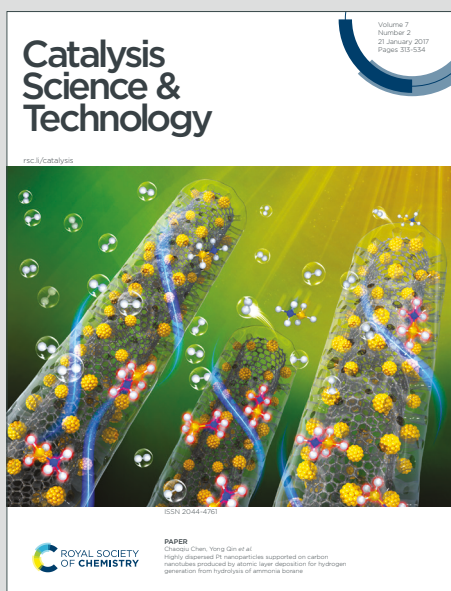


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ARTICLE

Towards practical earth abundant reduction catalysis: design of improved catalysts for manganese catalysed hydrogenation

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Manganese catalysts derived from tridentate *P,N,N* ligands can be activated easily using weak bases for both ketone and ester hydrogenations. Kinetic studies indicate the ketone hydrogenations are 0th order in acetophenone, positive order in hydrogen and 1st order in catalyst. This implies that the rate determining step of the reaction was the activation of hydrogen. New ligand systems with varying donor strength were studied and it was possible to make the hydrogen activation significantly more efficient; a catalyst displaying around a 3-fold increase in initial Turn-Over Frequencies for the hydrogenation of acetophenone relative to the parent system was discovered as a result of these kinetic investigations. Ester hydrogenations and ketone transfer hydrogenation (isopropanol as reductant) are first order for both the substrate and catalysts. Kinetic studies also gained insight into catalyst stability and identified a working range in which the catalysts is stable throughout the catalytic reaction (and a larger working range where high yields can still be achieved). The new more active catalyst, combining an electron-rich phosphine with an electron-rich pyridine is capable of hydrogenating acetophenone using as little as 0.01 mol% catalyst at 65 °C. In all, protocols for reduction of 21 ketones and 15 esters are described.

INTRODUCTION

Homogenous hydrogenation of ketones and esters is used in synthesis, and in the large-scale production of important chemicals. Alongside enzymatic routes, homogeneous hydrogenation catalysed by Ru, Ir and Rh are probably the core reactions used in the production of chiral alcohols in both the pharmaceutical, fine chemicals, and flavours and fragrance sector.¹ In the best cases, these are very efficient reactions indeed, but in some cases the amount of precious metal catalyst used can be a major contributor to cost of a product, and even lead to these atom-efficient routes becoming unviable. Despite the impressive performance of ruthenium and iridium ketone hydrogenation catalysts, there has been a very strong drive to replace these metals with earth abundant metal alternatives.² It is becoming clear there is untapped reactivity within earth abundant metal catalysts and hence many new opportunities to solve important problems of relevance to the chemical industry. Out of the earth abundant metal catalysts, manganese was almost ignored in hydrogenation catalysis until a seminal contribution from the Beller team demonstrated its promise.³ Since that paper there have been a number of articles published in the field of hydrogenation,⁴ and other reductive processes.^{4(h),5} Practical reasons that make manganese an especially good candidate

relate to it being one of the most abundant metals and hence the amounts of Mn needed for the catalysis industry should be sustainable more or less indefinitely. Since manganese is classified as a metal of limited concern in terms of toxicity, the limits for Mn in pharmaceuticals are 250 ppm relative to less than 10 ppm for all precious metal catalysts.⁶ This might mean less energetic purification of products to reach the required specification, or might mean reactions that tend to need higher catalyst loadings of precious metal may become economic for Mn, due to lower metal cost and lower purification cost. The use of manganese catalysts could lead to more sustainable hydrogenations. It is important to note that an earth abundant metal catalyst formed from bespoke ligands will still need to have significant activity (i.e. high TON) to be practical at larger scale. Advances that push earth abundant metal catalysts towards practicality are therefore urgently required, since it is only when these interesting approaches get used in commercial synthesis that the benefits regarding sustainability get properly realized. While Mn catalysed reductions are now being researched quite extensively, the majority of the papers make use of catalyst loadings in the range of 1-5 mol%. This is sometimes also accompanied by slightly less than ideal additives or solvents. In this article, we first describe the discovery of a chiral Mn catalyst for asymmetric ketone hydrogenation, development of more sustainable reaction conditions and synthetically useful ester hydrogenations. The use of kinetic studies was then used to develop a significantly more active second-generation catalyst that appears to be one of the most reactive of any earth abundant metal catalysts for the hydrogenation of ketones and esters.

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Electronic Supplementary Information (ESI) available: [Further tables and graphs of results, full data, NMR and HPLC spectra e]. See DOI: 10.1039/x0xx00000x

RESULTS AND DISCUSSION

As part of a programme studying a variety of metal catalysts derived from *P, N, N* ligands for hydrogenations,⁷ we became interested in Mn complexes of ferrocene derived *P, N, N* ligands.^{8,41} We recently communicated that manganese catalyst (*S_c, R_p*)-1 (Fig. 1) is a very promising hydrogenation catalyst. Selected previously communicated results are in Table 1 for comparative purposes.^{4(l),4(q)}

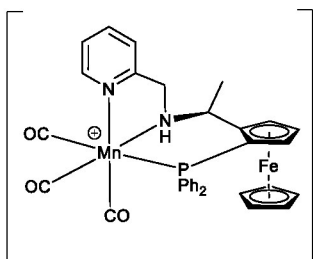


Fig. 1 Structure of manganese catalyst (*S_c, R_p*)-1

Using 1 mol% (*S_c, R_p*)-1 and 10 mol% KO^tBu we found that ketones could be successfully hydrogenated at moderate temperatures (50 °C) in ethanol. We found that both the substitution on the phenyl ring as well as the alkyl side of the ketone had an impact on the enantioselectivity. Acetophenone and 4'-chloroacetophenone were reduced with low enantioselectivity under the unoptimized conditions (Table 1. Entry 1 and 2, *er* 60:40 and 62:38). However, both isobutyrophenone (entry 3) and 2'-chloroacetophenone (entry 4) could be reduced with significantly higher enantioselectivity (*e.r.* 91:9 and 79:21 respectively). For more examples see reference 4(l). The impact of base on both conversion and enantioselectivity has been studied (Table 2 and Table S1). Although the conversion after 4 h was found to be dependent on the base used, the impact on the enantioselectivity was minor (Table 2 and Table S1). We could not see any major differences with regards to the counter-ion under these conditions. There are sporadic examples of using weak bases like carbonates, or more commonly the use of pre-activated metal hydrides catalysts.⁹ The latter requires an extra synthetic step, often using a large excess of hydride reagent, to make the active catalyst that then tends to be less stable. Being able to use a simple precursor and a simple cheap base is desirable, but Ru or Ir catalysts derived from most *P,N,N* ligands do not work well with bases weaker than alkoxides.^{7c,d} We were very surprised by the performance possible using potassium carbonate as base, especially in ester hydrogenation. Potassium carbonate is a cheap and green choice of base relative to a metal alkoxides, and since it is significantly less basic than hydroxide, less water sensitive.

