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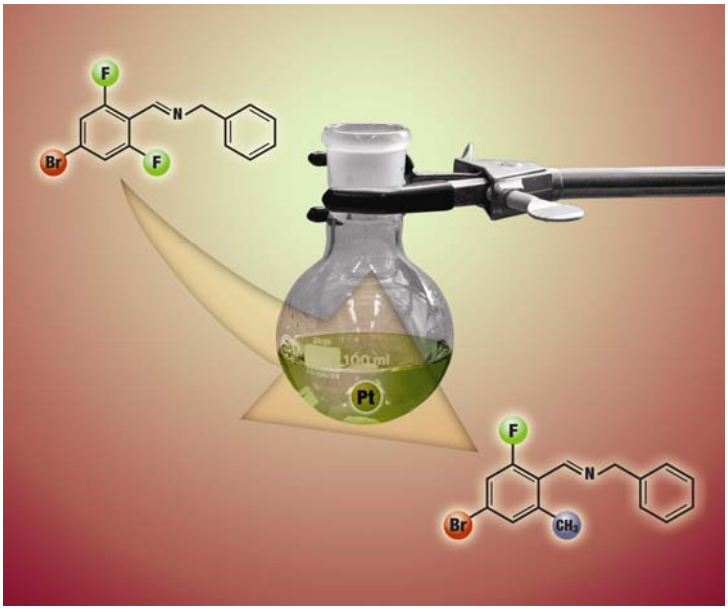

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The unexpected role of pyridine-2-carboxylic acid in manganese based oxidation catalysis with pyridin-2-yl based ligands†‡

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A number of manganese-based catalysts employing ligands whose structures incorporate pyridyl groups have been reported previously to achieve both high turnover numbers and selectivity in the oxidation of alkenes and alcohols, using H_2O_2 as terminal oxidant. Here we report our recent finding that these ligands decompose *in situ* to pyridine-2-carboxylic acid and its derivatives, in the presence of a manganese source, H_2O_2 and a base. Importantly, the decomposition occurs prior to the onset of catalysed oxidation of organic substrates. It is found that the pyridine-2-carboxylic acid formed, together with a manganese source, provides for the observed catalytic activity. The degradation of this series of pyridyl ligands to pyridine-2-carboxylic acid under reaction conditions is demonstrated by ^{1}H NMR spectroscopy. In all cases the activity and selectivity of the manganese/pyridyl containing ligand systems are identical to that observed with the corresponding number of equivalents of pyridine-2-carboxylic acid; except that, when pyridine-2-carboxylic acid is used directly, a lag phase is not observed and the efficiency in terms of the number of equivalents of H_2O_2 required decreases from 6–8 equiv. with the pyridin-2-yl based ligands to 1–1.5 equiv. with pyridine-2-carboxylic acid.

Introduction

The design of new ligands for 1st row transition metal oxidation catalysts has been driven by the desire to reduce the reliance on stoichiometric oxidants (*e.g.*, MnO_4^-, OsO_4, peracids *etc.*),[1] and to replace 2nd and 3rd row transition metal based oxidation catalysts.[2,3] A key challenge this presents is to achieve high activity while at the same time avoiding oxidative degradation of ligands during catalysis. Indeed ligand stability has been a longstanding issue in transition metal oxidation catalysis, as exemplified by the design rules proposed by Collins as early as 1994.[4,5]

The focus on ligand stability is important since, although ligand free oxidation catalysis can be achieved with manganese as demonstrated by Burgess and co-workers,[6] in order to control reactivity and especially (*enantio*) selectivity then it is almost certainly unavoidable that ligand metal complexes are employed. Over the last decades many ligand systems have been developed that have proven their effectiveness with iron and manganese during oxidation catalysis, including the pyridyl based ligand families (*e.g.*, TPEN,[20] BPMEN,[7] TPA[8] and N4Py,[9] Fig. 1) and the paradigm tmtacn ligand (where tmtacn is *N*,*N*′,*N*″-trimethyl-1,4,7-triazacylononane, Fig. 1),[10] which has proven one of the more effective ligands for manganese based oxidation catalysis.[11] The stability of these systems have allowed for stereospecific C–H activation,[12] (enantioselective) epoxidation[13,14] and (enantioselective) *cis*-dihydroxylation of alkenes,[15–18] often with high turnover numbers and efficiency in terminal oxidants, *e.g.*, peracetic acid and H_2O_2.

