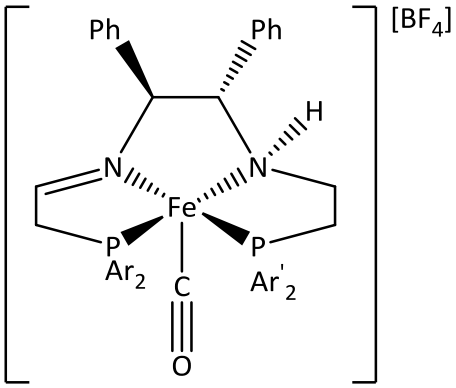
41 **42**

Figure 15 Inactive complexes compared to **38** [41]



41 **43** **40**

Scheme 11 Formation of the highly active catalytic species **43** from complex **41** [41]



44: Ar = *para*-MeC_6H_4, Ar' = Ph
45: Ar, Ar' = 3,5-$Me_2C_6H_3$

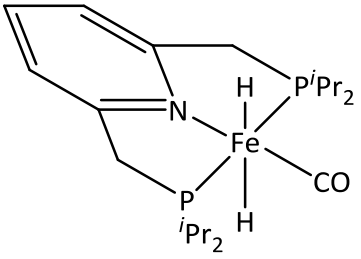
Figure 16 Complexes which showed the most promise developed by Zuo and co-workers [38]

As mentioned previously, Zuo and co-workers [38] studied the effectiveness of iron complexes with a PN(H)NP ligand. Of the group of PN(H)NP complexes formed, the highest TOF for acetophenone reduction to *(R)*-1-phenylethanol was for complex **44** (**Figure 16**) (TOF of 547,200 h^{-1} at 50% conversion, *ee* 86% at 10 s, 28 ^{O}C, substrate:catalyst:base ≈ 6000:1:8, base = KO^tBu). The highest *ee* was obtained with complex **45** (**Figure 16**) (TOF of 252,000 h^{-1} at 50% conversion, *ee* 92% at 10 s, same conditions as for complex **44**). In any case, for all the complexes trialled complete conversions were obtained in seconds, some TOF (including that of complex **44**) exceeded that of the osmium and ruthenium *(R,S)*-Josiphos complexes [42] (acetophenone to *(R)*-1-phenylethanol: TOF up to 320,400 h^{-1}, *ee* 89-92%, 60 ^{O}C in $^{i}PrOH$), and the high *ee* values obtained validate this family of catalysts as industrially viable replacements for the current ruthenium catalysts used. The team also note that the mirror image of the catalysts used should be able to produce the *(S)*- alcohols.

2.3 PNP

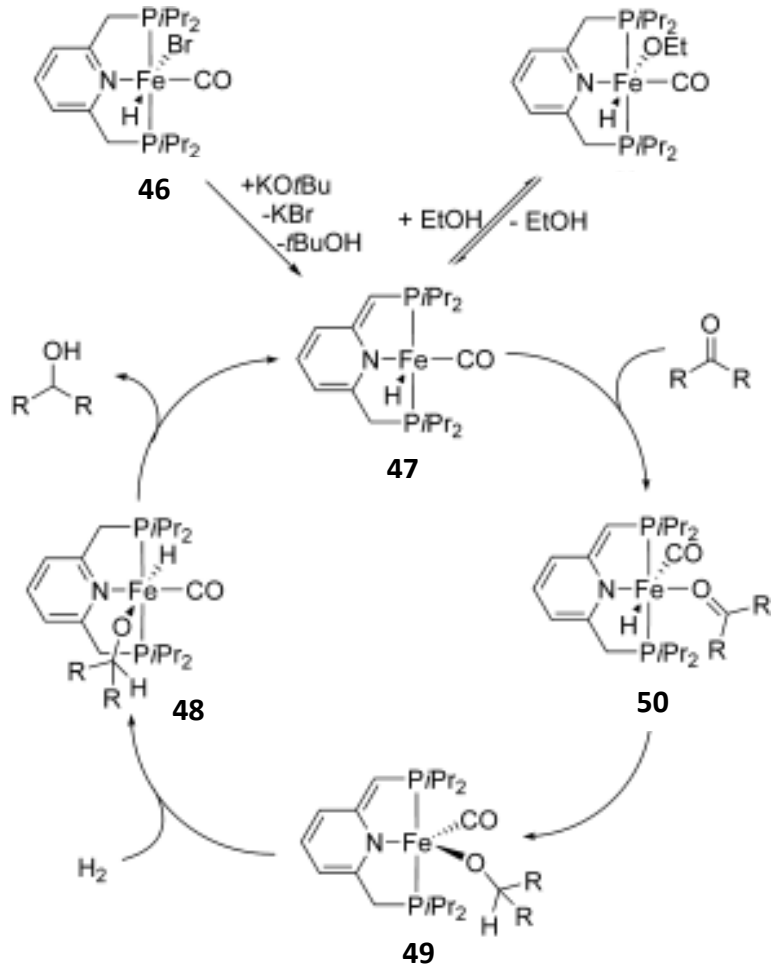
The biggest leap, it seems, has been the work of Milstein and co-workers in 2011, [43] who produced a novel monohydride iron (II) pincer complex, [Fe(Br)(CO)(H)(^{i}Pr-PNP)] (**46**, **Scheme 12**), which surpassed previous work in bifunctional iron catalysts for the ATH of ketones to alcohols. For the conversion of acetophenone to 1-phenylethanol, the team reported a TOF of 87 h^{-1}, 94% conversion in under 22 h (26-28 ^{O}C, 4.1 atm H_2, substrate:catalyst:base = 2000:1:2, base = KO^{t}Bu, solvent = EtOH). The mild conditions make the novel PNP ligand attractive for industrial usage – the team did note that increasing the temperature to 40 ^{O}C significantly increased the TOF from 87 h^{-1} (as mentioned above), to 430 h^{-1}. But *ee* values were not reported as the products obtained were racemic.