Table 1. Ketone hydrogenation using Mn catalysts^a

Entry	ketone	R ¹	R ²	Conversion (%) ^(b)	<i>e.r.</i> ^(c)
1	2a	Ph	CH ₃	99 (80)	60:40 (<i>R</i>)
2	2c	4-Cl-Ph	CH ₃	99 (90)	62:38 (<i>R</i>)
3	2b	Ph	CH(CH ₃) ₂	99 (87)	91:9 (<i>R</i>)
4	2d	2-Cl-Ph	CH ₃	99 (85)	79:21 (<i>R</i>)

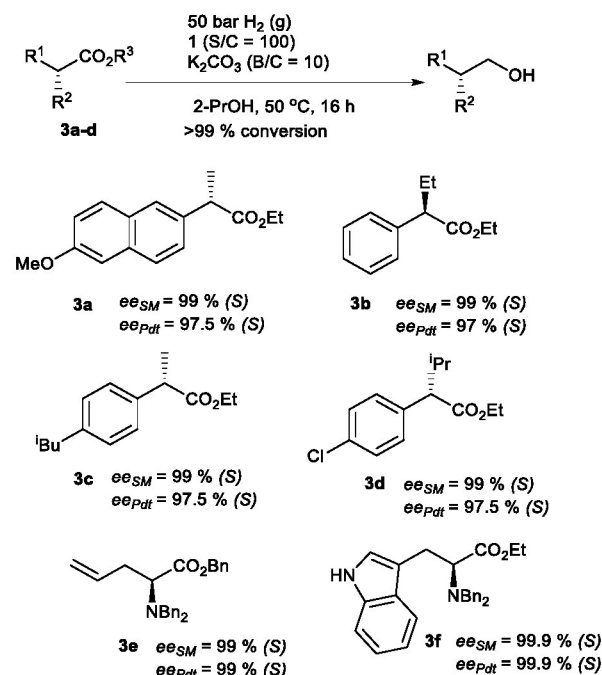
a. Typical reaction conditions: 0.34 mmol substrate, 0.003 mmol catalyst, 0.034 mmol base and internal standard (0.06 mmol) in 1.6 mL ethanol (0.2 M) under 50 bar of H₂ at 50 °C for 16 h; b. Conversion was estimated by ¹H-NMR using 1-methylnaphthalene as internal standard (8-10 μL). Isolated yield in brackets; c. *e.r.* was measured using chiral HPLC, known absolute configuration in brackets;

Table 2. Investigation of different bases on reactivity^a

Entry	Base	Time (h)	Conv. (%) ^b	<i>e.r.</i> ^c
1	KO ^t Bu	16	>99 (80)	75:25 (<i>R</i>)
2	-"	4	39 (ND)	81:19 (<i>R</i>)
3	K ₂ CO ₃	16	>99 (70)	85:15 (<i>R</i>)
4	-"	4	37 (ND)	81:19 (<i>R</i>)
5 ^e	-"	4	42 (ND)	81:19 (<i>R</i>)
6	NaO ^t Bu	4	43 (ND)	84:16 (<i>R</i>)
7 ^f	-"	4	51 (ND)	81:19 (<i>R</i>)
8	Na ₂ CO ₃	4	16 (ND)	84:16 (<i>R</i>)
9	DBU	4	12 (ND)	89:11 (<i>R</i>)
10 ^g	DBU	16	>99 (90)	80:20 (<i>R</i>)

a. Typical reaction conditions: 2.10 mmol substrate, 0.0021 mmol (*S_c, R_p*)-1, 0.21 mmol base and internal standard (0.21 mmol) in 3.0 mL ethanol (0.7 M) under 50 bar of H₂ at 50 °C for 4 or 16 h; b. Conversion was determined by ¹H-NMR using 1-methylnaphthalene as internal standard (8-10 μL). Isolated yield in brackets, ND = not determined; c. *e.r.* was measured using chiral HPLC, known absolute configuration in brackets; d. 1 mol% **1** and 10 mol% base used; e. 10 mol% 18-C-6 used as additive; f. 2 mol% base used; g. 0.2 mol% (*S_c, R_p*)-1.

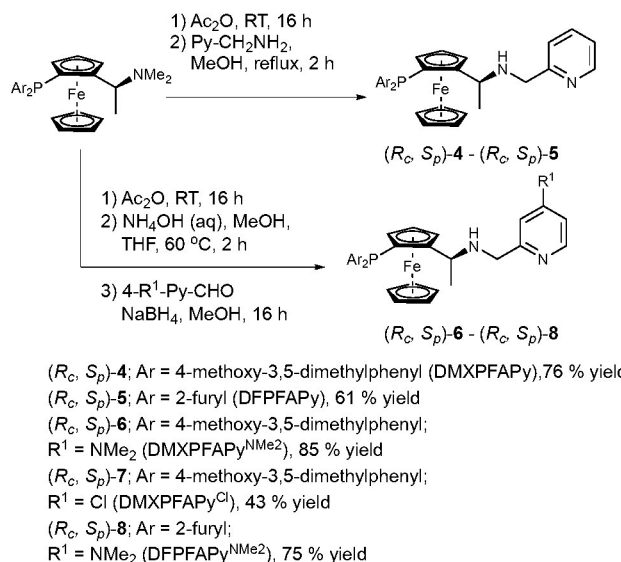
There are other synthetic consequences of using a weaker base. Turning to ester hydrogenation, some substrates are incompatible with strong bases. Scheme 1 illustrates selected examples using potassium carbonate as the base in the hydrogenation of chiral esters.^{4(a)} Reference 4 (q) show how, for example, (*S*)-Naproxen ethyl ester undergoes racemisation within a few minutes when exposed to the more common alkoxide bases,^{9(a)} but is stable to carbonate, and can be reduced clearly with very little racemization (Scheme 1).



a. Typical conditions: 1.00 mmol substrate, 0.010 mol **1**, 0.10 mmol K_2CO_3 , 50 bar hydrogen gas, ethanol or isopropanol (0.4 M), 50 °C, 16 h using 1-methylnaphthalene (0.35 mmol) as internal standard; b. 110 °C.