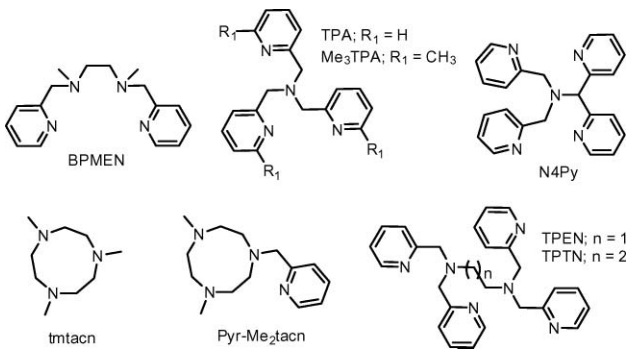

Fig. 1 Examples of pyridyl and triazacyclononane based ligands employed in Fe and Mn based oxidation catalysis.

Nevertheless, many ligand systems that have been employed in oxidation catalysis to date have been limited due to their propensity to undergo oxidative degradation, as demonstrated for instance by Banse, Girerd and coworkers[19] for the TPEN[20] class of ligands (Fig. 1). Oxidative ligand degradation can be inhibited, as shown by Banse and coworkers recently,[21] through introduction of steric hindrance in the TPEN ligand. Degradation *via* C–H abstraction was reduced, an effect ascribed to inhibition of bimolecular degradation pathways. Britovsek and coworkers[22] have reported also that catalytic activity and catalyst stability (with respect to ligand dissociation) correlate in the non-heme iron catalyst family.

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[b]*Rahu Catalytics BV, BioPartner Center Leiden, Wassenaarseweg 72, 2333, AL Leiden, The Netherlands*
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† Based on the presentation given at Dalton Discussion No. 12, 13–15th September 2010, Durham University, UK.

‡ Electronic supplementary information (ESI) available: Full synthesis and characterisation of ligand, details for catalysis experiments and ligand decomposition studies. CCDC reference number 768839. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0dt00452a

This may account for the stability observed in multidentate ligands where ligand dissociation is of limited importance (*vide supra*).

These observations are important as the primary tools available to tuning the catalytic activity and selectivity of transition metal complexes is to change reactions conditions, in particular solvent, co-catalysts and pH, and to vary the detailed structure of the ligands—both of which can affect coordinative stability and ligand robustness in addition to catalyst performance.

This aspect is exemplified for instance by the oxidation catalyst $[Mn^{IV}_2O_3(tmtacn)_2]^{2+}$. De Vos,[11b,11d] Berkessel,[11e] Lindsay Smith,[23] Feringa[15,17,18] and co-workers have demonstrated that varying the solvent and co-catalyst employed has a profound effect on its activity. For example tuning selectivity from selective epoxidation to selective *cis*-dihydroxylation of alkenes.[17] It has been demonstrated by Feringa and co-workers that the complex reacts with the carboxylic acid co-catalysts *in situ*, to complexes of the type $[Mn^{III}_2O(RCO_2)_2(tmtacn)_2]^{2+}$ that are responsible for the activity achieved.[17,18] An alternative strategy taken recently by Costas and co-workers is to tune reactivity by modifying the tmtacn ligand with an additional pyridyl group (Pyr-Me_2tacn, Fig. 1).[24] The catalysts formed by this complex with manganese[24] and iron[25] show markedly different reactivity and selectivity under acidic conditions compared with $[Mn^{IV}_2O_3(tmtacn)_2]^{2+}$. In both approaches the ligand itself has proven to be robust with catalyst deactivation proceeding by ligand dissociation rather than ligand oxidation.

In general, most research effort has focused on this latter approach, *i.e.* ligand modification, with attention being directed especially towards the design of novel ligands based on pyridyl metal binding moieties.[26]

Over a decade ago, we took such an approach by developing a family of manganese complexes, with TPEN/TPTN type of ligands (Fig. 1).[27,28] Manganese complexes based on these pyridyl ligands were indeed found to display high oxidation activity, both in the epoxidation of alkenes[27] and towards alcohol oxidation.[28]

An attractive feature of this type of ligands is that the synthetic route allows for facile introduction of different groups both on the central diamine unit or in replacing one or more of the pyridyl rings.[29] Although similar levels of activity could be achieved compared with the tmtacn family of complexes, the manganese catalysts based on these pyridyl containing ligands[27] typically require excess of oxidant (8–16 equiv. of H_2O_2) to overcome the extensive catalase activity that follows addition of the H_2O_2 at the start of the reaction.

An interesting question arises as to whether the intermediate compounds **2** and **3** in the synthetic route to the TPEN type ligands—*i.e.* intermediates containing an aminal ring motif (Fig. 2)— are also potential ligands in their own right.

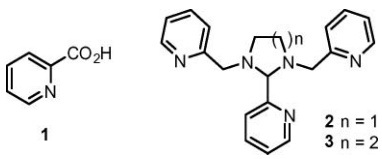


Fig. 2 Pyridine-2-carboxylic acid (**1**) and aminal ligands **2** and **3**.

In the present contribution we describe the catalytic activity observed with these aminal and other ligands with manganese in the oxidation of alkenes. With these ligands and a series of related ligands (**4–7**, **13–16**, Fig. 3) we obtain essentially identical reactivity and selectivity as that observed for the TPEN based ligands reported previously.

