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Manganese- and Iron-Catalyzed Oxidative Valorization of Unactivated Alkenes and Alkanes

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Statement of Authorship

I hereby affirm that I have written the present work by myself without outside assistance. No other resources were utilized than stated. All references as well as verbatim extracts were quoted, and all sources of information were specifically acknowledged.

Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe. Dazu habe ich keine außer den von mir angegebenen Hilfsmitteln und Quellen verwendet und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen habe ich als solche kenntlich gemacht.

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Though we cannot always control what happens to us,

we always have the freedom of choosing how to respond to it!

Wir können zwar nicht immer kontrollieren, was uns passiert, aber wir haben immer die Freiheit, unsere Einstellung zu den Dingen selbst zu wählen!

Summary

This dissertation summarizes the employment of simple, inexpensive, and easily accessible manganese and iron catalysts for the oxidative valorization of unactivated alkenes to epoxides and alkanes to ketones/alcohols. In a first project, *tert*-butyl hydroperoxide was used as terminal oxidant and quinoline was shown to be the crucial additive for manganese-catalyzed epoxidation of unactivated alkenes. In a consecutive project, the efficiency of this transformation was raised by developing an improved manganese catalyst using the more benign oxidant hydrogen peroxide. In this case, the employment of N-heterocycles also proved to be crucial for achieving high yields of epoxides. This system was additionally capable of selectively oxidizing alkanes to ketones, as well as secondary alcohols to ketones. In a last project, an iron catalyst was used to transform unactivated alkanes into corresponding mixtures of ketones and alcohols, using hydrogen peroxide as terminal oxidant.

Zusammenfassung

In der vorliegenden Dissertation wurden neuartige, *in situ* generierte Mangan- und Eisenkatalysatoren zur oxidativen Valorisierung von Alkenen zu Epoxiden und von Alkanen zu Ketonen/Alkoholen eingesetzt. Im ersten Projekt diente dazu *tert*-Butylhydroperoxid als Oxidationsmittel und Chinolin als entscheidendes Additiv, um Alkene zu epoxidieren. Im nachfolgenden Projekt konnte dann mit einem weiteren Mangankatalysator die Effizienz deutlich erhöht, sowie durch den Einsatz von Wasserstoffperoxid als Oxidationsmittel die Nachhaltigkeit der Reaktion verbessert werden. Auch hier spielte die Zugabe von N-Heterozyklen als Additiv eine wichtige Rolle, wobei dieses System neben der Epoxidierung auch die selektive C-H Oxidation zu Ketonen, sowie Oxidation von sekundären Alkoholen, ermöglichte. Im letzten Projekt konnte gezeigt werden, wie der Einsatz eines einfach zugänglichen Eisenkatalysators die Oxidation von nicht-aktivierten Alkanen zu den entsprechenden Ketonen und Alkoholen mithilfe von Wasserstoffperoxid ermöglicht.

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2-MQ	2-Methylquinoline
Ac	Acyl
Acac	Acetylacetone
AcOH	Acetic Acid
Ad	Adamantyl
aq.	Aqueous
BDE	Bond-dissociation Energy
BHT	2,6-di-*tert*-butyl-4-methylphenol
BPA	Bis(2-picolyl) amine
Bu	Butyl
cat.	Catalyst
CF_3	Trifluoromethyl
CH	Chlorohydrin
CHP	Cumene Hydroperoxide
COD	Cycloocta-1,5-diene
Conv.	Conversion
Cy	Cyclohexyl
DCM	Dichloromethane
e.g.	Example
ee	Enantiomeric excess
eq.	Equivalent(s)
Et	Ethyl
FAO	Fatty Acid Oxidation
GC	Gas Chromatography
h	hour
H_2O_2	Hydrogen Peroxide
H_2SO_4	Sulfuric Acid
HAT	Hydrogen Atom Transfer
HR	High Resolution
IR	Infrared
IST	Internal Standard
KA	Ketone Alcohol
KA Oil	Cyclohexanone and Cyclohexanol
m	milli
M	Molar
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mL	Milliliter
mmol	Millimole
MS	Mass Spectrometry
MTBE	methyl *tert*-butyl ether
MTO	Methyltrioxorhenium

NHPI	*N*-Hydroxyphthalimide
NMR	Nuclear Magnetic Resonance
NTf_2	Bis(trifluoromethane)sulfonimide (Triflimide)
ORTEP	Oak Ridge Thermal-Ellipsoid Plot Program
OTf	Trifluoromethanesulfonate (Triflate)
Ph	Phenyl
PicOH	Picolinic acid
Picolyl	Pyridine Methyl
PINO	Phthalimido-*N*-oxyl
PO	Propylene Oxide
PPO	Polypropylene oxide
Pr	Propyl
Py	Pyridyl
Q	Quinoline
QNO	Quinoline-N-oxide
R	Rest
rt	Room temperature
SAR	Structure-Activity-Relationship
Sel.	Selectivity
Select.	Selectivity
SM	Styrene Monomer
SET	Single-electron transfer
tacn	Triazacyclononane
TBA	*tert*-Butyl Alcohol
TBHP	*tert*-Butyl Hydroperoxide
***t*BuOOH**	*tert*-Butyl Hydroperoxide
TEMPO	2,2,6,6-Tetramethylpiperidinyloxyl

1. A Short Introduction to Chemistry

Everything is made up of atoms. The word atom is derived from the Greek adjective "*atomos*", meaning indivisible or uncuttable. Though this definition no longer stands true as was discovered in 1938 by the German chemist Otto Hahn,[1] it is still used today. The doctrine describing the formation or scission of bonds between atoms is called chemistry. So, in that regard, everything is chemistry.

There exist uncountable examples of chemical transformations, *i.e.*, the formation or scission of chemical bonds, that affect our lives on a daily basis, often without us even noticing. Our bodies, for example, derive energy from the food we eat or burn excess fat reserves for energy gain if we are on a diet. Similarly, our lives are greatly facilitated by all kinds of products that were created by chemical transformations. Famous examples are the infamous plastics which mostly are, with good reason, being criticized due to the environmental problems they cause or simple things like surfactants that help us with cleaning our clothes.

There are, in fact, two things that the creation of several plastic or surfactant precursors, *e.g.*, nylon or ethylene oxide, have in common with our bodies burning fat for energy gain:

First, both chemical reactions require the employment of a catalyst. Secondly, both transformations are oxidation reactions.

The objective of this doctoral thesis is the development of new catalysts for oxidation reactions.

One may now ask, why do we need new catalysts, or even catalysts at all? And why especially for oxidation reactions? The answers to these questions will be fully disclosed in the following chapters.

1.1. Catalysis and Green Chemistry in Today's Society

The chemical industry is largely reliant on the employment of catalysts to accommodate us with a plethora of necessary, as well as perhaps not entirely necessary, products, compounds, medicinal drugs etc. In fact, about 90% of all chemical reactions in industry make good use of a catalyst.[2] This clearly shows *that* catalysts are immensely important. Now we still need to elaborate *why* catalysts are that important, or rather, *how* they work. To that end we shall revert to the old, yet most famous first definition of a catalyst that was formulated by Wilhelm Ostwald in 1895:

> *"A catalyst is a substance, that increases the rate of a chemical reaction, without being consumed itself and without changing the final position of the thermodynamic equilibrium of that reaction."*

This definition holds two important implications: First, increasing the rate of a chemical reaction means that said reaction can be performed, for example, at lower temperatures or at shorter reaction times; both of which are less energy demanding than the uncatalyzed reaction. Secondly, the fact that the catalyst itself is not consumed means that it can be re-used, *i.e.*, low amounts of the catalyst are needed to convert a larger amount of the reactant(s) to the desired product(s); the catalyst is used in *catalytic amounts*. This is of course superior to an uncatalyzed reaction where large amounts of a certain compound would be required to help convert the reactant(s) to the desired

product(s). These features are accomplished by the catalyst through reducing the required activation energy of the reaction in question. The catalyst can open alternative reaction pathways, which require less activation energy that would otherwise not be accessible. Hence, though the overall thermodynamic equilibrium is unaffected, improving the kinetics of that reaction (see Figure 1 for a general example diagram).

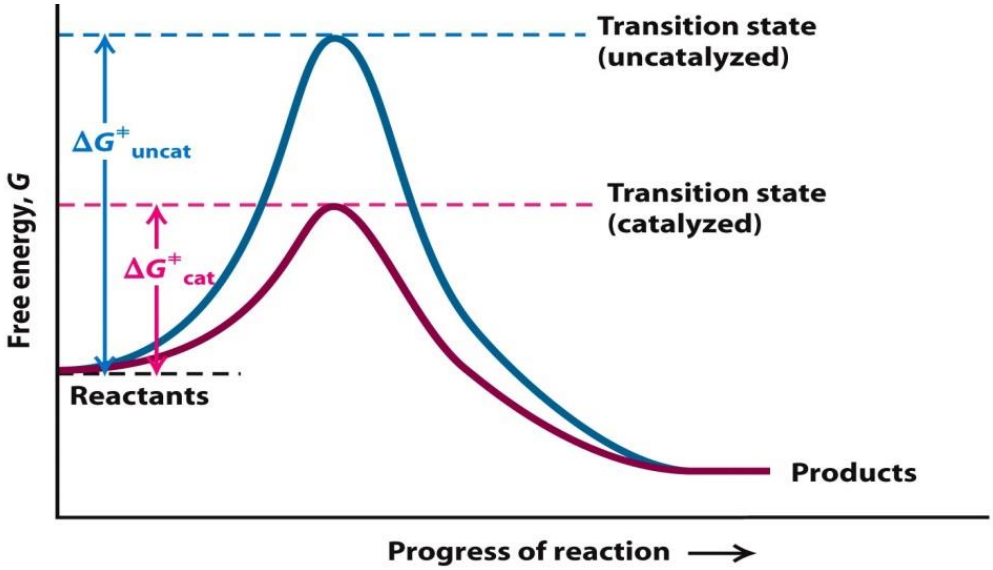


Figure 1: General reaction diagram of an uncatalyzed reaction (blue) and a catalyzed reaction (red).[3]

In addition to making reactions more energy efficient, catalysts thus also help in reducing the amount of chemical waste that is generated in uncatalyzed reactions. To understand the relevance of waste reduction one only has to watch the news or listen to any political discussion. Nowadays it is highly unlikely that environmental protection or pollution control is *not* mentioned. Therefore, it is exceedingly clear that making chemical processes more benign and more (energy) efficient, *i.e.*, "*greener*", is of utmost importance in today's society. To that end, by the time this thesis is being written, already a quarter century ago, Paul T. Anastas and John C. Warner postulated the famous twelve principles of green chemistry:[4]

1. *Prevention*. Preventing waste is better than treating or cleaning up waste after it is created.
2. *Atom economy.* Synthetic methods should try to maximize the incorporation of all materials used in the process into the final product. This means that less waste will be generated as a result.
3. *Less hazardous chemical syntheses.* Synthetic methods should avoid using or generating substances toxic to humans and/or the environment.
4. *Designing safer chemicals.* Chemical products should be designed to achieve their desired function while being as non-toxic as possible.
5. *Safer solvents and auxiliaries.* Auxiliary substances should be avoided wherever possible, and as non-hazardous as possible when they must be used.
6. *Design for energy efficiency.* Energy requirements should be minimized, and processes should be conducted at ambient temperature and pressure whenever possible.
7. *Use of renewable feedstocks.* Whenever it is practical to do so, renewable feedstocks or raw materials are preferable to non-renewable ones.

8. *Reduce derivatives.* Unnecessary generation of derivatives, such as the use of protecting groups, should be minimized or avoided if possible; such steps require additional reagents and may generate additional waste.
9. *Catalysis.* Catalytic reagents that can be used in small quantities to repeat a reaction are superior to stoichiometric reagents (ones that are consumed in a reaction).
10. *Design for degradation.* Chemical products should be designed so that they do not pollute the environment; when their function is complete, they should break down into non-harmful products.
11. *Real-time analysis for pollution prevention.* Analytical methodologies need to be further developed to permit real-time, in-process monitoring and control before hazardous substances form.
12. *Inherently safer chemistry for accident prevention.* Whenever possible, the substances in a process, and the forms of those substances, should be chosen to minimize risks such as explosions, fires, and accidental releases.

Why especially the field of oxidation chemistry is strongly impacted by these principles will be discussed in chapter 1.2.

1.1.1. Different Types of Catalysts

The catalysts that help accomplish the aforementioned goals can generally be divided into three different types:

Heterogeneous Catalysts

Here, the catalyst and the substrate are present in different phases, *e.g.*, the catalyst is a solid suspended in the liquid phase containing the substrate or the substrate is a gas. The majority of industrially catalyzed reactions, particularly bulk chemical syntheses, rely on the use of a heterogenous catalyst. The advantages are low cost, ease of preparation and separation from the reaction mixture and therefore high recyclability. Disadvantages are usually harsh reaction conditions and comparably medium to lower activity and selectivity. Possibly the two most famous examples for heterogeneously catalyzed reactions are the Haber-Bosch process (iron-catalyzed ammonia synthesis from nitrogen and hydrogen) and the catalytic converter present in cars which relies on noble metals such as platinum, rhodium, or palladium.

Homogeneous Catalysts

In this case, both the catalyst and the substrate are present in the same phase, *e.g.*, both are dissolved in the liquid phase. A much smaller portion of all industrial reactions is catalyzed by homogeneous catalysts, for example fine chemical syntheses like drug molecules. In general, these catalysts are quite complementary to heterogeneous ones. Usually, they are higher in cost, more difficult to synthesize and to separate from the reaction mixture. On the other hand, they display higher activities and selectivities and work under milder reaction conditions. Famous examples for homogeneously catalyzed industrial reactions are the Wacker oxidation[5] (palladium-catalyzed reaction from olefins to aldehydes) and the Halcon process[6] (molybdenum-catalyzed epoxidation of propylene to propylenoxide).

Biocatalysts

Biocatalysts, *i.e.*, enzymes, are present in living beings. For example, fatty acid oxidation (FAO) enzymes help you gain energy from fatty acids you ate or that are stored in your body[7]. Nowadays, some reactions in industry are also conducted using enzymes as catalysts, *e.g.*, monoamine oxidases in the pharmaceutical sector,[8] as these are highly specific and selective in their activity. However, they can be exceedingly difficult to synthesize for a certain reaction and are often limited to aqueous reaction conditions and ambient temperatures.

The focus of this thesis is the second type of catalyst: *The homogeneous catalysts*.

1.1.2. Noble Metals versus non-noble Metals as Homogeneous Catalysts

The metals that are the precursors for many homogeneous, or for that matter also for heterogeneous, catalysts can further be divided into sub-categories, *e.g.*, noble metals and non-noble/earth-abundant/base metals. Especially in the past, noble metals were predominantly used due to several advantages they offer over base metals: 4d and 5d transition metals usually exhibit much higher stability and activity and can therefore be employed with much lower catalyst loadings than their 3d counterparts. Numerous achievements have been made in the past using noble metals as catalysts expanding the toolbox of a chemist and thus contributing to facilitate the syntheses of many important compounds. One very famous example are palladium-catalyzed cross coupling reactions that have even been awarded the Nobel Prize in 2010.[9] However, the employment of noble metals as catalysts has several disadvantages, especially regarding the principles of green chemistry: On the one hand, they exhibit much higher levels of toxicity for human beings which is problematic, for example, in syntheses of drug molecules, where certain thresholds for metals are in place.[10] On the other hand, they are more expensive than earth-abundant metals because they are much rarer in the earth´s crust (10^{-4}–10^{-5} ppm vs 10^{1}–10^{5} ppm for non-noble metals).[11] They are not only very rare but the circumstances are getting worse in the future, where supply issues might arise due to the many processes that are still reliant on noble metals as catalysts. In Figure 2 it is apparent that continuous excessive use of certain (noble) metals is not a sustainable solution for the chemical industry. Hence, numerous endeavours by academia and industry have been and are being developed to circumvent these rising problems in the near future.

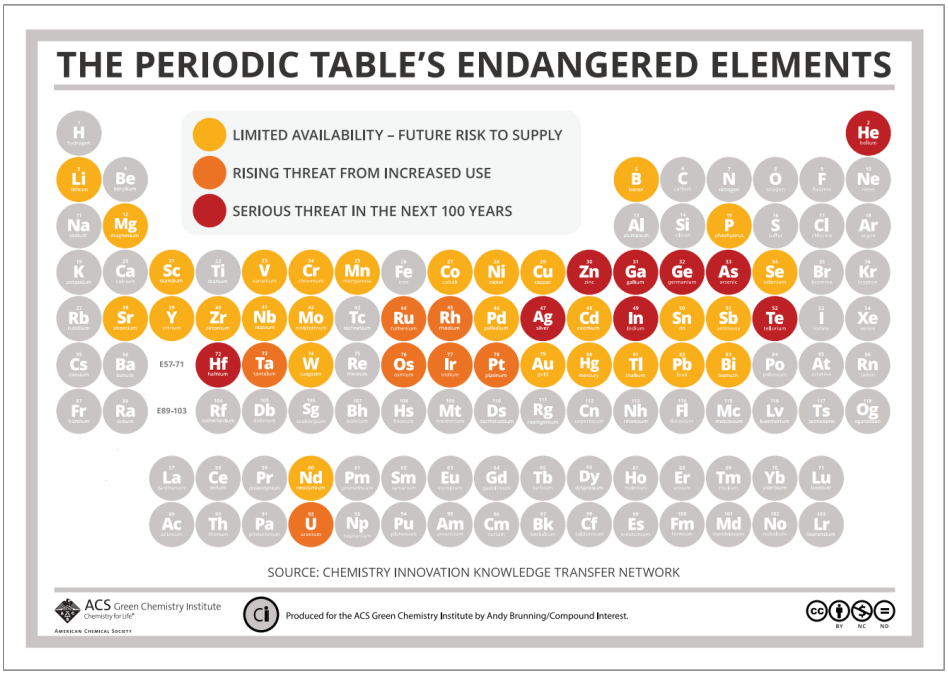


Figure 2: The periodic table's endangered elements.[12]

1.2. The Value and Hazards of Oxidation Chemistry

In accordance with the principles of green chemistry, not only the best product yield determines the quality of a given synthesis, but other factors such as minimizing the amount of generated waste, avoiding excess of reagents and additives, utilizing earth-abundant catalysts, as well as circumventing any risk stemming from the use of toxic, corrosive or hazardous materials.[4] These factors are especially relevant in oxidation chemistry, as most (highly concentrated) oxidants pose safety risks due to their explosive, toxic or corrosive nature.[13] In this respect, the use of molecular oxygen, hydrogen peroxide or *tert*-butyl hydroperoxide are clearly preferred compared to, for example, hypervalent iodine species, chlorine gas, hypochlorite or highly toxic metal oxides, *e.g.*, OsO_4.[14]

Consequently, although the aforementioned hazardous oxidants usually allowed for high product yields, the trend has shifted towards the employment of safer oxidants and more efficient synthetic routes, as can be seen in several examples of oxidation reactions in the chemical industry. The following chapter highlights some important industrial examples, namely epoxidation reactions and C-H oxidation reactions as these demonstrate the relevance of oxidation reactions for the generation of value-added products.

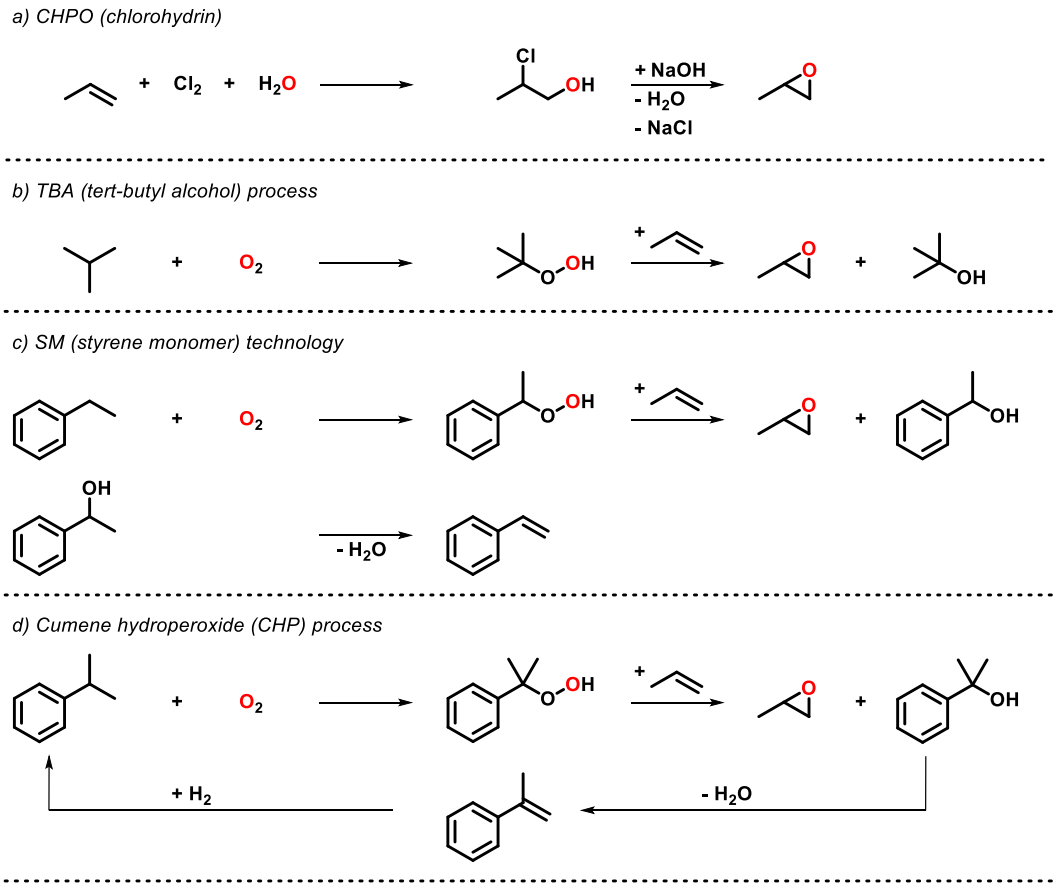
1.2.1. Oxidation Chemistry in Industry

Oxidation chemistry in industry is the tool of choice for the synthesis of important intermediate building blocks or monomers for the polymer industry.[14] Noteworthy examples are oxidized alkanes as nylon precursors or epoxides which enable access to a plethora of compounds.

Propylenoxide Production

Epoxides are a unique class of ethers containing a 3-membered ring of two carbon atoms and one oxygen atom. Due to the nature of this strained system, epoxides, especially terminal ones, are considered highly reactive, the two simplest examples being ethylenoxide and propylenoxide (PO). In general, terminal aliphatic epoxides are valuable building blocks for a variety of daily life products such as epoxy resins, paints, surfactants and health care related products.[15-18] Furthermore, they can easily be derivatized by reacting, for example, with ammonia to give β-hydroxyamines, with thiols to give β-hydroxy mercaptans, with alcohols to give β-hydroxy ethers or with cyano groups to give nitriles. In particular, propylenoxide held a market size of 11.9 million tons in 2022 which is projected to rise to over 20 million tons within the next ten years.[19] Therefore, it is not surprising that many efforts were dedicated to optimize standing, or to develop new procedures for the synthesis of propylenoxide where the principles of green chemistry are better integrated by employing safer oxidants and reduce by-product formation. In Scheme 1 a short overview of several processes for the oxidation of propene is given that emphasizes the aforementioned points.

One long-standing process is the so-called chlorohydrin process (CHPO) (Scheme 1a). Here, propene is oxidized by chlorine gas in the presence of water, yielding 2-chloro-1-propanol as intermediate. Consecutively, upon addition of a base, this intermediate is converted to the desired product propylenoxide. A major disadvantage of this technology is the massive amount of salt by-product that is generated in the process, therefore displaying poor atom economy. Hence, no new plants for this process are being built. A second process is the *tert*-butyl alcohol (TBA) process, where *iso*-butane is oxidized by O_2 yielding *tert*-butyl hydroperoxide (TBHP) which is then used as terminal oxidant to give propylenoxide from propene, generating *tert*-butanol as a by-product (Scheme 1b). Though this by-product is employed for methyl *tert*-butyl ether (MTBE) synthesis, no future investments in this process are expected. Another way of excessing PO is the styrene monomer (SM) technology (Scheme 1c). Analogously to the TBA process, here, ethylbenzene is oxidized to give ethylbenzene hydroperoxide which will followingly oxidize propene to propylenoxide, also yielding the corresponding benzyl alcohol as by-product. However, phenyl ethanol is then converted to styrene, which can be used as monomer for polystyrene (PS), or other value-added products. The disadvantage is a volatile economic performance due to market balancing problems between PO and the styrene by-product. The last technology is the cumene hydroperoxide (CHP) process. Similarly, cumene is oxidized to the corresponding peroxide. Advantageously, CHP is a more stable (and therefore safer) oxidant compared to the other peroxides, thus giving more selective oxidation. Additionally, a more efficient recovery of the reaction heat, as well as the recycling of the alcohol by-product, are other benefits of this process.[14] These are only a few examples from the chemical industry regarding advancements in epoxidation reactions. In chapter 1.2.2.1 we will discuss the scientific advances in academia in this field of chemistry.



Scheme 1: Industrial propylene oxide (PO) production processes.[14]

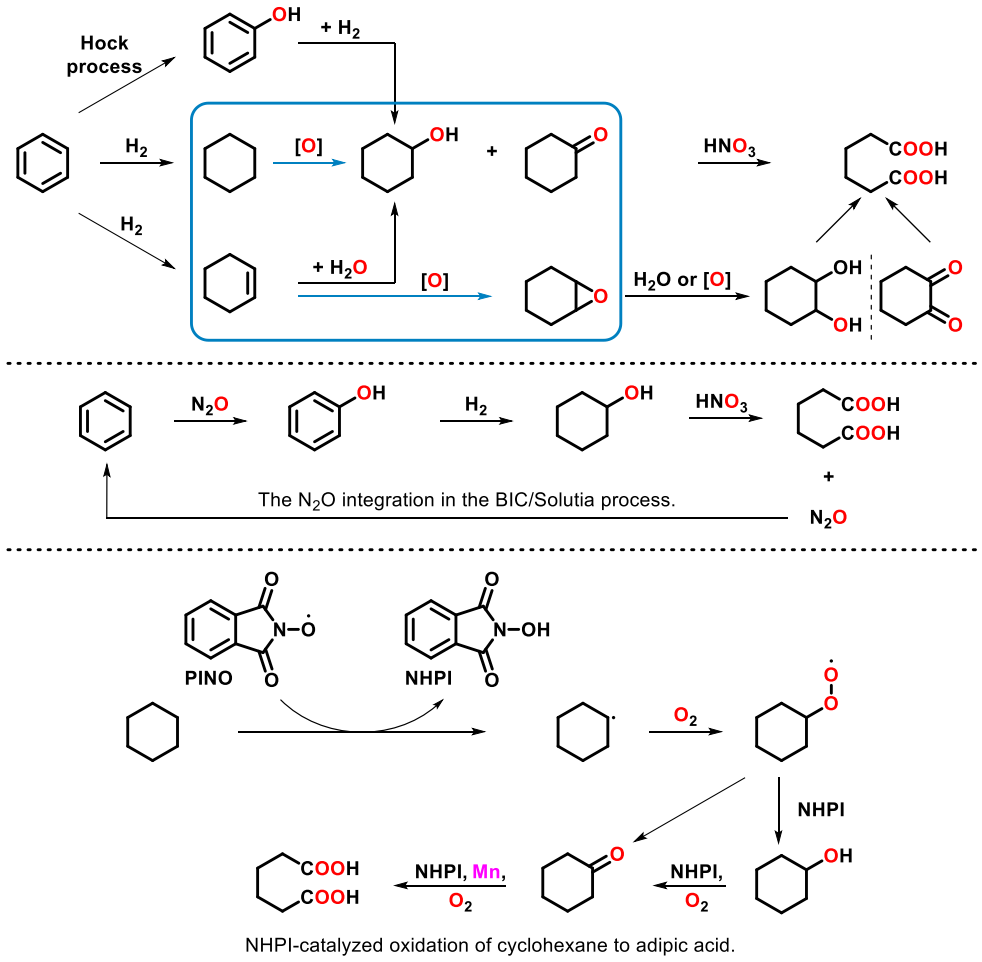
Adipic Acid Production

Another important sector in the chemical industry is the production of nylon and its precursors, namely adipic acid, as nylon-6,6 production accounts for over 63% of adipic acid consumption. Common uses of nylon are fishing lines, tire cords, carpets, furnishings and fabrics.[14] Hence, adipic acid annual production exceeded three million tons in 2021 and is still growing annually.[20] Naturally, there are many routes for the production of adipic acid (see Scheme 2). However, they are mostly reliant on the employment of cyclohexane as starting material, that is in turn accessed by the hydrogenation of benzene. Alternatively, benzene can be oxidized to phenol (Hock process) which will then be reduced to cyclohexanol. Partial reduction of benzene to cyclohexene and consecutive hydration of the C=C double bond will also lead to cyclohexanol. Analogously, oxidation of cyclohexane to cyclohexanol and/or cyclohexanone will give the same end result as the aforementioned steps. Thus, the obtained mixture of cyclohexanol and cyclohexanone is called “KA oil” and is commonly known as a precursor to adipic acid as its oxidation with nitric acid will generate the desired dicarboxylic acid. Going back to cyclohexene, from here, oxidation to the corresponding epoxide and consecutive oxidation or hydrolysis will lead to cyclohexane-1,2-diol or the analogous diketone, which will in turn also be transformed into adipic acid. Therefore, it is obvious that the C-H oxidation of cyclohexane or the epoxidation of cyclohexene are important steps in this industrial process chain (blue highlighted steps). Both reactions, that is C-H oxidation of unactivated alkanes and epoxidation of alkenes, are the focus of this thesis, as will be discussed in chapter 3.

In the chemical industry, due to its many steps, this route has several alternatives, one being the N_2O integration in the BIC/Solutia process. Here, benzene is oxidized using N_2O to yield phenol, followed by hydrogenation to

cyclohexanol and consecutive oxidation with nitric acid to adipic acid. One the one hand, the greenhouse gas by-product N_2O, which results from the reduction of the oxidant HNO_3, being recycled for its re-employment in the first step, can be regarded as an advantage from an environmental point of view. On the other hand, the recycled amount of N_2O is not sufficient to close the cycle depicted in Scheme 2, thus necessitating additional phenol acquisition and therefore limiting the benefits. Although alternative catalytic routes for KA oil oxidation, or even direct oxidation from cyclohexane, to adipic acid are known, they suffer from corrosion problems due to acetic acid as reaction solvent and/or lower selectivities than the uncatalyzed two-step nitric acid route.[14] One noteworthy achievement was the *N*-hydroxyphthalimide (NHPI) process. Here, NHPI serves as a precursor to phthalimido-*N*-oxyl (PINO), the radical abstracting species that converts cyclohexane to its corresponding radical. This will then react with dioxygen, forming an oxygen centered radical, which will either decompose to cyclohexanone, or react with NHPI, forming cyclohexanol. In turn, the alcohol will also be oxidized to the ketone, thus eventually yielding the KA oil mixture as adipic acid precursor. In this last step, a manganese and/or cobalt catalyst, as well as acetic acid/(MeCN) solvent, is necessary to convert the KA oil into the desired adipic acid product. One advantage of this process is the cheap cost of the NHPI catalyst, however, this method suffers from drawbacks like high catalyst loading (10 mol%) and rather low catalyst stability (decay to phthalimide).[14]

Although direct and “green” routes from cyclohexene to adipic acid exist, they tend to be economically unfeasible due to the comparably high cost of hydrogen peroxide and the starting material itself. Therefore, it would be desirable to establish direct routes that start from cyclohexane. In general, reducing benzene to cyclohexane or cyclohexene followed by re-oxidation of the formed products is both ecologically and economically problematic as changing redox states multiple times creates waste and necessitates additional reactants. Furthermore, the fact that there are so many different routes for adipic acid production demonstrates that there is still a lot of room for improvement which explains why also scientists in academia have devoted time and efforts to optimize on standing and find new oxidative procedures (see next chapter).