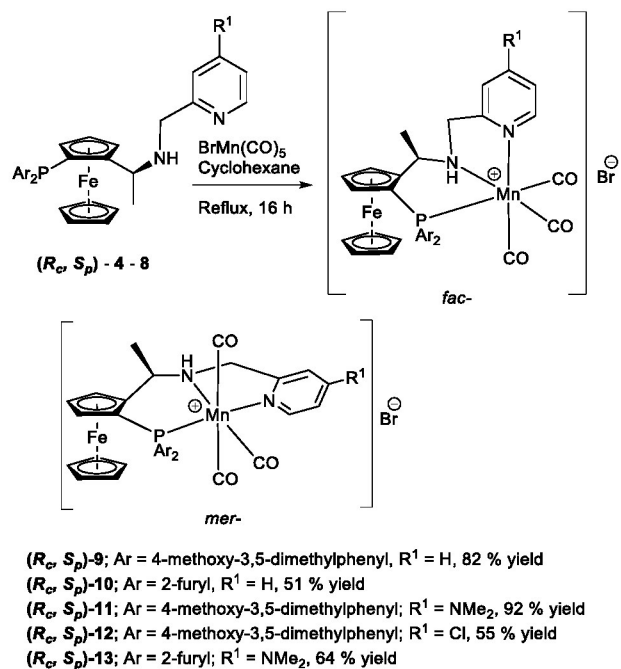
Scheme 1. Selected examples of hydrogenation of chiral esters using inorganic base and catalyst **1** (previously communicated work)⁹

Preliminary studies using the original catalyst indicated that the hydrogenation of ethyl *p*-fluorobenzoate was first order in substrate, while the ketone hydrogenations had a superior fit for a reaction that was zero order in substrate. This implies that a step that doesn't involve the ketone is rate-limiting, and hence most likely catalysis that is limited by slow activation of dihydrogen. As such, we felt it likely that the catalytic activity might be responsive to changes in the donor strength of the tridentate ligands. Ligands derived from both a more electron donating phosphine such as di(4-methoxy-3,5-dimethylphenyl)phosphine, from here-on DMXPFA (Di-(methoxyxylyl)phosphino derivative of PPFA, Scheme 2) or derived from a PPFA derivative containing the more electron-deficient di-(2-furyl)phosphine group (DFPFA, Scheme 2) allowed us to probe this hypothesis. To augment these electronic changes, a more electron donating and less electron donating pyridine unit was considered and we decided to investigate the impact of adding either a dimethylamino or a chloro group to the pyridine 4-position. The synthesis of the new ligands (**4-8**) followed already established protocols^{8(a), 8(e), 10} and are detailed below (Scheme 2). In short, the *N,N*-dimethyl phosphinoferrocenyl-1-ethylamine was reacted with acetic anhydride to form the acetate species with retention of stereochemistry.^{10(c)} This well studied substitution proceeds by assistance from the iron and is effectively a double inversion process. This species was then either displaced using 2-aminomethylpyridine (ligands **4-5**) or with ammonia to give the free amine again with retention.



Scheme 2. Synthesis of ligands **4-8** (overall yields starting from PPFA)

This free amine was then reductively alkylated with suitable 4-substituted pyridine-2-carboxaldehyde to give ligands **6-8**. The formed ligands were then reacted with $\text{BrMn}(\text{CO})_5$ in refluxing cyclohexane to give the manganese complexes as orange solids (Scheme 3).



Scheme 3. Synthesis of Mn complexes **9-13**

For ligand **7** both (R_C, S_P) and (S_C, R_P) enantiomers were prepared. Catalyst **1** is sparingly soluble in most solvents and a pleasing secondary outcome was enhanced solubility for the new catalysts. Analysis of the full range of Mn complexes by

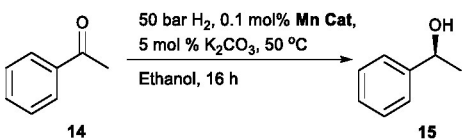
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NMR and IR spectroscopy enabled the geometry in alcohol solvents to be assigned with high confidence.

The reported crystal structure for (*S_c*, *R_p*)-**1** BAr^F was found to have a *fac*-coordination of the ligand around the Mn metal and showed a signal in the ³¹P-{¹H}-NMR at +45 ppm. This compound displays three bands in the carbonyl region of its IR spectrum (2036.8, 1961.6 and 1930.7 cm⁻¹).^{4(f)} The bromide complex (*S_c*, *R_p*)-**1** is sparingly soluble, making NMR analysis difficult, but in ethanol, the ³¹P-{¹H}-NMR also displays a peak at around +45 ppm. These are therefore assigned as the facial coordinated cationic complex. When (*S_c*, *R_p*)-**1** is isolated from a non-polar solvent, the IR spectrum in the solid state only displays 2 peaks at 1921 and 1842 cm⁻¹, and when analysed by ³¹P-{¹H}-NMR in acetone as solvent, the only peak present is a + 90 ppm. The number of IR bands is often not diagnostic due to weak or overlapping peaks, but the presence of two bands at these wavenumbers is similar to a complex with meridional geometry with only two carbon monoxide ligands and bromide coordinated, reported by Milstein and co-workers.^{4d} However, in contrast to reference 4d, MS analysis of (*S_c*, *R_p*)-**1** shows the presence of three carbon monoxide ligands. In the case of the more soluble complex **11**, (to be discussed further shortly) we found that you could switch between the δ_p= 45 ppm species and the δ_p= 90 ppm species by removing solvents and redissolving in the other solvent. This would not be expected to be possible if the difference between the species involves loss of a carbon monoxide ligand. It is worth noting that in alcoholic solvents, as used in catalysis, the species present is fully consistent with the cationic facially coordinating ligand, and for this reason all complexes are drawn this way. A consistent trend emerges when the other complexes are examined by NMR and IR spectroscopy. Complex **11** was the most soluble complex and easiest to handle and will be discussed comparatively to complex **1**, but similar observations were found for the other complexes. When **11** is isolated from a non-polar solvent, the solid state IR spectrum displays four carbonyl bands (2025.3, 1942.3, 1905.9 and 1830.5 cm⁻¹), while when dissolved in non-polar dichloromethane solvent, the ³¹P-{¹H}-NMR spectrum showed two peaks (89 ppm and 44 ppm) in an 8:1 ratio. This is therefore consistent with a composite of the two species discussed for complex **1**, and as one might expect, all the CO bands are at somewhat lower wavenumber, since the ligand is more electron donating. When **11** is dissolved in methanol, only the δ_p= 45 ppm species is visible. The behaviour is analogous to **1**, and also consistent with the pre-catalyst having a facially coordinating ligand, when dissolved in an alcoholic solvent as in every example of catalysis herein. The structure of the actual hydride species undertaking hydride transfer is unknown (as it is for almost all of the 100s of hydrogenation catalysts!), although we favour a facial arrangement, as will be discussed later.

