Selective oxidation catalysis with Mn and H2O2

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Conversion of alkenes to α-hydroxy ketones, C=C cleavage and mechanistic insights

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Table of Contents

Chapter 2 Towards attritional oxidation of 2- and 3-carene

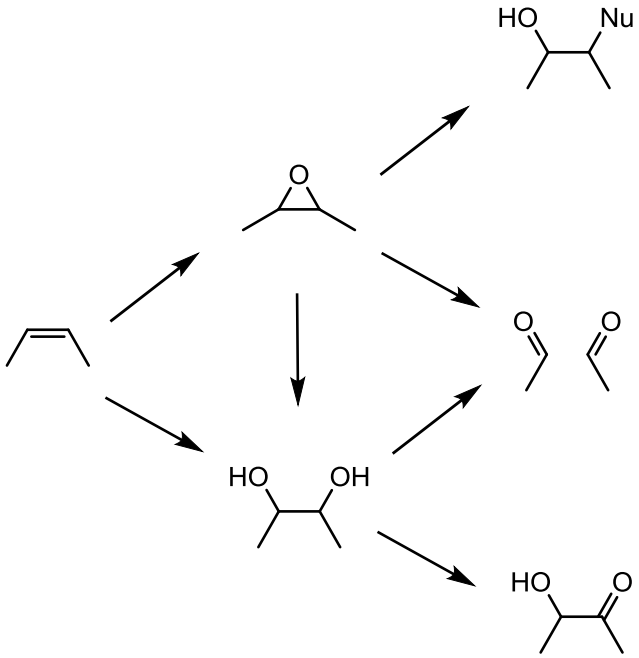
Chapter 3 Oxidative cleavage of alkene C=C bonds: an alternative to ozonolysis

Chapter 4 Oxidation of vicinal diols to α-hydroxy ketones with H_2O_2 and a simple manganese catalyst

Chapter 1

Selective oxidation of organic substrates with H_2O_2 catalyzed by manganese salts and pyridine-2-carboxylic acid; recent advances and mechanistic studies

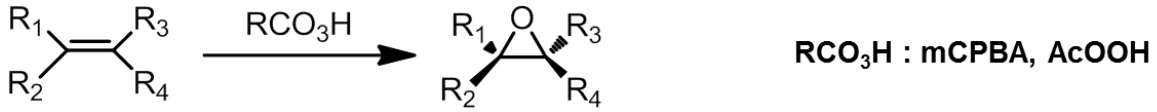
Abstract. Here, a general overview and discussion of the catalytic oxidation method based on H_2O_2, a ketone, a Mn(II) salt and pyridine-2-carboxylic acid is provided. Comparison with related oxidation methods using other transition metal catalysts and conventional oxidants is made also, which together forms a basis for the catalyst systems further development as a versatile general *syn*thetic tool.



Scheme 1 Multistep oxidations of alkenes

1.1 Introduction

The oxidation of alkenes is a central and indeed fundamental process in *syn*thetic organic chemistry, both for fine chemistry and bulk industrial processes, with the range of primary products (epoxides, diols, ketones and aldehydes) expanding dramatically in the range of their derivatives, including acyloins and carboxylic acids. The methods available to produce epoxides and diols are nevertheless limited to a few reaction classes with several including asymmetric protocols, with the Shi, [1,2,3,4,5,6,7] Prilezhaev [8,9,10,11,12] (scheme 2) and Sharpless [13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32] asymmetric methods being the best known. Indeed the success of the Sharpless asymmetric dihydroxylation is exemplified by the off-the-shelf availability of the AD-mix^{TM}! And its extensive use in total *syn*theses such as those of Corey *et al*.[30,33,34,,35,36,37] In contrast the direct *syn*thesis of further oxidized products, such as α-hydroxy ketones from alkenes, has only recently seen significant progress, in particular by Plietker and co-workers.[38,39,40,41,42,43,44]



Scheme 2. The Prilezhaev reaction.[8,9,10,11,12]

Evidence of the utility of the oxygenated alkene products as *syn*thons is ubiquitous as is their presence in natural products and pharmaceutically active compounds. Despite their utility the methods available for oxygenation of alkenes rely heavily on (atom) uneconomic oxidants (chromates, Oxone^{TM}, peracids, permanganate, etc), while catalytic methods employ expensive and often toxic 2nd and 3rd row transition metals (*e.g.*, OsO_4 for Sharpless *cis*-dihydroxylation, $RuCl_3$ also for dihydroxylation, ketohydroxylation etc).