Scheme 2: Industrial technologies for adipic acid production.[14]

1.2.2. Oxidation Chemistry in Academia

As described in the previous chapter, oxidation chemistry is an important instrument in the chemical industry due to its relevance in the synthesis of many commonly used products from available (fossil-based) feedstocks. Thus, unsurprisingly, academia has acted correspondingly for epoxidation reactions as well as for C-H oxidation reactions as will be laid out within the present chapter. In both cases, the relevant literature will be restricted to homogeneous catalysis as this is the topic of the present doctoral thesis.

1.2.2.1. Homogeneous Catalysis for Epoxidation Reactions

Metal-catalyzed epoxidation reactions of aliphatic olefins are widely used and studied tools not only in the chemical industry (see previous chapter) but also in academia.[16, 21-23]

More specifically, the selective epoxidation of terminal aliphatic olefins under environmentally benign conditions is desired as the corresponding 1,2-epoxides are valuable building blocks for a variety of daily life products (see chapter 1.2.1).[15-18] Hence, numerous epoxidation protocols based on a variety of different transition metals, such as Sc,[24] Ti,[25-27] Mn,[28-32] Fe,[33-35] Nb,[36] Mo,[37] Ru,[38-40] and Re[41-43] have been published in the past four decades. Among the non-noble metals, especially catalysts based on manganese or iron have the potential for further applications in epoxidation reactions.[22] Selected examples of epoxidation catalysts are depicted in Figure 3.

Going back to 1980, K. B. Sharpless published his now famous work about titanium-catalyzed asymmetric epoxidation of allylic alcohols.[25] His works,[25, 41, 44-46] as well as the works of W.S. Knowles[47-49] and R. Noyori[50, 51] about asymmetric syntheses were so impactful that they were awarded the Nobel Prize in 2001.[52] In 1997, a very efficient methodology was published by Sharpless and co-workers based on the earlier works of Herrmann and co-workers[53] that relies on the use of methyltrioxorhenium (MTO) as metal catalyst with pyridine derivatives as ligand. Employing hydrogen peroxide as oxidant, high yields of epoxides were achieved. However, the use of rhenium as a metal and reliance on dichloromethane (DCM) as reaction solvent are, from an environmental perspective, obvious drawbacks.[54]

Since the beginning of the 2000s, many manganese- and also iron-catalyzed epoxidation reactions were reported. Interestingly, most of them share quite common ligand features, employing tetradentate nitrogen based ligands or tridentate N,N,N-pincer ligands. For example, in 2001, Jacobsen and co-workers published their work about a tetradentate nitrogen-based iron catalyst for the epoxidation of both terminal and internal alkenes. Although their system is efficient in the amount of employed hydrogen peroxide, it depends on acetic acid as additive which results in corrosive reaction mixtures and undesirable by-products.[55] Nonetheless, achieving yields of >80% for terminal, aliphatic olefins can be regarded as state-of-the-art to this day. Similarly, in 2008, the Wong group developed a manganese-based catalyst system that was capable of epoxidizing the challenging terminal aliphatic olefins, though they relied on peracetic acid as oxidant which poses problems akin to a combination of hydrogen peroxide and large amounts of acetic acid.[17] In a related fashion, in 2009, Costas and co-workers demonstrated that high yields can also be achieved in these reactions utilizing environmentally friendly H_2O_2 as oxidant, but a large excess of acetic acid is needed to achieve decent yields here, too.[56]

A remarkably simple manganese-based oxidation catalyst system was published by Browne and co-workers in 2012. Previously, they showed that 2-picoline based ligand scaffolds often undergo oxidative degradation *in situ* to 2-picolinic acid that will than act as the active ligand in selected oxidative transformations.[57] Later on, they published their work about a 2-picolinic acid based manganese oxidation catalyst for epoxidation of olefins.[58] As oxidant a combination of benign hydrogen peroxide and a ketone activator was employed while the addition of a simple base was necessary to deprotonate the 2-picolinic acid to form the active catalytic species. Furthermore, their system was shown to promote dihydroxylation of electron deficient alkenes,[59] oxidation of vicinal diols,[60] as well as C-H oxidation of alkanes and O-H oxidation of alcohols.[61] Besides, the Browne group published several more papers about their system, its mechanism and the role of the respective employed compounds.[32, 62-64]

In 2015, Nam and Sun reported asymmetric epoxidation of olefins, which also included terminal aliphatic olefins.[65] However, when it comes to industrial applications for bulk chemical syntheses, *e.g.*, terminal epoxides from unactivated olefins, the requirement of rather complex procedures and elaborate ligand syntheses renders their protocol unsuitable.

Moreover, in 2020, Zhu and co-workers published their work about tetradentate nitrogen based ligands for manganese epoxidation catalysis, once more employing similar ligand scaffolds as were previously reported.[66] Here, akin to other drawbacks of several procedures, obligatory ligand syntheses and addition of acetic acid subtract from this protocol's utility for large scale applications.

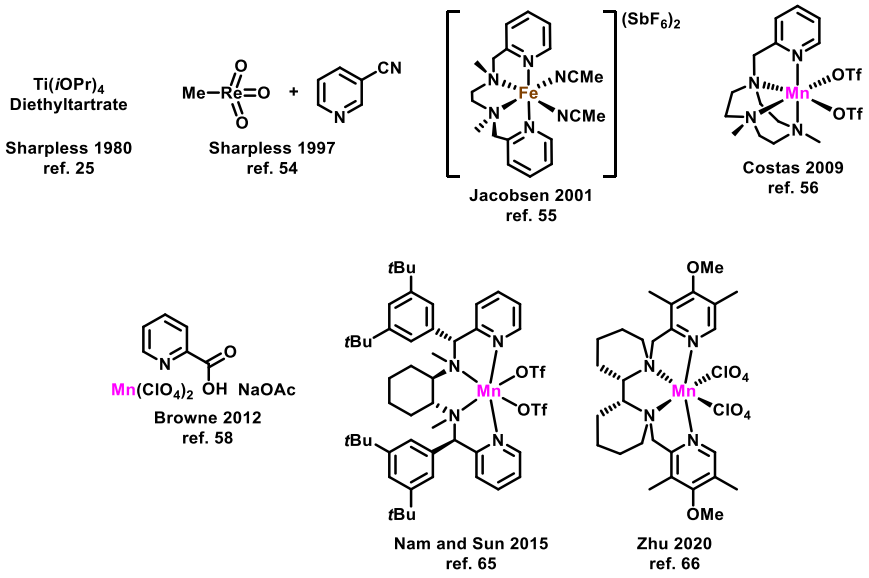


Figure 3: Selected examples of epoxidation catalysts.

Although further, valuable contributions were made in the field of manganese- and iron-catalyzed epoxidation reactions,[66-71] oxidant decomposition, product degradation, or free-diffusing radicals still render terminal olefins challenging substrates to be epoxidized in high yields under benign conditions.[72, 73] Ideally, those conditions are acid free, employ non-toxic, earth-abundant and cheap metals[74] as well as commercial and inexpensive ligands.

1.2.2.2. Homogeneous Catalysis for C-H Oxidation Reactions

Besides epoxidation, aliphatic C-H oxidation is also highly desirable as it allows to implement functional groups, *i.e.*, hydroxy or carbonyl groups, into unfunctionalized compounds, thus profoundly changing their physical (and biological) properties. Yet, this transformation is challenging due to high bond dissociation energies (BDE ~96 – 101 kcal/mol) of such unactivated C-H bonds.[75]

Therefore, unsurprisingly, next to the in chapter 1.2.1 mentioned industrial progression of C-H oxidation reactions, academia has also committed time and resources into developing more efficient and environmentally friendly earth-abundant metal-catalyzed oxidations of especially unactivated C-H bonds. The present chapter discusses these advancements and highlights certain achievements in manganese- and iron-based oxidations of alkanes (see Figure 4).

One important step towards this goal was achieved by the White group in 2007.[76] Here, an iron catalyst derived from her works with Jacobsen on epoxidation[55] was modified by introducing two ring structures into the amine backbone of the tetradentate ligand. This change led to a potent catalyst for oxidation of unactivated C-H bonds. However, high catalyst loadings (15 mol% total) and the fact that three consecutive additions of catalyst, oxidant and acetic acid were necessary to achieve decent yields are noticeable downsides of this system.

In 2012, Bryliakov and co-workers published a manganese-based catalyst system for C-H oxidation that was also originally developed for epoxidation of olefins.[77] In this case, too, only slight modifications were required to tune the reactivity of their epoxidation catalyst for C-H oxidation reactions. In contrast to some reported iron-based systems, much lower catalyst loadings were possible. However, again the addition of acetic acid was crucial for

achieving decent activity, while also cooling conditions (0 °C) were demanded due to the exothermic nature of the oxidation reaction.

One year later, the Costas group reported on their mechanistic works[78] about an iron catalyst system, employing Pytacn (pyridyl-substituted triazacyclononane) based ligands that previously showed reactivity for C-H hydroxylation of alkanes[79] and for *cis*-dihydroxylation or epoxidation of olefins.[80] In their mechanistic studies they drew the conclusion that these non-heme based iron catalysts operate *via* a mono-oxygenase-type reaction pathway, rather than a radical Fenton-type reaction pathway. In general, reactions which predominately follow the former pathway, allow for selective alkane oxidation to *either* the ketone or the alcohol. In the latter case, however, free diffusing radicals lead to roughly one-to-one ratios of ketone and alcohol, respectively. Thus, observing product ratios in alkane C-H oxidation reactions can provide initial insights into the reaction mechanism.

Later on, in 2013, the Browne group demonstrated the applicability of their simple manganese-based epoxidation system for C-H oxidation of alkanes,[61] once more showing that non-noble metal based oxidation catalysts occasionally exhibit activity for several oxidative transformations. Analogous to previously mentioned systems, slight modifications were conducted to obtain decent yields of alkane oxidation products, namely higher catalyst and additive loadings as well as higher excesses of peroxide. Interestingly, their system shows complete selectivity for the ketone product over the alcohol product, starting from the parent alkane substrate, indicative of a mono-oxygenase-type reaction pathway.

In 2017, Bietti, Costas and co-workers reported the first example of an asymmetric C-H oxidation of unactivated, but pre-functionalized, alkanes mediated by a non-enzymatic system, generating the ketone product.[81] The employment of very bulky ligands in combination with a manganese catalyst, as well as the addition of large amounts (17 eqs.) of carboxylic acids were crucial for achieving high enantiomeric excess (ee). The addition of acid contributes to defining the active catalytic species by binding *cis* to the site where H_2O_2 is activated, as is also observed with related manganese and iron catalysts for epoxidation reactions.[82-84] Interestingly, cyclopropanecarboxylic acid proved to be the best additive, partially due to its rigid structure and oxidative stability.

Nam and Wang published in 2022 and 2023, respectively, two papers employing similar tetradentate manganese catalysts for C-H hydroxylation reactions.[85, 86] In their works they showed selective oxidation of C-H bonds to alcohols without over-oxidation to the corresponding ketone. In both cases, however, bromoacetic acid was a necessary additive, while in their consecutive publication, the presence of fluorinated solvents was also required to achieve the desired selectivities. Of note, however, pre-functionalized alkanes with various C-H bonds present could be hydroxylated selectively at the desired sites, demonstrating the positive impact of the aforementioned less benign additives or solvents on the reaction outcome.

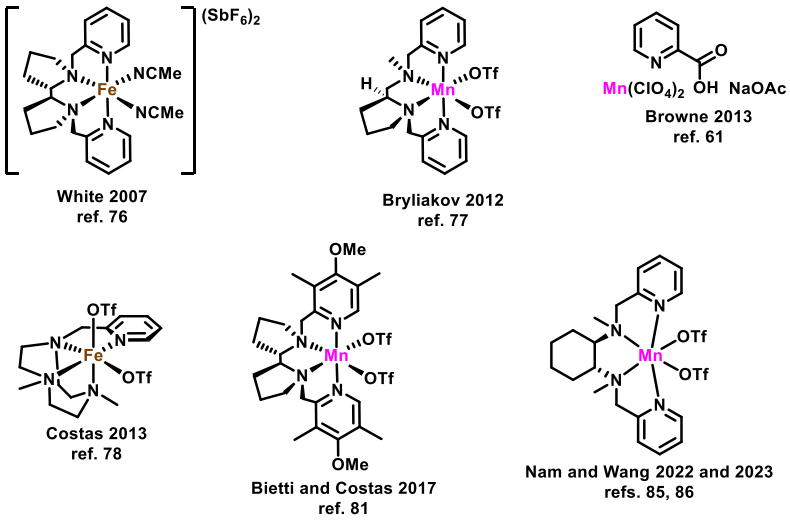


Figure 4: Selected examples of iron- and manganese-based C-H oxidation catalysts.

Upon reviewing the hitherto cited literature reports, and others,[87-90] it becomes clear that tetradentate, nitrogen-based ligands are privileged structures for catalyst design in epoxidation and C-H oxidation reactions. Especially scaffolds containing two aliphatic amine motifs as well as two aza-heterocyclic amine moieties, have proven to be a crucial instrument in said transformations, particularly regarding complex substrates or enantioselective processes.[91] As nature commonly relies on similar structures for highly selective oxidation reactions, it is, therefore, no wonder that scientists were inspired to mimic these naturally occurring structures when designing new manganese- or iron-based catalyst systems.[92] Between these two metals, manganese holds a unique position as it often displays superior catalytic traits compared to the iron equivalent for oxidation reactions.[93]

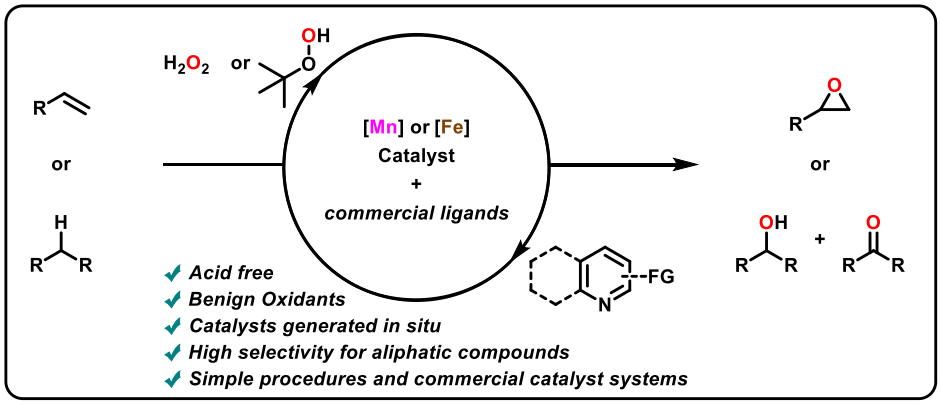
2. Objectives of this Work

Despite all the advantages of non-noble metal-based catalyst systems for oxidation reactions and the numerous scientific contributions that have already been made, it is noteworthy that most of those were focused on rather complex and pre-functionalized molecules or even enantioselective processes (see chapter 1.2.2). Furthermore, regarding bulk chemical syntheses in the chemical industry, cost-effectiveness and robustness remain major unsolved problems with established methodologies for epoxidation and C-H oxidation reactions (see chapter 1.2.1).

Therefore, especially for the latter case, there is still a large room for improvement regarding a catalytic system that focuses on a combination of the following points:

1) A protocol that specifically addresses the oxidation of unactivated, unsubstituted olefins and alkanes, which is of interest for bulk chemical syntheses,
2) the employment of an inexpensive catalytic system that does not require complicated procedures or elaborate ligand syntheses, and
3) the use of an environmentally benign oxidant without the necessity of large excesses of acids or similarly corrosive, toxic or otherwise harmful compounds.

Therefore, within the frame of this doctoral thesis, we sought to develop such systems based on the earth-abundant metals manganese and iron employing commercially available and inexpensive ligands and additives (Scheme 3).



Scheme 3: General concept of this thesis.

3. Summary of Research

The following chapter summarizes the research that was conducted during the time of this thesis. In detail, the development of two new manganese catalyst systems, as well as an iron catalyst system, for the oxidative valorization of alkenes and alkanes are presented.

3.1. Manganese N,N,N-Pincer Complex-Catalyzed Epoxidation of Unactivated Aliphatic Olefins

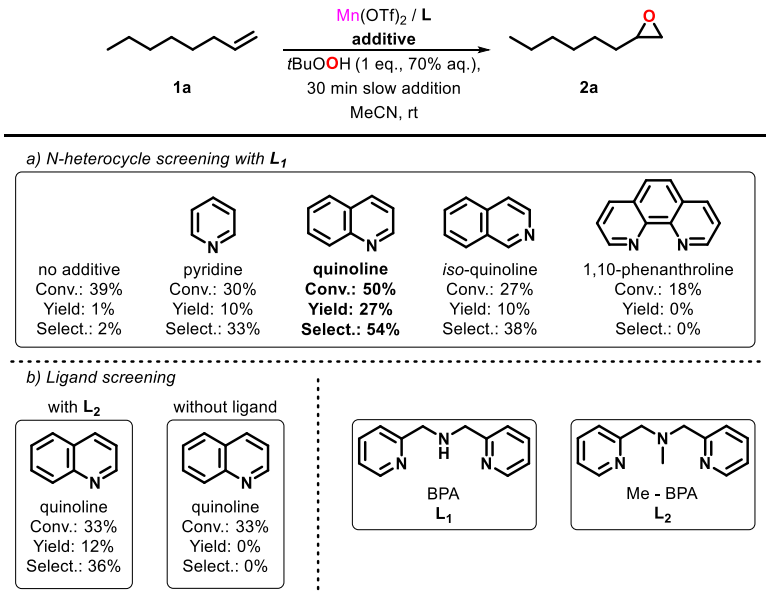
As discussed in the introduction, many valuable contributions in the field of manganese-catalyzed epoxidation reactions were realized in the past. However, we still sought to develop a new methodology, complementing the present state-of-the-art, by concentrating on a combination of the following points: (i) specifically address the epoxidation of terminal aliphatic olefins, which are of interest for bulk and fine chemical syntheses, (ii) employment of a cheap and easily accessible catalyst system without the requirement of complicated procedures or elaborate ligand syntheses, and (iii) using an environmentally benign oxidant without the necessity of large excesses of acids or similarly corrosive, toxic or otherwise harmful compounds.

3.1.1. Optimization of Reaction Conditions

Based on our previous experiences with non-noble metal pincer catalysts,[34, 94] we initiated our investigations by probing the reactivity of an *in situ* catalytic system utilizing manganese(II)triflate as precursor and bis(2-picolyl) amine **L1** as the employed N,N,N-pincer ligand for the epoxidation of the model substrate 1-octene **1a**. As *tert*-butyl hydroperoxide (TBHP) is industrially applied in the epoxidation of propylene (Halcon process)[6] we used it as terminal oxidant (70% aqueous solution). Employing 1 equivalent of TBHP at room temperature and 5 mol% of manganese precursor, only trace amounts of the desired product 1,2-epoxyoctane **2a** were detected (Table 1a) while no other major product could be identified. We thus assume that the starting material mainly underwent oxidative degradation to CO_2. However, the addition of N-heterocycles as co-ligands, which are known for their beneficial effects in selected metal-catalyzed oxidation reactions,[34, 54, 95, 96] surprisingly improved the reaction to a significant degree.

The results of the influence of various N-containing compounds on the reaction outcome are highlighted in Table 1. For example, in the presence of 30 mol% of pyridine, 10% of the desired epoxide were formed. Notably, exchanging pyridine with quinoline to test other aromatic heterocycles, showed a substantial improvement of this result, giving 27% yield of 1,2-epoxyoctane **2a** under the applied reaction conditions. Here, *iso*-quinoline yielded similar results to pyridine, while the bidentate 1,10-phenanthroline proved ineffective for this reaction (Table 1a). Predictably, no reaction occurred without employing a pincer ligand. Applying the N-methylated bis(2-picolyl) amine (Me – BPA) **L2** had a detrimental effect on the reactivity of this system, giving only 12% epoxide **2a** after GC analysis (see Table 1b). Hence, commercial BPA **L1** was chosen as ligand for this system.

Table 1: Initial screening of various N-heterocycles as additives.

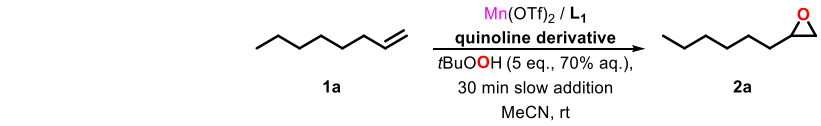


Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.125 M), 5 mol% $Mn(OTf)_2$, 6 mol% **L1** or **L2**, 30 mol% N-heterocycle, MeCN (4 mL), 25 °C, 30 min slow addition of TBHP (70% aq., 1 eq.) *via* syringe pump.

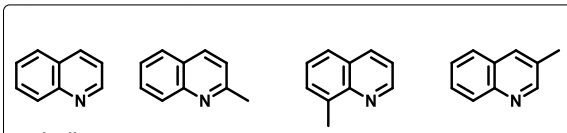
Interestingly, applying 5 eqs. of TBHP led to full conversion of **1a** giving 67% yield of the desired epoxide **2a** with simple quinoline as the additive (see Table 2a). Hence, the effect of different substituted and commercially available quinolines was elucidated in the model reaction. For our first experiments, we employed methylated quinolines as additives. While 2-methyl- and 8-methylquinoline led to a significantly reduced catalytic performance (possibly due to steric hindrance), the other methylated quinolines provided similar or marginally lower yields compared to unsubstituted quinoline (Table 2a).

Followingly, halogenated quinolines with electron-withdrawing substituents were investigated in the epoxidation reaction (see Table 2b). Here, 3-chloroquinoline gave a significantly reduced yield, while 4-chloroquinoline only gave a moderately reduced yield. On the other hand, 6-fluoroquinoline yielded an almost identical outcome to standard quinoline. Seemingly, either sterically impaired quinolines or electronically poor N-containing rings negatively impede on the reaction outcome. Thus, unsubstituted quinoline was selected as additive for further optimization studies.

Table 2: Selected results of quinoline additive screening.

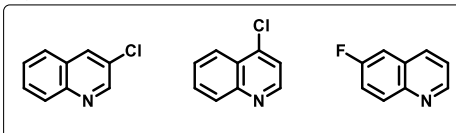


a) Quinoline and methylated quinolines



quinoline	2-methylquinoline	8-methylquinoline	3-methylquinoline
Conv.: >99%	Conv.: 65%	Conv.: 61%	Conv.: >99%
Yield: 67%	Yield: 29%	Yield: 6%	Yield: 65%
Select.: 67%	Select.: 45%	Select.: 9%	Select.: 65%

b) Halogenated quinolines



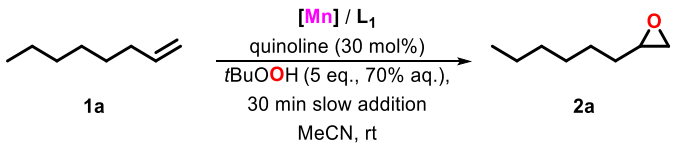
3-chloroquinoline	4-chloroquinoline	6-fluoroquinoline
Conv.: 50%	Conv.: 81%	Conv.: 97%
Yield: 10%	Yield: 46%	Yield: 65%
Select.: 21%	Select.: 56%	Select.: 68%

Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.125 M), 5 mol% $Mn(OTf)_2$, 6 mol% **L**$_1$, 30 mol% quinoline derivative, MeCN (4 mL), 25 °C, 30 min slow addition of TBHP (70% aq., 5 eq.) *via* syringe pump.

Variation of the amount of the quinoline additive revealed 30 mol% to be the most efficient. Subsequently, different metal precursors were screened for this reaction. To identify alterations in the reactivity more easily, we employed only 1 equivalent of TBHP, thus preventing full conversion of the starting material 1-octene **1a**. As shown in Table 3, only manganese precursors with weakly coordinating anions were effective for the epoxidation reaction (cf. Table 3, entry 9).

The best results were obtained in the presence of manganese(II)perchlorate, manganese(II)triflimide and manganese(II)triflate (Table 3, entries 1, 5, 7). Using an iron(II) pre-catalyst turned out to be incompatible with the present protocol, demonstrating the unique reactivity of manganese under present conditions (Table 3, entry 4). Besides TBHP, we also employed hydrogen peroxide (30% aq.) as terminal oxidant, which provided only low amounts of the desired product (12%) (Table 3, entry 3). Interestingly, no difference applying the *in situ* generated catalyst system compared to using the isolated complexes **Mn-1** and **Mn-2** as catalyst was observed (Table 3, entry 10).

Table 3: Screening of various precursors and oxidant variation for epoxidation reaction.



Entry	Precursor	TBHP [eq.]	Conv. (1a) [%]	Yield (2a) [%]	Sel. (2a) [%]
1	$Mn(OTf)_2$	1	50	27	54
2	**$Mn(OTf)_2$**	**5**	**>99**	**67**	**67**
3	$Mn(OTf)_2$	H_2O_2 (5 eq.)	21	12	57
4	$Fe(OTf)_2$	5	12	1	8
5	$Mn(ClO_4)_2$	1	43	24	55
6	$Mn(ClO_4)_2$	5	99	59	60
7	$Mn(NTf_2)_2$	1	42	26	62
8	$Mn(NTf_2)_2$	5	99	61	62
9	$Mn(OAc)_2$	1	22	0	0
10	**Mn-1** or **Mn-2**	5	>99	67	67

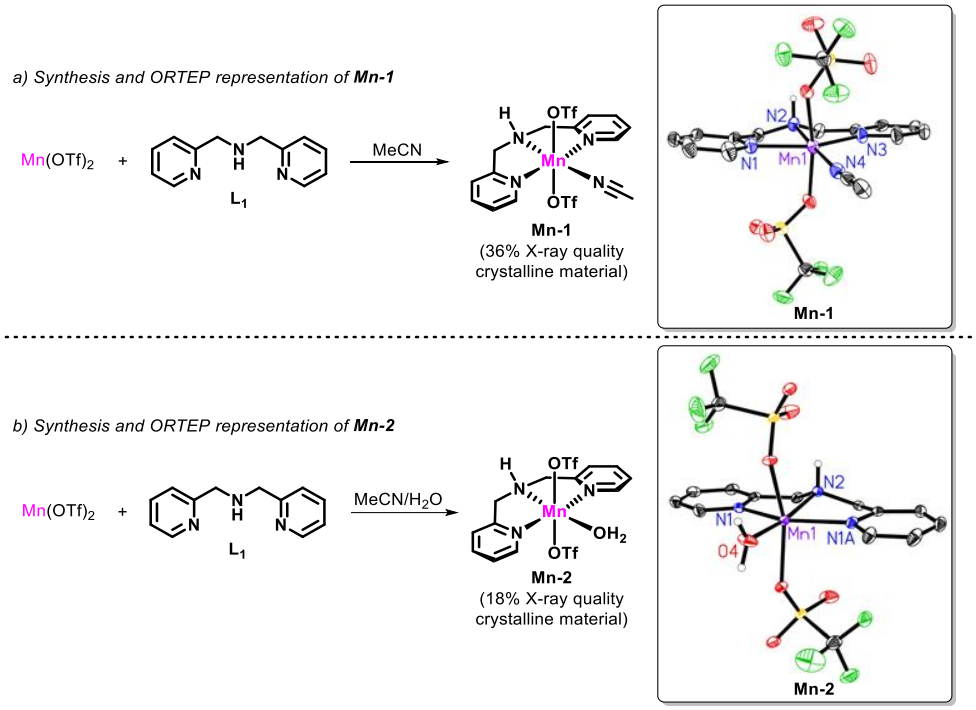
Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol 1-octene **1a** (0.125 M), 5 mol% manganese precursor, 6 mol% **L1**, 30 mol% quinoline, MeCN (4 mL), 25 °C, 30 min slow addition of oxidant *via* syringe pump.

Screening of other solvents revealed that only MeCN is suitable for this reaction, as it is often observed in epoxidation reactions.[22] On the one hand, MeCN is oxidatively stable and possesses mild coordinating abilities, stabilizing metal complexes. On the other hand, its polarity offers sufficient solubility for aqueous peroxide solutions, the employed catalyst systems, and for alkene substrates.[17] Furthermore, any deviations from these optimized reaction conditions did not increase the product yield or reaction efficiency (for more information check the ESI of the original publication).

3.1.2. Catalyst Preparation and Characterization

Following the investigations of the *in situ* model reaction, we were interested in synthesizing a defined manganese(II)-complex. Therefore, manganese(II)triflate and bis(2-picolyl) amine **L1** were mixed under inert conditions in dry MeCN and subsequently layered with dry Et_2O (see Scheme 4a). Gratifyingly, **Mn-1** was obtained as colorless needles after crystallization. The complex crystallizes in the triclinic space group $P\bar{1}$ with two molecules in the unit cell and a distorted octahedral geometry. Here, one MeCN molecule is coordinated to the manganese(II)center in addition to the three nitrogen atoms of the pincer ligand and two triflate groups with the ligand coordinating in an equatorial fashion. Elemental analysis confirms the formation of $Mn(II)(OTf)_2$ – **L1** as the coordinating MeCN is removed *in vacuo* when drying the crystals before measurement. Accordingly, HRMS shows $[M\text{-}OTf]^+$. In a second set up, the above procedure was repeated with undried MeCN to imitate the aqueous

reaction conditions. Here, layering the MeCN solution of the complex with benzene led to the formation of a different solvent complex **Mn-2**, which was obtained as colorless prismatic needles (see Scheme 4b). In contrast to **Mn-1**, the usage of undried MeCN led to an exchange of the additional coordinating MeCN with a water molecule. This complex crystallizes in the monoclinic space group *P*2/*n* with two molecules in the unit cell and a distorted octahedral geometry. The N,N,N-pincer ligand and the triflate anions coordinate in a similar fashion to **Mn-1**. Here, elemental analysis and HRMS also confirmed the formation of Mn(II)(OTf)$_2$ – **L$_1$** and [M-OTf]$^+$, respectively. Obviously, **Mn-1** is converted to **Mn-2** during the catalytic reaction, which accounts for the similar catalytic performance of the isolated complexes **Mn-1** and **Mn-2** and the *in situ* system.