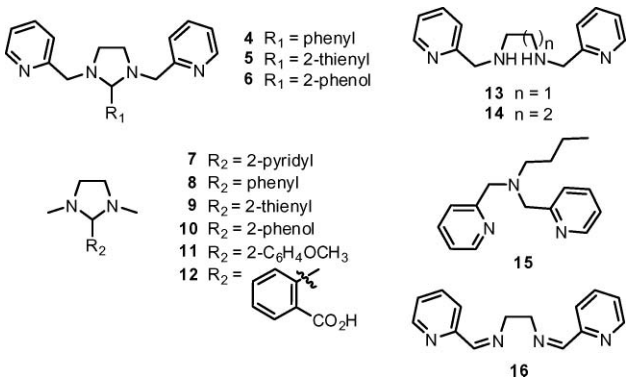
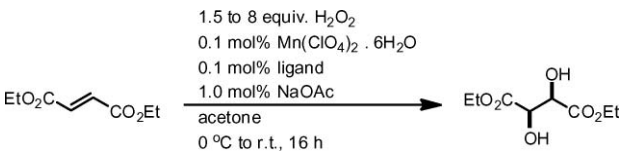


Fig. 3 Ligands employed in the present study.

The key finding we report is that in all cases these ligands (**2–7**, **13–16**) are highly unstable under the catalytic conditions employed and undergo rapid decomposition, ultimately, to pyridine-2-carboxylic acid. We show that the catalytic activity observed for a wide range of pyridyl based ligands (**2–7**, **13–16**) under certain conditions is as a direct result of the pyridine-2-carboxylic acid formed *in situ*. Unexpectedly, instead of leading to reduced activity, oxidative ligand degradation allowed for the discovery of a remarkably simple yet powerful four component catalytic system for a wide range of oxidative transformations (*i.e.* pyridine-2-carboxylic acid/Mn^{II}/NaOAc/carbonyl compound, Scheme 1).[29]



Scheme 1 Alkene oxidation with H_2O_2. For the electron deficient alkene diethyl fumarate full selectivity in favour of *cis*-dihydroxylation is observed with ligands TPTN, **2–7** and pyridine-2-carboxylic acid (for which 0.3 mol% and only 1.5 equiv. of H_2O_2 was required for full conversion, *vide infra*).

Results

Ligands **2–16** (Fig. 2 and 3) were prepared by standard methods based on the procedure described by Mialane *et al.*[30] and characterised by NMR spectroscopy, elemental analysis and HRMS (see ESI‡). TPTN (Fig. 1.) was described earlier.[28]

Catalytic activity of Mn^{II} with TPTN, 2 and 3

Previously we reported the activity of dinuclear Mn^{II} acetato complexes of the TPTN ligand in the oxidation of alkenes[27] and benzyl alcohols.[28] In the present study we have re-examined this ligand together with the immediate synthetic precursors of TPEN and TPTN, *i.e.* **2** and **3**, respectively.

A typical example of the conditions used in the manganese catalyzed oxidation reactions is shown in Scheme 1. The reaction was found to proceed with conversion in acetone and butanone

but not in acetonitrile or ^{t}BuOH/H_2O with TPTN, **2** and **3**. Furthermore, the addition of several equivalents of base, either with the manganese source (*e.g.*, $Mn^{II}(OAc)_2$, or $Mn^{III}(OAc)_3$) or as NaOAc, NaOH or Na_2CO_3 (when $Mn^{II}(ClO_4)_2$ is used) was found to be essential. With other carboxylates such as sodium trichloroacetate or benzoate the rate of reaction was substantially decreased but full conversion was nevertheless achieved.

As noted earlier,[27,28] the addition of at least 8 equiv. of H_2O_2 is required in order to obtain reasonable conversion of the alkene substrates, due to the extensive disproportionation that is observed initially upon addition of H_2O_2. The time dependence of product formation/substrate consumption indicates a substantial lag-time (~20–60 min) prior to the start of substrate conversion. The addition of acid, *e.g.*, acetic acid or trichloroacetic acid suppressed catalase type activity completely, however in these cases conversion of the substrate or even consumption of the H_2O_2 was not observed. For diethyl fumarate full conversion to the *cis*-diol product (*d*/*l*-diethyl tartrate) and for *cis*-cyclooctene full conversion to a 1 : 6 mixture of *cis*-diol and epoxide product was observed for TPTN, **2** and **3**.