They also proved, using NMR spectroscopic studies that the reaction proceeds via a dearomatisation-rearomatisation mechanism as shown in **Scheme 12**. Catalyst **46** is dearomatised by KO^{t}Bu to give catalytically active complex **47**. This then allows for insertion of ketone to **47** via ligation to the metal centre, to give **48**. Hydride transfer from FeH to the carbonyl carbon occurs to give **49**. Then H_2 insertion regenerates the Fe-H bond (**50**) and dissociation of alcohol regenerates **47** - thus completing the catalytic cycle. As the reaction could not occur without EtOH, it was thought that the alcohol stabilised complex **47**. One thing that was not considered was the complex **51** (**Figure 17**) which was observed during the reaction but not included in the catalytic mechanism (**Scheme 12**).



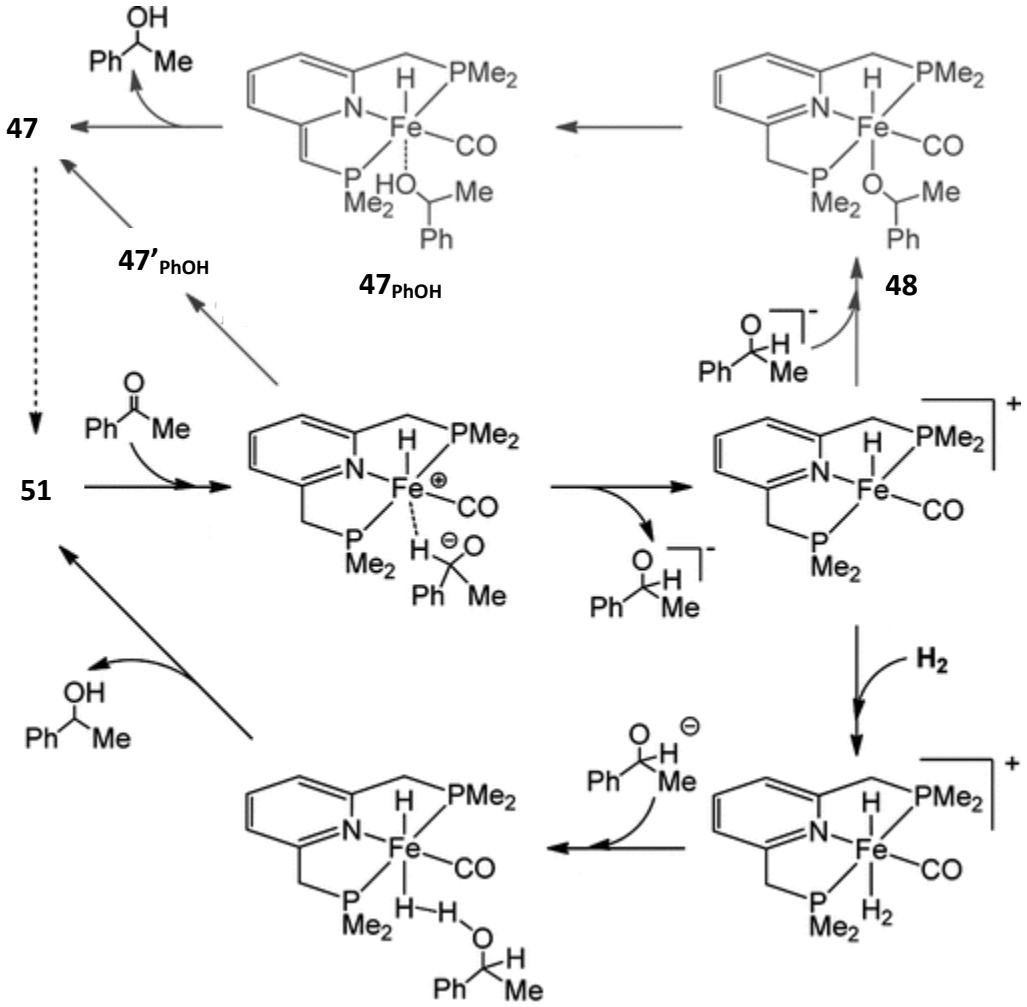
51

Figure 17 Species observed but not accounted for by Milstein and co-workers [43]