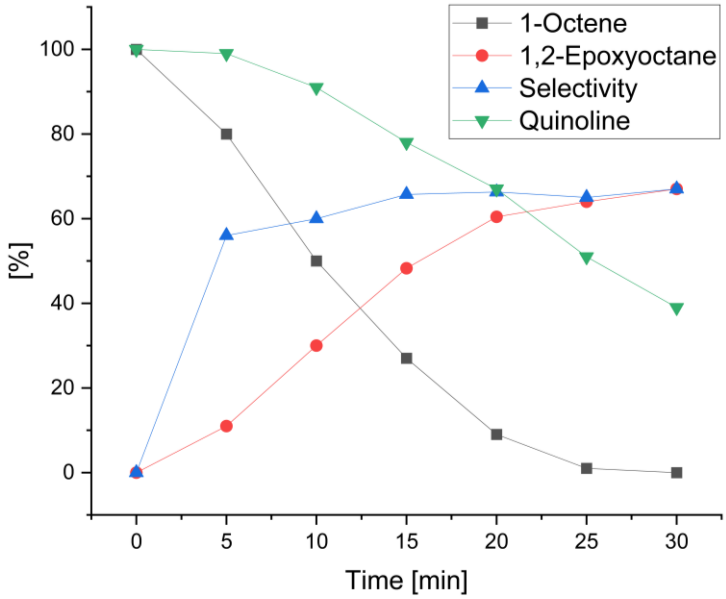


a): **Mn-1**. (S yellow, O red, F green). Displacement ellipsoids correspond to 30% probability. C-bound hydrogen atoms and one position of the disordered triflate ligands are omitted for clarity.
b): **Mn-2**. (S yellow, F green). Displacement ellipsoids correspond to 30% probability. C-bound hydrogen atoms and one position of the disordered parts of the complex are omitted for clarity.

*Scheme 4: Syntheses and ORTEP representations of manganese catalysts **Mn-1** and **Mn-2**.*[97]

3.1.3. Mechanistic Investigations

With the optimized reaction conditions and two crystal structures in hand, we focused on a more profound understanding of this catalytic system. We initiated our investigations of the reaction pathway by recording the kinetic profile of the epoxidation of the model substrate 1-octene **1a** (see Figure 5). Here, we found that the selectivity stays rather constant at approximately 60 – 67% after the first ~10 minutes. Intriguingly, we also observed that quinoline is partially consumed during the reaction, as only 39% of the initially employed amount is detected by GC analysis after the reaction is completed.

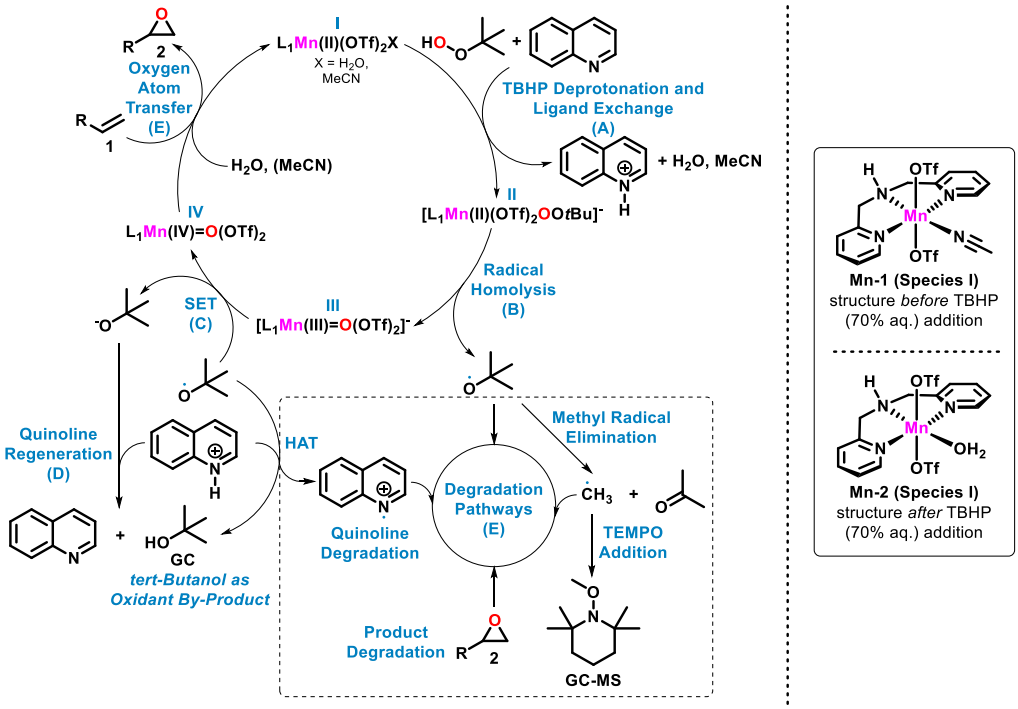


Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol 1-octene (0.125 M), 5 mol% $Mn(OTf)_2$, 6 mol% **L**$_1$, 30 mol% quinoline, MeCN (4 mL), 25 °C, 30 min slow addition of TBHP (70% aq., 5 eq.) *via* syringe pump. Six reactions were set up in parallel and at every 5-minute mark one reaction was stopped and analyzed.

Figure 5: Kinetic profile of 1-octene epoxidation.

To shed light on the nature of the reaction and possible side- or follow-up reactions as well as on the intriguing role of quinoline, several control experiments were performed: First, the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinyloxyl) (1 eq.) was added to the model reaction under otherwise standard conditions, which completely inhibited product formation, thus pointing towards the importance of radical intermediates in this reaction. When adding 1 eq. of BHT (2,6-di-*tert*-butyl-4-methylphenol) to the reaction mixture, a similar yet less pronounced effect was observed with 45% conversion of 1-octene and 26% epoxide yield. Furthermore, the product 1,2-epoxyoctane **2a** was subjected to the standard reaction conditions to analyze its stability. Interestingly, only 72% of the epoxide and 19% of the employed quinoline were detected by GC analysis after 30 minutes. This clearly suggests that the product is not entirely stable under the present reaction conditions and that the inherent limitation of this system is more likely a follow-up reaction of the product with the quinoline rather than a side-reaction of the starting material. Repetition of this experiment with the addition of 1 eq. TEMPO revealed that both the product **2a** and quinoline remain completely unreacted, which indicates that the presumed follow-up reaction of the epoxide with the quinoline is also of a radical nature. Unfortunately, all efforts to isolate the decomposition product(s) failed and it was not possible to identify its structure(s). Additionally, we subjected the product to our standard reaction protocol and evaluated the effect of all employed compounds for its degradation. Indeed, the presence of all compounds is essential for quinoline and product degradation. Summarizing all these results, we can deduce that the presence of quinoline or related heterocycles is, on the one hand, essential for the desired product formation. On the other hand, it also promotes an unwanted follow-up reaction with the formed epoxide. Both reactions are mediated by our manganese-pincer catalyst under oxidative conditions. Based on these results the following catalytic cycle was postulated (see Scheme 5): After mixing the metal precursor and the ligand, species **I** is formed. In the first reaction step **A**, quinoline acts as a base deprotonating TBHP to facilitate the ligand exchange of $L_1Mn(II)(OTf)_2X$ (with X = MeCN, H_2O) (species **I**) to form $L_1Mn(II)(OTf)_2OO$*t*Bu (**II**) and the protonated quinolyl cation $[Q\text{-}H]^+$. Then, species **II** undergoes homolysis generating the oxo-species $[L_1Mn(III)=O(OTf)_2]^-$ **III** and a *tert*-butyl alkoxy radical (step **B**). Consecutively, a single-electron transfer (SET)

from species **III** to the *tert*-butoxy radical occurs, thus forming a manganese(IV)oxo-species **IV** and *tert*-butanolat (step **C**). In step **D**, the quinoline additive is regenerated by protonating the *tert*-butanolat anion, forming the oxidant by-product *tert*-butanol, which is also observed by GC analysis. In the last step (**E**), the olefin **1** is oxidized to the epoxide **2** by the previously formed Mn(IV)=O species **IV**. After the free coordination site is saturated by H_2O (see crystal structures), species **I** is reformed again. As quinoline and the epoxide are partly consumed during the reaction, the following degradation pathways **E** are proposed: The protonated quinoline $[Q\text{-}H]^+$ can react with a *tert*-butyl alkoxy radical in a hydrogen atom transfer (HAT) reaction, also generating *tert*-butanol and an oxidized quinolyl radical. Tertiary alkoxy radicals are known to eliminate methyl radicals, generating the corresponding ketone.[65] The presence of these methyl radicals was indirectly confirmed by the formation of the methylated adduct 1-methoxy-2,2,6,6-tetramethylpiperidine, when TEMPO was added to the reaction mixture. Such methyl radicals, as well as the *tert*-butyl alkoxy radicals can be responsible for quinoline and product degradation.



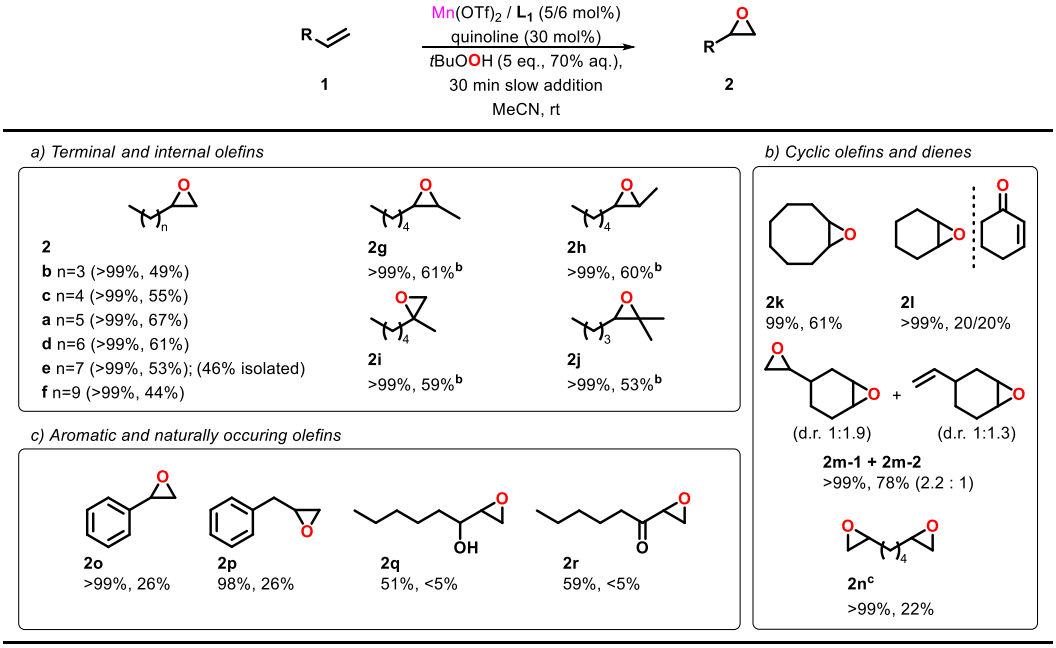
Scheme 5: Mechanistic Proposal and possible degradation pathways for manganese-catalyzed epoxidation reaction.

3.1.4. Substrate Scope

Finally, we studied the scope of the developed novel catalytic protocol applying other terminal and internal olefins (Table 4a). Both, linear and terminal epoxides bearing shorter alkyl chains **2b** and **2c** were obtained in moderate yields of 49% and 45%, respectively, possibly due to higher product volatility. As expected, 1-nonene was converted in 61% yield to the desired epoxide **2d**. Further increase of the chain length, however, led to somewhat reduced yields, as is observed with 1,2-epoxydecane **2e** (53%) and 1,2-epoxydodecane **2f** (44%), possibly due to lower solubility of the starting materials. Employing the internal olefins 2-methyl-1-heptene (**1i**) and 2-methyl-2-heptene (**1j**) gave similar epoxide yields of 59% and 53%, respectively. Additionally, *cis* and *trans* 2-octene displayed identical reactivity to 1-octene giving epoxide yields of >60%. Applying cyclic alkenes and dienes (see Table 4b), *e.g.*, cyclohexene (**1l**), less selective oxidizations occurred under these conditions. Here, allylic oxidation competes with the desired epoxidation, as is in accordance with the radical nature of this system.

Hence, the reaction gave a 1 : 1 mixture of both possible products in 20% yield, respectively. On the other hand, cyclooctene was epoxidized in good yield of 61% to **2k**. Next, we subjected the more challenging substrate 4-vinyl-cyclohexene **1m** to our optimized conditions to probe the selectivity of ring epoxidation versus epoxidation of the vinyl side chain. To our delight we observed an overall yield of epoxidation products of 78% with a selectivity of 2.2 : 1 (double epoxidation : ring epoxidation). Lastly, 1,7-octadiene **1n** was applied in the present protocol. Here, halving the amount of substrate led to full conversion to the desired di-epoxide **2n** in lower yield (22%).

Table 4: Scope of olefins for manganese-catalyzed epoxidation reaction.



Conversion and yield determined by GC analysis with hexadecane as IST, a: isolated yield, b: yield determined by NMR analysis with dibromomethane as IST, c: 0.25 mmol substrate. Reaction conditions: 0.5 mmol substrate (0.125 M), 5 mol% $Mn(OTf)_2$, 6 mol% **L**$_1$, 30 mol% quinoline, MeCN (4 mL), 25 °C, 30 min slow addition of TBHP (70% aq., 5 eq.) *via* syringe pump.

Finally, we tested the epoxidation of aromatic olefins, which are usually more reactive than terminal aliphatic olefins.[42] However, with the here presented catalytic protocol only ~27% of styrene oxide **2o** and benzyloxiran **2p** were formed. GC analyses did not reveal the formation of major side-products in either of these cases. Furthermore, we found that the naturally occurring 1-octene-3-ol or the corresponding ketone are not well tolerated under our reaction conditions. In both cases only trace amounts of the epoxide products **2q** and **2r** (< 5%), and much lower conversions were obtained (see Table 4c).

Summarizing this chapter, a new synthetic protocol for the epoxidation of the challenging terminal aliphatic olefins was developed. Two crystal structures of the manganese-complex, as well as some information about the role of quinoline were obtained during this project. However, a few shortcomings regarding the applicability and detailed (mechanistic) understanding of this protocol remain. Hence, we tried to solve these issues (see next chapter).

3.2. A Manganese-based Catalyst System for General Oxidations of Unactivated Olefins, Alkanes, and Alcohols

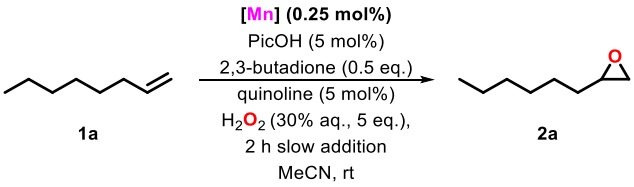
Encouraged by the discovery of the intriguing role of N-heterocycles in our previously published work about manganese-catalyzed epoxidation reactions,[97] and also inspired by the works of Browne and co-workers,[58] we saw great potential in the improvement of such a system. These improvements should include, (i) a deeper understanding of the detailed role of the applied N-heterocycles, (ii) a broader applicability regarding the substrate scope and (iii), a higher efficiency, *i.e.,* lower catalyst loading and a more benign oxidant.

3.2.1. Optimization of Reaction Conditions

Based on our previously reported system,[97] we envisioned utilizing $Mn(OTf)_2$ as metal precursor and quinoline as N-heterocyclic additive. As established in the literature,[58] a combination of hydrogen peroxide with 2,3-butadione as peroxide activator should fulfill the role of terminal oxidant while picolinic acid should serve as cheap and commercially available ligand. We started our investigations of the catalytic activity of this manganese-based picolinic acid – quinoline system by choosing 1-octene **1a** as model substrate for epoxidation. Therefore, we first varied in the numerical parameters, *i.e.*, catalyst loading, additive amounts, and their respective ratios to find conditions that we deemed sufficiently satisfying for further investigations (see supporting information of the original publication for more details). Concluding this initial screening, we achieved 79% conversion and obtained 37% yield of 1,2-epoxyoctane **2a** when employing 0.25 mol% $Mn(OTf)_2$, 5 mol% picolinic acid, 5 mol% quinoline, 0.5 equivalent 2,3-butadione, and 5 equivalents H_2O_2 (30% aq.).

We then embarked on an in-depth precursor screening to improve activity and selectivity. Obviously, there are many examples in the literature where weakly coordinating anions are effective in manganese-catalyzed oxidation or epoxidation reactions.[22] As expected, such anions, *e.g.*, perchlorate, triflate and triflimide all produced virtually identical results of 78% conversion and 37% epoxide yield (see Table 5, entries 1 – 3). Switching to hexafluoropenta-2,4-dione as anion, a slightly higher conversion and yield of 40% was obtained (Table 5, entry 5). Following this surprising trend, we then employed stronger coordinating anions in this protocol. To our delight, acetate and acetylacetonate produced better yields then the initially employed precursors, giving almost full conversion of the starting material and yields of 40 – 45% of the desired epoxide **2a** (Table 5, entries 6 – 8). Manganese(II)bromide also yielded the product in 42% yield with full conversion of the starting material (Table 5, entry 11). Next to $MnBr_2$ we also tested other halogen derived manganese salts. We gratefully obtained 51% yield of the epoxide **2a** with simple and cheap $MnCl_2$ (Table 5, entry 12). Interestingly, almost identical results were obtained with $MnSO_4$ and $Mn(NO_3)_2$, giving 50% and 48% of 1,2-epoxyoctane, respectively (Table 5, entries 9, 10). To better distinguish between the best working precursors, we tested $MnCl_2$ and $Mn(NO_3)_2$ with only 2.5 equivalents of oxidant and found that $MnCl_2$ yielded almost identical results as before, while $Mn(NO_3)_2$ gave a slightly reduced conversion and a correspondingly lower yield. Therefore, $MnCl_2$ was chosen as precursor for further studies. Of note, iron was found not to be compatible with the present protocol (Table 5, entry 4).

Table 5: Precursor screening for picolinate based manganese-catalyzed epoxidation of 1-octene.



Entry	Precursor	Conv. (1a) [%]	Yield (2a) [%]	Sel. (2a) [%]
1	$Mn(OTf)_2$	79	37	47
2	$Mn(ClO_4)_2$	77	37	48
3	$Mn(NTf_2)_2$	78	37	47
4	$Fe(ClO_4)_3$	34	0	0
6	$Mn(OAc)_2$	99	45	45
7	$Mn(acac)_2$	99	42	42
9	$MnSO_4$	99	50	50
10	$Mn(NO_3)_2$	99/87[a]	48/43[a]	48/49[a]
11	$MnBr_2$	99	42	42
12	**$MnCl_2$**	**99/97[a]**	**51/49[a]**	**51/51[a]**

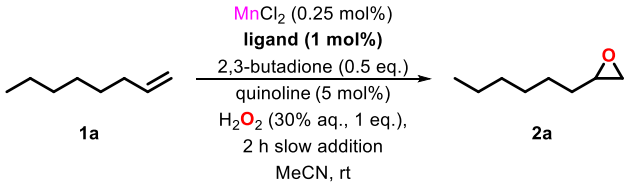
Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.25 mol% manganese precursor, 5 mol% picolinic acid, 5 mol% quinoline, 0.5 eq. 2,3-butadione, MeCN (2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 5 eq., diluted in MeCN) *via* syringe pump. a: 2.5 eq. of H_2O_2 (30% aq.) used.

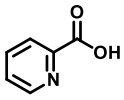
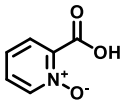
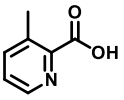
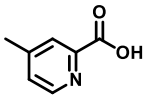
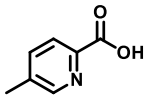
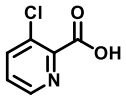
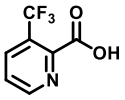
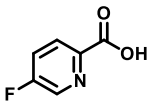
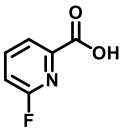
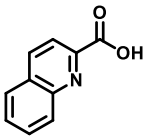
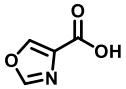
Further reduction of oxidant to 1.0 equivalent gave results more suitable for upcoming screening efforts (66% conversion and 26% yield), thus facilitating the comparison of respective variations. Next, we varied the amount of picolinic acid. Starting with an initial [PicOH]:[Mn] ratio of 20:1, we found that a ratio of 4:1 gave the best results of 35% yield of 1,2-epoxyoctane **2a**. As this ratio deviates from previously reported findings[63, 98, 99] we further investigated the role and influence of the picolinic acid on the reaction outcome by conducting a thorough ligand screening.

First off, the addition of picolinic acid is necessary, as we observe no epoxide formation in its absence. Presumably, the starting material undergoes oxidative decomposition, as no major side-product is observed during GC analysis. Secondly, the formation of picolinic acid-*N*-oxide as the active ligand can be excluded, as its employment did not result in any product formation. Next, we investigated the influence of the substitution pattern on the picolinic acid. Here, we observed slightly reduced activity of the catalyst system when employing methylated picolinic acids (3-Me, 4-Me and 5-Me) and obtained almost identical yields of ~28% in all three cases. Electron-withdrawing substituents, *i.e.*, 3-Cl and 3-CF_3 provided the product **2a** in similar yields of ~26%. Furthermore, 5-fluoropicolinic acid proved less suitable, yielding 22% of epoxide. Finally, blocking the 6-position, either by employing quinoline-2-carboxylic acid or 6-fluoropicolinic acid led to no product formation whatsoever, as in the absence of any ligand. Therefore, we assume that the active complex does not form if the 6-position of the ligand is blocked.

The same result was observed for 4-oxazolecarboxylic acid, indicating that no active complex is formed (see Table 6).

Table 6: Screening of picolinic acid derivatives as ligands for manganese-catalyzed epoxidation of 1-octene.

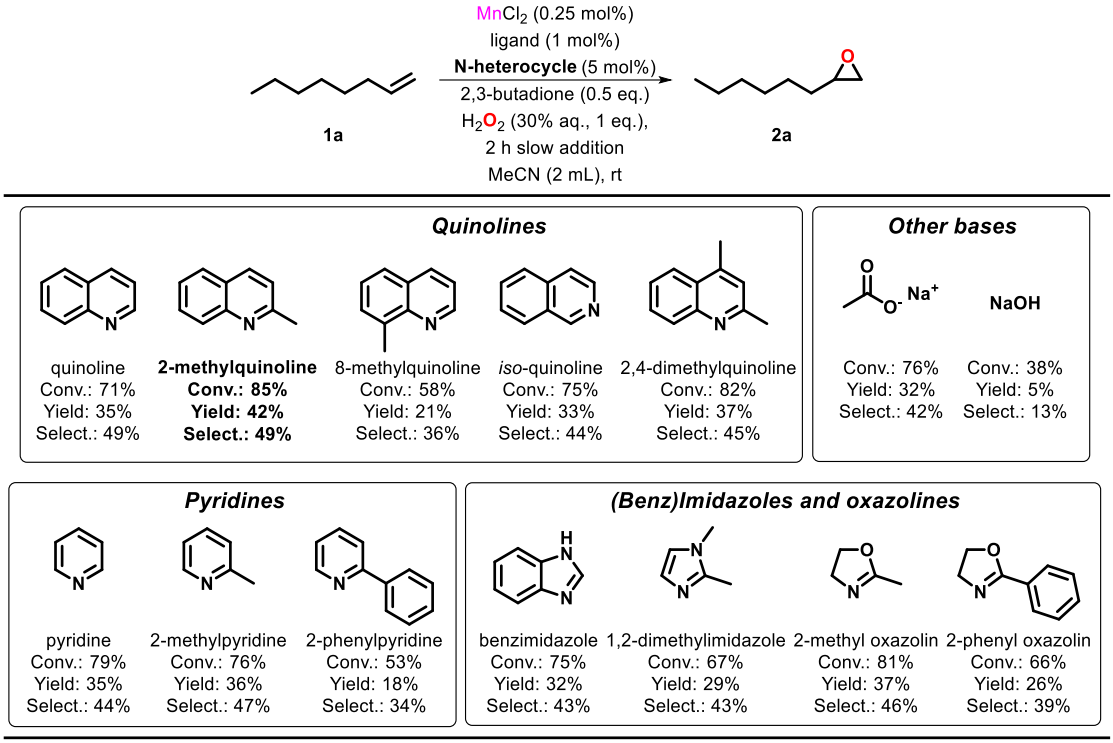


 No Ligand Conv.: 32% Yield: 0% Select.: 0%	picolinic acid Conv.: 71% Yield: 35% Select.: 49%	 picolinic acid *N*-oxide Conv.: 36% Yield: 0% Select.: 0%	 3-methylpicolinic acid Conv.: 66% Yield: 27% Select.: 41%	 4-methylpicolinic acid Conv.: 67% Yield: 28% Select.: 42%	 5-methylpicolinic acid Conv.: 69% Yield: 28% Select.: 41%
 3-chloropicolinic acid Conv.: 67% Yield: 27% Select.: 40%	 3-(trifluoromethyl)picolinic acid Conv.: 69% Yield: 26% Select.: 38%	 5-fluoropicolinic acid Conv.: 64% Yield: 22% Select.: 34%	 6-fluoropicolinic acid Conv.: 33% Yield: 0% Select.: 0%	 quinoline-2-carboxylic acid Conv.: 30% Yield: 0% Select.: 0%	 4-oxazolecarboxylic acid Conv.: 34% Yield: 0% Select.: 0%

Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.25 mol% manganese(II)chloride, 1 mol% picolinic acid derivative, 5 mol% quinoline, 0.5 eq. 2,3-butadione, MeCN (2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 1 eq., diluted in MeCN) *via* syringe pump.

Furthermore, the influence of the N-heterocycle with varying steric effects was investigated (see Table 7). Here, we found that 2-methylquinoline gave a slightly improved yield of the desired epoxide **2a** of 42% compared to quinoline. In contrast, the introduction of a methyl group in the 8-position of quinoline severely hindered the reaction and only yielded 21% of the epoxide (for a more detailed discussion see supporting information of the original publication). Other quinoline derivatives yielded the epoxide in similar yields of 33 – 37%. Pyridines proved similarly or slightly less efficient than quinolines with the bulky 2-phenylpyridine providing the epoxide only in low yield (18%). While in the presence of (benz)imidazoles the desired products were obtained in yields around 30%, 2-methyloxazoline proved similarly suitable as quinoline. Here, 2-phenyloxazoline was also less efficient as additive. Considering the negative effect of very bulky substituents in the vicinity of the nitrogen-atom, a coordination of the heterocycle to the metal center during the catalytic reaction seems reasonable. Additionally, we also employed the simple bases NaOAc and NaOH for comparative reasons. While the former is a suitable, though less effective base compared to 2-methylquinoline for this transformation, the latter provided a poor yield of the epoxide. Taken together, these results suggest than the employed heterocycle fulfills multiple roles in this reaction, *i.e.*, being a basic additive enabling complex formation but also acting as a potentially stabilizing co-ligand for the metal catalyst.

Table 7: Screening of selected N-heterocycles and bases for epoxidation reaction.



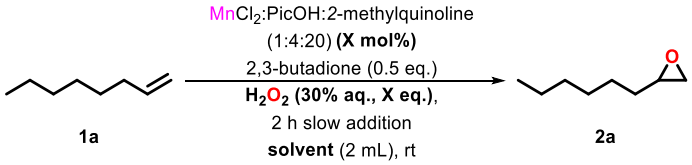
Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.25 mol% manganese(II)chloride, 1 mol% picolinic acid, 5 mol% N-heterocycle or base, 0.5 eq. 2,3-butadione, MeCN (2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 1 eq., diluted in MeCN) *via* syringe pump.

Having identified the most suitable heterocycle, we then varied in the amount of the employed 2-methylquinoline. Here, we found that a ratio of $MnCl_2$:PicOH:2-methylquinoline of 1:4:20 is most efficient, giving the best yield of 42%. Further optimization attempts regarding the ketone additive, which assists in activating hydrogen peroxide,[58] turned out unsuccessful.

After determining the optimal stoichiometries of all employed additives, the catalyst amount was varied at the aforementioned ratio. Increasing the amount of catalyst to 1 mol% led to slightly lower conversion of starting material and accordingly lower yields (Table 8, entry 1). As described in the literature,[64] higher catalyst loadings can increase H_2O_2 disproportionation. Lowering the catalyst loading to 0.05 mol% we still achieved 38% epoxide yield which could be increased again to 42% by simply changing the reaction solvent to a more polar mixture (MeCN:H_2O = 75:25, vol%:vol%), possibly due to better solubility of the manganese precursor and picolinic acid (Table 8, entries 3 – 5). Further variation of the reaction solvent did not improve upon these results, demonstrating again the unique features of MeCN.[97]

Finally, the amount of the employed hydrogen peroxide (30% aq.) was studied (Table 8, entries 6 – 9). Using 1.0 equivalent of H_2O_2 already 42% of the desired product **2a** were obtained, which is comparable to previously reported catalyst systems composed of $Mn(ClO_4)_2$, picolinic acid, and hydrogen peroxide solutions (50% aq.).[58] Interestingly, employing 2.0 equivalents of H_2O_2, we obtained the highest yield of 61% (Table 8, entry 8). Further increase led to full conversion of **1a**, however, the yield of **2a** could not be improved (Table 8, entry 9). Thus, we chose the conditions depicted in entry 8 as the final reaction conditions.

Table 8: Final optimization studies of manganese-catalyzed epoxidation.