The identical reactivity and selectivity observed for TPTN and ligands **2** and **3** was unexpected (*vide infra*). The observation of a significant induction period during which extensive disproportionation of H_2O_2 was observed prior to onset of substrate conversion indicated that the formation of the active catalyst system was slow. Mass spectral analysis of samples from the reaction mixture using TPTN over the course of the catalyzed oxidation of alkenes with H_2O_2, Mn^{II} and TPTN, indicated that TPTN undergoes conversion to ligand **3** in this period.[31]

Stability of ligands 2 and 3 in the presence of iron salts and under acid and basic conditions

The stability of TPEN and TPTN in the presence of iron and manganese salts under non-oxidative conditions is evidenced by the ability to prepare iron and manganese complexes from these ligands (*vide supra*).[19,20,27,28] However, for the ligands containing an aminal motif, the stability is expected to be less. The stability of ligand **2** was determined by ^{1}H NMR spectroscopy under both acidic and basic conditions in acetone and in the absence and presence of H_2O_2.

In the presence of excess trichloroacetic acid (4 equiv.) in acetone ligand **2** was found to convert to a mixture of species within 2 h both in the absence and presence of H_2O_2 (see ESI, Section 4a‡). After 24 h, however, where only trichloroacetic acid was added, the ^{1}H NMR spectrum recovered to show only absorptions due to ligand **2**. In the presence of H_2O_2 and trichloroacetic acid the absorptions of **2** reappeared partially after 24 h (see ESI, Section 4b‡). This recovery of the original spectra with time is indicative of partial hydrolysis under strongly acidic conditions, which reverses as moisture from the air reduces the acidity of the solution.

In the presence of NaOH (4 equiv.) and/or H_2O_2 (8 equiv.) ligand **2** was found to be stable with no change in the ^{1}H NMR spectrum over 24 h (see ESI, Section 4c/d‡). This indicates that under the conditions relevant to the catalysed reactions, *i.e.* in acetone/H_2O with a base and H_2O_2, the aminal based ligands are in fact stable to ring opening in the absence of metal ions.

An indication of the intrinsic instability of the aminal ligands in the presence of metal ions was obtained during attempts to isolate the corresponding Fe^{II} complexes. Reaction of ligand **2** or **3** with one equivalent of $Fe^{II}(ClO_4)_2$ in methanol/acetontrile lead over 30 min to 1 h to the appearance of an intense purple coloration. Slow evaporation of solvent provided crystals of a complex obtained from **3** suitable for single crystal structure determination (see the experimental section, Fig. 4). From X-ray crystallographic analysis together with elemental analysis it is apparent that the central aminal ring of ligand **3** is opened to release pyridin-2-carboxaldehyde (as a methoxy-hemiacetal) followed by coordination of the ligand fragments to Fe^{II}. Attempts to isolate Mn^{II} complexes of ligands **2** and **3** were unsuccessful to date, however it should be noted that similar ligands have been employed previously[32] with Mn^{II} ions and in these cases the aminal ring was found to be stable.

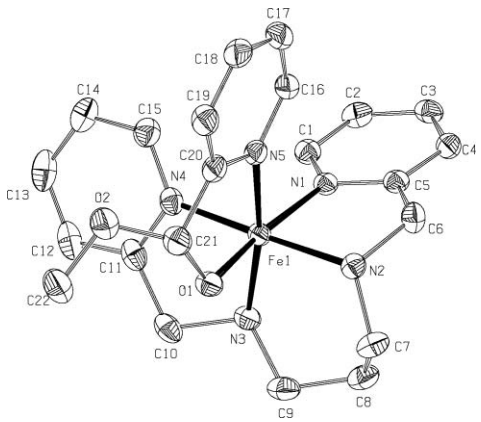


Fig. 4 Ortep representation of the iron complex isolated from the reaction of $Fe^{II}(ClO_4)_2$ with ligand **3** in acetonitrile–methanol. Counter ions and solvent of crystallisation are omitted for clarity.

The stability of TPEN and TPTN with iron[33] contrasts markedly with the instability of their aminal precursors (*e.g.*, **2** and **3**). This makes the observation of essentially identical reactivity and selectivity with Mn/H_2O_2 all the more remarkable. A structure activity study was therefore carried out to identify the key ligand components required to achieve full activity.

Catalytic activity of Mn^{II}/ligand in relation to ligand structure

The dependence of the observed reactivity and the structure of the aminal ligand was investigated using a series of ligands shown in Fig. 3. In this series of ligands the pyridyl groups were systematically removed from the aminal ring and replaced with other aromatic rings or else methyl groups. Furthermore the non-cyclic ligands **13–16** (Fig. 3) were examined including ligands containing the 6-methyl-pyridyl motif.

The catalytic activity of the series of aminal based ligands **2–12** in the oxidation of *cis*-cyclooctene was examined. Full conversion with ligands **2–7**, all of which contained at least one pyridin-2-yl moiety, was observed with the *cis*-diol:epoxide ratio being identical in all cases. By contrast ligands **8–12**, which do not contain a pyridine-2-yl unit, showed no activity in the oxidation of *cis*-cyclooctene.