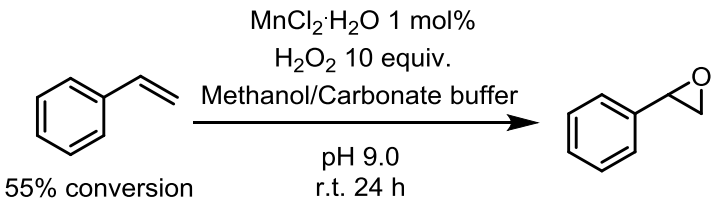
There is increasing interest in the development of atom-efficient and environmental friendly methods for alkene oxidations, preferably with the use of oxidants that lead to minimal formation of byproducts, with O_2 and H_2O_2 as the "champions" (their only byproduct being water). Activation of small molecule oxidants by catalysts has focused on first row transition metals both for environmental and especially economic reasons. The control of catalytic activity has focused on the use of ligands to tune the mode of action of the catalysts, which has more recently raised issues with regard to the stability of the ligands: in particular with respect to oxidative ligand degradation under reaction conditions, leading to reduced conversion and selectivity in most cases, but also to an increase in activity!

In the recent years, our group has been focused on developing methods for the oxidation of electron rich olefins to epoxides,[45] and for electron poor alkenes to *syn*-diols.[46] The method is based on an *in situ* prepared catalyst using a manganese salt, 2-pyridine carboxylic acid (PCA), a mild base, such as NaOAc and sub-stoichiometric butanedione; all of which are readily available chemicals, and H_2O_2 as terminal oxidant. The method is facile to implement and can provide excellent yields and selectivities for the conversion of alkenes to epoxides and diols under ambient conditions.

This catalytic system was more recently applied to C-H oxidation of alkanes to alcohols and ketones[47] in compounds that do not bear an alkene. In this chapter, an overview of the development of this catalytic system and comparison with the related oxidation methods is presented.

1.2 'Ligand free' metal catalyzed oxidations

The potential of a 'Ligand free' approach to transition metal oxidation catalysis has been recognized for over two decades, in the case of manganese in the reports by Burgess and co-workers.[48]



Scheme 3. Oxidation of styrene reported by Hage and co-workers using a Mn/tmtacn catalyst.[49]

A key drawback of such an approach is that it is not obvious how reactivity and especially (enantio)selectivity can be controlled and the paradigm in oxidation chemistry is that ligand metal complexes are employed. However, the use of a ligand in a particular reaction does not necessarily mean that the ligand is retained or even responsible for the reactivity observed. The tmtacn class of ligands (where tmtacn is N,N',N''-trimethyl-1,4,7-triazacylononane), for example,[50] have proven to be one of the more effective ligands for manganese based oxidation catalysis.[49,51,52,53,54,55,56,57,58]

Indeed, in recent years the consequences of oxidative degradation of ligands in regard to activity have received increased attention. A case in point are the manganese complexes based on the TPEN/TPTN class of pyridylamine ligands used to catalyze the oxidation of alcohols and epoxidation of alkenes (scheme 3).[59,60,61,62,63,64]

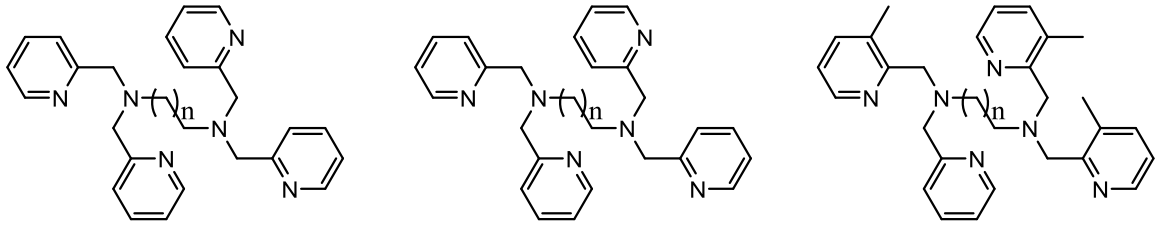


Figure 1. Structure of TPEN/TPTN ligands and their derivatives.[64]