Entry	H_2O_2 [eq.]	$MnCl_2$ [mol%]	Solvent	Slow Addition Time [h]	Conv. (1a) [%]	Yield (2a) [%]	Sel. (2a) [%]
1	1.0	1.0	MeCN	2	71	31	44
2	1.0	0.25	MeCN	2	85	42	49
3	1.0	0.05	MeCN	2	79	38	48
4	1.0	0.01	MeCN:H_2O (95:5)	2	75	31	41
5	1.0	0.05	MeCN:H_2O (75:25)	2	82	42	51
6	1.25	0.05	MeCN:H_2O (75:25)	2	87	44	51
7	1.5	0.05	MeCN:H_2O (75:25)	2	92	50	54
8	**2.0**	**0.05**	**MeCN:H_2O (75:25)**	**2**	**97**	**61**	**63**
9	2.5	0.05	MeCN:H_2O (75:25)	2	>99	57	57

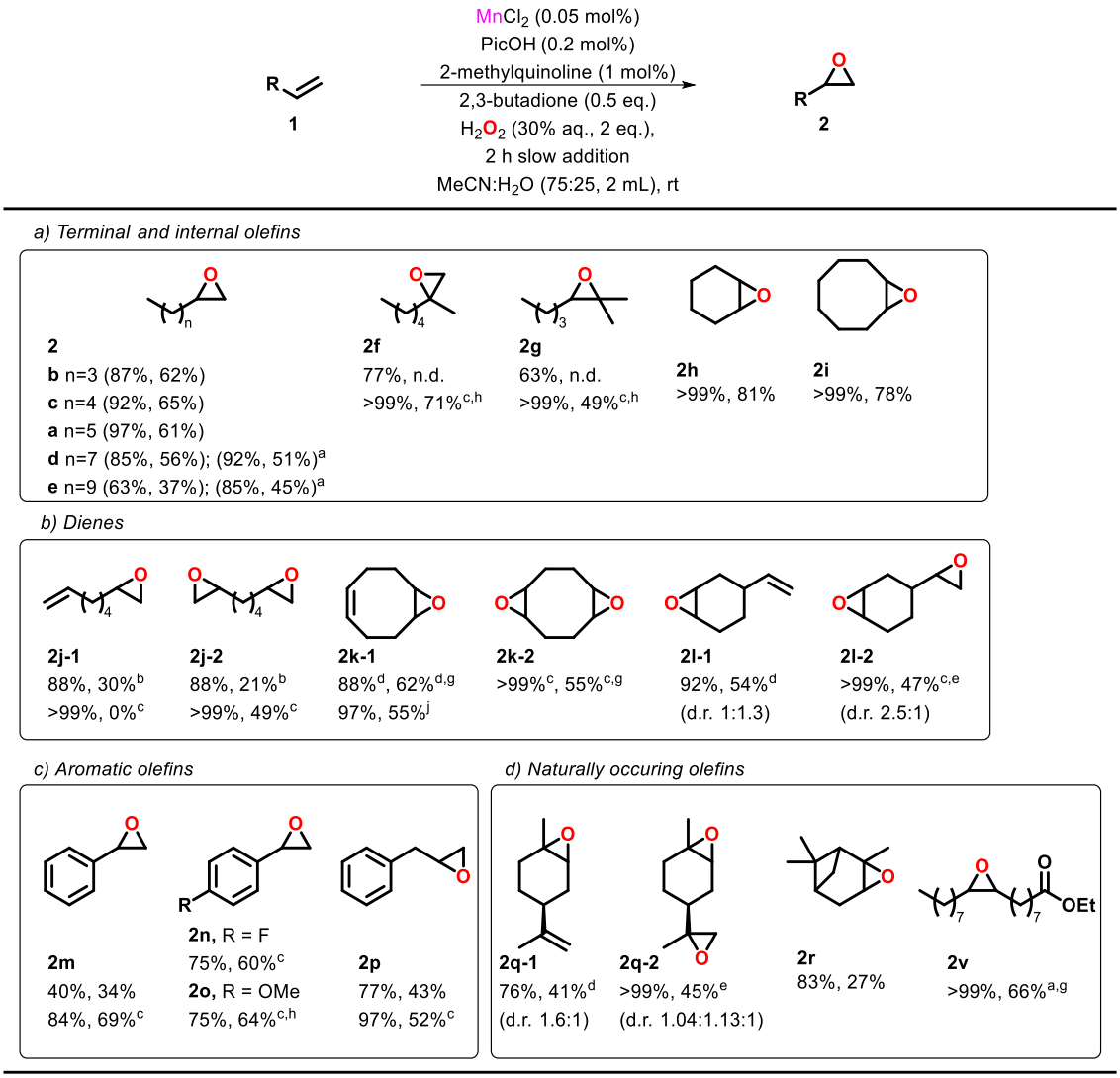
Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), X mol% $MnCl_2$:PicOH:2-methylquinoline (1:4:20), 0.5 eq. 2,3-butadione, solvent (2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., X eq., diluted in MeCN) *via* syringe pump.

3.2.2. Substrate Scope

Investigating the scope of this manganese-catalyzed oxidation protocol, we first employed different terminal and internal alkenes as substrates (Table 9a). 1-Hexene (**1b**), 1-heptene (**1c**) and 1-octene (**1a**) were all converted in good yields of 61 – 65% to their corresponding epoxides **2a-c**. These results are superior to our previous epoxidation protocol, where much higher catalyst loadings, more expensive ligands and higher amounts of less benign oxidant were necessary. Further extension of the chain length, however, led to slightly decreased yields (56% **1d**, 37% **1e**), probably due to lower solubility of the starting materials. Therefore, a less polar solvent ratio (95:5) was employed for these substrates giving 51% of 1-epoxydecane **2d** and 45% of 1,2-epoxydodecane **2e**. Employing higher substituted olefins showed an interesting trend: With 2-methyl-1-heptene **1f**, an improved yield of 71% of the desired epoxide **2f** was obtained, while with 2-methyl-2-heptene **1g** only 49% epoxide **2g** was obtained. Obviously, disubstituted olefins are more nucleophilic and therefore more reactive, accounting for the better performance. Though the electronic properties of trisubstituted olefins are even more nucleophilic, here, steric influence starts to interfere with the reaction, demonstrating the selectivity of this catalytic system for electronically less activated, *i.e.*, sterically less demanding olefins. Switching to cyclic olefins, the reaction proceeded with much higher selectivities/mass balances. For cyclohexene **1h** and cyclooctene **1i** the desired epoxides **2h** and **2i** were obtained in ~80% yield. In both cases, no allylic oxidation products were observed, indicating that this reaction does not proceed *via* a radical/Fenton-type reactivity pathway.

Investigating dienes as substrates (Table 9b), we first employed 1,7-octadiene **1j** under present reaction conditions. Here, 88% conversion and 21% of the diepoxide **2j-2** were observed with about 30% of the mono-epoxide **2j-1** product remaining. However, halving the amount of employed substrate **1j** to 0.25 mmol, significantly increased the yield and selectivity giving the di-epoxide **2j-2** as sole major product in 49% yield. Due to its industrial relevance in the fragrance industry, we also investigated the selective mono- or di-epoxidation of cyclooctadiene **1k** (COD). When employing only 1.5 eq. of H_2O_2 (30% aq.) to prevent over-oxidation to the di-epoxide **2k-2**, 88% conversion were achieved, and the desired mono-epoxide **2k-1** was isolated in 62% yield. Halving the substrate concentration and using 5 eqs. of peroxide gave the di-epoxide **2k-2** as single major product in 55% isolated yield. To further demonstrate this systems applicability, we also performed a large scale (5 g) reaction of the mono-epoxidation of COD. Here, we isolated 3.1 g of the desired product **2k-1** (55% yield). As seen before, cyclic olefins are more reactive than terminal olefins, thus, we employed 4-vinyl-cyclohexene **1l** as starting material to investigate the selectivity. Under optimized conditions, 97% conversion of the diene **1l**, 53% yield of the ring epoxidation product **2l-1**, and 16% of the di-epoxide **2l-2** were observed. No sole side-chain epoxidation product was formed. The same yield of the **2l-1** was obtained when using only 1.5 equivalent of oxidant. Again, when employing only 0.25 mmol of the diene and 5 equivalents of oxidant, full conversion and 47% of the desired di-epoxide **2l-2** as single major product were obtained.

Table 9: Scope of olefins for manganese-catalyzed epoxidation reaction.



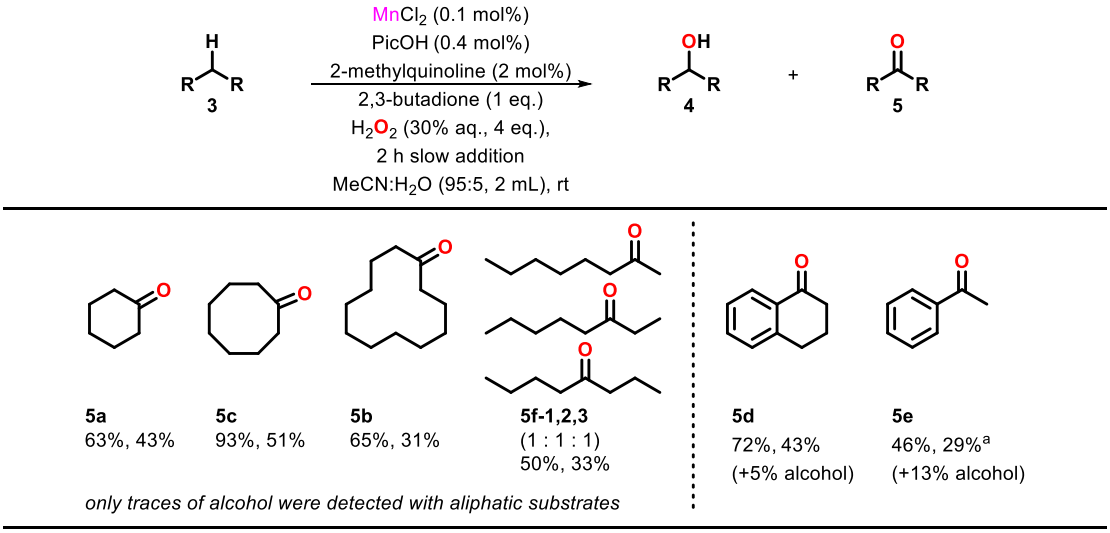
Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.05 mol% $MnCl_2$, 0.2 mol% picolinic acid, 1 mol% 2-methylquinoline, 0.5 eq. 2,3-butadione, MeCN:H_2O (75:25, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 2 eq., diluted in MeCN) *via* syringe pump. a: MeCN:H_2O (95:5) as solvent, b: Same results were obtained employing 4 eq. of H_2O_2, c: 0.25 mmol of substrate employed, d: 1.5 eq. of H_2O_2 were employed, e: 5 eq. of H_2O_2 were employed, f: 1.5 eq. of 2,3-butadione were employed, g: isolated yield, h: yield determined by NMR analysis with dibromomethane as IST, j: 5 g scale reaction.

Though this protocol was initially optimized for aliphatic alkenes, we also employed aromatic alkenes as substrates (Table 9c). Subjecting styrene **1m** to the present reaction conditions, we observed a reduced conversion of 40% and a yield of styrenoxide **2m** of 34%. Halving the concentration of styrene to 0.125 M led to much better results, approximately doubling conversion and yield to 84% and 69%, respectively. Investigating electronic effects of substituents in the 4-position of styrene did not reveal significant changes in the outcome. Both with 4-F and 4-MeO styrene **1n** and **1o** the same conversions of 75% were achieved, while similar yields of 60% and 64% were obtained, respectively, demonstrating the robustness of this system towards varying electronic properties. With allylbenzene **1p**, we observed 77% conversion and 43% of the desired epoxide **2p** under standard conditions. Employing 0.25 mmol of substrate led to almost full conversion (97%), however, a lower selectivity than with styrene was obtained, giving the desired product in 52% yield. Trace amounts of benzylic oxidation products were observed here.

To further expand on this protocol's applications, we then turned our attention to the epoxidation of naturally occurring alkenes (Table 9d), *e.g.*, terpenes. Therefore, we first employed (–)-limonene **1q** as substrate under standard reaction conditions. Here, we obtained 41% of the ring epoxidation compound **2q-1** as major product and 11% of the di-epoxide product **2q-2**. Fine tuning the reaction conditions to obtain the di-epoxide **2q-2** as major product was easily accomplished by halving the substrate concentration and increasing the amount of H_2O_2 (30% aq.) to 5 equivalents. Here, the desired di-epoxide **2q-2** was obtained in 45% yield. In case of α-pinene **1r**, 83% conversion but only 27% yield of the desired product **2r** were obtained. We observed minor amounts of other unselective oxidation or follow-up products upon GC-MS analysis, *e.g.*, campholenic aldehyde. Since aldehydes are easily oxidized to the corresponding carboxylic acids, this would account for the lower selectivity with this substrate, as the formation of certain amounts of acids negatively impede on the performance of this catalyst system. Finally, the fatty acid ester ethyl oleate **1v** was employed as substrate and the desired epoxide product **2v** was isolated in 66% yield, demonstrating the high selectivity of this system towards aliphatic unactivated C=C double bonds.

Besides epoxidation, aliphatic C-H oxidation is also highly desirable as it allows to implement functional groups, *i.e.*, hydroxy or carbonyl groups, into unfunctionalized alkanes. Yet, this transformation is challenging due to high bond dissociation energies of such unactivated C-H bonds[75] (see introduction). Therefore, we also investigated C-H oxidation reactions with the present catalytic protocol as trace amounts of C-H oxidation products were observed when employing allylbenzene as substrate. Also, similar systems for oxidation of C-H bonds in alkanes have been reported in the literature.[61] As model substrates we chose cyclohexane **3a** and cyclododecane **3b** due to their industrial relevance and equivalence of all present C-H bonds. After a short optimization, we delightfully obtained 43% yield of cyclohexanone **5a** from cyclohexane with complete selectivity for the ketone **5** over the alcohol **4**. Similarly, cyclododecane **3b** was converted to cyclododecanone **5b** in 31% yield as the sole major product (the limiting factor here seems to be the solubility, see ESI of the original publication for more information). Consequently, we subjected various alkanes to our now slightly modified catalytic protocol (see Table 10). Employing cyclooctane **3c** we observed high conversion of 93% and a good yield of 51% of the desired ketone product **5c**. With *n*-octane **3f** as substrate no selectivity for the 2, 3, or 4-position is observed, resulting in a 1:1:1 mixture of the three possible ketone products **5f-1–3** with 33% combined yield (50% conversion). In all cases, no alcohol formation was detected. Next, we tested alkanes bearing aromatic rings, *i.e.*, benzylic C-H groups, as substrates. Here, tetrahydronaphthalene **3d** gave 72% conversion and 43% of the corresponding ketone **5d**, while small amounts of the alcohol **4d** were detected. For Ethylbenzene **3e** the more polar solvent mixture was applied, giving 46% conversion and 29% of acetophenone **5e**. Similar to our epoxidation studies, aromatic substrates, *e.g.*, styrene, performed worse than aliphatic substrates under identical reaction conditions, demonstrating the selectivity of this catalytic protocol for the oxidation of unactivated aliphatic compounds.

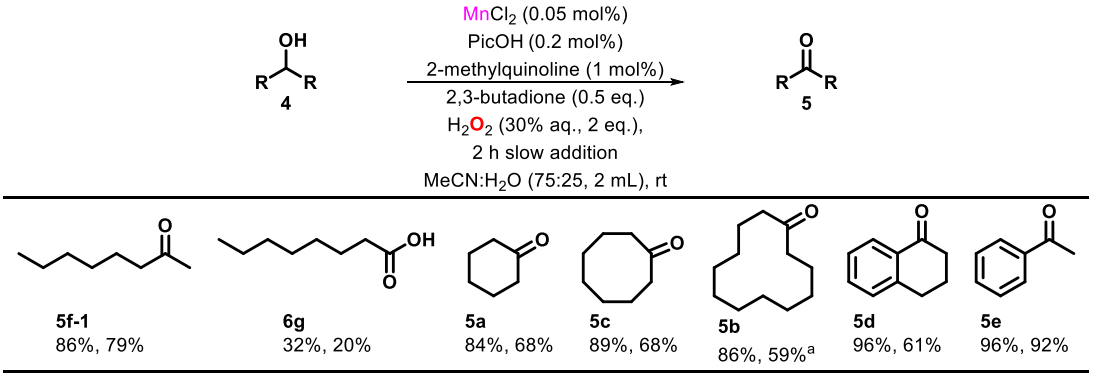
Table 10: Scope of alkanes for manganese-catalyzed C-H oxidation reaction.



Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.25 mmol substrate (0.125 M), 0.1 mol% $MnCl_2$, 0.4 mol% picolinic acid, 2 mol% 2-methylquinoline, 1 eq. 2,3-butadione, MeCN:H_2O (95:5, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 4 eq., diluted in MeCN) *via* syringe pump. a: MeCN:H_2O (75:25) as solvent.

Finally, we investigated the oxidation of alcohols to ketones under epoxidation reaction conditions as we also observed O-H oxidation with certain epoxidation substrates (see original publication for more information). First, we compared primary to secondary alcohols, verifying the standing thesis that primary alcohols are indeed not tolerated under present reaction conditions due to the formation of carboxylic acids (Table 11). With 2-octanol **4f** as substrate 86% conversion and 79% yield of 2-octanone **5f** were achieved. In contrast, 1-octanol **4g** is not suitable for this current protocol, as low conversions (30%) and ~20% of octanoic acid were detected. Since this catalyst system relies on the deprotonation of picolinic acid by the additive 2-methylquinoline to form the active complex, the formation of high amounts of acid obviously impedes on the catalytic activity. Followingly, several secondary alcohols were subjected to our catalytic protocol. With cyclohexanol **4a** and cyclooctanol **4c**, identical yields of 68% of the desired ketones **5a** and **5c** were obtained. Using cyclododecanol **4b** as substrate, switching to the less polar solvent mixture (MeCN:H_2O = 95:5), resulted in 59% yield of cyclododecanone **5b**. Moving to aromatic substrates, phenylethanol **4e** proved to be an excellent substrate with almost quantitative conversion and full selectivity yielding acetophenone **5e** in 92% yield. Lastly, with tetrahydronaphthalene-1-ol **4d** 96% conversion and 61% yield of 1-tetralone **5d** were achieved. Here, small amounts of over-oxidation products, *e.g.*, the diketone, were observed upon GC analysis.

Table 11: Scope of alcohols for manganese-catalyzed O-H oxidation reaction.



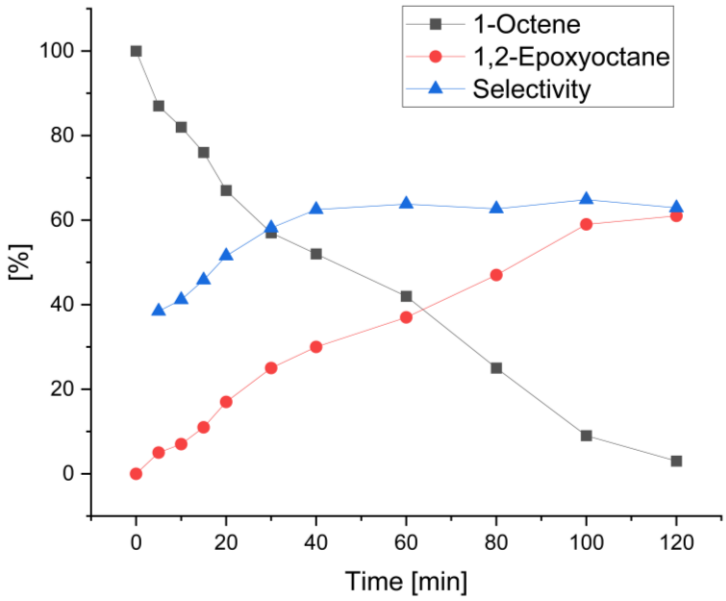
Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.05 mol% $MnCl_2$, 0.2 mol% picolinic acid, 1 mol% 2-methylquinoline, 0.5 eq. 2,3-butadione, MeCN:H_2O (75:25, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 2 eq., diluted in MeCN) *via* syringe pump. a: MeCN:H_2O (95:5) as solvent.

3.2.3. Mechanistic Considerations

While investigating the scope of our catalytic protocol, significant information related to the mechanism of this system was already obtained. Nonetheless, we were still interested to gain more knowledge about the specific nature of this catalyst, the oxidative transformation it catalyzes, and additional possible limitations.

Therefore, we investigated the involvement of radical species conducting several control experiments employing the radical scavengers TEMPO and BHT. While the addition of either of said compounds impede on the reactivity, it was found that they do not act as radical scavengers, rather they seem to interfere with the catalyst, as even the addition of only 5 mol% TEMPO reduces the catalytic activity by 20%. This is in accordance with the result of the cyclohexene epoxidation, where no allylic oxidation products were formed. Since we detected follow-up and over-oxidation products when employing certain substrates, we followingly subjected 1,2-epoxyoctane **2a** to the present reaction conditions and found that only 80% could be recovered after 2 hours. As we observed inhibition of this system by the addition of TEMPO, we repeated the experiments with 1,2-epoxyoctane **2a** as substrate in the presence of TEMPO and found that it could be completely recovered. Therefore, we assume that the same species that converts 1-octene **1a** to the corresponding epoxide **2a**, also partially degrades the desired product (see ESI of the original publication for more information).

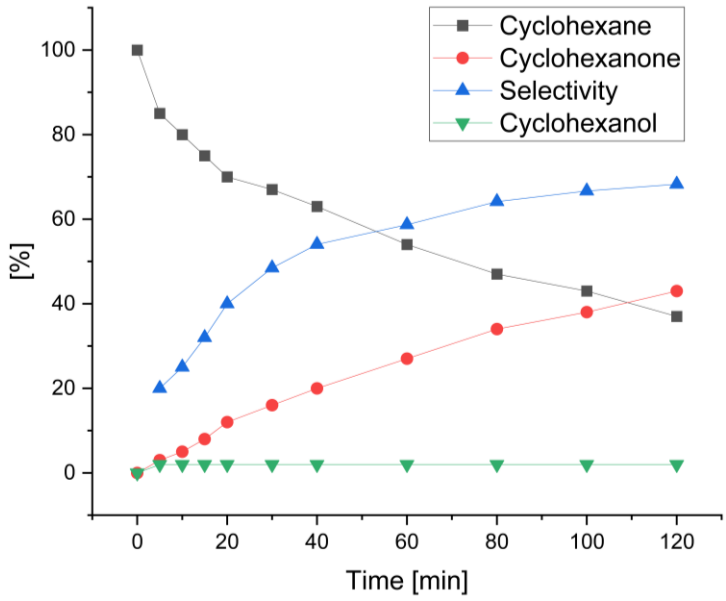
This prompted us to record a kinetic profile of the epoxidation of 1-octene **1a** to identify possible intermediates or follow-up products. As is in accordance with the literature,[32] the kinetic profile of the epoxidation of 1-octene **1a** shows that both the substrate consumption and the product formation follow an approximately linear course. Nevertheless, at the beginning the conversion is slightly faster than the product formation, indicating that the active epoxidation catalytic species might not be formed immediately upon H_2O_2 addition. Therefore, the selectivity towards the desired product **2a** at the start of the reaction is about 40% until it rises to ~60% after 40 minutes staying constant for the rest of the reaction (see Figure 6). Additionally, no major side-product or decrease of the product amount, indicating follow-up reactions, were observed. Therefore, we assume that substrate over-oxidation or degradation takes place at the very beginning of the reaction. In any case, similar to our previous works with N-heterocycles as epoxidation promotors,[34, 97] we assume eventual oxidative degradation to small molecules such as CO_2.



Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.05 mol% $MnCl_2$, 0.2 mol% picolinic acid, 1 mol% 2-methylquinoline, 0.5 eq. 2,3-butadione, MeCN:H_2O (75:25, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 2 eq., diluted in MeCN) *via* syringe pump. For each point in time a separate reaction was set up and analyzed after the indicated slow addition time.

Figure 6: Kinetic profile of manganese-catalyzed epoxidation of 1-octene.

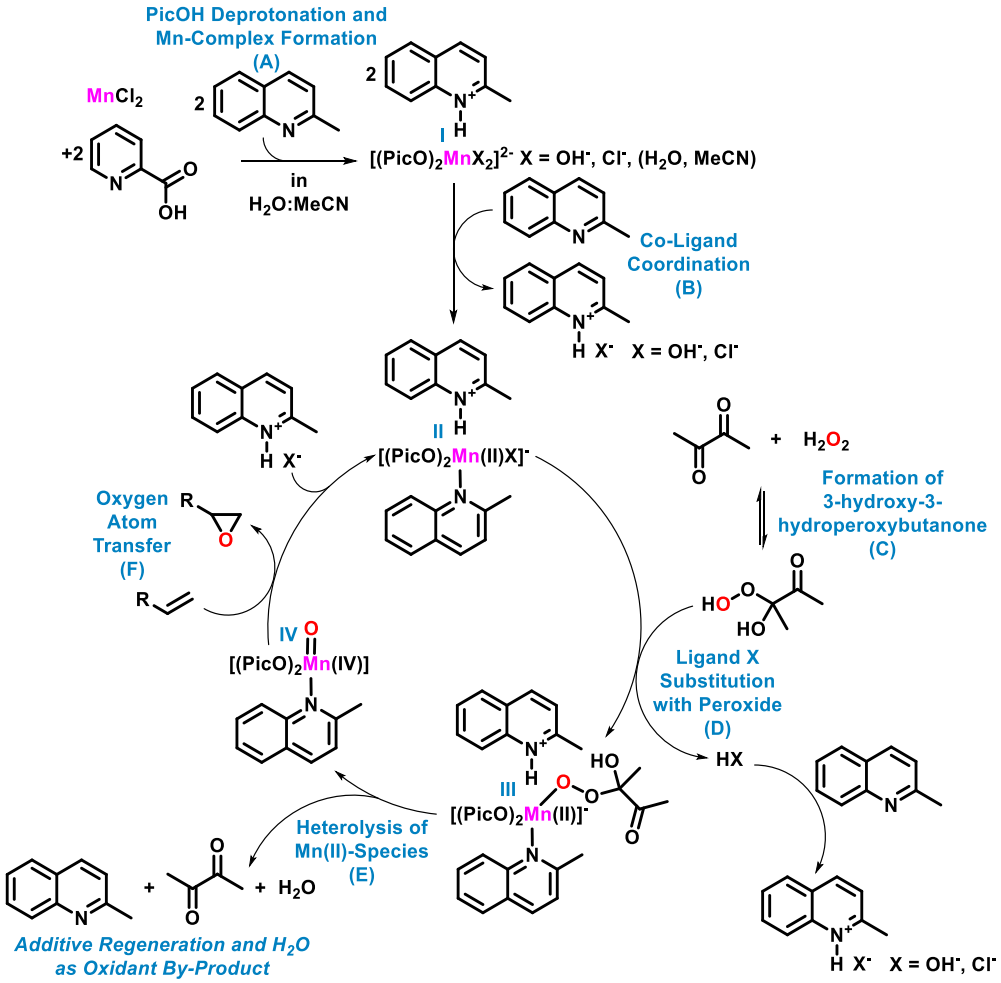
Furthermore, we recorded the kinetic profile of the C-H oxidation of cyclohexane **3a** to cyclohexanone **5a** to compare both oxidative transformations. At the beginning, a lower selectivity is observed that reaches ~60% after 60 minutes staying in the range of 60 – 70% for the remaining reaction time. Also in this case, the lower selectivity towards the desired product at the beginning of the reaction might indicate a lag period during which the active catalytic species is not yet formed. In contrast to 1-octene epoxidation, no quantitative conversion of cyclohexane **3a** is achieved under present optimized reaction conditions. Finally, there is no accumulation of cyclohexanol **4a** as an intermediate as only trace amounts of the alcohol are observed during the whole reaction time (see Figure 7). Taken these results into consideration, we suggest similar reaction pathways and reactive intermediates for both types of oxidation reactions.



Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.25 mmol substrate (0.125 M), 0.1 mol% $MnCl_2$, 0.4 mol% picolinic acid, 2 mol% 2-methylquinoline, 1 eq. 2,3-butadione, MeCN:H_2O (95:5, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 4 eq., diluted in MeCN) *via* syringe pump. For each point in time a separate reaction was set up and analyzed after the indicated slow addition time.

Figure 7: Kinetic profile of manganese-catalyzed oxidation of cyclohexane.

Based on all the previously made observations we propose the following catalytic cycle for this newly developed oxidation catalyst (see Scheme 6): In the first step **A**, the postulated $[(PicO)_2MnX_2]^{2-}$ – complex is generated by deprotonation of PicOH by 2-methylquinoline resulting in the negatively charged species **I**, with two protonated quinolyl species $[2\text{-MQ-H}]^+$ as counterions. Here, the nature of the two ligands X^- occupying the two additional coordination sites of the manganese center remain unclear. Two chloride ligands derived from the precursor or OH-groups from the hydrolysis of $MnCl_2$ to $Mn(OH)_2$ as well as solvent coordination (H_2O, MeCN) seem to be possible. In the second step **B**, one of the ligands X^- can be exchanged by coordination of the co-ligand, 2-methylquinoline, leading to the formation of species **II** (though species **I** and **II** are possibly in equilibrium). Here, the formal charge of X^- would be compensated by the present protonated quinolyl species $[2\text{-MQ-H}]^+$. As is described in the literature, 2,3-butadione and hydrogen peroxide are in equilibrium (**C**) with 3-hydroxy-3-hydroperoxybutanone.[63] In the following step **D**, this formed adduct substitutes the remaining X^- ligand, resulting in H_2O or HCl elimination. These would in turn be deprotonated by another 2-methylquinoline, forming an additional $[2\text{-MQ-H}]^+$ and manganese species **III**. Considering the results from the co-ligand screening, where 8-methylquinoline performed much worse than 2-methylquinoline, the formation of species **III** could be severely hindered by the steric effect of the 8-methyl group in case of 8-MQ as co-ligand. This Mn(II)-species **III** undergoes heterolysis of the O-O bond from the coordinated 3-hydroxy-3-hydroperoxybutanone, resulting in the formation of species **IV** with a manganese(IV)-center (step **E**). This step is facilitated by the present counter-cation, *i.e.*, acid, $[2\text{-MQ-H}]^+$ which further activates the O-O bond either by forming a hydrogen bond or even promoting a protonolysis[100] of species **III** resulting in the regeneration of the 2-MQ. Followingly, 2,3-butadione is regenerated and H_2O is formed as by-product. The high valent manganese-oxo species **IV** is presumed to be the active oxidation catalyst (stabilized by the co-ligand),[101, 102] oxidizing the present alkene to the corresponding epoxide (step **F**). Upon regeneration of the manganese(II)-species **II**, the free coordination site is occupied again by ligand X^-.



Scheme 6: Mechanistic proposal for manganese-catalyzed epoxidation of 1-octene.

Within this chapter, the potential of an easily accessible manganese-based catalyst system for the selective oxidation of bulk chemicals, *e.g.*, unactivated alkenes and alkanes, and secondary alcohols was demonstrated. To the best of our knowledge, this non-noble metal catalyst system offers the highest efficiency especially for the epoxidation of the challenging terminal aliphatic olefins of any acid free *in situ* system. Furthermore, the roles of the employed N-heterocycles as a base and a co-ligand were (partially) elucidated in several experiments. For future endeavors, synthesizing a defined complex, ideally with a coordinated quinoline species, would be highly desirable.

3.3. Homogeneous Iron-Catalyzed Oxidation of Non-Activated Alkanes with Hydrogen Peroxide

Recently, our group published a paper about the iron-catalyzed epoxidation of linear and terminal olefins.[34] The employed catalyst system was comprised of $Fe(OTf)_2$ as precursor with Me – BPA (**L2**) as ligand and picolinic acid as co-ligand. There, we discovered that addition of the internal standard hexadecane *prior* to hydrogen peroxide addition leads to partial oxidation of hexadecane, next to the desired epoxidation reaction. Hence, we postulated that this system would also be capable of selectively oxidizing unactivated alkanes leading to a more detailed exploration of its applications.

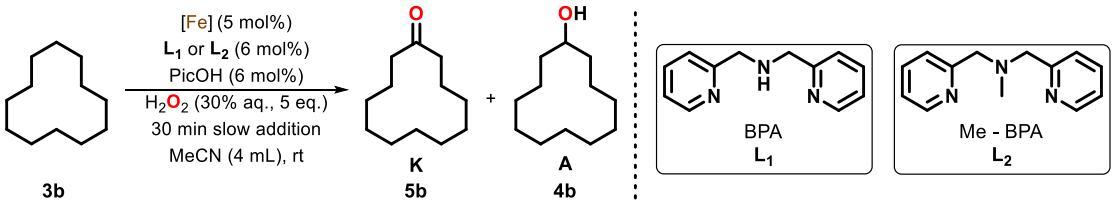
3.3.1. Optimization of Reaction Conditions

The investigations were initiated by choosing cyclododecane **3b** as model substrate due to its industrial relevance (*vide infra*) and equivalence of all present C-H bonds. The corresponding cyclododecanone is of interest as a fragrance and precursor to 1,12-dodecanedioic acid and laurolactam, which are used for specialized polyamides syntheses.[103]

Applying the reaction conditions from our previous epoxidation protocol,[34] *i.e.,* 5 mol% $Fe(OTf)_2$, 6 mol% **L2**, 6 mol% PicOH as co-ligand and H_2O_2 (30% aq., 5 eqs.) as terminal oxidant in acetonitrile a conversion of 61% and an overall selectivity of 56% for the KA-mixture of the corresponding ketone (K, **5b**) (16% yield) and alcohol (A, **4b**) (18% yield) was achieved (see Table 12, entry 1). A control experiment under inert atmosphere excluded the influence of air on the reaction outcome. Conducting the reaction without an iron source led to low conversion (Table 12, entry 2), while in the absence of any ligand a reduced activity was observed giving low amounts of the desired product mixture (Table 12, entry 3).