The relative selectivity observed for four substrates with ligands **2–8** was examined (Table 1). The substrates chosen were diethyl fumarate and *n*-butylacrylate, which are converted to the (*cis*-)diol product exclusively, styrene, which shows an approximately equal

Table 1 Conversions and product distributions using ligands **2**, **4**, **7** and **8**

Substrate	Ligand	Conversion[a]	Product distribution[b]
EtO_2C CO_2Et	**2**	100%	
	4	100%	*cis*-diol product only
	7	100%	(*d*/*l*-diethyl tartrate)
	8	0%	
$CO_2(n\text{-Bu})$	**2**	82%	
	4	80%	diol product only
	7	75%	
	8	0%	
	2	25%	
	4	20%	epoxide : diol 1 : 2
	7	22%	
	8	0%	
	2	100%	
	4	100%	epoxide : diol 6 : 1
	7	95%	
	8	0%	
			yield of epoxide
	2		79%[c]
	13		48%[c]
	15	100%	79%[c]
	16		80%[c]
	TPTN		58%[c]

[a] Reaction conditions: at 0 °C, substrate (1 M), $Mn(ClO_4)_2 \cdot 6H_2O$ (0.1 mM), ligand (0.1 mM), NaOAc (1.0 mM) in acetone with 8 equiv. of H_2O_2. Conversion of substrate was determined by *in situ* Raman spectroscopy by monitoring the decrease of the alkene stretching band at *ca.* 1620 cm^{-1} with 1,2-dichlorobenzene as internal standard and confirmed by ^1H NMR spectroscopy, [b] Product yield was determined by ^1H NMR spectroscopy. [c] Reaction conditions: at 0 °C, *cis*-cyclooctene (1 M), $Mn(OAc)_3 \cdot 2H_2O$ (0.1 mM), ligand (0.1 mM) in acetone with 9.6 equiv. of H_2O_2. Conversion of substrate and yield of epoxide product was determined by GC (diol not determined).

mixture of epoxide and *cis*-diol products and *cis*-cyclooctene, which leads the epoxide product primarily but with a minor amount of the *cis*-diol product also.

For ligand **8** no activity was observed for any of the substrates examined. By contrast for ligands **2**, **4** and **7** essentially identical conversion and selectivity was observed for all substrates.

From Table 1 it is apparent that a minimum of one pyridine-2-yl group is required in the structure of the ligand in order to obtain substrate conversion, since for ligands **8–12**, which lack a pyridin-2-yl group in their structures, conversion is not observed. These observations could be assigned to simply the denticity of the ligand especially considering that in the presence of iron the aminal ring is opened readily yielding ligands analogous to those shown in Fig. 1. Furthermore, no significant effect of ligand structure on conversion or product distributions are observed between ligands **2**, **4** and **7**. The instability of the aminal ring in the case of ligands **2**, **3** and **7**, could indicate that the loss of pyridine-2-carboxaldehyde is the cause of the activity seen. However, for ligands **4–6** the opening of the aminal ring does not lead immediately to free pyridin-2-carboxaldehyde, yet full activity is nevertheless observed for these ligands.

Notably, the activity observed for ligands such as **13–15** (Fig. 3) indicates that opening of aminal ring and/or facile loss of pyridine-2-yl units from the ligand is not required to achieve full activity. What is certain, however, is that in the absence of a pyridin-2-yl unit, activity is not observed. For ligands **13–15**, which do not have the aminal structural motif, essentially identical selectivity and activity was observed in the oxidation of *cis*-cyclooctene compared to ligand **2**.

Ligand stability under reaction conditions

The stability of the ligands TPTN, **2**, **3** and **4** under reaction conditions was determined by ^1H NMR spectroscopic analysis of the reaction mixture after catalysed oxidation of 2,3-dimethyl-but-2-ene in acetone-d_6. The ^1H NMR spectrum of the diluted reaction mixture was recorded 16 h after addition of H_2O_2 was complete (Fig. 5).

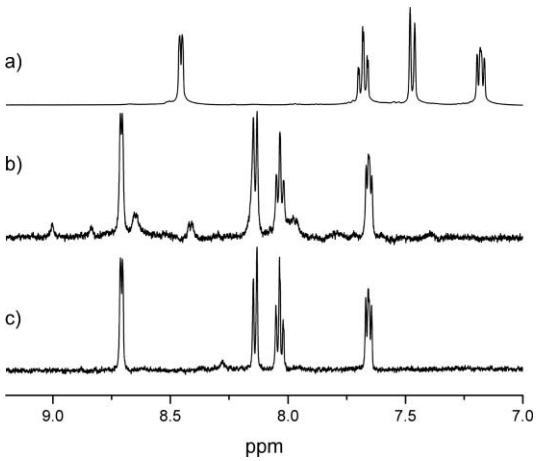
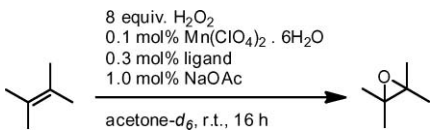


Fig. 5 ^1H NMR (400 MHz) spectra of the reaction mixture (Scheme 2) with TPTN in acetone-d_6 a) before and b) 16 h after addition of H_2O_2 and c) pyridine-2-carboxylic acid (Scheme 2 and ESI‡ for details).