Despite their activity, this class of complexes required a large excess of oxidant (between 8 and 16 equiv. of H_2O_2) to overcome the losses due to H_2O_2 disproportionation and it eventually emerged through mechanistic studies that these ligands are unstable under

reaction conditions. Unexpectedly, pyridine-2-carboxylic acid, the degradation product of the pyridyl based ligands tested, was responsible for the catalytic conversion of the substrate employed.[65]

In contrast Britovsek and co-workers[66] reported that catalytic activity and catalyst stability (with respect to ligand dissociation) correlate in the non-heme iron catalyst family, and Banse an coworkers[67] showed that ligand degradation in Mn/TPEN complexes can be prevented[59,68] if bulky substituents are introduced in the backbone of the ligand.

Nevertheless the focus on ligand modification has represented the leitmotif in oxidation chemistry over the last decades with particular attention directed to towards the design of pyridyl amine ligands due to the facile *syn*thesis of a wide range of modified ligands in which one or more pyridyl ligands can be substituted for by other groups.

1.3 Discovery of the Mn/PCA based catalytic system and its impact on ligand design

A key strategy in the optimization of catalyst systems is the modification of ligands to tune both activity and selectivity. In the case of the TPEN class of ligands, such an approach was taken by Pijper *et al*.[65] using a series of derivatives and precursors (Figure 2) For all ligands examined, remarkably essentially identical substrate conversion and product distributions were observed provided that the ligand contained at list one pyridyl moiety in which the 6-position was a hydrogen. Extensive disproportionation of hydrogen peroxide, as previously mentioned, required a gross (8-fold) excess of H_2O_2 in order to obtain reasonable conversion of substrates and although disproportionation is suppressed, as in other manganese based systems,[59,60,61,62,63,64] by addition of carboxylic acids (*e.g.*, acetic, trichloroacetic acid etc.), it also lead in this system to a loss of conversion.