Table 3. Initial ketone hydrogenation investigation^a

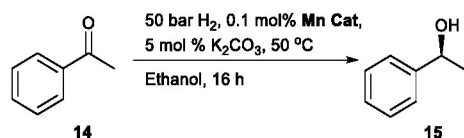


Entry	Cat	Conversion (%) ^b	<i>er</i> ^c
1	(<i>R_c</i> , <i>S_p</i>)- 9	>99 (ND)	81:19 (<i>S</i>)
2	(<i>R_c</i> , <i>S_p</i>)- 10	83 (ND)	84:16 (<i>S</i>)
3	(<i>R_c</i> , <i>S_p</i>)- 11	>99 (98)	84:16 (<i>S</i>)
4	(<i>R_c</i> , <i>S_p</i>)- 12	83 (ND)	83:17 (<i>S</i>)
5	(<i>R_c</i> , <i>S_p</i>)- 13	>99 (ND)	88:12 (<i>S</i>)

a. Experimental conditions: 3.1 mmol acetophenone, 0.0031 mmol catalyst, 0.15 mmol K₂CO₃, 50 bar H₂, 50 °C, 16 h, ethanol (0.62 M); b. determined by ¹H-NMR using internal standard, isolated yields in brackets; c. determined by chiral HPLC, known configuration in brackets.

Initial tests established how the new catalysts performed in hydrogenation using acetophenone (**14**) as the substrate. Table 3 shows the results. The reaction conditions used just 0.1 mol% catalyst, 5 mol% K₂CO₃ and a reaction time of 16 h under 50 °C and 50 bar H₂ in ethanol. The initial investigation showed that electron-poor phosphines had a detrimental impact on the catalytic activity. Interestingly, the data suggest that the impact on enantioselectivity is minimal regardless of substitution on the phosphine or the pyridine (4-position).

To further investigate the impact of ligand structure on the catalyst activity kinetic studies on the hydrogenation of acetophenone were carried out (Table 4 and Fig. 2). These were carried out at the less effective pressure of 20 bar (for technical reasons), with pressure kept constant and topped up with a gas burette, the rate of which was measured. The kinetic data shown in Table 4 show that, compared to **1**, Mn complexes with an electron-rich phosphine (**9**) increase the rate of conversion a little, but that an electron-poor phosphine (**10**) reduce the rate of conversion. The impact on the activity when the ligand has an electron-donating group in the 4-position of the pyridine, as well as the donating (dimethoxy-xylyl)phosphino group, (**11**) is significantly faster rates of reaction (around 3 times faster than **1**). A ligand with an electron-withdrawing group (**12**) in the 4-position of the pyridine, but an electron-rich (dimethoxy-xylyl)phosphino group gives catalysts with diminished rates relative to the parent catalyst with unsubstituted pyridine, **9**. Adding an electron-donating group in the pyridine 4-position, combined with the electron-poor difurylphosphino group, (**13**) not only showed an increase in rate of conversion compared to the other difurylphosphino containing ligand, **10**, but proved to be more active than the original catalyst **1**. This indicates that the electronics of the pyridine are more important to activity than the nature of the phosphine (Fig S1 and S2). The TOF highlighted the difference more clearly (Table 4 entries 1, 3 and 6).

Table 4. Effect of catalyst electronics on the hydrogenation of acetophenone^a

Entry	Cat	TOF (h ⁻¹) ^b	t _{1/2} (h) ^c	Conv. (2 h) (%) ^d
1	1	69	6.7	11.5
2	9	112	4.7	22.6
3	10	35	15.4	11.0
4	11	200	2.6	38.7
5	12	77	6.4	17.6
6	13	85	4.8	15.2
7 ^e	1	47	N/A	9.0
8 ^e	9	90	N/A	18.0
9 ^e	10	24	N/A	5.0
10 ^e	11	283	N/A	57.0
11 ^f	11	325	N/A	26.0

a. experimental conditions: *entries 1-6*: 20.81 mmol acetophenone, 0.021 mmol catalyst, 1.04 mmol K₂CO₃, 20 bar H₂, 50 °C, 16 h, ethanol (0.62 M), *entries 7-11*: 3.1 mmol acetophenone, 0.0031 mmol catalyst, 0.15 mmol K₂CO₃, 50 bar H₂, 50 °C, 2 h, ethanol (0.62 M); b. for entries 1-6: calculated at 25 % conversion, with entry 4 an average of 3 expts. (see ESI Table S2); for entries 7-10 calculated after 2 h reaction time; c. time at which 50 % conversion was achieved; d. Conversion after 2 h reaction time; e. reaction carried out in vials using 3.1 mmol acetophenone, 0.0031 mmol catalyst, 0.15 mmol K₂CO₃, 50 bar H₂, 50 °C EtOH (1.2 M), 2 h; f. Reaction run at 70 °C using 0.04 mol% **11**.

The use of an electron-rich phosphine together with an electron-donating group in the pyridine 4-position (e.g. **11**) showed around a 3-fold increase in rate compared to **1** (Table 4 and Fig. 2). The less-active, **1** was already demonstrated to be significantly more active than other ketone hydrogenation catalysts based on Mn.^{4(f), 5} Separate 'batch' experiments measuring conversion after 2 h (Table 4, entries 7-10 and Fig. S3) showed a similar trend as the gas-uptake measurements; electron-donating substituents increases reaction rate.

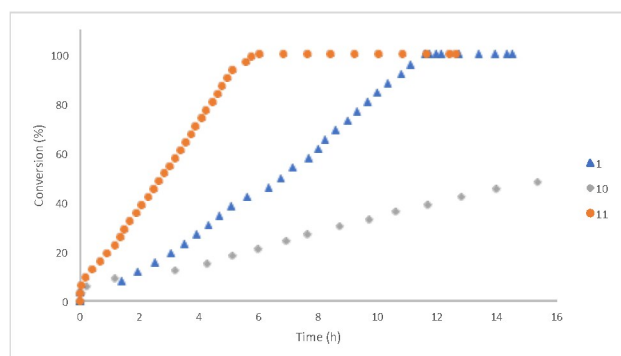


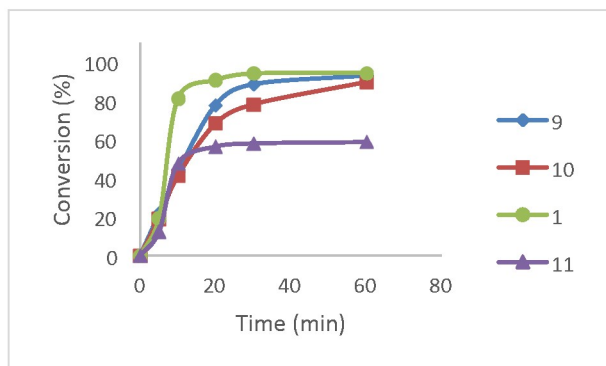
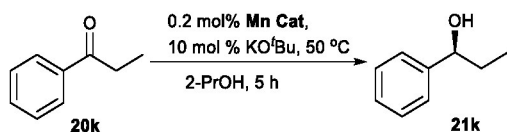
Fig. 2. Conversion over time for the hydrogenation of acetophenone at 20 bar H₂ using Mn complexes **10** and **11** compared with **1**. The data from catalyst **11** is an average of three runs (see ESI Table S2)