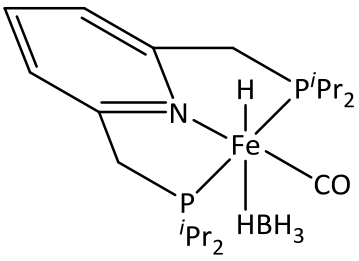


Scheme 12 Catalytic mechanism proposed for PNP complex **46** [43]

The lack of investigation into complex **51** was picked up on by Yang, [44] whom studied the role of EtOH in the mechanism further, and scrutinised the mechanism proposed by Milstein and co-workers (**Scheme 12**). What Yang found through DFT studies on a simplified version of **51** was a direct ketone reduction mechanism catalysed by complex **51** (**Scheme 13**). The team found that the solvent (EtOH) was not only needed to stabilise **47** but also to an "assistant catalyst" for the formation of stable catalytically active species **51**. They also found that increasing the H_2 pressure accelerated the reaction.



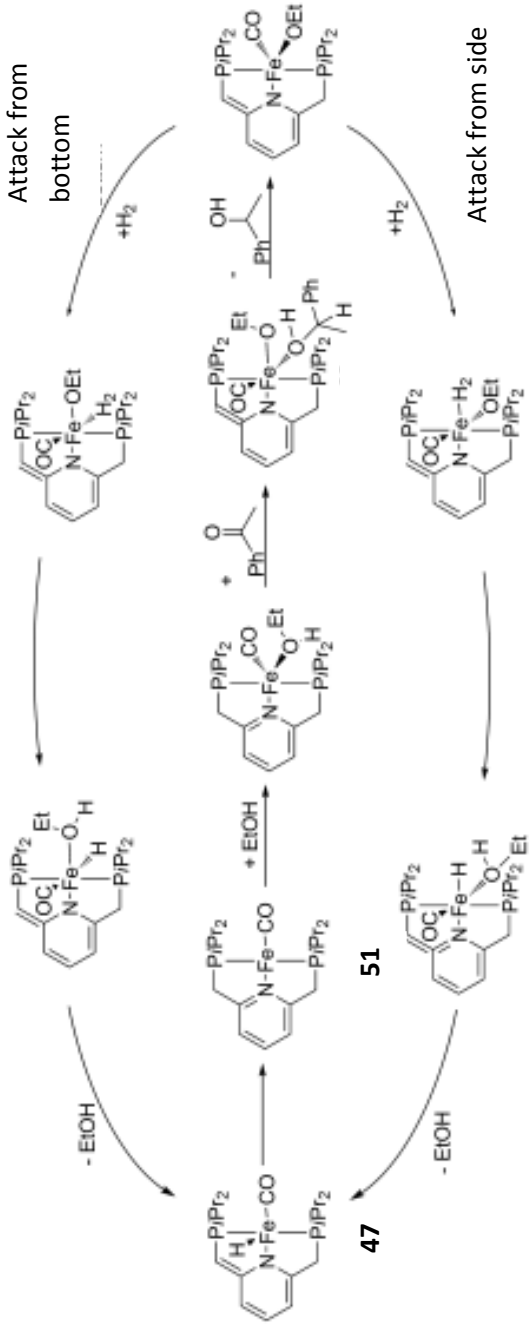
Scheme 13 Proposed "direct reduction mechanism for the hydrogenation of acetophenone catalysed by **51** [44]