Consecutively, different iron precursors were tested for this reaction. Here, almost now product formation was observed using $FeCl_2$ or $FeBr_2$ in combination with **L2** as catalyst system (Table 12, entries 4, 5). The stronger coordination of halide ions compared to the triflate anion presumably blocks the active site of the iron catalyst to be accessed. Accordingly, other iron precursors with non-coordinating anions were tested. The best results were achieved applying $Fe(OTf)_3$ and $Fe(ClO_4)_3xH_2O$ (Table 12, entries 6, 7). The latter was selected for further studies due to its comparably lower cost and easier handling. Followingly, solvent screening revealed that MeCN is the only suitable solvent for this transformation (see ESI of original publication), as was also observed with our manganese-based catalyst systems.

Table 12: Optimization of reaction conditions for iron-catalyzed oxidation of cyclododecane.



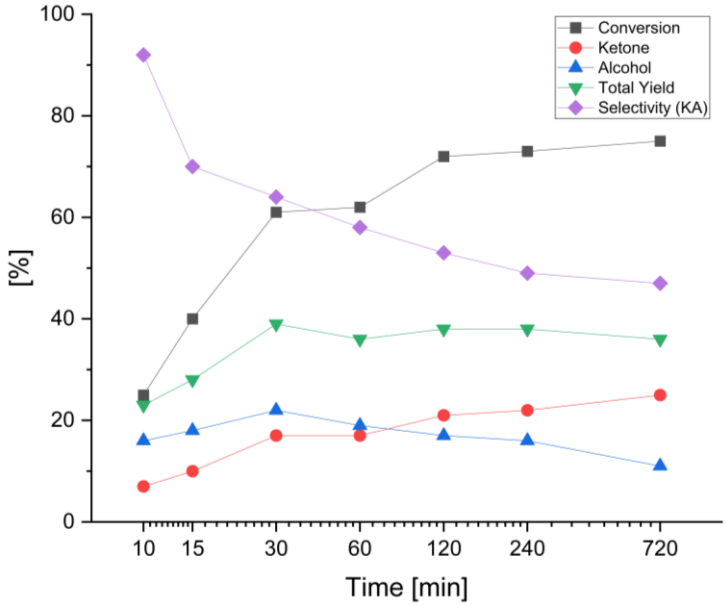
Entry	Precursor	Ligand	Conv. (4b) [%]	Yield (K+A) [%]	Sel. (KA) [%]
1	$Fe(OTf)_2$	**L_2**	61[a]	16 + 18	56
2	---	**L_2**	<1	0	0
3	$Fe(OTf)_2$	---	27	8 + 5	48
4	$FeCl_2*6H_2O$	**L_2**	8	1 + 2	38
5	$FeBr_2$	**L_2**	<5	<5	n.d.
6	$Fe(OTf)_3$	**L_2**	69	18 + 20	55
7	**$Fe(ClO_4)_3xH_2O$**	**L_2**	**61**	**16 + 23**	**64**
8	$Fe(OTf)_2$	**L_1**	29	17 + 8	86
9	$Fe(OTf)_2$	**L_1**	75[b]	21 + 18	52

Conversion and yield determined by GC analysis with hexadecane as IST . Reaction conditions: 0.5 mmol cyclododecane (0.125 M), 5 mol% iron precursor, 6 mol% ligand, 6 mol% PicOH, MeCN (4 mL), 25 °C, 30 min slow addition of H_2O_2 (5 eq., 30% aq.) *via* syringe pump under ambient conditions. Selectivity is the total yield of ketone and alcohol in relation to the substrate conversion. a: The same results were obtained when performing the reaction under an inert atmosphere of argon, b: 16 h of slow addition time.

In contrast to the previously discussed manganese system (see chapter 3.1), applying BPA **L_1**, led to reduced conversion but higher selectivity. However, when the reaction time was increased to 16 h, the selectivity dropped again (Table 12, entry 9) giving slightly worse results than **L_2**. Nonetheless, other accessible and commercially available N-derived ligands, *e.g.*, free amine or oxazoline moieties, were examined (see original publication). Unfortunately, none of the other tested ligands showed any reactivity at all demonstrating the specific features of this ligand scaffold. Further optimization attempts did not improve the reaction outcome (see ESI of original publication). Thus, the best result was obtained using the *in situ* catalyst system generated form $Fe(ClO_4)_3xH_2O$ – **L_2**, PicOH, and 5 equivalents of H_2O_2 (30% aq.), giving 61% conversion and 39% yield of the KA-mixture (Table 12, entry 7).

3.3.2. Kinetic Investigations

To gain a deeper understanding of this reaction we recorded a time-dependent reaction profile to analyze the ratio of the ketone to the alcohol, as well as the conversion of the model substrate and selectivity towards the KA-mixture over time. Therefore, slow addition times between 10 minutes and 12 hours were applied (see Figure 8). Here, a drastic increase in conversion is observed between 10 minutes (25%) and 30 minutes (61%). Accordingly, the yield of the product mixture increases from 23% to 39% in that time. Interestingly, the ratio of the ketone to the alcohol changes from 1:2.3 to 1:1.4, indicating that longer reaction times favor formation of the ketone over the alcohol. With even longer reaction times, the initial ratio completely inverts to 2.2:1 in favor of the ketone. The overall yield, however, barely changes with slow addition times longer than 30 minutes. Despite this, the conversion increases slightly with longer reaction times, accounting for the lower mass balances compared to shorter reaction times. Taken together, these results implicate a metal-centered mono-oxygenase-type of reaction where the ketone is formed from over-oxidation of the alcohol rather than a free-radical driven mechanism where both products are formed in parallel with similar rates.



Reaction conditions: 0.5 mmol cyclododecane (0.125 M), 5 mol% $Fe(ClO_4)_3xH_2O$, 6 mol% ligand, 6 mol% PicOH, MeCN (4 mL), 25 °C, H_2O_2 (5 eq., 30% aq.) added over the indicated time *via* syringe pump under ambient conditions. Substrate conversion and product yield were determined by GC using hexadecane as IST.

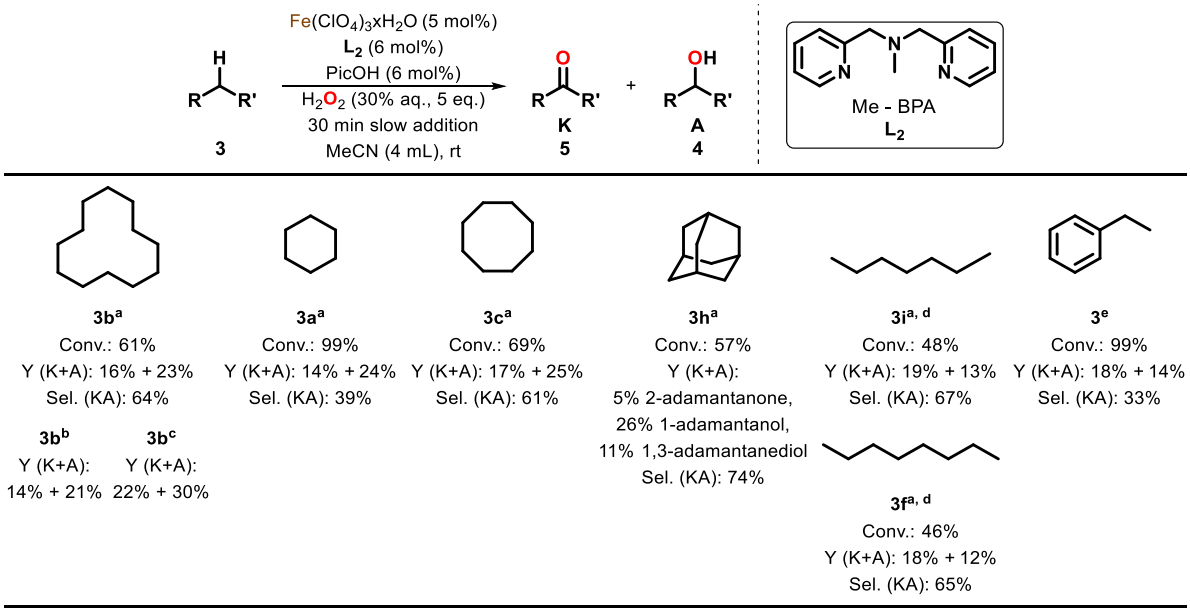
Figure 8: Reaction profile of iron-catalyzed oxidation of cyclododecane.[104]

Although the mass balances of the performed reactions, especially with longer reactions times, are rather low, no major side-product(s) could be isolated. Thus, apart from the oxidation to the desired KA-mixture and similar to our previous works,[34, 97] we assume that the starting material underwent oxidative degradation to small molecules like formic acid and CO_2.

3.3.3. Substrate Scope

Finally, the applicability of the optimized iron catalyst system was studied for different alkanes (see Table 13). Subjecting cyclohexane **3a** or cyclooctane **3c** to standard reaction conditions, similar yields of the desired KA-mixtures around 40% were obtained. When cyclododecane **3b** was utilized as substrate, the reaction was scaled up to multi-g scale (5 g) and no significant reduction of reactivity was observed (**3b**[b]). Of note, the yield of the KA-mixtures can further be improved to 52%, by adding a second portion of the catalyst and fresh H_2O_2 (30% aq., 5 eqs.) to the reaction mixture after the first 30 minutes of slow addition time (**3b**[c]). More complex alkanes like adamantane can also be oxidized to the corresponding ketone and alcohols. Here, tertiary C-H groups are oxidized preferentially, giving only 5% of the ketone product from secondary C-H group oxidation and a combined 37% yield of the alcohol and diol from tertiary C-H group oxidation (**3h**). Linear alkanes such as heptane or octane can similarly be converted to the respective KA-mixtures in slightly reduced yields but with low regioselectivity (**3i, 3f**). Furthermore, this iron catalyst can oxidize preferentially benzylic C–H bonds in ethylbenzene **3e** giving a lower yield of 32% of the KA-mixture, possibly due to over-oxidation of the substrate and/or products.[105, 106]

Table 13: Iron-catalyzed oxidation of cyclic, linear and aryl-substituted alkanes.



Reaction conditions: 0.5 mmol alkane (0.125 M), 5 mol% $Fe(ClO_4)_3xH_2O$, 6 mol% **L2**, 6 mol% PicOH, MeCN (4 mL), 25 °C, 30 min slow addition of H_2O_2 (5 eq., 30% aq.) *via* syringe pump under ambient conditions. Yield (Y) refers to the total amount of ketone and alcohol product(s) formed from the indicated substrate. Selectivity (Sel.) is the total yield of ketone and alcohol in relation to the substrate conversion. a: Substrate conversion and product yield were determined by GC using hexadecane as IST, b: 5 g scale reaction, c: another portion of catalyst and H_2O_2 were added after the reaction, d: a mixture of oxidation products in the 2, 3 and 4-position with a ~1:1:1 ratio was obtained, e: 56% of benzoic acid was obtained.

Concluding this chapter, an *in situ* generated iron catalyst system which was initially developed for epoxidation of olefins required only slight modifications to be applied for the direct oxidation of unactivated cyclic and linear alkanes. The optimized system is generated from $Fe(ClO_4)_3xH_2O$ and Me – BPA (**L2**) as ligand, using picolinic acid as co-ligand and H_2O_2 as terminal oxidant.

4. Summary and Outlook

In summary, three new non-noble metal catalyst systems for the oxidative valorization of alkenes and alkanes have been developed within the constraints of this doctoral thesis.

First, a new manganese – N,N,N-pincer catalyst system was designed for the epoxidation of the industrially relevant terminal, aliphatic olefins. Key features of this system are the commercial availability of the employed bis(2-picolyl) amine ligand and the convenient *in situ* generation of the employed catalyst BPA – $Mn(OTf)_2$ that was also characterized by single-crystal X-ray diffraction. In the course of this project, the crucial, yet intriguing role of the additive quinoline was revealed as being both essential for product formation whilst simultaneously being detrimental to the product stability. However, the detailed influence of the heterocyclic additive could not be fully disclosed. Using *tert*-butyl hydroperoxide as oxidant, terminal epoxides were obtained with yields of up to 67%.

Followingly, the development of a second, even simpler manganese-based catalyst system for the oxidation of alkenes to epoxides, as well as the selective oxidation of alkanes or alcohols to ketones was described within the frame of this work. Here, much lower catalyst loadings, a more benign oxidant, and a larger variety of substrates and higher yields compared to the first system were realized. This system relies on inexpensive $MnCl_2$ as precursor and picolinic acid as ligand. The additive 2-methylquinoline fulfilled multiple roles, *e.g.*, acting as a base deprotonating picolinic acid, thus generating the active catalyst and also acting as a co-ligand that has beneficial effects on the reaction progress overall.

Lastly, an iron-based catalyst system, relying on N-methyl bis(2-picolyl) amine (Me – BPA) as ligand, was developed for the oxidation of unactivated alkanes to mixtures of the corresponding ketones and alcohols. This system is also conveniently generated *in situ* using cheap and easy to handle $Fe(ClO_4)_3xH_2O$ as metal precursor. Employing picolinic acid as co-ligand and the environmentally friendly hydrogen peroxide as terminal oxidant, cyclic and linear alkanes were converted to the desired ketone and alcohol products in moderate yields.

Concluding this thesis, the importance of N-heterocycles in non-noble metal-catalyzed oxidation reactions was elucidated. Fulfilling the role(s) of a base, a ligand, a co-ligand, a simple “additive” or even a combination of those, clearly shows their value in this field of research.

In general, many recent publications demonstrate that chemists still, or rather now more than ever, strive to find more efficient, selective, and, probably most importantly, environmentally friendly ways to accommodate the needs of this planet’s inhabitants. Though we are still a long journey from realizing all relevant chemical reactions with minimal waste, highest efficiency, and lowest possible costs, there is the common phrase: Even the longest journey begins with a single step.

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6. Selected Publications

The following chapter displays the original publications where the herein presented research was initially reported. My contribution to each publication is described in the respective subchapter.

6.1. Manganese N,N,N-Pincer Complex-Catalyzed Epoxidation of Unactivated Aliphatic Olefins

Dennis Verspeek, Sebastian Ahrens, Anke Spannenberg, Xiaodong Wen, Yong Yang, Yong-Wang Li, Kathrin Junge* and Matthias Beller*

Catal. Sci. Technol., **2022**, *12*, 7341 – 7348.

DOI: 10.1039/d2cy01472f

Electronic supporting information is available online. CCDC 2187359 and 2187360 contain the supplementary crystallographic data for this paper.

Contribution

For this manuscript I co-conceived and designed the project, performed all the experiments (except crystallization-related experiments), including optimization of reaction conditions, preparing the substrate scope and data analysis. Furthermore, I co-wrote and co-edited the manuscript, wrote the supporting information and performed the revisions after peer-review. My overall contribution accounts for approximately 75%.

_____	_____
Signature of the student	Signature of the supervisor
Dennis Verspeek	Prof. Matthias Beller

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Manganese *N,N,N*-pincer complex-catalyzed epoxidation of unactivated aliphatic olefins†

Dennis Verspeek, [a] Sebastian Ahrens, [a] Anke Spannenberg,[a] Xiaodong Wen, [bc] Yong Yang, [bc] Yong-Wang Li,[bc] Kathrin Junge *[a] and Matthias Beller *[a]

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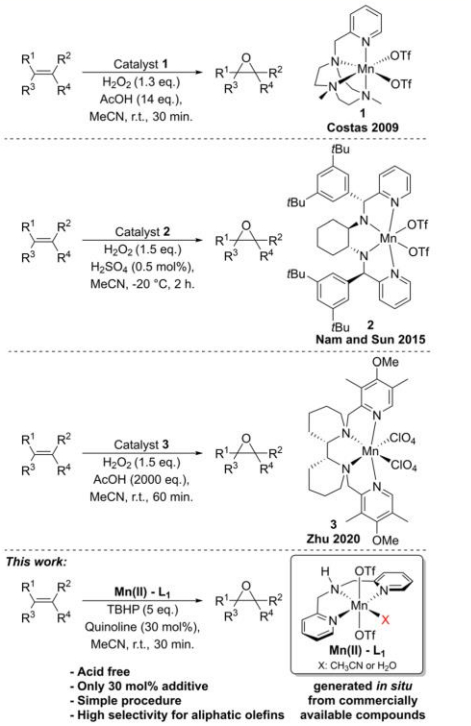
A practical *in situ* generated manganese(II) catalyst system with the commercially available bis(2-picolyl) amine ligand enables epoxidation of terminal aliphatic olefins in good yields with *tert*-butyl hydroperoxide as oxidant. Crystallization experiments revealed the formation of two manganese solvent complexes with MeCN and H_2O, respectively. Furthermore, a detailed investigation of the quinoline additive identified its crucial role in this transformation as being both essential for the epoxide formation while simultaneously being detrimental to its stability.

Introduction

Metal-catalyzed epoxidation reactions of aliphatic olefins are widely used and studied tools in organic synthesis and the chemical industry.[1–4] More specifically, the selective epoxidation of terminal aliphatic olefins under environmentally benign conditions is desired as the corresponding 1,2-epoxides are valuable building blocks for a variety of daily life products ranging from epoxy resins, paints, surfactants to health care.[1,5–7] Thus, numerous epoxidation protocols based on a variety of different transition-metals, such as Sc,[8] Ti,[9–11] Mn,[12–16] Fe,[17–19] Nb,[20] Mo,[21] Ru,[22–24] and Rh[25,26] have been published in the past four decades. However, until now terminal olefins are difficult to be epoxidized in high yields.[27,28] With respect to the catalyst system, the use of non-noble metal complexes to enable such reactions would be preferred due to their non-toxic and ecologically friendly traits as well as their abundance and therefore inexpensive price.[29]

Among the non-noble metals, especially catalysts based on manganese have the potential for further applications in epoxidation reactions.[3] Despite all the advantages of non-noble metal catalysts, in general cost-effectiveness and robustness remain major unsolved problems with



Scheme 1 Manganese(II) complexes applied in epoxidation reactions of alkenes.

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† Electronic supplementary information (ESI) available. CCDC 2187359 and 2187360 contain the supplementary crystallographic data for this paper. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d2cy01472f**

established manganese-catalyzed methodologies. Interestingly, in 2008 the group of Wong showed that even terminal aliphatic olefins can be epoxidized in high yields following a simple procedure, though they relied on the use of peracetic acid as the oxidant, which results in undesirable side-products.[6]

One year later, Costas and co-workers demonstrated that high yields can also be achieved in these reactions utilizing environmentally friendly H_2O_2 as oxidant, but a large excess of acetic acid is needed to achieve decent yields (Scheme 1).[30]

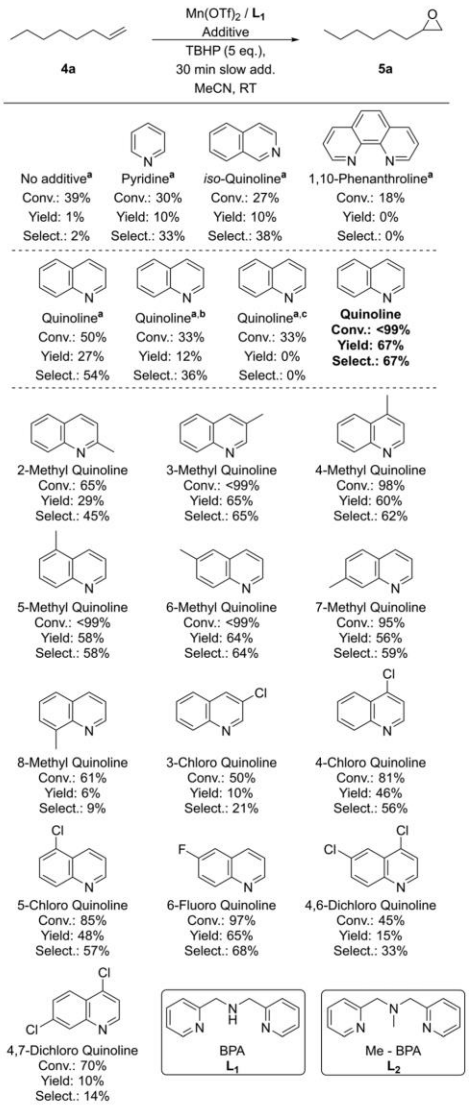
In 2015, Nam and Sun reported the asymmetric epoxidation of olefins, which also included terminal aliphatic olefins.[31] However, the requirement of rather complex procedures and elaborate ligand syntheses renders their protocol unsuitable for industrial application of inexpensive bulk chemical syntheses. Although further, valuable contributions were made in the field of manganese-catalyzed epoxidation reactions,[32–37] there is still a general lack of a method that focuses on a combination of the following points: 1) a protocol that specifically addresses the epoxidation of terminal aliphatic olefins, which is of interest for bulk and fine chemical syntheses, 2) the employment of a cheap catalytic system that does not require complicated procedures or elaborate ligand syntheses, and 3) the use of an environmentally benign oxidant without the necessity of large excesses of acids or similarly corrosive, toxic or otherwise unbenign compounds. In this paper, we present our development of a simple and accessible *in situ* manganese(II)-catalyzed reaction that is designed for the environmentally friendly and cost-effective epoxidation of terminal aliphatic olefins. Furthermore, we provide a detailed investigation of this system, its advantages and ultimately, its limitations.

Results and discussion

Catalytic experiments

Based on our previous works with non-noble metal pincer catalysts,[18,38] we started our investigations by probing the reactivity of the *in situ* catalytic system of manganese(II) – triflate as precursor and bis(2-picolyl amine) $\mathbf{L_1}$ as the employed *N*,*N*,*N* – pincer ligand for the epoxidation of the model substrate 1-octene **4a**. As the terminal oxidant, an aqueous solution of *tert*-butyl hydroperoxide (TBHP) was used, which is also industrially applied in the epoxidation of propylene (Halcon process).[39] Employing 1 equivalent of TBHP at room temperature and 5 mol% of manganese precursor only trace amounts of the desired product 1,2-epoxyoctane **5a** were detected by GC analysis (Table 1). Here, no major product could be identified assuming that the starting material mainly underwent oxidative degradation to CO_2. However, the addition of *N*-heterocyclic compounds as co-ligands, which are known for their beneficial effects in selected metal-catalyzed oxidation reactions,[18,40,41] surprisingly improved the reaction to a significant degree. Selected results of the influence of different *N*-containing compounds on the reaction outcome are shown in Table 1.

Table 1 Screening of different additives and ligands



Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.125 M), 5 mol% $Mn(OTf)_2$, 6 mol% $\mathbf{L_1}$, 30 mol% quinoline derivative, MeCN (4 mL), 25 °C, 30 min slow addition of TBHP (70% aq., 5 eq.) *via* syringe pump. [a] 1 eq. of TBHP employed. [b] 6 mol% $\mathbf{L_2}$. [c] No ligand employed.

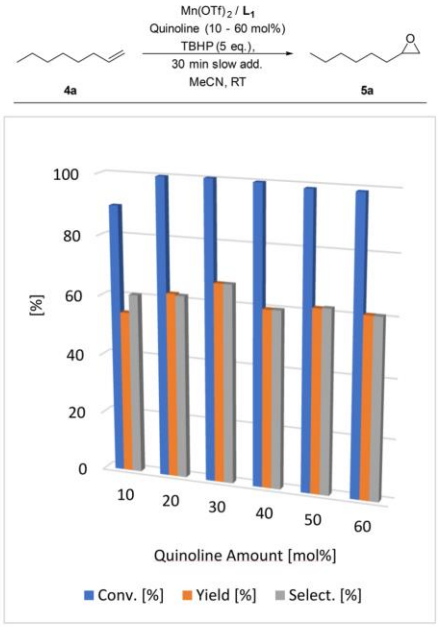


Fig. 1 Variation of the quinoline amount for epoxidation reaction. Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.125 M), 5 mol% $Mn(OTf)_2$, 6 mol% L_1, 10–60 mol% quinoline, MeCN (4 mL), 25 °C, 30 min slow addition of TBHP (70% aq., 5 eq.) *via* syringe pump.

For example, in the presence of 30 mol% of pyridine, 10% of the corresponding epoxide was formed. Notably, switching from pyridine to quinoline to test other aromatic heterocycles, showed a significant improvement of this result, giving 27% yield of 1,2-epoxyoctane **5a** under the applied reaction conditions. Here, *iso*-quinoline yielded very similar results to pyridine, and the bidentate 1,10-phenanthroline was not suitable for this reaction. Interestingly, applying 5 eq. of TBHP led to full conversion of **4a** giving 67% yield of the desired epoxide **5a** with simple quinoline as the additive. Therefore, the effect of different substituted and commercially available quinolines was investigated in the model reaction. In a first set of experiments, we used methylated quinolines as additives.

While 2-methyl- and 8-methylquinoline led to a significantly reduced catalytic performance, all other methylated quinolines provided similar or slightly lower yields compared to unsubstituted quinoline. Next, halogenated quinolines with electron-withdrawing substituents were investigated in the epoxidation reaction. Here, 6-fluoroquinoline yielded the epoxide **5a** in good yield, and 4- and 5-chloroquinoline provided more moderate yields. On the other hand, 3-chloroquinoline and di-chlorinated quinolines caused lower conversions and low selectivity towards the desired epoxide (see Table 1). Obviously, there is no clear structure–activity relationship of the influence of the substituted quinolines on the reaction outcome. Since none of the tested quinoline derivatives increased the product yields, the parent quinoline was the additive of choice for further optimization studies. As expected, no reaction occurred without employing a pincer ligand. Applying the *N*-methylated bis(2-picolyl amine) L_2 had a detrimental effect on the reactivity of this system, giving only 12% epoxide **5a** after GC analysis.

Next, the amount of the quinoline additive was varied (Fig. 1 and Table S1†). Employing only 10 mol% of quinoline led to a slightly reduced conversion and an accordingly lower yield. Similar conversions were obtained with loadings of quinoline between 20 and 40 mol%, while 30 mol% of quinoline seemed to be the reactions "sweet-spot".

In contrast, higher amounts of the additive (up to 60 mol%) do not further improve the reaction outcome giving yields around 60%.

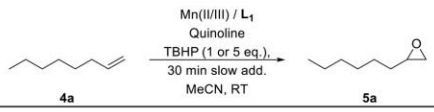
Subsequently, different manganese precursors were tested for this reaction. To identify differences in the reactivity more easily, we employed only 1 eq. of TBHP. As shown in Table 2 and Fig. S1,† only precursors with weakly coordinating anions were effective for the epoxidation reaction. Optimal results were obtained in the presence of manganese(II) perchlorate, manganese(II) triflimide and manganese(II) triflate (Table 2, entries 1, 5 and 7). Using an iron(II) pre-catalyst was found to be not compatible with the present protocol, demonstrating the unique reactivity of manganese under these conditions (Table 2, entry 4). Next to TBHP, we tested hydrogen peroxide as final oxidant, which provided only low amounts of the desired product (12%) (Table 2, entry 3). Interestingly, no difference applying the *in situ* generated catalyst system compared to using the isolated complexes **Mn-1** and **Mn-2** as catalyst was observed (Table 2, entry 13). It should be noted that no extra time for pre-stirring of the *in situ* system is required.

Here, the full catalytic potential is achieved shortly after mixing the precursor, the ligand, and the additive, indicating a fast complexation of the pincer ligand to the metal. Further screening efforts revealed that MeCN is the most suitable solvent for this reaction, as it is often observed in epoxidation reactions (Table S2†).[3] Any deviations from these optimized reaction conditions within the numerical parameters of this system, *e.g.*, reaction time, temperature, catalyst loading or the amount of employed oxidant, either had no positive effect on the yield, or gave (slightly) worse results (Table S3†).

Catalyst characterisation

Following the investigations of the model reaction, we focused our attention on synthesizing the defined manganese(II) complex catalyst. Therefore, manganese(II) triflate and bis(2-picolyl amine) L_1 were mixed under inert conditions in dry MeCN and subsequently layered with dry Et_2O.

Table 2 Screening of different metal-precursors and amounts of peroxide



Entry	Precursor	TBHP [eq.]	Conv.[a] [%]	Yield[a] (**5a**) [%]	Sel. (**5a**) [%]
1	$Mn(OTf)_2$	1	50	27	54
2	$Mn(OTf)_2$	5	>99	67	67
3	$Mn(OTf)_2$	H_2O_2 (5 eq.)	21	12	57
4	$Fe(OTf)_2$	5	12	1	8
5	$Mn(ClO_4)_2$	1	43	24	55
6	$Mn(ClO_4)_2$	5	99	59	60
7	$Mn(NTf_2)_2$	1	42	26	62
8	$Mn(NTf_2)_2$	5	99	61	62
9	$MnCl_2$	1	17	1	6
10	$Mn(OAc)_2$	1	22	0	0
11	$Mn(acac)_2$	1	14	0	0
12	$Mn(acac)_3$	1	21	0	0
13	**Mn-1** or **Mn-2**	5	>99	67	67

[a] Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.125 M), 5 mol% manganese precursor, 6 mol% $\mathbf{L_1}$, 30 mol% quinoline, MeCN (4 mL), 25 °C, 30 min slow addition of oxidant *via* syringe pump.

Gratifyingly, **Mn-1** was obtained as colourless needles after crystallization. The complex crystallizes in the triclinic space group $P\bar{1}$ with two molecules in the unit cell and a distorted octahedral geometry. Here, one MeCN molecule is coordinated to the manganese(II) center in addition to the three nitrogen atoms of the pincer ligand and two triflate groups with the ligand coordinating in an equatorial fashion (Fig. 2). There are reports known where the employed ligands coordinate in a facial manner to the transition metal, especially when a twofold excess of ligand is used.[42–45] Elemental analysis confirms the formation of $Mn(II)(OTf)_2$ – $\mathbf{L_1}$ as the coordinating MeCN is removed *in vacuo* when drying the crystals before measurement. Accordingly, HRMS shows $[M\text{-}OTf]^+$. In a second set up, the above procedure was repeated, however, in this case undried MeCN was used to mimic the reaction conditions, where aqueous TBHP solution is applied. Here, layering the MeCN solution of the complex with benzene led to the formation of a different solvent complex **Mn-2**, which was obtained as colourless prismatic needles. In contrast to **Mn-1**, the usage of undried MeCN led to an exchange of the additional coordinating MeCN with a water molecule. This complex crystallizes in the monoclinic space group $P2/n$ with two molecules in the unit cell and a distorted octahedral geometry. The pincer ligand and the triflates coordinate in a similar fashion to **Mn-1** (Fig. 3). Here, elemental analysis and HRMS also confirm the formation of $Mn(II)(OTf)_2$ – $\mathbf{L_1}$ and $[M\text{-}OTf]^+$, respectively.