Due to the relatively low concentration of the ligand, the spectrum is dominated by the absorptions of the substrate, solvent and water. However, the absorptions corresponding to the aromatic protons of the ligand are well-resolved.[34] Fig. 5 shows the ^1H NMR spectrum of pyridine-2-carboxylic acid in acetone-d_6, together with the spectrum of the reaction mixture (Scheme 2) after 16 h where the ligand employed is TPTN. The spectrum shows the ligand has decomposed to pyridine-2-carboxylic acid. For ligands **2**, **4** and **5** (see ESI‡) essentially the same effect was observed with pyridine-2-carboxylic acid being detected (together with benzoic and thiophene carboxylic acids, respectively) as the principle aromatic component after oxidation reactions (see ESI‡).



Scheme 2 Conditions employed for studying ligand decomposition during the oxidation of alkenes with H_2O_2 in acetone-d_6.

Confirmation that the degradation products of the ligands, *e.g.* **7**, were responsible for the catalytic activity observed was obtained from the comparison of the oxidation of *cis*-cyclooctene and diethyl fumarate where 8 and 4 equiv., respectively, of H_2O_2 were

added in a single addition or batchwise (see ESI‡). For both *cis*-cyclooctene and diethyl fumarate, full conversion was observed overnight when all the H_2O_2 was added at once. By contrast addition of half of the H_2O_2 achieved only partial conversion (<20%) overnight. Addition of the remaining H_2O_2 to these reactions resulted in full conversion.

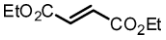
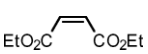
Oxidation catalysis with pyridine-2-carboxylic acid/Mn^{II}

Recently, we reported a remarkably simple system capable of efficient *cis*-dihydroxylation of electron deficient alkenes and epoxidation of electron rich alkenes.[29] This system comprises of pyridine-2-carboxylic acid, a base (*e.g.*, NaOH, or NaOAc) and Mn^{II} source (typically at 0.1–0.3 mol%) in combination with acetone and H_2O_2. The discovery of this system was as a direct result of the mechanistic studies of the series of Mn/ligand catalysts (Fig. 3) systems involving polypyridyl based ligands reported here.

The observation of pyridine-2-carboxylic acid as the principle decomposition product of ligands **1**, **2**, **4**, **5** and TPTN indicates that it may either be a manifestation of catalyst deactivation only or that pyridine-2-carboxylic acid could in fact be responsible for the catalytic activity observed. The observation that a lag period is present after addition of H_2O_2 to the, *e.g.*, **2**/Mn catalysed reactions, during which extensive disproportionation of H_2O_2 is observed, followed by an second phase in which H_2O_2 is not disproportionated and oxidation of substrates proceeds provides a strong indication that decomposition products of the ligands are responsible for catalysis.

The ability of pyridine-2-carboxylic acid together with Mn^{II} to catalyse oxidation of alkenes was compared with that of ligand **2** (Table 2). For three substrates used for comparison identical results in terms of conversion and product formation using either the aminal ligand or pyridine-2-carboxylic acid were observed (Scheme 1, Table 2). Furthermore, whereas 4–8 equiv. of H_2O_2 are required to achieve full conversion with the pyridyl ligands, with pyridine-2-carboxylic acid the efficiency in oxidant is substantially higher with only 1.5–2 equiv. of H_2O_2 required for full conversion. These data provide compelling evidence that under the reaction conditions, it is pyridine-2-carboxylic acid rather than the pyridine-2-yl ligands (including TPTN, ligands **2–7** *etc.*) that, together with manganese ions, is responsible for the catalytic activity observed.

Table 2 Conversions and product distributions using aminal ligands **2** or pyridine-2-carboxylic acid (**1**)

Substrate	Ligand	Conversion[a]	Product distribution[b]
	**2**	100%	*cis*-diol product
	1	100%	(*d*/*l*-diethyl tartrate)
	**2**	20%	*cis*-diol product
	1	20%	(*meso*-diethyl tartrate)
	**2**	100%	epoxide : *cis*-diol 6 : 1
	1	100%	

[a] Conditions: 0.1 mol% $Mn(ClO_4)_2$. $6H_2O$, 0.1 mol% **2** or 0.3 mol% pyridine-2-carboxylic acid, 1.0 mol% NaOAc and 8 equiv. H_2O_2 in acetone at 20 °C. Conversion of substrate was determined by Raman spectroscopy after 16 h. [b] Product yield and distribution were determined by ^1H NMR spectroscopy.