The electronics of both the pyridine and the phosphine has an impact on the catalytic activity of the Mn complex due to facilitating hydrogen activation. All reactions were zero order in ketone (as illustrated by essentially constant rates regardless of substrate concentration in Fig. 2). Hence hydrogen activation should be rate-determining in acetophenone hydrogenation. The order in catalyst was determined using Burés method to be 1 (Fig. S4).¹¹ The catalysts operate well at pressures around 10 bar and above (Fig. S5). The hydrogen is in excess, but further increases in hydrogen pressure lead to faster rates (i.e. the reactions have a positive order in hydrogen (presumably 1), although not measured as an excess reagent). Increasing concentration of base (Fig. S6) is beneficial up to a certain level then becomes less important presumably due to solubility.

Transfer hydrogenation

In order to confirm that this pronounced electronic effect on the rates of reaction was solely originating in improved hydrogen activation, the transfer hydrogenation of propiophenone was also studied using catalysts **1**, **9**, **10** and **11**. Initial individual batch experiments stopped just before reaching full conversion indeed suggests there are no longer huge differences in reactivity between the **1**, **9** and **10** catalysts in this reaction (Table S3). This is confirmed by the graphs of conversion versus time (Fig. 3) that are very similar and give consistent with a first order dependence in substrate concentration. We used KO^tBu as the activator / base with these experiments as K₂CO₃ was did not activate the catalyst under the reaction conditions (0.2 mol% catalyst, 5 mol% base, 50 °C, isopropanol).

The data show that there are only small differences in TOF and enantioselectivity between catalysts **1**, **9** and **10**. This indicated that the nature of the phosphines has more of an impact on hydrogenation of ketones than under transfer hydrogenation conditions, since the electronic effects impact on the hydrogen activation. Catalyst **11** was found to be quickly deactivated during the reaction and failed to go to > 60 % conversion after 5 h reaction time. In a separate experiment, a lower amount of KO^tBu was used, but this gave even poorer conversion (Fig. 3 entry 5). Using potassium hydroxide as the base showed minimal conversion after 2 h (Fig. 3 entry 6). Transfer hydrogenations using manganese catalyst have attracted significant interest recently.^{4(h), 5(k)-(m)} Catalyst **1** appears to have broadly similar activity, but our catalysts are more selective and productive in pressure hydrogenation. Further results for transfer hydrogenation are archived in Table S3.



Entry ^a	Cat	TOF (h ⁻¹) ^b	<i>er</i> ^c	Conv. (%) ^d
1	(<i>R_oS_p</i>)-1	1360	88:12 (S)	98
2	(<i>R_oS_p</i>)-9	1167	79:21 (S) ^e	96
3	(<i>R_oS_p</i>)-10	1024	83:17 (S)	93
4	(<i>R_oS_p</i>)-11	845	89:11 (S) ^f	59
5 ^g	(<i>R_oS_p</i>)-11	ND	ND	19
6 ^h	(<i>R_oS_p</i>)-11	ND	ND	7

a. Typical reaction conditions: 3.00 mmol substrate, 0.006 mmol catalyst, 0.15 mmol KO^tBu and internal standard (0.06 mmol) isopropanol (0.3 M) 50 °C for 5 h; b. Calculated from conversion after 20 min reaction time; c. *er* was measured using chiral HPLC, known absolute configuration of the major enantiomer in brackets; d. Conversion after 5 h reaction time; e. the *er* was determined to be 88:12 (S) under hydrogenation conditions; f. the *er* was determined to be 86:14 (S) under hydrogenation conditions; g. 2 mol% KO^tBu as base; h. 5 mol% KOH (s) as base.

Fig. 3. Conversion over time for the transfer hydrogenation of propiophenone using Mn complexes **1**, **9**, **10** and **11**

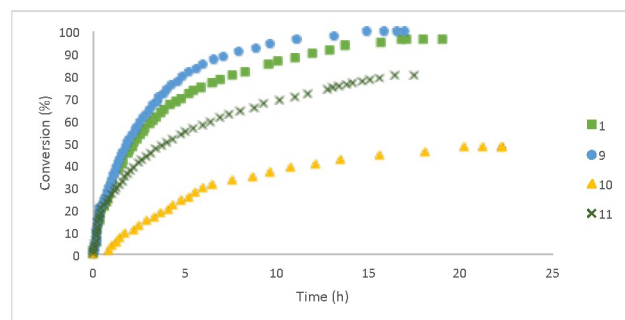
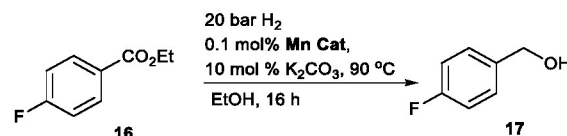
Ester hydrogenation

Since **1** is a good catalyst for the reduction of esters^{4(a)} we were curious as to the outcome of ester hydrogenation using catalysts **1** and **9-11** (Fig. 4 and 5).

Since ester hydrogenation was found to be first order in substrate using catalyst, **1** (Fig. 4 and 5) then it is also expected that smaller differences between the catalysts would be observed, since activation of dihydrogen was no longer rate determining. **1** and **9** are indeed similar but **10** or **11** did not reach complete conversion easily (Fig. 4). The kinetics of ethyl *para*-fluorobenzoate hydrogenation at 90 °C were complicated by catalyst **11** showing evidence of decomposition. The original curves of conversion versus time are reprocessed in the form of plots of TOF against [S] during the catalytic reaction (i.e. the beginning of the reaction [S] is around 0.5 M). Fig. 5, red line shows that the rate in this experiment drops off faster than would be predicted given the ester hydrogenation was first order in substrate, unlike the rate data for catalyst **1**.

Catalyst **1** shows quite good stability and a fairly linear relationship between TOF and [S]. Excess experiments reveal there is no product inhibition but some evidence of the

catalyst beginning to degrade after several hours, since the TOF measured at [S] = 0.15 M after 6.5 h is lower than after 1.7 h (Table 5 entry 2 and 3).