Obviously, **Mn-1** is converted to **Mn-2** during the catalytic reaction, which would also explain the similar catalytic performance of the isolated complexes **Mn-1** and **Mn-2** and the *in situ* system. A detailed discussion about the bond length and angles of **Mn-1** and **Mn-2** is not possible because

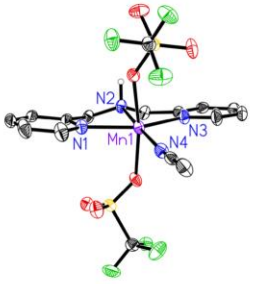


Fig. 2 ORTEP representation of **Mn-1**. (S yellow, O red, F green). Displacement ellipsoids correspond to 30% probability. C-bound hydrogen atoms and one position of the disordered triflate ligands are omitted for clarity.

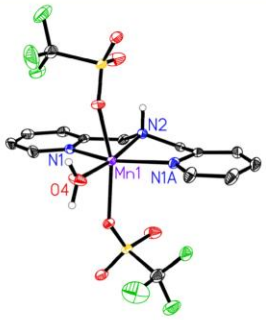


Fig. 3 ORTEP representation of **Mn-2**. (S yellow, F green). Displacement ellipsoids correspond to 30% probability. C-bound hydrogen atoms and one position of the disordered parts of the complex are omitted for clarity.

the triflate groups of both complexes as well as the ligand backbone of **Mn-2** are disordered over two sites (see ESI†).

Mechanistic studies and scope

With the optimized reaction conditions and two crystal structures in hand, we focused on a more profound understanding of this catalytic system. Therefore, we started to investigate the reaction pathway by recording the kinetic profile of the epoxidation of the model substrate 1-octene **4a** (Fig. 4). When plotting the selectivity *versus* the reaction time, we found that it stays rather constant at approx. 60–67% after the starting period. Intriguingly, we also observed that the quinoline is partially consumed during the reaction, as only 39% of the initially employed amount is detected by GC analysis after 30 minutes.

To shed light on the nature of the reaction and possible side or follow-up reaction as well as on the intriguing role of quinoline, many control experiments were performed (Scheme 2): first, the radical scavenger TEMPO (1 eq.) was applied in the model reaction under optimized conditions, which completely inhibited product formation and pointed towards the importance of radical intermediates in this novel reaction. When adding 1 eq. of BHT to the reaction mixture, a similar yet less pronounced effect was observed with 45% conversion and 26% yield.

Furthermore, the product 1,2-epoxyoctane **5a** was subjected under the standard reaction conditions to test its stability. Interestingly, only 72% of **5a** and 19% of the employed quinoline were detected by GC analysis after 30 minutes. This clearly suggests that the product is not entirely stable under reaction conditions and that the inherent limitation of this system is more likely a follow-up reaction of the product with the quinoline rather than a side reaction of the starting material. Repetition of this experiment in the presence of 1 eq. TEMPO revealed that both the product **5a** and the quinoline remain completely unreacted, which indicates that the presumed follow-up reaction of the epoxide with the quinoline is also of radical nature. Unfortunately, all efforts to isolate the decomposition product (more than 20 attempts, see below) failed and it was not possible to identify its structure. In addition, we subjected the product to our standard reaction protocol without the addition of quinoline. Indeed, 100% of the epoxide could be recovered after 30 minutes reaction time, also indicating that these two compounds could react together in a follow-up reaction. Further control experiments revealed that a simple Lewis-acid catalyzed reaction between the quinoline and the epoxide can be excluded. Additionally, no reaction occurs in the absence of TBHP, revealing that the decomposition reaction only takes place under oxidative conditions. Interestingly, even the presence of the pincer ligand is also necessary for the decomposition step. Summarizing all these results, we can conclude that the

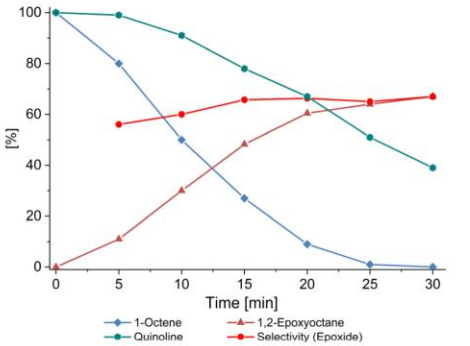
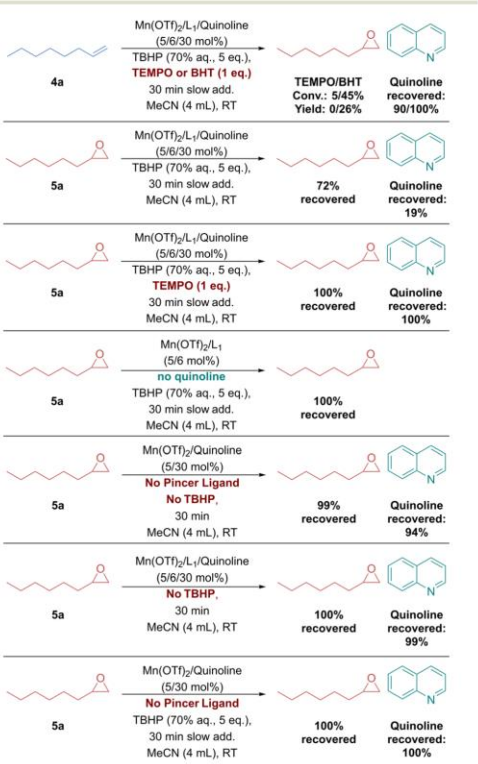


Fig. 4 Kinetic profile of epoxidation of 1-octene **4a**. Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate **4a** (0.125 M), 5 mol% $Mn(OTf)_2$, 6 mol% L_1, 30 mol% quinoline, MeCN (4 mL), 25 °C, 30 min slow addition of TBHP (70% aq., 5 eq.) *via* syringe pump. Six reactions were set up in parallel and at every 5-minute mark one reaction was stopped and analyzed.



Scheme 2 Mechanistic experiments with 1-octene and 1,2-epoxyoctane. Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol 1-octene **4a** or 1,2-epoxyoctane **5a** (0.125 M), 5 mol% $Mn(OTf)_2$, 6 mol% L_1, 30 mol% quinoline, MeCN (4 mL), 25 °C, 30 min slow addition of TBHP (70% aq., 5 eq.) *via* syringe pump.

presence of quinoline or related heterocycles is essential for the desired product formation, while on the other hand it also promotes an unwanted follow-up reaction with the formed epoxide, which both are mediated by our manganese-pincer catalyst under oxidative conditions.

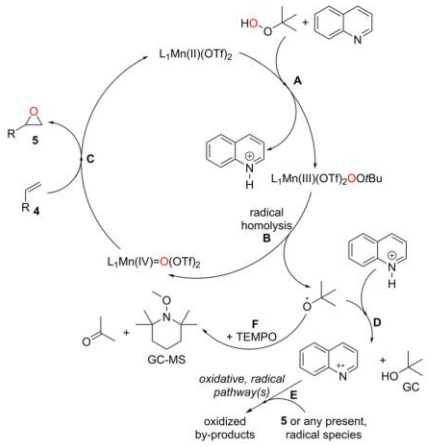
Further attempts were made to identify potential side products such as the mono-hydroxylated octenes **6** and **7**, 1,2-octanediol **8**, octanal **9** or octanoic acid **10**. Also, the formation of olefin cleavage products, such as heptanoic or hexanoic acid was considered (ESI†). However, none of them could be detected by GC and LC-MS analysis of the reaction mixture. Also, neither of these compounds appears to be an intermediate in the reaction, as their employment as starting materials did not yield the desired epoxide as product. Additionally, LC-MS analysis of reaction mixtures did not reveal the formation of quinoline-*N*-oxide, which could be formed under these oxidizing reaction conditions (Scheme S1 and Table S4†).

Besides, Browne and co-workers[15,16] describe the oxidative degradation of the ligand scaffolds to 2-picolinic acid which forms the active catalyst. Hence, several control experiments were realized, applying 2-picolinic acid or 2-picolyl amine as ligands in the model reaction. However, no catalytic activity was observed demonstrating that this reaction likely occurs through a different mechanism. Furthermore, the addition of picolinic acid in the presence of the pincer ligand BPA had only minor (6 mol% acid) or detrimental effect (15 mol% acid) on the reaction outcome. Based on these findings the involvement of 2-picolinic acid in the formation of the active catalyst can be excluded.

Furthermore, the potential formation of quinoline-*N*-oxide and its involvement in the catalytic reaction was explored. Using quinoline-*N*-oxide as additive only 18% of epoxide were formed underlining the beneficial role of quinoline for our catalytic protocol (see Table S5†).

Based on these results the following catalytic cycle was postulated (Scheme 3): in the first step (**A**), quinoline acts as a base deprotonating TBHP to facilitate the oxidation of $L_1Mn(II)(OTf)_2$ to $L_1Mn(III)(OTf)_2OO^tBu$. A similar behaviour is reported by the group of Todisco using imidazole for the activation of TBHP in a manganese-catalyzed oxidation reaction.[46] Then, the manganese(III) species undergoes homolysis generating the oxo-species $L_1Mn(IV)=O(OTf)_2$ and a *tert*-butyl radical (step **B**). In the last step (**C**), the olefin **4** is oxidized to the epoxide **5** by the previously formed Mn(IV)=O species. As quinoline is partly consumed during the reaction, the following pathway **D** is proposed: The protonated quinoline can react with a *tert*-butyl radical, generating *tert*-butanol (observed by GC) and an oxidized quinolyl radical. Tertiary alkoxy radicals are known to eliminate methyl radicals and to generate the corresponding ketone.[31] Such methyl radicals can be responsible for quinoline degradation.

Notably, in the presence of TEMPO quinoline is fully recovered, while the formation of the alkylated adduct 1-methoxy-2,2,6,6-tetramethylpiperidine is observed by GC-MS (step **F**).



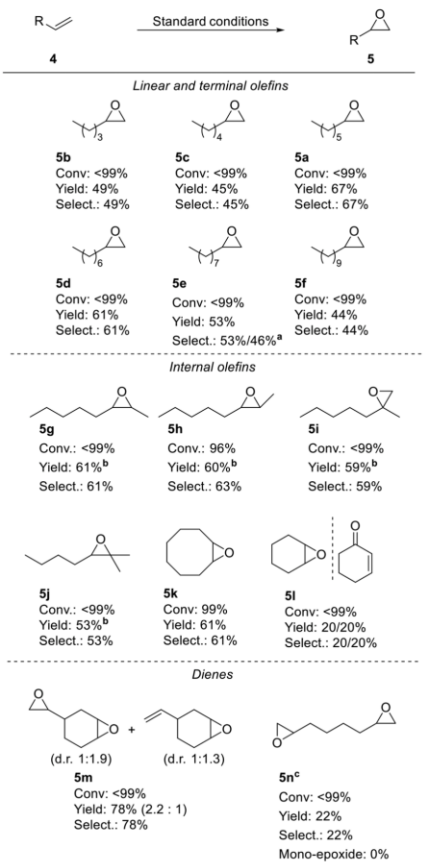
Scheme 3 Proposed catalytic cycle and quinoline degradation pathways of the epoxidation of simple olefins.

Finally, we studied the scope of this catalytic protocol applying other aliphatic olefins (Table 3). Both, linear and terminal epoxides bearing shorter alkyl chains **5b** and **5c** were obtained in moderate yields of 49% and 45%, respectively, possibly due to higher volatility of the corresponding products. Linear olefins with longer alkyl chains gave similar epoxide yields around 60% (see Table 3). Notably, the presented catalyst system is also suitable for the epoxidation of internal olefins. Switching to this class of substrates, we found that 2-methyl-1-heptene (**4i**) and 2-methyl-2-heptene (**4j**) gave epoxide yields of 59% and 53%, respectively. Applying cyclic alkenes, *e.g.*, cyclohexene (**4m**), less selective oxidizations occurred under these conditions, as an allylic oxidation also happens as a competing reaction, giving both products in a one-to-one ratio.

On the other hand, cyclooctene was epoxidized in good yield of 61%. Next, we subjected the more challenging substrate 4-vinyl cyclohexene to our optimized conditions to probe the selectivity of ring epoxidation *versus* epoxidation of the vinyl side chain. To our delight we observed an overall yield of epoxidation products of 78% with a selectivity of 2.2 : 1 (double epoxidation : ring epoxidation). Only trace amounts of the vinyl chain epoxidation product were observed.

Lastly, we tested the epoxidation of few selected aromatic olefins, which are in most epoxidation procedures more reactive substrates than terminal aliphatic olefins.[47] However, with the here presented catalytic protocol only 26% of styrene oxide were formed. Analogously, allylbenzene also led to a rather moderate epoxide yield of 27%. In both cases no major side product was observed by GC analysis. Furthermore, we found that the naturally occurring 1-octene-3-ol or the corresponding ketone are not well tolerated under our reaction conditions. In both cases only trace amounts of product (<5%), and much lower conversions were obtained (see Table S6†).

Table 3 Manganese-catalyzed epoxidation with aliphatic olefins



Conversion and yield determined by GC analysis with hexadecane as IST. [a] Isolated yield. [b] Yield determined by NMR analysis with dibromomethane as IST. [c] 0.25 mmol substrate. Reaction conditions: 0.5 mmol substrate (0.125 M), 5 mol% $Mn(OTf)_2$, 6 mol% $\mathbf{L_1}$, 30 mol% quinoline, MeCN (4 mL), 25 °C, 30 min slow addition of TBHP (70% aq., 5 eq.) *via* syringe pump.

Conclusions

In summary, we present a novel non-noble metal catalyst system for the epoxidation of industrially relevant aliphatic olefins. Key features of this system are the use of the commercially available tridentate *N*,*N*,*N*-ligand BPA and quinoline as additive. The active catalyst can be conveniently generated *in situ* from several cationic manganese salts, *e.g.*, $Mn(OTf)_2$ and BPA. Crystal structures of the formed pincer complexes are also provided. Mechanistic experiments underlined the crucial role of the addition of quinoline for this catalytic reaction as being essential for product formation, but also detrimental to product stability. Although the detailed influence of quinoline on these reactions is not entirely clear, we assume these results will inspire other researchers using quinoline and related derivatives in related reactions, too. Under optimized conditions, epoxide yields up to 67% could be achieved, which provides potential for further applications.

Experimental

General procedure for epoxidation of simple olefins

An 8 mL glass vial equipped with a Teflon coated stirring bar was charged with stock solutions of $Mn(OTf)_2$ (0.025 mmol, 8.8 mg, 5 mol% catalyst loading), bis(2-picolyl amine) (0.03 mmol, 6.0 mg, 6 mol%) and freshly distilled quinoline (0.15 mmol, 19.4 mg, 30 mol%). The resulting mixture was further diluted with MeCN to a total volume of 4 mL and stirred for 5 minutes. Then, 1-octene (0.5 mmol, 56.1 mg, 0.125 M) was added. Next, a solution of *tert*-butyl hydroperoxide (TBHP) (2.5 mmol, 5 eq., 340 μL, 70% aq.) in MeCN (660 μL) was added *via* a syringe pump to the reaction mixture over the course of 30 minutes. Afterwards, the reaction was terminated by the addition of a few drops of a saturated aqueous $Na_2S_2O_3$ solution (note: in most cased the addition of $Na_2S_2O_3$ is not necessary as all TBHP was already consumed at this point).

For GC analysis the reaction mixture was then diluted with EtOAc, filtered, and analyzed using hexadecane (30 μL) as an internal standard to determine conversion and yield.

Author contributions

M. B., K. J., and D. V. conceived and designed the project; D. V. and S. A. performed the experiments and analyzed the data; A. S. was responsible for the SC-XRD needed for the project; K. J., and M. B., supervised the research activities at the corresponding institutions, X. W., Y. Y. and Y.-W. L. supported the project with funding acquisition, M. B., K. J., and D. V. coedited the manuscript; D. V., S. A., K. J., and M. B. cowrote the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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6.2. A Manganese-based Catalyst System for General Oxidations of Unactivated Olefins, Alkanes, and Alcohols

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Electronic supporting information is available online.

Contribution

For this manuscript I conceived and designed the project, performed all the experiments, including optimization of reaction conditions, preparing the majority of the substrate scope and data analysis. Furthermore, I co-wrote and co-edited the manuscript and wrote the supporting information. My overall contribution accounts for approximately 80%.

_____	_____
Signature of the student	Signature of the supervisor
Dennis Verspeek	Prof. Matthias Beller

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A manganese-based catalyst system for general oxidation of unactivated olefins, alkanes, and alcohols†

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Non-noble metal-based catalyst systems consisting of inexpensive manganese salts, picolinic acid and various heterocycles enable epoxidation of the challenging (terminal) unactivated olefins, selective C–H oxidation of unactivated alkanes, and O–H oxidation of secondary alcohols with aqueous hydrogen peroxide. In the presence of the *in situ* generated optimal manganese catalyst, epoxides are generated with up to 81% yield from alkenes and ketone products with up to 51% yield from unactivated alkanes. This convenient protocol allows the formation of the desired products under ambient conditions (room temperature, 1 bar) by employing only a slight excess of hydrogen peroxide with 2,3-butadione as a sub-stoichiometric additive.

Introduction

Finding and designing more efficient and environmentally friendly catalytic reactions continues to be an important task for synthetic chemists in industry and academia. To a greater extent, achieving this task is becoming more and more difficult as already existing synthetic routes, especially in the area of bulk chemical syntheses, have been optimized for decades. Nowadays, not only the best product yield but also other factors such as minimizing the amount of generated waste, avoiding excess use of reagents and additives, utilizing Earth-abundant catalysts, and circumventing any risk stemming from the use of toxic, corrosive or hazardous materials determine the quality of a given synthesis.[1] The latter is especially true for oxidation reactions, as most (highly concentrated) oxidants pose serious safety risks.[2] In this respect, the use of molecular oxygen, hydrogen peroxide or *tert*-butyl hydroperoxide is clearly preferred compared to, for example, hypervalent iodine species, hypochlorite or toxic metal oxides, *e.g.*, OsO_4.[3] More specifically, the ultimate clean oxidant for liquid phase oxidation at ambient pressure is aqueous hydrogen peroxide, which unfortunately can be easily decomposed, especially by non-noble metal salts, thus limiting its general applicability. To improve the selectivity and prevent decomposition reactions of peroxides, N-heterocyclic compounds have been used as (co-)ligands,[4–8] additives,[9] or bases[10] in metal-catalysed oxidation reactions. In fact, several multidentate ligands, *e.g.*, pincer-type or tetradentate ligands, showed higher selectivities in oxidation reactions with oxidants like hydrogen peroxide or *tert*-butyl hydroperoxide (TBHP).[4,5,11–19] In addition, the application of structurally simpler pyridine derivatives is a useful tool if a base is needed to deprotonate a peroxide species to enhance its nucleophilicity.[10,14] Other examples include functionalized N-heterocycles, such as picolinic acid derivatives, that have found application in iron- or manganese-catalysed oxidation reactions, *e.g.*, (ep)oxidation of olefins,[5,20–22] alcohol oxidation,[23] or C–H oxidation of (unactivated) alkanes.[4,23,24]

Furthermore, picolinic acid derivatives have been used for (noble)metal-catalysed reactions in the fields of water oxidation,[25] photochemistry,[26,27] and others.[28–32]

As part of our ongoing efforts regarding the valorization of terminal aliphatic olefins, we recently reported a novel protocol for manganese-catalysed epoxidation of olefins.[14] Here, the addition of quinoline was crucial to obtain high selectivity towards the desired epoxide products. Although N-heterocycles of similar structures are known to promote analogous metal-catalysed oxidation reactions,[5,19,33] the exact role of quinoline has not been revealed. However, we postulated a mechanism where quinoline acts as a base to deprotonate TBHP. Following our previous findings[4,5,14] regarding the employment of N-heterocycles as additives and inspired by the works of

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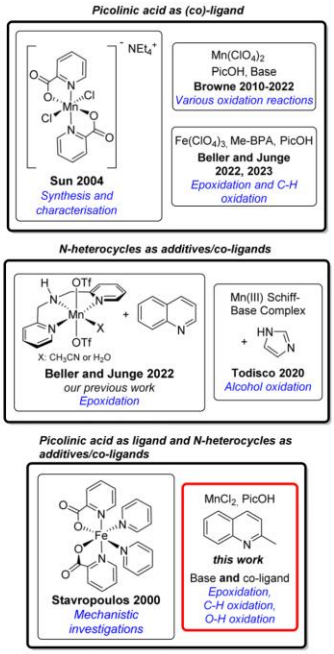


Scheme 1 Selected examples and applications (blue) of iron and manganese catalysts with picolinic acid and/or N-heterocycles as (co)-ligands and/or additives.

Browne and co-workers,[8,20,21,23,34–38] Stack,[22] and others[10,24,39] employing picolinic acid as a ligand (see Scheme 1), we had the idea to combine both features in one catalyst system for the valorization of terminal aliphatic olefins as well as other oxidation reactions. Despite many developments in (non)noble metal-catalysed epoxidation reactions in recent years,[5,9,15,16,40–53] this approach, *i.e.*, combining a picolinate-based manganese system with N-heterocycles, has not been implemented. Furthermore, product degradation, oxidant decomposition and/or free-diffusing radicals still make terminal aliphatic olefins difficult to be epoxidized in high yields under benign and acid-free conditions.[54,55] To address these issues, we propose manganese–picolinate complexes[39,56,57] in combination with different N-heterocycles as active and selective catalysts for diverse oxidation reactions.

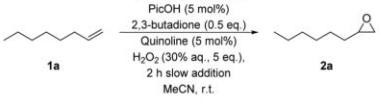
Results and discussion

Based on our previously reported system,[14] we envisioned the use of $Mn(OTf)_2$ as a metal precursor, picolinic acid as a simple and cheap ligand with quinoline as an additive as the starting point of our investigation. Firstly, the epoxidation of 1-octene **1a** as the model, yet challenging[54,55] substrate using a combination of hydrogen peroxide with 2,3-butadione as the peroxide activator[20] was performed in aqueous acetonitrile at room temperature. The epoxidation of terminal aliphatic olefins, *e.g.*, propylene, with aqueous hydrogen peroxide is of high industrial relevance and currently used on a >600 000 tons/a scale. Thus, a systematic variation of reaction parameters, *i.e.*, catalysts, additives, oxidants, and their respective ratios was performed. In the first numerical variation, a 37% yield of 1,2-epoxyoctane **2a** at 79% conversion was obtained by employing 0.25 mol% $Mn(OTf)_2$, 5 mol% picolinic acid, 5 mol% quinoline, 0.5 equivalents of 2,3-butadione, and 5 equivalents of H_2O_2 (30% aq.) (see Table S1† for more details).

To improve the selectivity and activity, we then embarked on in-depth metal precursor screening. In general, weakly coordinating anions are especially effective in manganese-catalysed oxidation or epoxidation reactions.[58] Thus, manganese(II) perchlorate, triflate, and triflimide all produced virtually identical results of 77–79% conversion and 37% epoxide yield (Table 1, entries 1–3). Switching to hexafluoropenta-2,4-dione as an anion, a slightly higher conversion and a yield of 40% was obtained (Table 1, entry 5). We then employed stronger coordinating anions in this protocol. To our delight, both Mn (II) acetate and acetylacetonate produced better yields than the initially employed precursors, giving almost full conversion of the starting material and yields of 40–45% of the desired epoxide **2a** (Table 1, entries 6–8).

Similar results were obtained with Mn(II) bromide and Mn (III) fluoride (Table 1, entries 11 and 13). Surprisingly, inexpensive Mn(II) chloride and $MnSO_4$ and $Mn(NO_3)_2$ gave best

Table 1 Mn-catalysed epoxidation of 1-octene: screening of metal precursors



Entry	Precursor	Conv. (**1a**) [%]	Yield (**2a**) [%]	Sel. (**2a**) [%]
1	$Mn(OTf)_2$	79	37	47
2	$Mn(ClO_4)_2$	77	37	48
3	$Mn(NTf_2)_2$	78	37	47
4	$Fe(ClO_4)_3$	34	0	0
5	$Mn(F_6\text{-acac})_2$	83	40	48
6	$Mn(OAc)_2$	99	45	45
7	$Mn(acac)_2$	99	42	42
8	$Mn(acac)_3$	99	40	40
9	$MnSO_4$	99	50	50
10	$Mn(NO_3)_2$	99/87[a]	48/43[a]	48/49[a]
11	$MnBr_2$	99	42	42
12	**$MnCl_2$**	**99/97**[a]	**51/49**[a]	**51/51**[a]
13	MnF_3	>99	40	40

Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.25 mol% precursor, 5 mol% picolinic acid, 5 mol% quinoline, 0.5 eq. of 2,3-butadione, MeCN (2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 5 eq., diluted in MeCN) *via* a syringe pump. [a] 2.5 eq. of H_2O_2 (30% aq.) was used.

results with around 50% yield of 1,2-epoxyoctane **2a** (Table 1, entries 9, 10 and 12). To better distinguish between the best working precursors, we tested $MnCl_2$ and $Mn(NO_3)_2$ again with only 2.5 equivalents of oxidant and found that $MnCl_2$ yielded almost identical results as before, while $Mn(NO_3)_2$ gave a slightly reduced conversion and a lower yield. Therefore, for all further experiments, $MnCl_2$ was used as the metal precursor.

At this point, it should be also noted that a related iron system showed significantly lower conversion and no desired product yield in the present protocol (Table 1, entry 4). Notably, reducing the amount of the oxidant even further to 1.0 equivalent with $MnCl_2$ as the precursor, we still achieved 66% conversion and 26% yield of **2a** (see the ESI, Table S2,† entry 3), indicating the high selectivity of this system against hydrogen peroxide decomposition.

To study the influence of picolinic acid ligands and ligand concentration, we considered these latter results (66% conversion and 26% yield) to be more suitable for observing both positive and negative effects. Starting with an initial [PicOH] : [Mn] ratio of 20 : 1, we consecutively reduced the amount of picolinic acid by a factor of ten up to 0.5 mol%, *i.e.*, a ratio of 2 : 1. Interestingly, 4 equivalents of picolinic acid with respect to the metal gave the best result and slightly increased yield (35%) of 1,2-epoxyoctane **2a** (see Fig. S2†). Noteworthily, in the absence of picolinic acid, around 30% conversion was observed but no epoxide formation was detected.

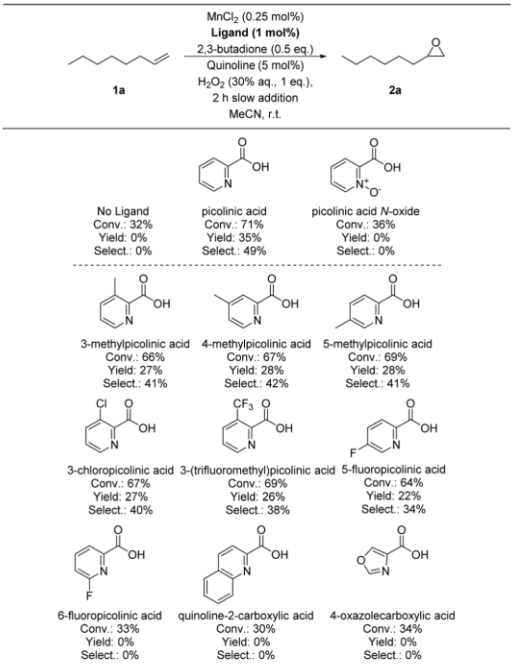
Presumably, the starting material undergoes complete oxidative decomposition as no major side products were observed by GC analysis. A control experiment utilizing picolinic acid-*N*-oxide also did not result in any product formation. Hence, the formation of this species as the active ligand can be excluded under catalytic conditions.

Next, we investigated the influence of the substitution pattern on picolinic acid (see Table 2). Both electron-donating substituents (3-Me, 4-Me, and 5-Me) and electron-withdrawing substituents, *i.e.*, 3-Cl and 3-CF_3 provided product **2a** in similar yields of ~27%. 5-Fluoropicolinic acid proved less suitable, yielding 22% of epoxide. Finally, blocking the 6-position, either by employing quinoline-2-carboxylic acid or 6-fluoropicolinic acid, led to no product formation whatsoever, as in the absence of any ligand. Therefore, we assume that the active complex does not form if the 6-position of the ligand is blocked, which is in accordance with the works of Stack.[22] The same result was observed for 4-oxazolecarboxylic acid, indicating that no active complex is formed.

To investigate the influence of the N-heterocycle, the model reaction was performed in the presence of several quinolines, pyridines and other heterocycles (Table 3). Applying 2-methylquinoline gave a slightly improved yield of epoxide **2a** (42%) compared to quinoline. In contrast, the introduction of a methyl group at the 8-position of quinoline severely hindered the reaction and only yielded 21% of epoxide (for a more detailed discussion about this difference see the ESI†). Other quinoline derivatives yielded the epoxide in similar yields of 33–37%. Pyridines proved to be similarly or slightly less efficient than quinolines with bulky 2-phenylpyridine providing the epoxide only in low yield (18%). While imidazoles yielded the desired products in yields below 30%, 2-methyloxazoline proved suitable similar to quinoline. Here, 2-phenyloxazoline was also less efficient. Lastly, various benzimidazoles provided the desired products in almost identical yields of slightly above 30% with little effects of methyl substituents being observed. Considering the negative effect of very bulky substituents in the vicinity of the nitrogen-atom, a coordination of the heterocycle to the metal centre during the catalytic reaction seems reasonable. Additionally, we also employed two simple bases NaOAc and NaOH for comparison. While the former is suitable, though less effective compared to 2-methylquinoline, the latter provided a poor yield of epoxide. Taken together, these results suggest that the employed heterocycle fulfils multiple roles in this reaction, *i.e.*, not only being a basic additive but also acting as a potentially stabilizing co-ligand for the metal catalyst.

Having identified suitable heterocycles, we then varied the amount of the employed 2-methylquinoline. As expected,

Table 2 Mn-catalysed epoxidation of 1-octene: screening of picolinic acid derivatives



Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.25 mol% manganese(II)chloride, 1 mol% picolinic acid derivative, 5 mol% quinoline, 0.5 eq. of 2,3-butadione, MeCN (2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 1 eq., diluted in MeCN) *via* a syringe pump.

employing (sub)stoichiometric amounts of 2-methylquinoline in relation to picolinic acid, much lower conversions and yields of epoxide are obtained as the postulated manganese–picolinate complex cannot be formed if the picolinic acid is not (fully) deprotonated. With 2.5 mol% or more, *i.e.*, 2.5 equivalents of 2-methylquinoline in relation to picolinic acid, comparable results are achieved.