52

Figure 18 Catalyst used by Langer and co-workers [45]

Soon after, Langer and co-workers [45] gave mechanistic insight into the catalytic activity of complex **52** (**Figure 18**) which is related **46** except for the Br group being replaced with a HBH_3 group. **52** reduced acetophenone to 1-phenylethanol with a conversion of 99% and TOF of 247 h^{-1} with a 5 mmol acetophenone, 0.0033 mmol **52**, 1 mmol *meta*-xylene and 3 mL ethanol in 4.1 atm H_2, 40 ^{O}C in 6 h – without the need for base. The team found the mechanism of acetophenone hydrogenation by **47** as shown in **Scheme 14**.

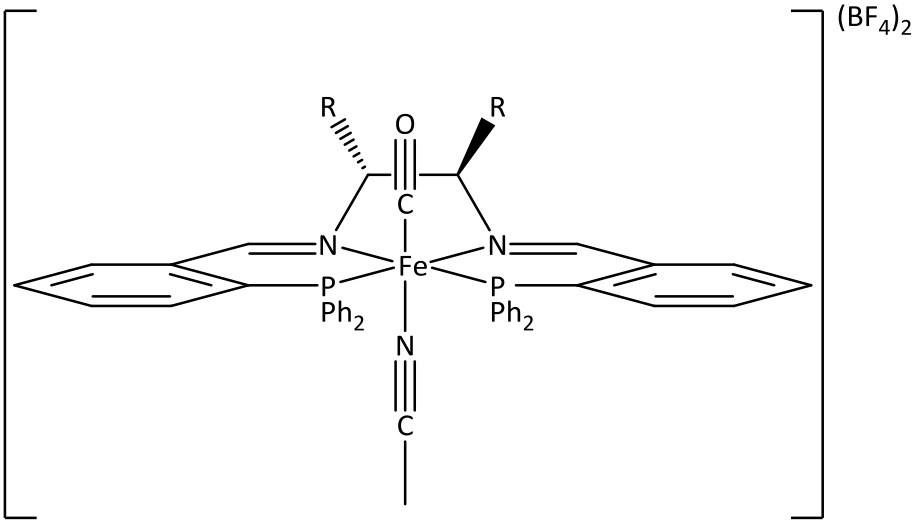


Scheme 14 Mechanism for acetophenone reduction without the use of base using catalyst **47** [45]

3 NANOPARTICLES

Transition metals used in catalysis as well characterised nanoparticles has been reported numerous times. Fe_3O_4 nanoparticles have been reported as a support for a rhodium catalyst in the ATH of aromatic ketones.[46] The magnetic property of these iron nanoparticles anchored to the rhodium catalyst makes for a recoverable catalyst – an industrially attractive aspect.

Recently, a mechanistic study of transfer hydrogenation with *trans*-[Fe(NCMe)CO($PPh_2C_6H_4CH$=NCHR-)$_2$][BF_4]$_2$ where R = H (compound **53**) or R = Ph (compound **54**)(**Figure 19**) was carried out by Sonnenberg and co-workers.[37]



53: R = H
54: R = Ph

Figure 19 Precatalysts investigated by Sonnenberg and co-workers [37]

The team hypothesised the active catalytic species was heterogeneous. To prove this, the team carried out a series of experiments. First, the reaction profiles for catalytic systems **53** and **54** both exhibited a sigmoidal curve. This indicated a 6-8 min induction period, a period of sudden catalytic activity, and a plateau region where the reaction reached equilibrium. This sigmoidal curve is usually suggestive of a heterogeneous catalytic system involving autocatalysis or colloid formation. Autocatalysis refers to when the reaction product itself (in this case, the product alcohol 1-phenylethanol) is involved in catalysis. Thus catalysis is slow at first until enough alcohol is formed. To disprove autocatalysis for this system, 1-phenylethanol was added to the catalyst and substrate (acetophenone) mixture. There was

no discernible difference in the resultant induction period and the same sigmoidal curve was obtained – thus disproving autocatalysis. Furthermore, the rate of catalysis decreased and equilibrium was reached sooner – owing to Le Châtelier's Principle.