C–H activation and alcohol oxidation with pyridine-2-carboxylic acid/Mn^{II}/NaOAc

The ability of the system pyridine-2-carboxylic acid/Mn^{II}/NaOAc to engage in oxidative degradation of the pyridyl ligands investigated in the present study requires that the system can engage in activation of C–H bonds and as well as in aryl-alcohol and aldehyde oxidation. Although C–H activation[35] is not observed when alkene substrates are employed; for cyclooctane and tetraline, good conversion (>70%) and good selectivity to the monoketone at (40–50%) is observed using both pyridin-2-carboxylic acid or ligands **2–7**. Furthermore, as for TPTN,[28] toluene and benzyl alcohol can be oxidised to benzaldehyde and eventually benzoic acid with pyridine-2-carboxylic acid/Mn^{II}/NaOAc (see ESI‡ for details).

Discussion

In the present study we have shown that pyridin-2-yl ligands (**2–7**, **13–16**) undergo facile decomposition under mildly basic conditions in acetone with Mn/H_2O_2 to yield pyridine-2-carboxylic acids. It is apparent that the pyridine-2-carboxylic acid formed by this ligand decomposition can fully account for the reactivity observed towards oxidation of alkenes, alcohols and for the C–H activation observed for ligands **2–7**, **14**, **15** and TPTN with Mn/H_2O_2.

It is important to note that the conditions employed determine the activity observed. For example under acidic conditions these complexes show relatively little activity and especially those ligands that do not incorporate an aminal ring motif are stable towards decomposition. Furthermore, under mildly acidic conditions (1–20 mol% acetic acid w.r.t. substrate) the reactivity of the pyridine-2-carboxylic acid system is reduced considerably.[29]

For (chiral) ligand systems similar to those under consideration in the present study, Stack and co-workers,[36] have reported under acidic conditions with peracetic acid and Costas and co-workers,[24] with acetic acid/H_2O_2 that with Mn^{II} activity is observed which cannot be ascribed to the formation of pyridine-2-carboxylic acids.

Furthermore, it is important to stress that in acetonitrile or other non-ketone containing solvent systems, the system pyridine-2-carboxylic acid/Mn/NaOAc is essentially inactive.[29] The only, and perhaps key, exception to this is that pyridine-2-carboxaldehyde is oxidised readily to pyridine-2-carboxylic acid in acetonitrile in the presence of Mn and H_2O_2.[29] Hence, in these solvent systems oxidative ligand degradation will lead to a suppression of activity, as indeed has been noted by Banse, Girerd and co-workers for TPEN.[19]

Notwithstanding this, it is clear that the methylene C–Hs of pyridine-2-yl based ligands are susceptible to oxidation *via* C–H activation as certainly occurs for the ligands (**2–6**) examined here. In the case of the aminal based ligands the susceptibility to ring opening and hydrolysis with a Lewis acidic metal could be viewed as key to the *in situ* formation of pyridine-2-carboxylic acid. In the case of ligands **4**, **15** and TPTN, however, activity comparable to that observed for an equivalent amount of pyridine-2-carboxylic

acid was observed (*vide supra*) and hence the opening of the aminal ring is not an only factor.

Conclusions

In conclusion, we have found that for a class of ligands (**2–16** and TPTN) that feature *ortho*-pyridyl functionalities, which have proven, when combined with manganese salts, to be active oxidation catalysts in acetone using H_2O_2, it is actually the pyridine-2-carboxylic acid formed *in situ via* decomposition of the ligand under the oxidative conditions, that is responsible for the observed catalytic activity. We have demonstrated the degradation of the ligand to pyridine-2-carboxylic acid by ^{1}H NMR spectroscopy, and that replacement of ligand **2** by equivalent amounts of pyridine-2-carboxylic acid in the oxidation reactions results in identical activity and selectivity for a broad range of substrates. The only notable difference being that with pyridine-2-carboxylic acid much less H_2O_2 is required to achieve the same levels of conversion.

Ligand degradation is typically considered as a cause of catalyst deactivation. The observation in this case is that *in situ* ligand degradation to relatively simple compounds results in a highly active oxidation system. This demonstrates the relevance of mechanistic understanding of catalyzed reactions, not only in the sense of elucidating catalytic cycles, but crucially in understanding the catalytic system. For example, activity observed with the ligand TPTN in acetonitrile with peracetic acid[36] is due to very different species than those involved in acetone with H_2O_2. This includes the interplay of all of its components, as a whole through speciation analysis. This is especially the case when understanding the effect of variation in ligand structure on reactivity and selectivity. Furthermore, it is an important consideration when understanding how changes in solvent and additives tune the reactivity of a particular system.