Experimental conditions: 20.81 mmol ethyl *p*-fluorobenzoate, 0.021 mmol catalyst, 2.08 mmol K₂CO₃, 20 bar H₂, 90 °C, 16 h, ethanol (0.62 M);

Fig. 4. Conversion over time for the hydrogenation of ethyl *p*-fluorobenzoate (**16**) using Mn complexes **1**, **9**, **10** and **11**.

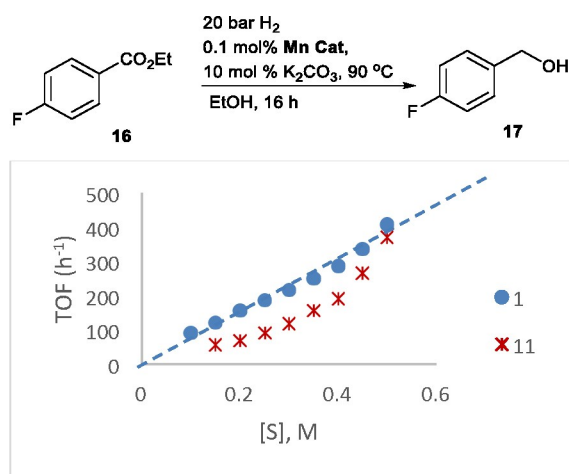
Table 5. Excess experiments using catalyst **1**^a

[S] ₀ ^b	Reaction Time (h) ^c	TOF at [S] = 0.15 M (h ⁻¹)
0.62 M	6.5	122
0.31 M	1.7	143
0.31 M ^d	1.8	139

a. Experimental conditions: 10.41-20.81 mmol ethyl *p*-fluorobenzoate, 0.021 mmol **1**, 2.08 mmol K₂CO₃, 20 bar H₂, 90 °C, 16 h, ethanol (0.3-0.6 M); b. starting concentration of substrate; c. time at which [S] = 0.15 M; d. 50/50 mixture of substrate and product

This decomposition / deactivation pathway is more pronounced for **11** as evident by TOF dropping off as reaction progressed (Fig. 5 red). The reaction of **11** was monitored using gas uptake at 70 and 90 °C (Fig. S7), and this clearly shows the decomposition and lowering of the rate with time at 90 °C as opposed to normal first order kinetics at 70 °C. The TOF_{20%} for **11** at 70 and 90 °C was found to be nearly the same (Table 6 entries 5 and 6).

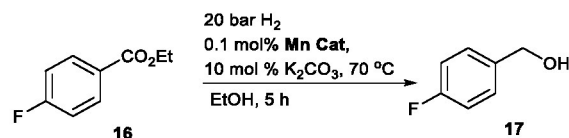
Table 6 show that experiments show that **11** was more active than the other catalysts followed by catalyst **9** at lower temperature. The TOF and the fact that the reaction using **11** as catalyst failed to go to full conversion at 90 °C but did so at 70 °C clearly showed that **11** was unstable at temperatures >75 °C. It may find some niche for ester hydrogenations that need lower temperatures, but preparative ester reductions can be carried out to good effect using 0.1 mol% catalyst loading at 90 °C using the more stable catalyst **9**. A few examples on ester hydrogenation promoted by the new catalyst can be found below (Scheme 4).



Experimental conditions: 20.81 mmol ethyl *p*-fluorobenzoate, 0.021 mmol catalyst, 2.08 mmol K_2CO_3 , 20 bar H_2 , 90 °C, 16 h, ethanol (0.62 M);

Fig. 5. TOF vs [S] for the hydrogenation of ethyl *p*-fluorobenzoate using catalyst **1** and **11** (data obtained from two experiments by calculating [S] based on conversion data).

Table 6. Comparing the activity of Mn catalysts in ester hydrogenation at 70 °C^a

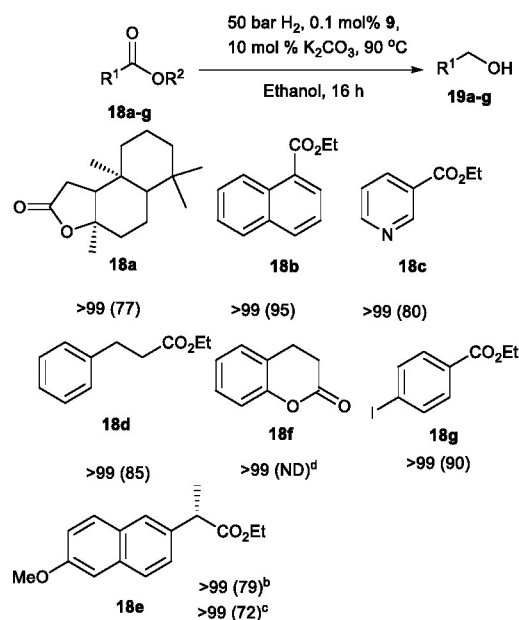


Entry	Catalyst	Conv. (%) ^b	Prod. (%) ^b	TOF (h ⁻¹) ^c
1	1	11.5	10.5	22
2	9	25	21	46
3	10	9.3	7.9	17
4	11	46.7	43.3	90
5 ^d	11	20	20	368 ^d
6 ^e	11	20	20	372 ^e
7 ^e	9	20	20	490

a. Experimental conditions: 1.78 mmol ethyl *p*-fluorobenzoate, 0.002 mmol catalyst, 0.18 mmol K_2CO_3 , 30 μ L internal standard (1-methylnaphthalene), 50 bar H_2 , 70 °C, 5 h, ethanol (0.6 M); b. determined by ¹H-NMR using internal standard; c. Calculated from conversion at 5 h reaction time using vessel with magnetic stirring; d. calculated from gas uptake data at 20 % conversion at 70 °C in mechanically-stirred vessel (>99% conversion after 17h); e. calculated from gas uptake data at 20 % conversion at 90 °C in mechanically-stirred vessel.