To prove colloid formation, the induction period was further investigated. Precatalysts **53** and **54** were reacted with KO^{t}Bu in isopropanol prior to acetophenone addition. The induction period was subsequently absent. This indicated that an active species was formed by the reaction of **53** and **54** with KO^{t}Bu – hence the induction period was due to activation of the precatalyst, not substrate uptake. The team also found that allowing precatalyst activation to occur before the addition of substrate increased the *ee* from 64% to 70% - possibly due to the complete formation of "the ligand-coated nanoparticles" unhindered by surrounding substrate, which allowed for "a more optimised coating of the chiral ligand on the surface" of the nanoparticles.

The other experiments carried out were a series of poisoning experiments. Poisoning experiments involve the addition of a poisoning agent (such as mercury) to suppress the catalytic activity of bulk metal which would be in heterogeneous catalysis. [47] A good poisoning agent should not, however, suppress the homogenous catalytic activity of the metal. Suppression of heterogeneous catalytic activity is carried out by amalgamation or physisorption (or physical adsorption – where the electronic structure of the catalyst is unaffected upon adsorption with the poisoning agent). In this way, it can be deduced whether a catalyst is heterogeneous or homogeneous.

The most common poisoning agent is mercury. However, due to the unstable iron complex – mercury (0) amalgam – mercury (0) addition yielded no effect on the catalytic reaction. [48] Another poisoning agent, PMe_3 in toluene, proved a successful poisoning agent for the catalytic reaction with **53** and **54**. Small phosphines such as PMe_3 used as poisoning agents in substoichiometric amounts have been well reported to give strong evidence for nanoparticles formation during catalysis. [49] Sonnenberg and co-workers found that a minimum of 10% PMe_3 added *in operand* (as the reaction progresses) was needed to stop catalysis. Thus, this suggests that Fe nanoparticles are the active species in the catalytic reaction. Moreover, it suggests that 10% of the surface of each Fe nanoparticle is present as active sites for catalysis.

Finally, Scanning Transmission Electron Microscopy (STEM) showed that the nanoparticles had a diameter of approximately 4.5 nm, Superconducting Quantum

Interference Device (SQUID) gave evidence that the catalytic mixture consisted mainly of a superparamagnetic species and X-ray Photon Spectroscopy (XPS) confirmed the production of an Fe(0) species. The team concluded that this system was "a rare example of highly active asymmetric catalysis using zerovalent nanoparticles not based on precious metals."

4 CONCLUSION

CATALYST (Ligand type in parentheses)	TOF (h^{-1})	ENANTIOSELECTIVTY (% *ee*/(R/S)*)*	SCOPE	CONDITIONS (Substrate:Catalyst: Base loading = S:C:B)	REF
20 (PNNP)	30 000	84 *(R)*		28 ^{O}C, S:C:B = 1000:1:8, ^{i}PrOH solvent	[33]
22 (PNNP)	26 000	90 *(R)*		28 ^{O}C, S:C:B = 1000:1:8, ^{i}PrOH solvent	[33]
44 (PN(H)NP)	547 000*	86 *(R)*$^{\#}$		28 ^{O}C, S:C:B = 6000:1:8, KO^{t}Bu base	[38]
45 (PN(H)NP)	252 000*	92 *(R)*$^{\#}$		28 ^{O}C, S:C:B = 6000:1:8, KO^{t}Bu base	[38]
52 (PNP)	247	N/A		28 ^{O}C, S:C = 1500:1, no base required, 1 mmol *meta*-xylene, EtOH solvent, 4.1 atm H_2	[45]

Table 1 A summary of the most prominent iron catalysts developed to date. All data is based on acetophenone reduction to (*R/S*)-1-phenylethanol. * TOF at 50% conversion – however, full conversion was achieved in a matter of seconds. $^{\#}$ *ee* at 10 s.

In summary, the development in recent years into iron catalysis for ketone hydrogenation has expanded rapidly. In **Table 1**, the most promising iron catalysts have been listed – in particular complexes **44**, **45**, and **52**. **44** and **45** have the highest TOFs to date along with very attractive *ee* values (especially for **45**). The need for base means that **44** and **45** use a transfer hydrogenation mechanism. **52** has very impressive activity, the TOF is not as high as that for **44** and **45**, but the fact that no base is required is industrially attractive (although H_2 gas is needed) – thus **52** uses a direct hydrogenation mechanism.

In my opinion, compounds **44** and **45** could replace current ruthenium catalysts for the hydrogenation of prochiral ketones into chiral alcohols. PNP ligands have only recently emerged in iron catalysis for ketone hydrogenation. Therefore, even though **52** is not as impressive as **44** and **45**, it gives hope of another family of iron catalysts that can be used for ketone hydrogenation – especially with the aspect of no base used for the reaction.

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