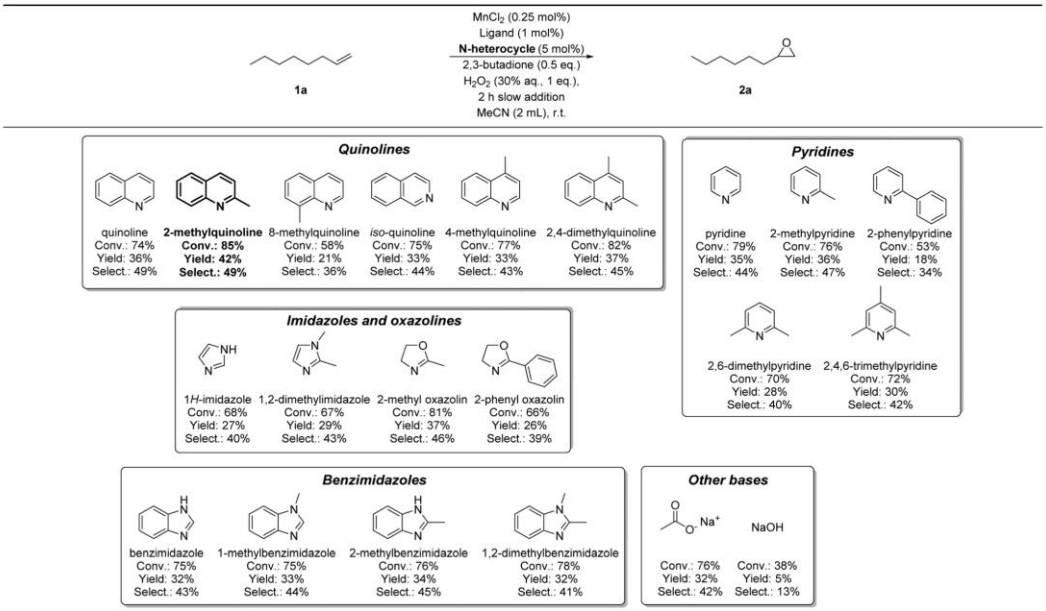
However, employing more than 5 mol% does not further improve the best yield of 42% obtained so far (see Fig. S3†), which is why we settled for a $MnCl_2$: PicOH : 2-methylquinoline ratio of 1 : 4 : 20.

As established in the literature,[20] diketones such as 2,3-butadione can form hydroxy–hydroperoxy adducts with hydrogen peroxide. These adducts are able to oxidize the metal catalyst, *e.g.*, manganese(II/III) species that will then transfer the oxygen atom(s) to the substrate, generating the desired product. Besides 2,3-butadione, we also tested two other ketone additives in this reaction. Here, methyl pyruvate yielded the desired epoxide in 33% yield, whereas pyruvonitrile was less efficient, giving only 13% yield of 1,2-epoxyoctane under the employed reaction conditions. Performing the reaction without the ketone additive led to no product formation, whatsoever. Also, reducing or increasing the amount of 2,3-butadione to 0.25 or 1.0 equivalent, respectively, did not improve the reaction efficiency (see Table S4† for more information).

After having determined the optimal ratios and stoichiometry of all employed additives, the catalyst amount was varied at a 1 : 4 : 20 ratio of $MnCl_2$: PicOH : 2-methylquinoline. Increasing the amount of catalyst to 1 mol% led to slightly lower conversion of the starting material and accordingly lower yields (Table 4, entry 1). This behaviour can be explained by increased H_2O_2 disproportionation as described in other oxidation reactions.[38] In contrast, lowering the amount of catalyst to only 0.05 mol% Mn, still achieved 38% epoxide yield. Simply changing the reaction solvent to a more polar mixture (MeCN : H_2O = 75 : 25, vol% : vol%) again provided 42% yield of **2a**, possibly due to better solubility of the manganese precursor and picolinic acid (Table 4, entry 6). However, using larger amounts of water led to solubility problems of the starting material and poor conversions. Using EtOH or an EtOH : H_2O (75 : 25) mixture as reaction solvent led to poor results, giving only 7% and 12% yields, respectively (possibly due to EtOH oxidation competing with the substrate and/or blocking of the catalyst, see below) (Table 4, entries 7 and 8).

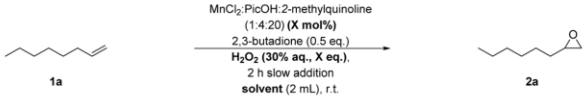
Finally, the amount of the employed hydrogen peroxide (30% aq.) was studied (Table 4, entries 9–13). Using 1.0 equivalent of H_2O_2 in the presence of 0.05 mol% Mn already gave

Table 3 Mn-catalysed epoxidation of 1-octene: screening of various N-heterocycles and bases



Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.25 mol% manganese(II)chloride, 1 mol% picolinic acid, 5 mol% N-heterocycle or base, 0.5 eq. of 2,3-butadione, MeCN (2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 1 eq., diluted in MeCN) *via* a syringe pump.

Table 4 Mn-catalysed epoxidation of 1-octene: variations of the catalyst loading, solvent, and oxidant



Entry	H_2O_2 [eq.]	$MnCl_2$ [mol%]	Solvent	Time [h]	Conv. (**1a**) [%]	Yield (**2a**) [%]	Sel. (**2a**) [%]
1	1.0	1.0	MeCN	2	71	31	44
2	1.0	0.25	MeCN	2	85	42	49
3	1.0	0.125	MeCN	2	79	37	47
4	1.0	0.05	MeCN	2	79	38	48
5	1.0	0.01	MeCN : H_2O (95 : 5)	2	75	31	41
6	1.0	0.05	MeCN : H_2O (75 : 25)	2	82	42	51
7	1.0	0.05	EtOH	2	35	7	20
8	1.0	0.05	EtOH : H_2O (75 : 25)	2	44	12	27
9	1.25	0.05	MeCN : H_2O (75 : 25)	2	87	44	51
10	1.5	0.05	MeCN : H_2O (75 : 25)	2	92	50	54
11	**2.0**	**0.05**	**MeCN : H_2O (75 : 25)**	**2**	**97**	**61**	**63**
12	2.25	0.05	MeCN : H_2O (75 : 25)	2	99	59	60
13	2.5	0.05	MeCN : H_2O (75 : 25)	2	>99	57	57
14	1.5	0.05	MeCN : H_2O (75 : 25)	4	89	47	53
15	1.5	0.01	MeCN : H_2O (95 : 5)	4	83	40	48

Conversion and yield determined by GC analysis with hexadecane as the IST. Reaction conditions: 0.5 mmol substrate (0.250 M), *X* mol% $MnCl_2$: PicOH : 2-methylquinoline (1 : 4 : 20), 0.5 eq. of 2,3-butadione, solvent (2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., *X* eq., diluted in MeCN) *via* a syringe pump.

42% yield of the desired product **2a**. Interestingly, by employing 2.0 equivalents of H_2O_2, we obtained a significantly higher yield of 61% and selectivity towards epoxide **2a** of 63% (Table 4, entry 11). A further increase in H_2O_2 led to full conversion of **1a**, however, the yields of **2a** could not be improved (Table 4, entries 12 and 13).

Scope

Investigating the scope of this manganese-catalysed oxidation protocol, we first employed different terminal and linear alkenes as substrates. 1-Hexene (**1b**), 1-heptene (**1c**) and 1-octene (**1a**) were all converted to their corresponding epoxides **2a–c** in good yields of 61–65%. These results are superior to previously reported protocols for aliphatic olefins (either in terms of yield or in terms of sustainability), where either much higher (noble-metal) catalyst loadings, more expensive ligands, or higher amounts of less benign oxidants, or (corrosive) additives were necessary.[5,9,11,14,17,20,22,53,59–62] Of note, around 80% yields for these substrates can be achieved with non-noble metals (as demonstrated by Stack and co-workers);[22] however, here, the less benign oxidant peracetic acid was employed which resulted in undesirable by-product formation. Further extension of the chain length, however, led to a decrease in conversion and correspondingly lower yields. With 1-decene **1d** and 1-dodecene **1e**, moderate yields of 56% and 37% were achieved, respectively, probably due to lower solubility of the starting materials in the polar MeCN : H_2O (75 : 25) solvent mixture. Indeed, employing a less polar solvent mixture (MeCN : H_2O = 95 : 5) for these substrates led to slightly varying yields of 51% of 1,2-epoxydecane **2d** and 45% of 1,2-epoxydodecane **2e**.

Applying di- and tri-substituted olefins showed an interesting trend: with 2-methyl-1-heptene **1f**, an improved yield of 71% of the desired epoxide **2f** was obtained, while with 2-methyl-2-heptene **1g**, only 49% of epoxide **2g** was obtained. Disubstituted olefins are more nucleophilic and therefore more reactive, accounting for better performance. Though the electronic properties of trisubstituted olefins are even more nucleophilic, here, steric influence starts to interfere with the reaction, demonstrating the selectivity of this catalytic system for sterically less demanding olefins.

Testing cyclic olefins, the reaction proceeded with much higher selectivity. With cyclohexene **1h** and cyclooctene **1i**, the desired epoxides **2h** and **2i** were obtained in ~80% yield. In both cases, no allylic oxidation products were observed, indicating that this reaction does not proceed *via* a radical/Fenton-type reactivity pathway.

Investigating dienes as substrates, we first employed 1,7-octadiene **1j** under the standard reaction conditions. Here, 88% conversion and 21% of diepoxide **2j-2** were observed with about 30% of the mono-epoxide **2j-1** product. Obviously, with dienes, the total concentration of olefinic functionalities is twice as high as that with simple olefins. Therefore, we doubled the amount of hydrogen peroxide to 4 equivalents. Interestingly, this did not change the result. However, reducing the amount of the employed substrate **1j** to 0.25 mmol, *i.e.*, operating with the same concentration of olefinic functionalities as that under the optimized conditions, a significant increase of the yield and selectivity was observed. In this case, full conversion of the starting material **1j** was observed, and no mono-epoxide **2j-1** remained after 2 h reaction time, obtaining 49% of the desired di-epoxide **2j-2**. It should be noted that

such di-epoxidation reactions have been scarcely investigated but offer interesting possibilities for oligomerisation and polymerisation.

Due to its industrial relevance in the fragrance industry, we also investigated the selective mono- and di-epoxidation of cyclooctadiene **1k** (COD). When employing only 1.5 eq. of H_2O_2 (30% aq.) to prevent over-oxidation to di-epoxide **2k-2**, 88% conversion was achieved, and the desired mono-epoxide **2k-1** was isolated in 62% yield. Halving the substrate concentration and using 5 eq. of peroxide, we were able to selectively obtain di-epoxide **2k-2** as single major product in 55% isolated yield. To further demonstrate the applicability of this system, we also performed a multi-gram scale (5 g of substrate) reaction of the mono-epoxidation of COD. Here, we isolated 3.1 g of the desired product **2k-1** (55% yield).

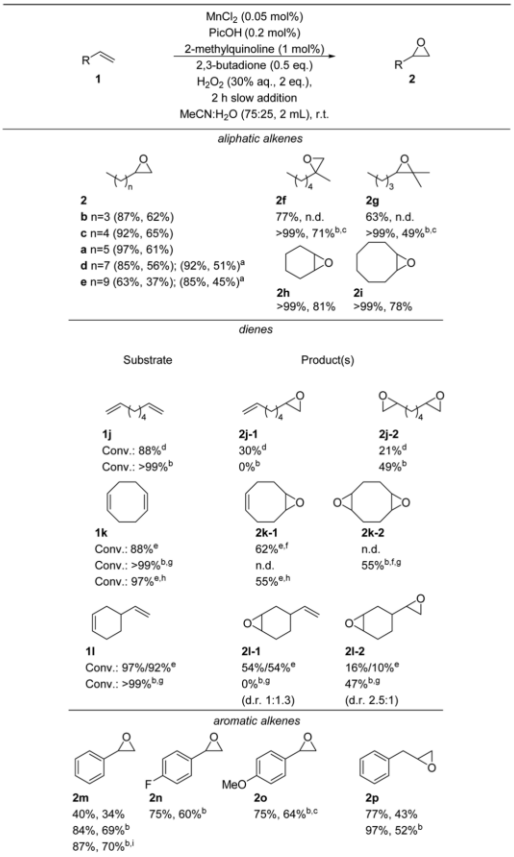
As mentioned *vide supra*, cyclic olefins are more reactive than terminal olefins, thus, we employed 4-vinyl-cyclohexene **1l** as the starting material to investigate the selectivity. Under standard conditions, 97% conversion of diene **1l** was achieved with 53% yield of the ring epoxidation product **2l-1** (dr 1 : 1.3) and 16% yield of di-epoxide **2l-2** (dr 2.5 : 1). No sole side-chain epoxidation product was observed. Reducing the amount of oxidant to 1.5 equivalents increased the reaction efficiency by obtaining the same yield of the desired ring epoxide **2l-1** but less overoxidation to di-epoxide **2l-2** was observed. Again, when employing only 0.25 mmol of diene and 5 equivalents of oxidant, full conversion and 47% yield of di-epoxide **2l-2** were obtained as the single major product (Table 5).

Though this protocol was initially optimised for aliphatic alkenes, we also employed aromatic alkenes as substrates under the same conditions. In the case of styrene **1m**, we observed a reduced conversion of 40% and a 34% yield of styrenoxide **2m**. Though the yield is comparably low, a high selectivity of 85% was achieved here. This prompted us to further investigate styrene as the model substrate for aromatic olefins. As only low conversion was observed, we reduced the concentration of styrene to 0.125 M. This change led to much better results, approximately doubling the conversion and yield to 84% and 69%, respectively. Further increasing the amount of 2,3-butadione did not lead to full conversion. Investigating the effect of electron-withdrawing and electron-donating substituents at the 4-position of styrene did not reveal significant changes in the outcome. With both 4-F- and 4-MeO-substituents (see substrates **1n** and **1o**), the same conversions of 75% were achieved, while similar yields of 60% and 64% were obtained, respectively, demonstrating the robustness of this system towards electronic effects of substituted aromatic substrates.

Switching from styrenes to allylbenzene **1p**, we obtained 77% conversion and 43% of the desired epoxide **2p** under standard conditions. Employing 0.25 mmol of substrate led to almost full conversion (97%); however, a lower selectivity compared to styrene was obtained, giving the desired product **2p** in 52% yield. Trace amounts of benzylic oxidation products were observed here.

To further expand the applications of this protocol, we then turned our attention to the epoxidation of naturally occurring alkenes, *e.g.*, terpenes. Here, we first employed (−)-limonene **1q** as a substrate, using only 1.5 equivalents of oxidant under otherwise standard reaction conditions. In this case, we obtained 41% of the ring epoxidation compound **2q-1** as the major product and 11% of the di-epoxide product **2q-2**. Fine tuning the reaction conditions to obtain the di-epoxide as major product was easily accomplished first by halving the

Table 5 Manganese-catalysed epoxidation reaction: scope of aliphatic olefins



Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.05 mol% $MnCl_2$, 0.2 mol% picolinic acid, 1 mol% 2-methylquinoline, 0.5 eq. of 2,3-butadione, MeCN : H_2O (75 : 25, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 2 eq., diluted in MeCN) *via* a syringe pump. [a]MeCN : H_2O (95 : 5) as solvent. [b]0.25 mmol of substrate employed. [c]Yield determined by NMR analysis with dibromomethane as the IST. [d]Same results were obtained employing 4 eq. of H_2O_2. [e]1.5 eq. of H_2O_2 were employed. [f]Isolated yield. [g]5 eq. of H_2O_2 were employed. [h]5 g scale reaction. [i]1.5 eq. of 2,3-butadione were employed, n.d.: not determined.

substrate concentration which resulted in a roughly one to one mixture of both products and consecutively raising the amount of H_2O_2 (30% aq.) to 5 equivalents, which then yielded the desired di-epoxide product **2q-2** in 45% yield as the sole major product. Next, we subjected α-pinene **1r** to our epoxidation reaction conditions. In this case, 83% conversion but only 27% yield of the desired product **2r** were obtained, while minor amounts of other unselective oxidation/decomposition products were detected upon GC-MS analysis, *e.g.*, campholenic aldehyde. Since aldehydes are easily oxidized to the corresponding carboxylic acids, this would account for the lower selectivity with this substrate, as the formation of large amounts of acids negatively impede the performance of this catalyst system. In the case of myrcene **1s**, high conversion of all three C=C double bonds (~76% after 1 h and ~83% after 2 h), but unselective product formation was detected.

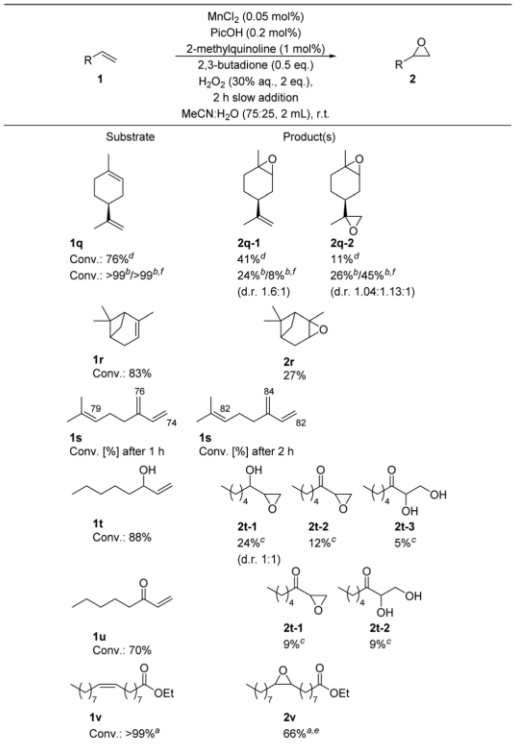
In addition to terpenes, we also investigated the "mushroom alcohol" 1-octene-3-ol **1t** and the analogous ketone **1u** as substrates. Interestingly, with the former substrate, NMR analysis indicated the formation of three major products. First, the epoxidation of the C=C double bond to the corresponding hydroxy-epoxide diastereomers **2t-1** (d.r. 1 : 1) is observed with 24% yield. In addition, the O–H group is also further oxidized to the ketone epoxide **2t-2** in 12% yield. As this class of compound easily undergoes epoxide ring-opening, the corresponding diol **2t-3** is formed with 5% yield. A similar reaction outcome was observed with 1-octene-3-one **1u** as the substrate. Finally, the fatty acid ester ethyl oleate **1v** was employed as substrate and the desired epoxide product **2v** was isolated in 66% yield, again demonstrating the high selectivity of this system towards aliphatic unactivated C=C double bonds (see Table 6).

Besides epoxidation, selective aliphatic C–H oxidation with non-noble metal catalysts is even more challenging. Obviously, such transformations allow the implementation of functional groups, *i.e.*, hydroxy or carbonyl groups, into unfunctionalized compounds, thus profoundly changing the physical (and biological) properties of the starting materials.[63] Therefore, we also investigated C–H oxidation reactions with the present catalytic protocol as trace amounts of C–H oxidation products were observed when employing allylbenzene as the substrate.

Also, similar systems for oxidation of C–H bonds in alkanes have been reported in the literature.[23] As the model substrate for C–H functionalization reactions, we chose cyclohexane **3a** due to its industrial relevance and equivalence of all present C–H bonds. In fact, "KA oil", a mixture of cyclohexanone and cyclohexanol, is used as a precursor for adipic acid whose production exceeds three million tons per anum and is still growing annually.[64] After a short optimization (see the ESI and Table S5† for more information), we were delighted to obtain 43% yield of cyclohexanone **5a** from cyclohexane with complete selectivity for ketone **5a** over alcohol **4a**.

Consequently, we subjected various alkanes to this slightly modified catalytic protocol. Using cyclododecane **3b**, we obtained cyclododecanone **5b** (a precursor to laurolactam) in 31% yield as the sole major product (the limiting factor here seems to be the solubility). Employing cyclooctane **3c**, we observed a high conversion of 93% and a good yield of 51% of the desired ketone product **5c**. Again, only traces of alcohol **4c** were detected. Next, we tested alkanes bearing aromatic rings as substrates. Here, tetrahydronaphthalene **3d** performed similarly well with 72% conversion and 43% of the corresponding ketone **5d**, while small amounts of alcohol **4d** were detected in this case. Switching to non-cyclic alkanes, such as ethylbenzene **3e** bearing an activated benzylic position, a different reactivity is expected. Indeed, 38% conversion was observed, resulting in a mixture of 13% phenylethanol **4e** and 24% acetophenone **5e**. Applying a more polar solvent mixture, slightly improved this result, giving 46% conversion and 29% of aceto-

Table 6 Manganese-catalysed epoxidation reaction: scope of naturally occurring alkenes

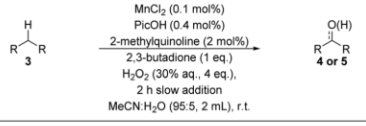


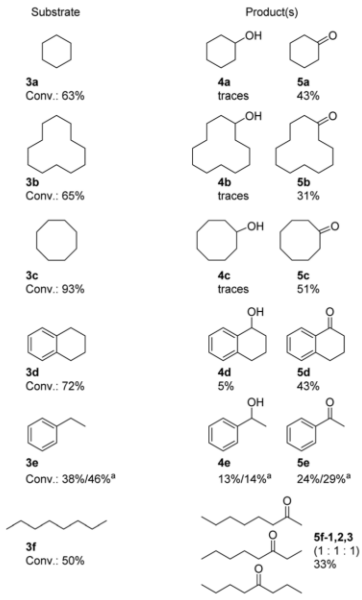
Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.05 mol% $MnCl_2$, 0.2 mol% picolinic acid, 1 mol% 2-methylquinoline, 0.5 eq. of 2,3-butadione, MeCN : H_2O (75 : 25, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 2 eq., diluted in MeCN) *via* a syringe pump. [a]MeCN : H_2O (95 : 5) as solvent. [b]0.25 mmol of substrate employed. [c]Yield determined by NMR analysis with dibromomethane as the IST. [d]1.5 eq. of H_2O_2 were employed. [e]Isolated yield. [f]5 eq. of H_2O_2 were employed.

phenone **5e**. In the case of *n*-octane **3f**, 50% conversion resulting in a 1 : 1 : 1 mixture of the three possible ketone products **5f-1–3** with 33% combined yield with no alcohol formation observed (see Table 7).

Finally, we investigated the oxidation of alcohols with the present protocol since we also observed O–H oxidation employing 1-octene-3-ol as the epoxidation substrate (see Table 8) and mainly ketones resulted from C–H oxidation. First, we compared primary and secondary alcohols to verify the standing thesis that primary alcohols are indeed not tolerated under present reaction conditions due to the formation of carboxylic acids. With 2-octanol **4f** as the substrate, we were delighted to achieve 86% conversion and 79% yield of 2-octanone **5f** under standard epoxidation reaction conditions. In contrast, oxidation of 1-octanol **4g** did not take place selectively under the standard reaction conditions and low conversion (30%) and

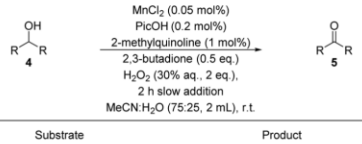
Table 7 Manganese-catalysed C–H oxidation reactions: scope of alkanes

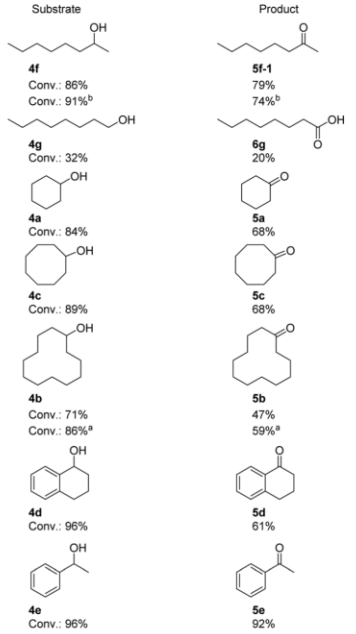




Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.25 mmol substrate (0.125 M), 0.1 mol% $MnCl_2$, 0.4 mol% picolinic acid, 2 mol% 2-methylquinoline, 1 eq. of 2,3-butadione, MeCN : H_2O (95 : 5, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 4 eq., diluted in MeCN) *via* a syringe pump. [a]MeCN : H_2O (75 : 25) as solvent.

Table 8 Scope of manganese-catalysed oxidation of alcohols





Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.05 mol% $MnCl_2$, 0.2 mol% picolinic acid, 1 mol% 2-methylquinoline, 0.5 eq. of 2,3-butadione, MeCN : H_2O (75 : 25, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 2 eq., diluted in MeCN) *via* a syringe pump. [a]MeCN : H_2O (95 : 5) as solvent. [b]0.25 mmol of substrate employed.

ca. 20% of octanoic acid **6g** were detected. Since this catalytic system relies on the deprotonation of picolinic acid by the 2-methylquinoline additive to form the active complex, the formation of significant amounts of acid obviously impedes the catalytic activity. Consequently, various secondary alcohols were subjected to our catalytic protocol. When employing cyclohexanol **4a** and cyclooctanol **4c** as substates, identical yields of 68% of the desired ketones **5a** and **5c** were obtained. Using the less polar cyclododecanol **4b** as substrate, a reduced yield of 47% was obtained. However, this was improved upon by switching to a less polar solvent mixture (MeCN : H_2O = 95 : 5), resulting in 59% yield of cyclododecanone **5b**. Furthermore, phenylethanol **4e** proved to be an excellent substrate with almost full conversion and selectivity, yielding acetophenone **5e** in 92% yield. Lastly, with tetrahydronaphthalene-

1-ol **4d**, 96% conversion and 61% yield of 1-tetralone **5d** were achieved. Here, small amounts of over-oxidation products, *e.g.*, the diketone, were observed upon GC analysis, accounting for the lower mass balance. In general, however, higher mass balances are achieved with O–H oxidation reactions compared to C–H oxidation or epoxidation reactions with this catalytic system.

Mechanistic investigations and proposal

Upon investigating the scope of our catalytic protocol, several interesting information on the activity of this novel system was obtained. To gain more knowledge about the detailed action of this manganese catalyst, we investigated the involvement of radical species by conducting control experiments employing the radical scavengers TEMPO and BHT. Both compounds impede the reactivity but do not block the catalyst. For example, the addition of 5 mol% TEMPO reduces the catalytic activity by 20% (see Scheme S1 and the ESI† for more information). To prove whether the observed over-oxidation products are a result of radical side-reactions, we reacted 1,2-epoxyoctane **2a** under the standard reaction conditions and found that 80% of **2a** could be recovered after 2 hours. Interestingly, performing the same experiment in the presence of TEMPO, we found that **2a** could be completely recovered. Therefore, we assume that the partial degradation of the epoxide products is a result of unwanted radical reactions.

Next, we recorded a kinetic profile of the epoxidation of 1-octene **1a** to identify possible intermediates or follow-up products that might be formed in small amounts during the reaction. In accordance with related studies,[35] it is apparent that both the substrate consumption and the product formation follow an approximately linear course. Nevertheless, in the beginning, substrate conversion is slightly faster than the product formation, indicating that the active epoxidation catalytic species might not be formed immediately upon H_2O_2 addition. Therefore, the selectivity towards the desired product **2a** at the beginning of the reaction is about 40% until it rises to ~60% after 40 minutes and remains constant for the rest of the reaction (see Fig. 1). Additionally, no major side-products or decrease in the yield of the product were observed. Therefore, we assume that substrate over-oxidation or degradation takes place at the very beginning of the reaction, as the active catalytic species is not yet formed. This is also in agreement with previous works.[5,14] Furthermore, we recorded the kinetic profile of the C–H oxidation of cyclohexane **3a** to cyclohexanone **5a** to compare both oxidative transformations. Here, at the beginning of the reaction, a lower selectivity is observed that reaches ~60% after 60 minutes and stays in the range of 60–70% for the remaining reaction time. Again, the lower selectivity towards the desired product at the beginning of the reaction indicates a lag period during which the active catalytic species is not yet formed. In contrast to 1-octene epoxidation, no quantitative conversion of cyclohexane **3a** is achieved under the present reaction conditions. Finally, there is no accumulation of cyclohexanol **4a** as an intermediate as only trace amounts of the alcohol are observed during the whole reaction

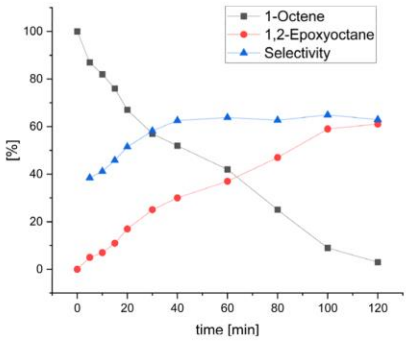


Fig. 1 Kinetic profile of manganese-catalysed epoxidation of 1-octene. Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.5 mmol substrate (0.250 M), 0.05 mol% $MnCl_2$, 0.2 mol% picolinic acid, 1 mol% 2-methylquinoline, 0.5 eq. of 2,3-butadione, MeCN : H_2O (75 : 25, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 2 eq., diluted in MeCN) *via* a syringe pump. For each point in time, a separate reaction was set up and analysed after the indicated slow addition time.

time (see Fig. 2). Taking these results and previous works[34] into consideration, we propose similar reaction pathways and reactive intermediates for both types of oxidation reactions.

While investigating the scope, we observed that aromatic alkenes required higher catalyst loadings than aliphatic alkenes to achieve comparable yields. Furthermore, allylbenzene was preferentially oxidized to the epoxide, although (benzylic) C–H oxidation is also possible. Also, 1-octene-3-ol

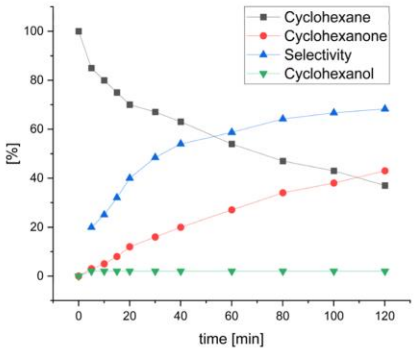
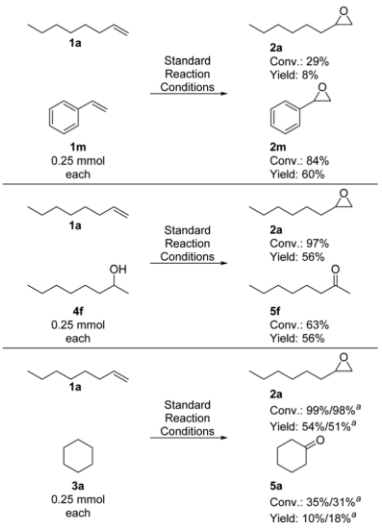


Fig. 2 Kinetic profile of manganese-catalysed C–H oxidation of cyclohexane. Conversion and yield determined by GC analysis with hexadecane as IST. Reaction conditions: 0.25 mmol substrate (0.125 M), 0.1 mol% $MnCl_2$, 0.4 mol% picolinic acid, 2 mol% 2-methylquinoline, 1 eq. of 2,3-butadione, MeCN : H_2O (95 : 5, 2 mL), 25 °C, 2 h slow addition of H_2O_2 (30% aq., 4 eq., diluted in MeCN) *via* a syringe pump. For each point in time, a separate reaction was set up and analysed after the indicated slow addition time.

was primarily oxidized to the corresponding epoxide though in lower yield due to several follow-up oxidations. These results show that epoxidation seems to be preferred over C–H and O–H oxidation, while O–H oxidation is preferred compared to C–H oxidation. To prove these assumptions, competition experiments of 1-octene with selected other substrate classes were performed. First, equal amounts of 1-octene **1a** and styrene **1m** (0.25 mmol each) were subjected to our standard reaction conditions. Interestingly, styrene performed similarly well in this competition experiment (60% yield of **2m**), while 1-octene was converted in poor yield (8%) to 1,2-epoxyoctane **2a**.