Experimental

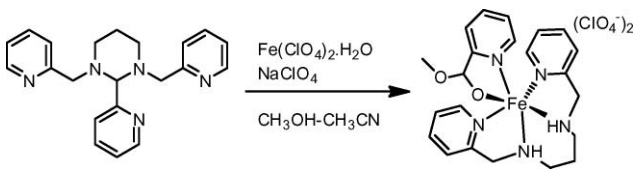
All reagents are of commercial grade and used as received unless stated otherwise. Hydrogen peroxide was used as received as a 50% wt solution in water; note that the grade of H_2O_2 employed can affect the reaction negatively where sequestrants are present as stabilizers. Diethyl-2-methylfumarate[37] was prepared by literature procedures. NMR spectra were recorded at ^{1}H-NMR (400.0 MHz) and ^{13}C-NMR (100.6 MHz). Chemical shifts are denoted relative to the residual solvent absorption (^{1}H: $CDCl_3$ 7.26 ppm; ^{13}C: $CDCl_3$ 77 ppm, acetone-d_6 2.05 ppm).[38] Raman spectra were recorded using a fibre optic equipped dispersive Raman spectrometer (785 nm, Perkin Elmer RamanFlex). Temperature was controlled using a cuvette holder equipped with a custom made fibre optic probe holder (Quantum Northwest). 1,2-Dichlorobenzene was employed as internal standard for Raman spectroscopy. GC analyses were performed on a Hewlett Packard 6890 Gas Chromatograph equipped with an autosampler, using a HP-1 dimethyl polysiloxane column or a HP-5 5% phenylmethylsiloxane column. Calibration was performed using authentic samples of the alkenes and epoxides. Conversions, yields and turnover numbers are the average of 2–4 experiments (uncertainty ± 10%) and were determined using bromobenzene or 1,2-dichlorobenzene as internal standard. Data for quantification of *cis*-diol products is omitted due to unreliability in their quantification by the GC method used.

Caution. The drying or concentration of acetone solutions that potentially contain hydrogen peroxide should be avoided. Prior to drying or concentrating, because of the potential presence of H_2O_2 and other peroxides neutralisation on solid $NaHSO_3$ or another suitable reducing agent should be performed. When working with H_2O_2, especially in acetone, suitable protective safeguards should be in place at all times.[39]

Caution. Perchlorate salts are potentially explosive in combination with organic solids and solvents. In the present study $Mn(OAc)_2$, $Mn(OAc)_3$ or $MnSO_4$ were found to give essentially identical reactivity and should be used above 2 gram reaction scales.

Synthesis and characterisation of [Fe(*N*,*N*′-Bis(pyridin-2-ylmethyl)propane-1,3-diamine)(pryidyl-2-aldehyde-methoxy-hemiacetal)](BF$_4$)$_2$·CH$_3$CN

A solution of $Fe(ClO_4)_2{\cdot}H_2O$ (0.15 g, 0.58 mmol) in acetonitrile (2 mL) was added to a solution of ligand **3** (0.2 g, 0.58 mmol) in methanol (4 mL) (Scheme 3). $NaClO_4$ (0.14 g, 1.16 mmol) was added to the mixture and the resulting solution was placed in an EtOAc bath for three days changing colour from yellow to intense purple within 1 h. The solvent was removed *in vacuo* and the residue washed with Et_2O and pentane to remove free ligand. The residue was redissolved in a minimum of acetonitrile and placed in an EtOAc bath yielding red coloured crystals (0.35 g, 0.52 mmol, 89%). Elemental analysis calcd for $C_{23}H_{29.5}Cl_2FeN_{5.5}O_{10}^{2-}$: C 41.25%, H 4.44%, N 11.50%; found C 41.31%, H 4.51%, N 11.53%.



Scheme 3

X-Ray crystallography $[C_{22}H_{28}FeN_5O_2]^{2+}{\cdot}2[ClO_4]^-{\cdot}0.5(C_2H_3N)$, $M_r = 669.77$, monoclinic, $C2/c$, $a = 37.597(4)$, $b = 9.1237(10)$, $c = 16.3513(18)$ Å, $\beta = 102.216(1)°$, $V = 5481.9(10)$ Å^3, $Z = 8$, $D_x = 1.623$ g cm^{-3}, $F(000) = 2768$, $\mu = 8.12$ cm^{-1}, λ(Mo-Kα) = 0.71073 Å, $T = 100(1)$ K, 21142 reflections measured, $GooF = 1.058$, $wR(F^2) = 0.1118$ for 5616 unique reflections and 397 parameters, and $R(F) = 0.0444$ for 4780 reflections obeying $F_o \geq 4.0\,\sigma(F_o)$ criterion of observability. The asymmetric unit consists of four moieties: a cationic Fe-complex, two perchlorate anions and an half of an acetonitrile solvate molecule. The acetonitrile molecule is located on a twofold axis. CCDC reference number 768839.‡

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