Sclareolide (**18a**) was readily reduced under the reaction conditions (0.1 mol% **9**, 10 mol% K_2CO_3 , 50 bar H_2 , 90 °C in ethanol). This is similar performance to the previously communicated experiment using catalyst **1** at 5 gram scale (archived in the ESI for completeness). Ethyl 1-naphthanoate (**18b**) was shown to be readily reduced. Ethyl nicotinate (**18c**) was also reduced at 90 °C to the alcohol with good conversion

and yield. Ethyl dihydrocinnamate (**18d**) was also readily hydrogenated at 90 °C. Using published conditions, (*S*)-ethyl naproxen (**18e**) was reduced using either 1.0 mol% or 0.5 mol% **9** with similar e.r. as reported using Mn complex **1**.^{4(a)} Finally, dihydrocoumarin (**18f**) was tested and found to be only converted in 76 % to product under the reaction conditions with the remaining substrate had been converted to the ethyl ester. The final substrate was ethyl *p*-iodobenzoate (**18g**) which was reduced to the *p*-iodobenzyl alcohol in excellent yields.



a. Typical reaction conditions: 1.40 mmol substrate, 0.0014 mmol **9**, 0.14 mmol K_2CO_3 and internal standard (0.06 mmol) in ethanol (0.5 M) under 50 bar of H_2 at 90 °C for 16 h; Conversion was estimated by ¹H-NMR using 1-methylnaphthalene as internal standard; Isolated yield in brackets, ND = not determined; b. reaction run with 1 mol% **9** in isopropanol, e.r. was determined by chiral HPLC to be 99.3:0.7 (S); c. reaction run with 0.5 mol% **9** in isopropanol, e.r. was determined by chiral HPLC to be 98:2 (S); d. 76 % product, the rest the ethyl ester.

Scheme 4. Ester hydrogenation using Mn complex **9**^a

Returning to ketone hydrogenation, the scope of the second-generation ketone hydrogenation catalyst **11** is summarized in Tables 7 and 8 with standard conditions of 0.1 mol% catalyst, 16 h reaction time and 50 °C reaction temperature for most examples. Using acetophenone as substrate we were able to reduce the catalyst loading to 0.02 and even 0.01 mol% albeit at higher temperature (60 and 65 °C, Table 7, entries 2-3). Substitution on the aromatic ring was investigated next and we found that *ortho* substituted ketones were reduced with lower enantioselectivity than either *meta* or *para* substituted ketones (Table 7, entries 4-8). Both bromine and iodide substituted acetophenone could be tolerated (Table 7 entries 9-10). 4'-cyanoacetophenone could be reduced to full conversion at 30 °C but with ~7 % by-product which was tentatively assigned as the ethyl ester (Table 7, entry 11). This chemoselectivity for C=O over nitrile reduction is interesting,

since some Mn catalysts are known to reduce nitriles well.^{3b} We note here also that attempts to hydrogenate imines were entirely unsuccessful using these catalysts. 2,6-dichloro-3-fluoroacetophenone (Table 7, entry 12) was readily reduced with an *er* of 91:9 (*S*). The product alcohol (**21i**) is a component in the synthesis of the pharmaceutical Critoizinib.¹² The 3,4,5-trimethoxyacetophenone (**20j**) Table 7, entry 13) was reduced to a product with *er* of 90:10 (*S*).

Table 7. Ketone hydrogenation using Mn complex **11**^a

Entry	R ¹	R ²	Conv. (%) ^b	<i>er</i> ^c	
1	Ph	CH ₃	14	>99 (98)	84:16 (<i>S</i>)
2 ^d	Ph	CH ₃	14	>99 (98)	80:20 (<i>S</i>)
3 ^e	Ph	CH ₃	14	>99 (98)	79:21 (<i>S</i>)
4	2-Cl-C ₆ H ₄	CH ₃	20a	>99 (83)	78:22 (<i>S</i>)
5	2-MeO-C ₆ H ₄	CH ₃	20b	>99 (91)	82:18 (<i>S</i>)
6 ^f	3-Cl-C ₆ H ₄	CH ₃	20c	>99 (85)	85:15 (<i>R</i>)
7	3-MeO-C ₆ H ₄	CH ₃	20d	>99 (99)	85:15 (<i>S</i>)
8	4-Cl-C ₆ H ₄	CH ₃	20e	>99 (99)	90:10 (<i>S</i>)
9	4-Br-C ₆ H ₄	CH ₃	20f	>99 (89)	89:11 (<i>S</i>)
10	4-I-C ₆ H ₄	CH ₃	20g	>99 (82)	90:10 (<i>S</i>)
11 ^g	4-CN-C ₆ H ₄	CH ₃	20h	>99 (90)	85:15 (<i>S</i>)
12	2, 6-Cl-3-F-C ₆ H ₂	CH ₃	20i	>99 (90)	91:9 (<i>S</i>)
13	3, 4, 5-MeO-C ₆ H ₂	CH ₃	20j	>99 (86)	90:10 (<i>S</i>)

Typical reaction conditions: 1.36 mmol substrate, 0.0014 mmol (*R_S*, *S_P*)-**11**, 0.068 mmol K₂CO₃ and internal standard (0.06 mmol), 50 bar H₂, ethanol (0.67 M), 50 °C, 16 h; b. conversion determined by ¹H-NMR using internal standard; c. *er* was measured using chiral HPLC, known absolute configuration of the major enantiomer in brackets; d. 0.02 mol% **11** at 60 °C for 24 h; e. 0.01 mol% **11** at 65 °C for 24 h; f. using (*S_O*, *R_P*)-**11**; g. reaction run at 30 °C.

The results from hydrogenation of ketones with R² substituents other than methyl are shown in Table 8. Propiophenone (**20k**) was reduced with an *er* of 86:14 (*S*), whilst both 4'-chloropropiophenone (**20l**) and 4'-methoxypropiophenone (**20m**) gave products with slightly higher *er* (93:7 and 91:9, Table 8, entries 1-3). The base sensitive *N,N*-dimethyl-3-aminopropiophenone (**20o**) a precursor to fluoxetine¹³ was readily reduced under the reaction conditions with an *er* of 86:14 (*S*) (Table 8, entry 6). *N,N*-dimethyl-3-amino-1-(4-chlorophenyl)propylpropylphenone (**20p**, Table 8, entry 7) gave a product with an *er* of 89:11. 1-(4-bromophenyl)-3-piperidin-1-ylpropylphenone (**20q**) was also reduced with good enantioselectivity and yield (Table 8, entry 8). The bulkier ketones isobutyrophenone, 2,2,2-trimethylacetophenone (**20r**) and cyclohexylphenyl ketone (**20s**) (Table 8, entries 4-5 and 9-11) gave alcohols with good *er* using either (*R_O*, *S_P*)-**9** or (*R_O*, *S_P*)-**11** with slightly higher *er* observed for (*R_O*, *S_P*)-**9**. The final entry 2-methyl-1-phenylpropylphenone (**20t**) gave an alcohol product (**21t**) with an *er* of 91:9. The enantioselectivity is biased towards (*R*) for (*S_O*, *R_P*)-**1** and (*S*) for (*R_O*, *S_P*)-**9-13**. There

is no discernible impact on the enantioselectivity from altering the aryl groups on the phosphine.