Although this system was optimized for the epoxidation of aliphatic alkenes, their aromatic, activated counterparts are more reactive when both substrates are employed in a single reaction. In the second set up, we compared 1-octene **1a** as an epoxidation substrate to 2-octanol **4f** as an alcohol oxidation substrate. Here, 1,2-epoxyoctane **2a** was formed in a similar yield as before from the former substrate (56%), while 2-octanone **5f** was obtained in a somewhat reduced yield of 56%, confirming the previously observed trend that epoxidation takes precedent over O–H oxidation when both functional groups are present. Finally, subjecting equal amounts of 1-octene **1a** and cyclohexane **3a** to our standard reaction conditions, 1,2-epoxyoctane **2a** was again obtained in a similar yield as before (54%) while cyclohexanone **5a** was only obtained in 10% yield (18% when the less polar solvent mixture is used, see Scheme 2). Taken together, these results show that the presented manganese catalyst system preferentially oxidizes alkenes in the presence of alcohols and in the presence of C–H oxidation substrates. Furthermore, under optimized reaction conditions, 1-octene requires lower catalyst loading and fewer peroxide equivalents than styrene; however, with higher loadings and more peroxide, styrene outcompetes 1-octene as a substrate when both compounds are present in the same reaction set-up.



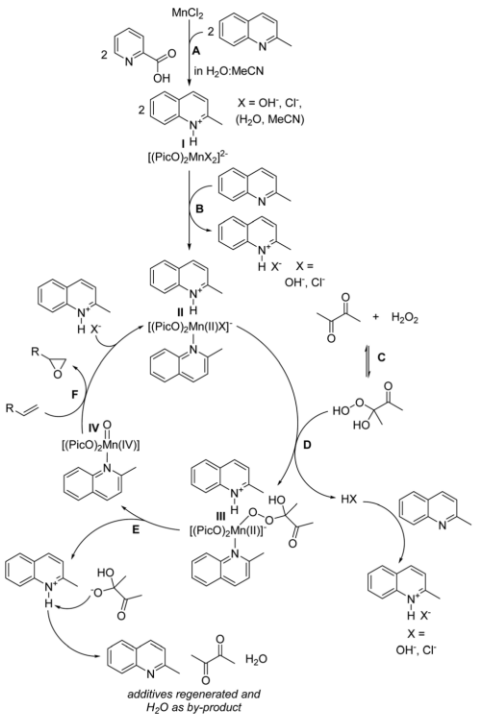
Scheme 2 Competitions experiments of 1-octene with selected other substrate classes. Conversion and yield determined by GC analysis with hexadecane as IST. [a] MeCN:H_2O (95 : 5) as solvent.

Based on all these observations, we propose the following catalytic cycle for this newly developed oxidation catalyst: in the first step **A**, the generation of the postulated $[(PicO)_2MnX_2]^{2-}$ - complex occurs, enabled by deprotonation of PicOH by 2-methylquinoline resulting in the negatively charged species **I**, with two protonated quinolyl species $[2\text{-MQ-H}]^+$ as counterions. Here, the nature of the two ligands X^- occupying the two additional coordination sites of the manganese centre remains unclear. Two chloride ligands derived from the precursor or OH-groups from hydrolysis of $MnCl_2$ to $Mn(OH)_2$ and solvent coordination (H_2O, MeCN) seem to be possible.

In the second step **B**, one of the ligands X^- is exchanged by the coordination of the co-ligand, 2-methylquinoline, leading to the formation of species **II** (though species **I** and **II** are possibly in equilibrium). Here, the formal charge of X^- would be compensated by the present protonated quinolyl species $[2\text{-MQ-H}]^+$. In accordance with the literature, 2,3-butadione and hydrogen peroxide are in equilibrium (**C**) with 3-hydroxy-3-hydroperoxybutanone.[34] In the following step **D**, this formed adduct substitutes the remaining X^- ligand, resulting in H_2O or HCl elimination, which in turn is deprotonated by another 2-methylquinoline, forming an additional $[2\text{-MQ-H}]^+$ and manganese species **III**. Considering the results from the co-ligand screening, where 8-methylquinoline exhibited a much worse performance than 2-methylquinoline, the formation of species **III** could be severely hindered by the steric effect of the 8-methyl group in the case of 8-MQ as the co-ligand. Additionally, the presence of TEMPO could either compete with picolinic acid as the ligand, or impede step **D**, by coordinating to the manganese centre and preventing 3-hydroxy-3-hydroperoxybutanone from coordinating, thus accounting for the negative effect TEMPO had on the reaction outcome.

Species **III**, in which manganese is still in the oxidation state (II) undergoes heterolysis of the O–O bond from the coordinated 3-hydroxy-3-hydroperoxybutanone, resulting in the formation of species **IV** with a manganese(IV) centre (step **E**). This step is facilitated by the present acidic counter-cation $[2\text{-MQ-H}]^+$ which further activates the O–O bond by either forming a hydrogen bond or even promoting protonolysis[65] of species **III** resulting in the immediate regeneration of the 2-MQ.

Alternatively, 2-MQ would be regenerated in a consecutive step by deprotonation of $[2\text{-MQ-H}]^+$ with concomitant regeneration of 2,3-butadione and formation of H_2O as the oxidant by-products. High-valent manganese oxo-species **IV**, which is stabilised by the present donor-ligand 2-methylquinoline,[10,66] is presumed to be the active oxidation catalyst, thus oxidizing the present alkene to the corresponding epoxide (step **F**). Upon regeneration of the manganese(II) species **II**, the free



Scheme 3 Mechanistic proposal for the manganese-catalysed (ep)oxidation reaction.

coordination site is stabilized again by ligand X^- (see Scheme 3).

Conclusions

In summary, we demonstrated the general potential of an easily accessible manganese-based catalyst system for the selective oxidation of olefins, alkanes, and alcohols, which are of importance for bulk chemicals as well as naturally occurring feedstocks. To the best of our knowledge, this non-noble metal catalyst system offers the highest efficiency of any acid-free *in situ* system especially for the epoxidation of unactivated terminal aliphatic olefins with yields of up to 65%. Additionally, unactivated (cyclic) alkanes can be converted selectively with yields of up to 51% to their corresponding ketones, streamlining industrially relevant processes, *e.g.*, adipic acid production. Furthermore, the role of the employed N-heterocycles was investigated in detail. On the one hand, 2-methylquinoline acts as a base deprotonating picolinic acid and generating the active catalyst system. On the other hand, it can be regarded as a co-ligand which has a beneficial effect on the reaction outcome.

Experimental

Important safety note

Hydrogen peroxide may cause explosion upon contact with metal catalysts. Therefore, we are working with the safer 30% aqueous hydrogen peroxide solution instead of the higher concentrated 50% solution.

General procedure for the epoxidation of olefins

An 8 mL glass vial equipped with a Teflon coated stirring bar was charged with stock solutions of $MnCl_2$ (0.25 μmol, 31.5 μg, 0.05 mol% in 250 μL H_2O), picolinic acid (1 μmol, 0.123 mg, 0.2 mol% in 250 μL H_2O) and freshly distilled 2-methylquinoline (5.0 μmol, 0.716 mg, 1.0 mol% in 250 μL MeCN). The resulting mixture was stirred for 5 minutes. Next, a solution of 2,3-butadione (0.25 mmol, 43 mg, 0.5 eq. in 250 μL MeCN) was added. The resulting mixture was further diluted with MeCN to a total volume of 2 mL (MeCN : H_2O = 75 : 25) and stirred for additional 5 min. Then, 1-octene (0.5 mmol, 56.1 mg, 0.250 M) was added. Next, a solution of hydrogen peroxide (H_2O_2) (1.0 mmol, 2.0 eq., 104 μL, 30% aq.) in MeCN (906 μL) was added *via* a syringe pump to the reaction mixture over a course of 2 h.

For GC analysis, the reaction mixture was then diluted with EtOAc, filtered, and analysed using hexadecane (30 μL) as an internal standard to determine the conversion and yield by 5-point calibration of the respective compounds.

The same procedure was applied for alcohol oxidation. For C–H oxidation of alkanes, a slightly modified protocol was applied (see the ESI† for more information).

Author contributions

D. V. conceived and conceptualised the project, co-wrote and co-edited the manuscript, performed the experiments, and analysed the data; S. A. co-performed the experiments; X. W., Y. Y. and Y.-W. L. supported the project with funding acquisition; K. J. and M. B. provided the infrastructure, performed discussions of the project results, and co-wrote and edited the manuscript.

Conflicts of interest

There are no conflicts to declare.

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6.3. Homogeneous Iron-Catalysed Oxidation of Non-Activated Alkanes with Hydrogen Peroxide

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Contribution

For this manuscript I helped with the optimization, the substrate scope and the ligand comparison. Furthermore, I helped with the data analysis and co-performed the revisions after peer-review. My overall contribution accounts for approximately 20%.

_____	_____
Signature of the student	Signature of the supervisor
Dennis Verspeek	Prof. Matthias Beller

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Homogeneous Iron-Catalysed Oxidation Of Non-Activated Alkanes With Hydrogen Peroxide

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A novel synthetic protocol for the direct oxidation of alkanes, including cyclic and linear ones, to give ketones and alcohols using hydrogen peroxide as terminal oxidant under ambient conditions is presented. The active catalyst for this challenging transformation is conveniently generated by combination of simple Fe salts with N-methyl bis(picolylamine) (Me-bpa). Utilizing picolinic acid as additive leads to improved yields of ketones and alcohols (32-57%). The reaction can be conveniently scaled up to multi-g scale.

Introduction

The introduction of functional groups into molecules is a fundamental process in organic chemistry and materials synthesis. Hence, countless methodologies for this kind of transformations have been developed in the past. In this respect, specifically direct C–H functionalization reactions represent a powerful tool,[1,2] which allows to streamline the synthesis of many products. Among the different classes of C–H bonds, the selective activation of C(sp^3)–H bonds is particularly interesting and at the same time highly challenging.[3] Apart from organic synthesis the activation of these C(sp^3)–H bonds especially by direct oxidation is of great potential for the chemical industry. Indeed, in the bulk chemical industry, direct oxidation of cyclic alkanes to ketones and alcohols, particularly of cyclohexane to KA oil is an efficient way for the synthesis of adipic acid, a key monomer of nylon-6,6.[4] The functionalization of vinylic polymers *via* direct oxidation of the C(sp^3)–H bond has also become of significant interest in recent years.[5] However, the high bond dissociation energies of C(sp^3)–H bonds (BDEs around 100 kcal/mol)[2,6] and the inert nature of the C(sp^3)–H bond make it thermodynamically and kinetically unreactive. Other than that, the corresponding alcohols are usually more reactive under similar conditions than the alkane substrates, which in general leads to over oxidation to the ketone. In the case of primary alcohols, the formed aldehyde easily over-oxidizes to the corresponding carboxylic acid, unless special conditions (*i.e.* Swern-oxidation) are used.

During the past decades, many different methods have been developed for this kind of transformation. For example, alkanes can be directly oxidized with strong oxidants such as dioxirane,[7] peracids,[8] and ozone.[9] Clearly, applying stoichiometric amounts of these reagents limits their applications due to their explosive nature as well as concomitant waste formation. On the other hand, utilizing transition metal catalysts, *e.g.*, Pt,[10] and Pd[11] it is possible to use more benign oxidants like hydrogen peroxide or molecular oxygen, though low productivity, utilization of precious metals and requirement of directing groups are drawbacks here.

Compared to other metals, iron is an ideal candidate for new catalysts due to its abundance, low toxicity, and environmentally benign character. Thus, more and more new potential catalysts as well as novel Fe-catalysed oxidative transformations of alkanes were reported in recent years.[12–19]

In this respect, specifically the development of iron-based catalysts for C–H oxidations of aliphatic alkanes has been a goal for many years. For example, in the 1990s Barton and co-workers reported different generations of so-called Gif systems using simple iron(III) salts and *t*-BuOOH or H_2O_2 in combination with pyridine.[20] Furthermore, Bolm and co-workers presented the use of simple iron perchlorate with acetic acid as an additive for C–H oxidation of alkanes and alkylarenes in 2005.[21] Notably, in biological systems, the oxidation of C(sp^3)–H bonds with iron centred enzymes, such as cytochrome P450 and Rieske oxygenases, is also well known.[22,23] In addition, Groves and co-workers developed an iron-porphyrin catalyst using PhIO as oxidant for oxidation of alkanes.[24] More recently, the groups of Que,[25] White,[26] and Costas[27] reported related biomimetic systems: the so called non-heme iron catalysts (Scheme 1), for selective oxidation of aliphatic alkanes using H_2O_2 as terminal oxidant, which showed very good reactivity

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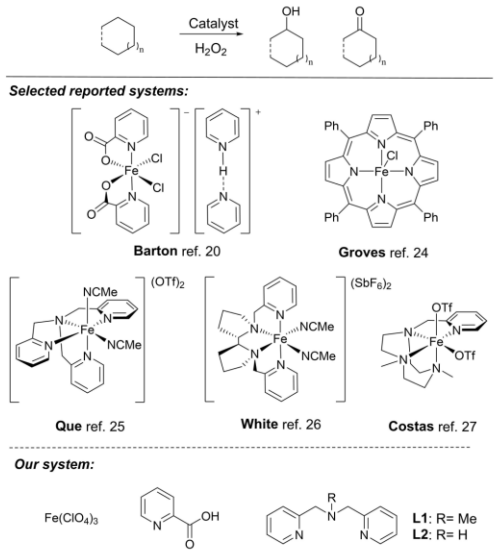


Scheme 1. Selected examples of Fe-catalysed oxidations of aliphatic alkanes.

and selectivity. Despite all these elegant developments, still a practical and selective iron catalyst is desired for such transformations as most systems are either less selective or need elaborate ligand synthesis and stoichiometric amounts of acids as additive. Complementary to the known works on Fe-catalysed direct alkane oxidation with H_2O_2 as terminal oxidant, herein we report an easy and convenient novel iron-based catalyst system with readily available tridentate ligands and picolinic acid (PicOH) as co-ligand.

Results and Discussion

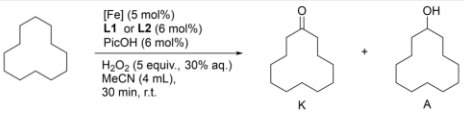
Recently, we demonstrated that the combination of N-methyl-bis-(2-picolyl)amine **L1** with $Fe(OTf)_2$ in the presence of PicOH showed selective reactivity for epoxidation of linear α-olefins.[28] While studying the epoxidation of 1-decene, we observed partial oxidation of the GC-standard hexadecane as an unwanted side reaction. Thus, we assumed that this system could have the potential for the oxidation of non-activated alkanes as well.

For the more detailed investigations, cyclododecane was applied as a model substrate owing to its relatively high boiling point and ready availability. Furthermore, the equivalence of C–H bonds in cyclododecane facilitates product analysis and obviates the problem of site selectivity. In addition, the corresponding cyclododecanone is of interest as a fragrance and precursor to 1,12-dodecanedioic acid and laurolactam, which are precursors for specialized polyamides. For practical reasons, we used *in-situ* generated catalytic systems formed from iron precursors and N-derived ligands. To our delight, with the combination of 5 mol% of $Fe(OTf)_2$, 6 mol% of **L1**, 6 mol% of PicOH as co-ligand and 5 equiv. of H_2O_2 (30% aq.) in acetonitrile, a conversion of 61% and an overall selectivity of 56% for a mixture of the corresponding ketone (K) (16% yield) and alcohol (A) (18% yield) was achieved (Table 1, entry 1). In general, the ratio of K to A in this experiment and the following ones was in the range of 1:1.2 to 2.1:1. When the reaction was realized under an argon atmosphere the same results were obtained. Performing the reaction without an iron source led to nearly no conversion (Table 1, entry 2), while in the absence of any ligand a reduced activity of $Fe(OTf)_2$ was observed giving low amounts of the desired products (Table 1, entry 3).

To further improve the reactivity and selectivity, the effect of different iron precursors was investigated. Very low reactivity was obtained using $FeCl_2$ or $FeBr_2$ in combination with **L1** as catalyst systems (Table 1, entries 4, 5). This may be due to the strong coordination of halide ions which prohibits the active site of iron catalysts. Furthermore, other iron precursors with less strong coordinating anions were tested. Best results were obtained applying $Fe(OTf)_3$ and $Fe(ClO_4)_3xH_2O$ (Table 1, entries 6, 7). As $Fe(ClO_4)_3xH_2O$ is much cheaper and easier to handle than $Fe(OTf)_3$, it was selected for further optimization of reaction parameters. Next, the effect of solvents was explored.

Neither more polar solvents such as DMSO and H_2O nor less polar solvents like DCM provided a better yield (see SI). This can be explained by the balance between a moderate coordinating ability to iron which stabilizes the catalyst and the good solubility for both organic and inorganic compounds in acetonitrile. Interestingly, when **L2** (bis-(2-picolyl)amine) was

Table 1. Fe-catalysed oxidation of cyclododecane: Variation of reaction conditions.[a]



Entry	[Fe]	L	Conv. (%)[b]	Yield (%) (K+A)	Sel. (%)[b] (K+A)
1	$Fe(OTf)_2$[c]	**L1**	61	16+18	56
2	—	**L1**	<1	0	0
3	$Fe(OTf)_2$	—	27	8+5	48
4	$FeCl_2$*$6H_2O$	**L1**	8	1+2	38
5	$FeBr_2$	**L1**	<5	<5	n.d.
6	$Fe(OTf)_3$	**L1**	69	18+20	55
7	**$Fe(ClO_4)_3xH_2O$**	**L1**	**61**	**16+23**	**64**
8	$Fe(OTf)_2$	**L2**	29	17+8	86
9[d]	$Fe(OTf)_2$	**L2**	75	21+18	52

[a] Reaction conditions: Cyclododecane (0.5 mmol), $Fe(OTf)_2$ (5 mol%), ligand **L1** (6 mol%), PicOH (6 mol%) acetonitrile (4 mL), H_2O_2 (5 equiv., 30% aq.) added over 30 minutes by syringe pump under ambient conditions. [b] Substrate conversion and selectivity were determined by GC using hexadecane as an internal standard. Selectivity is the total yield of ketone and alcohol in relation to the substrate conversion. [c] The same results were obtained when performing the reaction under an inert atmosphere of argon. [d] 16 h.

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applied as ligand, despite the low yield, a much higher selectivity was achieved. However, when the reaction time was increased to 16 h, the selectivity dropped again (Table 1, entry 9) giving even worse results than with **L1**.

Nevertheless, other easily accessible N-derived ligands including ligands with free amines or oxazoline moieties were further examined to obtain a better activity and/or selectivity (Figure 1). However, none of the other ligands showed any reactivity at all demonstrating the specific features of this ligand scaffold. After optimization of reaction parameters such as metal precursors, ligands, solvents, and additives (see SI), the best result was obtained using the *in-situ* catalyst system generated form 5 mol% of $Fe(ClO_4)_3xH_2O$, 6 mol% of **L1**, 6 mol% of PicOH, and 5 equiv. of H_2O_2 (30% aq.) as oxidant in acetonitrile at room temperature (61% conv. and 39% yield of ketone and alcohol (16% A + 23% K)).

To determine the side products of this reaction, a kinetic profile was performed under the optimized conditions. As shown in Figure 2, the reaction proceeds very fast even at room temperature. The chemoselectivity towards the KA mixture is relatively high at the very beginning of the reaction. Obviously, with the increase of conversion, the selectivity dropped gradually. The overall yield of the corresponding ketone and alcohol stopped increasing after 30 min, while the conversion of starting material is still increasing. Noteworthy, the ratio of the ketone to the alcohol changes from K:A = 1:2 in the beginning to roughly K:A = 2:1 towards longer reaction times.

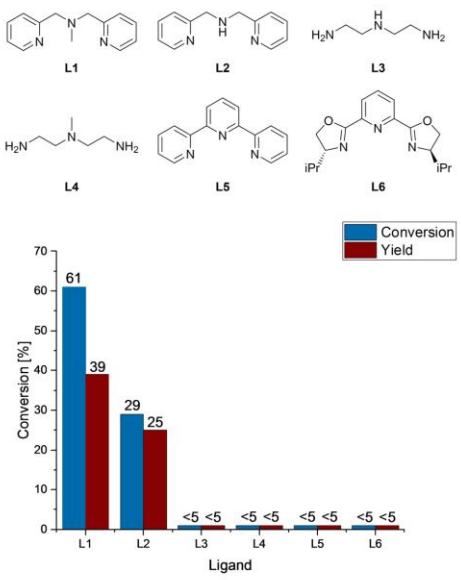

Figure 1. Screening of ligands for the oxidation of cyclododecane. Reaction conditions: Cyclododecane (0.5 mmol), $Fe(ClO_4)_3xH_2O$ (5 mol%), ligand (6 mol%), PicOH (6 mol%) acetonitrile (4 mL), H_2O_2 (5 equiv., 30% aq.) added over 30 minutes by syringe pump under ambient conditions. a: Substrate conversion and product yield were determined by GC using hexadecane as an internal standard.

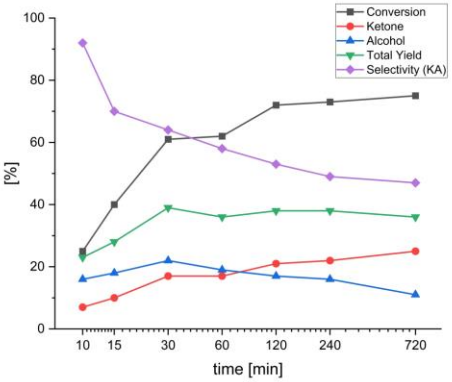

Figure 2. Reaction profile of the oxidation of cyclododecane using **L1** as ligand. Reaction conditions: Cyclododecane (0.5 mmol), $Fe(ClO_4)_3xH_2O$ (5 mol%), ligand (6 mol%), PicOH (6 mol%), acetonitrile (4 mL), H_2O_2 (5 equiv., 30% aq.) added over the indicated time by syringe pump under ambient conditions. Substrate conversion and product yield were determined by GC using hexadecane as an internal standard.

This indicates a metal-centred mono-oxygenase type of reaction where the ketone is formed from over-oxidation of the alcohol rather than a free-radical driven mechanism where both products are formed in parallel with similar rates.

Furthermore, no major side-products could be isolated and only trace amounts of over-oxidation products were observed by GC, GC-MS, and NMR spectroscopy. Thus, apart from the selective oxidation, we assume that the starting material underwent oxidative degradation to give volatile small molecules like formic acid and CO_2.

Next, the applicability of the optimized catalytic system was studied for different alkanes (Scheme 2). Other cyclic alkanes such as cyclododecane, cyclooctane and cyclohexane also reacted with overall moderate yield to the mixtures of the corresponding ketones and alcohols (Scheme 2, **2a**–**2c**). When cyclododecane was utilized as substrate, the reaction was scaled up to multi-g scale (5 g) and no significant loss of reactivity was observed (Scheme 2, **2a**[b]). Notably, the yield of the ketone/alcohol mixtures can be further improved to 52%, by adding a second portion of the catalyst and fresh H_2O_2 to the reaction mixture (Scheme 2, **2a**[c]). Other cyclic alkanes like adamantane can also be oxidized to the corresponding ketone and alcohols. Here, tertiary C–H groups are oxidized preferentially, giving only 5% of the ketone product from secondary C–H group oxidation and a combined 37% of the alcohol and diol from tertiary C–H group oxidation (Scheme 2, **2d**). In addition to cyclic alkanes also linear ones such as heptane or octane can be converted to the respective ketone/alcohol mixture in similar yield but with low regioselectivity regarding the 2, 3 and 4-position (Scheme 2, **2e**–**2f**). Furthermore, this Fe catalyst can oxidise preferentially benzylic C–H bonds in ethylbenzene. Here, a lower yield of 32% of the ketone/alcohol mixture was obtained (Scheme 2, **2g**). On the one hand, the lower product yield could be a result of the over oxidation of

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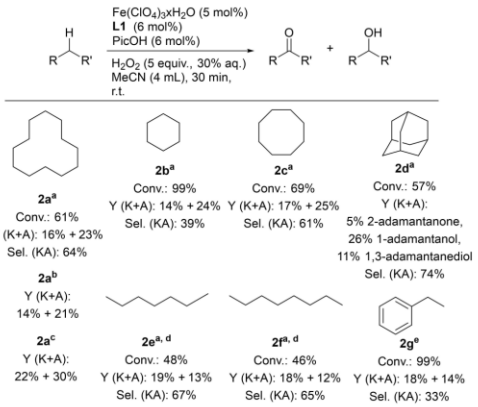
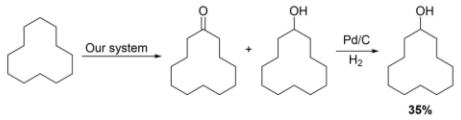


Scheme 2. Fe-catalysed oxidation of cyclic, linear, and aryl-substituted alkanes. Reaction conditions: Alkane (0.5 mmol), $Fe(ClO_4)_3xH_2O$ (5 mol%), **L1** (6 mol%), PicOH (6 mol%) acetonitrile (4 mL), H_2O_2 (5 equiv., 30% aq.) added over 30 minutes by syringe pump under ambient conditions. a: Product yield was determined by GC using hexadecane as an internal standard. Yield refers to the total amount of ketone and alcohol product(s) formed from the indicated substrate. b: 5 g scale. c: another portion of catalyst and H_2O_2 (5 equiv., 30% aq.) was added after the reaction. d: a mixture of oxidation products in the 2, 3 and 4-position with a ~1 : 1 : 1 ratio was obtained. e: 56% of benzoic acid was obtained.



Scheme 3. Selective two-step synthesis of cyclododecanol from cyclododecane (see supporting information for detailed reaction conditions).

the formed phenyl ethanol and acetophenone to benzoic acid. These products are known to undergo C–C bond cleavage under oxidizing conditions to form the analogous carboxylic acid.[29] Furthermore, ethylbenzene itself is known to undergo C–C bond cleavage under oxidizing conditions.[30]

Finally, considering the importance of cyclododecanol as intermediate for the synthesis of nylon 12 and some fragrances, a selective and atom-efficient two-step synthesis of cyclododecanol from cyclododecane was developed by combining our iron-catalysed oxidation with a well-known hydrogenation reaction (Scheme 3). Thus, a total yield of 35% of cyclododecanol directly from cyclododecane was obtained.

Conclusions

In conclusion, we presented a novel *in-situ* generated iron catalyst for the direct oxidation of alkanes. The optimal system is conveniently generated from $Fe(ClO_4)_3xH_2O$ and **L1** and it shows promising reactivity for the oxidation of unfunctionalized alkanes with H_2O_2. Apart from cyclic alkanes, a selection of different alkanes, mainly cyclic and linear ones were transformed to mixtures of the corresponding ketones and alcohols with moderate yields by utilizing the catalyst system. The reaction can be easily scaled up to multi-g scale.

Experimental Section

General procedure: An 8 mL glass vial equipped with a Teflon coated stirring bar and a plastic cap with a Teflon septum was charged with iron salt (0.025 mmol), ligand (0.03 mmol) and acetonitrile (4 mL) at room temperature under air (ambient conditions). The mixture was stirred for 30 minutes. Co-ligand (0.03 mmol) was then added to the solution and the mixture was stirred for a further 30 minutes. Then, alkane (0.5 mmol) was added to the solution and stirred for 5 minutes to dissolve. An acetonitrile solution (1 mL) of H_2O_2 (2.5 mmol) was added dropwise over 30 minutes by syringe pump under ambient conditions. The reaction was terminated by addition of several drops of $NaHCO_3$ solution and diluted with Et_2O. The conversion and yield were analysed by GC using a known amount of hexadecane (30 µL) as internal standard.

Supporting Information

Supporting Information are available.

Important safety note

Hydrogen peroxide may cause explosion upon contact with metal catalysts or when solutions containing hydrogen peroxide are concentrated. We are working with the safer 30% aqueous hydrogen peroxide solution instead of the higher concentrated 50% solution. Proper safety measurements should be in place at all times.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Homogeneous catalysis · CH-oxidation · iron · H_2O_2 · KA oil

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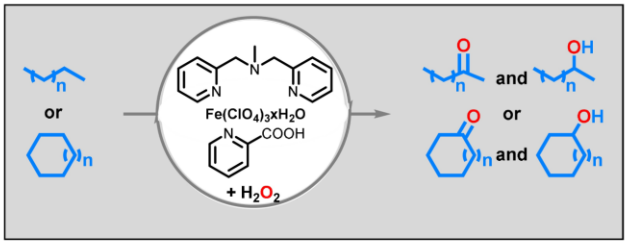

Dr. S. Mao, D. Verspeek, Prof. X. Wen, Prof. Y. Yang, Prof. Y.-W. Li, Dr. K. Junge, Prof. M. Beller**

Homogeneous Iron-Catalysed Oxidation Of Non-Activated Alkanes With Hydrogen Peroxide

A novel synthetic protocol for the direct oxidation of alkanes, including cyclic and linear ones, to give ketones and alcohols using hydrogen peroxide as terminal oxidant under ambient conditions is presented. The active catalyst for this challenging transformation is conveniently generated by combination of simple Fe salts with N-methyl bis(picolylamine).

7. Curriculum Vitae

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IT	MS Office (Word, Excel, PowerPoint), MestreNova, Endnote

Publications

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1. **D. Verspeek**, S. Ahrens, X. Wen, Y. Yang, Y.-W. Li, K. Junge, Prof. M. Beller, *Org. Biomol. Chem.*, **2024**, *22*, 2630 – 2642.
   "A Manganese-based Catalyst System for General Oxidations of Unactivated Olefins, Alkanes, and Alcohols"
2. S. Mao, **D. Verspeek**, X. Wen, Y. Yang, Y.-W. Li, K. Junge, Prof. M. Beller, *ChemCatChem*, **2023**, e202300735.
   "Homogeneous Iron-Catalysed Oxidation of Non-Activated Alkanes with Hydrogen Peroxide"
3. **D. Verspeek**, S. Ahrens, A. Spannenberg, X. Wen, Y. Yang, Y.-W. Li, K. Junge, Prof. M. Beller, *Catal. Sci. Technol.*, **2022**, *12*, 7341 – 7348.
   "Manganese N,N,N-Pincer Complex-Catalyzed Epoxidation of Unactivated Aliphatic Olefins"
4. C. Empel, **D. Verspeek**, S. Jana, Prof. R. M. Koenigs, *Adv. Synth. Catal.* **2020**, *362*, 4716 – 4722.
   "Photochemical O−H Functionalization Reactions of Cyclic Diazoamides"
5. S. Jana, F. Li, C. Empel, **D. Verspeek**, P. Aseeva, Prof. R. M. Koenigs, *Chem. Eur. J.* **2020**, *26*, 2586 – 2591.
   "Stoichiometric Photochemical Carbene Transfer by Bamford-Stevens Reaction"

Conference Participations and Poster Presentations

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1. *56th German Catalysis Meeting*, Weimar, Germany, March 2023, Poster-Presentation: "Manganese N,N,N-Pincer Complex-Catalyzed Epoxidation of Unactivated Aliphatic Olefins"
2. *12th New Year's Symposium RWTH Aachen University*, Aachen, Germany, January 2020, Poster-Presentation: "Stoichiometric Photochemical Carbene Transfer by Bamford–Stevens Reaction"

8. Selbstständigkeitserklärung

4. Erklärung gemäß § 4 Absatz 1 Buchstaben g und h der Promotionsordnung

Doktorandinnen/Doktoranden-Erklärung gemäß § 4 Absatz 1 Buchstaben g und h der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock

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(Straße, PLZ, Wohnort)

Ich habe eine Dissertation zum Thema

Manganese- and Iron-catalyzed Oxidative Valorization of Unactivated Alkenes and Alkanes

an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock angefertigt. Dabei wurde ich von Frau/Herrn

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