Table 8. Ketone hydrogenation using Mn complex **11**^a

Entry	R ¹	R ²	Conv. (%) ^b	<i>er</i> ^c	
1	Ph	CH ₂ CH ₃	20k	>99 (81)	86:14
2	4-Cl-C ₆ H ₄	CH ₂ CH ₃	20l	>99 (86)	93:7
3	4-MeO-C ₆ H ₄	CH ₂ CH ₃	20m	>99 (89)	91:9
4	Ph	CH(CH ₃) ₂	20n	>99 (96)	82:18
5 ^d	Ph	CH(CH ₃) ₂	20n	>99 (85)	93:7
6	Ph	CH ₂ CH ₂ N(CH ₃) ₂	20o	>99 (89)	86:14
7	4-Cl-C ₆ H ₄	CH ₂ CH ₂ N(CH ₃) ₂	20p	>99 (82)	89:11
8	4-Br-C ₆ H ₄	CH ₂ CH ₂ N(CH ₂) ₅	20q	>99 (84)	90:10
9	Ph	C(CH ₃) ₃	20r	>99 (97)	90:10
10 ^d	Ph	C(CH ₃) ₃	20r	>99 (85)	93:7
11	Ph	CH(CH ₂) ₅	20s	>99 (89)	91:9
12	Ph	C(CH ₃) ₂ Ph	20t	>99 (85)	91:9

Typical reaction conditions: 1.36 mmol substrate, 0.0014 mmol (*R_O*, *S_P*)-**11**, 0.068 mmol K₂CO₃ and internal standard (0.06 mmol), 50 bar H₂, ethanol (0.67 M), 50 °C, 16 h; b. conversion determined by ¹H-NMR using internal standard; c. *er* was measured using chiral HPLC; d. (*R_O*, *S_P*)-**9** used as catalyst.

We considered either a *fac*- or a *mer*- configuration of the ligand around the Mn hydride (Fig. 6). In the *fac*-coordination mode, if the aromatic moiety is aligned with the ligand pyridine in the (*S_O*, *R_P*)-**1** derived catalyst, the resulting alcohol will have the (*R*)-configuration. The alignment of the aromatic rings in a substrate with a heterocycle on a catalyst is quite widespread as an effective control element in asymmetric catalysis,¹⁴ although here substrates like acetophenone, that lack sterically different substituents give somewhat lower enantioselectivity. The model shows that a bulky substituent, R, on the aliphatic side of the ketone, would stick out unhindered (Fig. 6, left). In the case of the *mer*-coordination mode the aliphatic part of the ketone is expected to clash with the phenyl groups on the phosphine. Since the substitution of the arylphosphine in the ligands also does not impact the enantioselectivity, the meridional structure seems unlikely, and we believe the *fac*-coordinated Mn hydride is more likely the correct form. Several attempts to detect or isolate this Mn-hydride were unsuccessful.

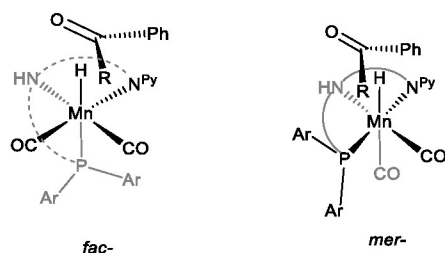


Fig. 6. Hypothetical *fac*- and *mer*- structures of the (*S*, *R_p*)-1-H with an aromatic ketone overlaid.

Conclusions

In conclusion, we have synthesised new *P,N,N* ligands and successfully coordinated these to manganese, and deliver active hydrogenation catalysts. Kinetic studies indicate that for ketone hydrogenation the reaction was zero order in acetophenone, but first order with regards to the catalyst. In ester hydrogenation we found that the substrate and the catalyst was first order. Electronic effects on the rates of reaction have been studied and found to be profound. The introduction of an electron rich phosphine combined with an electron rich pyridine gave a very active Mn catalyst capable of hydrogenating acetophenone with as little as 0.01 mol% catalyst load. This is competitive with any other earth abundant metal catalyst, to our knowledge. The lowest catalyst loadings for a Fe system for pressure hydrogenation seem to be 0.05 mol%,²¹ while Fe-based ester hydrogenation catalyst use 1 mol% of catalyst or higher.²⁵ After this work was completed, another Mn system has been reported to operate readily at 1 mol% of loading, but with an example at 0.01 mol% using alkoxide base as a promoter.⁴⁵ The exact mechanism for reduction using a variety of Mn systems would benefit from further elucidation in the future; it seems essential that a CO ligand leaves the Mn to be replaced with an Mn-hydride. It seems reasonable that dihydrogen could bind to the Mn complex, which maybe more Lewis acidic than analogous Ru or Ir complexes. As a result of this deprotonation of this dihydrogen can be readily accomplished with just a weak base. While this becomes possible for this Mn catalyst (rather than impossible with Ru), the kinetic studies show this step is more energetic than the reduction step for acetophenone reduction, since the reactions are zero order in this substrate. Catalyst stability has also been studied to clarify the temperature range that the catalysts should be used at. Quantifying catalyst stability by studying TOF versus [S] at different temperatures is perhaps underused as a means to ensure a catalyst behaves predictably.

A wide variety of functional groups within ketone and ester substrates can be tolerated using the new catalyst and the mild and economic reaction conditions (ethanol solvent, K₂CO₃ base). As higher enantioselectivity is often desirable for many applications, it is envisaged structural modification of Mn/*P,N,N* systems is likely to lead to improved enantioselectivity. Hopefully this can be done in a way that retains the key lessons from this work to ensure reactivity and stability. For

the well-established substrates, the catalyst loadings used are not competitive with the most productive examples using precious metal catalysts. However, the possibility of a lower catalyst cost per gram, lower purification cost, alongside the use of economic additives and functional group tolerance does at least open the possibility that Mn catalysts might be assessed for large scale usage, or only need further research that is readily within reach to reach that level.

Conflicts of interest

There are no conflicts to declare

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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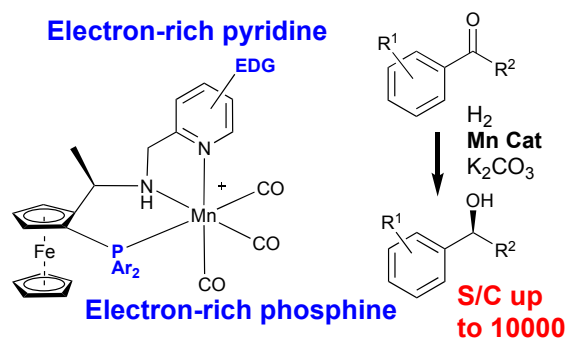
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Towards practical earth abundant reduction catalysis: design of improved catalysts for manganese catalysed hydrogenation

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Rational design using kinetic studies has led to a 3-fold-increase in the reaction-rates using an already-promising lead catalyst for the reduction of ketones and esters.