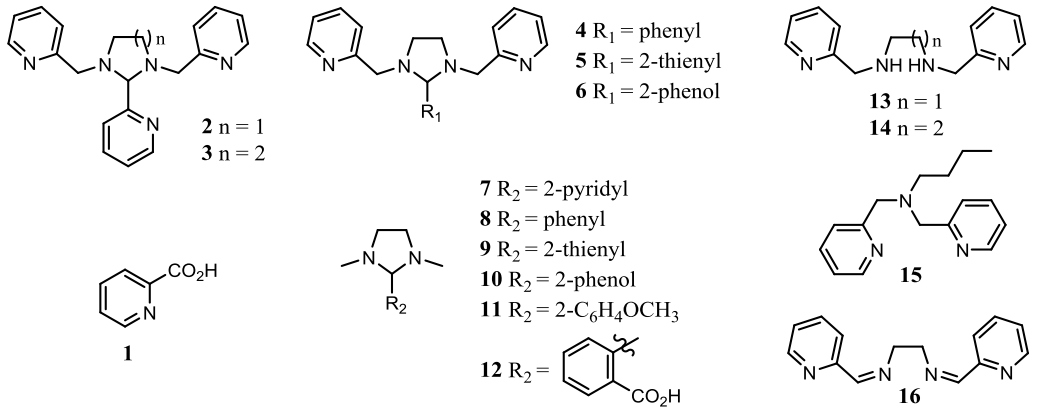


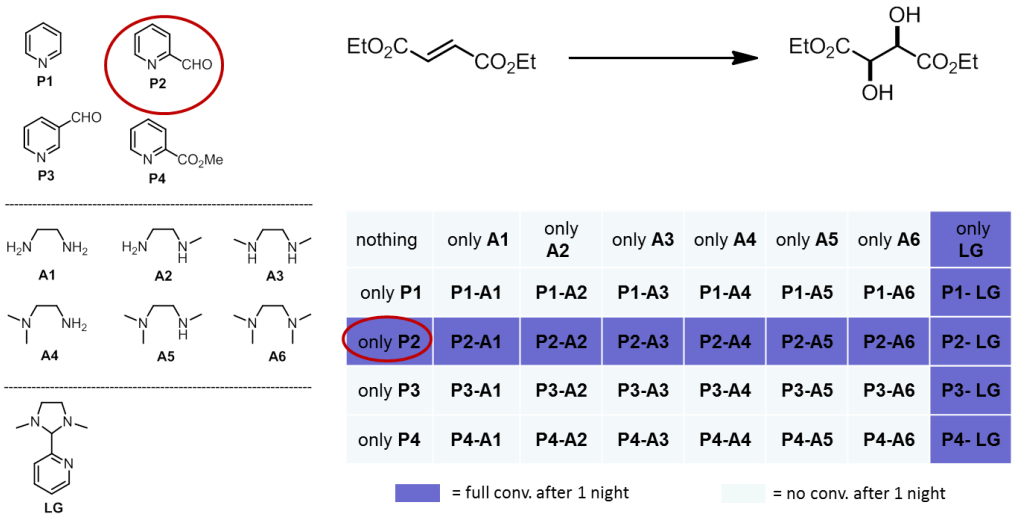
Figure 2. Ligands discussed in the text.[65]

The decomposition of H_2O_2 continued over the entire lag phase (20-60 min) but ceased once conversion of substrate commenced. This last observation indicates that the active catalyst forms at the end of the lag period. ESI-MS analysis of the reaction noted the

presence of ligand **1** (Figure 2), providing the first indication that ligand breakdown was occurring during the lag period.

1.3.1 Structure activity relation and in situ ligand *syn*thesis

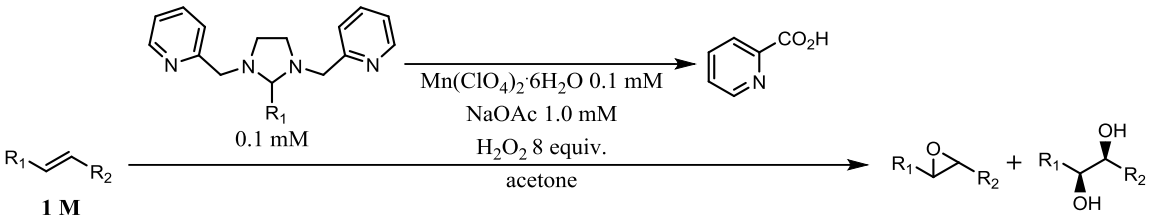
A structure/activity study using a series of aminal ligand (from which pyridyl groups were systematically removed from the aminal ring an replaced with other substituents) and non-cyclic ligands (containing the 2-methyamino-pyridyl motif) in the oxidation of *cis*-cyclooctene revealed that full conversion was obtained with all ligands containing at least one pyridyl moiety, while those not bearing such a moiety did not give conversion. Remarkably, the *cis*-diol to epoxide ratio was identical also in all the case in which conversion was achieved (for a series of structurally related ligands). Taken together, these data indicated that oxidative ligand degradation may lead to the formation of pyridyl fragments that were common in all reactions in which conversion was observed. A key experiment in understanding the structure activity relation was to screen a matrix of combinations of ligand 2, its precursors and a series of pyridyl and amine derivatives in the oxidation of cyclooctene and diethylfumarate with Mn(II) salts (scheme 4). Conversion was determined by high throughput screening with Raman spectroscopy and it was observed only where either pyridine-2-carboxaldehyde (used to form the aminal based ligands) or ligand 2 was present.



nothing	only **A1**	only **A2**	only **A3**	only **A4**	only **A5**	only **A6**	only **LG**
only **P1**	**P1-A1**	**P1-A2**	**P1-A3**	**P1-A4**	**P1-A5**	**P1-A6**	**P1- LG**
only **P2**	**P2-A1**	**P2-A2**	**P2-A3**	**P2-A4**	**P2-A5**	**P2-A6**	**P2- LG**
only **P3**	**P3-A1**	**P3-A2**	**P3-A3**	**P3-A4**	**P3-A5**	**P3-A6**	**P3- LG**
only **P4**	**P4-A1**	**P4-A2**	**P4-A3**	**P4-A4**	**P4-A5**	**P4-A6**	**P4- LG**

Scheme 4. Screening of combinations of pyridines and amines used in the identification of pyridine-2-carboxaldhyde (and later PCA) as the essential component in the oxidation of diethyl fumarate. LG = **2**

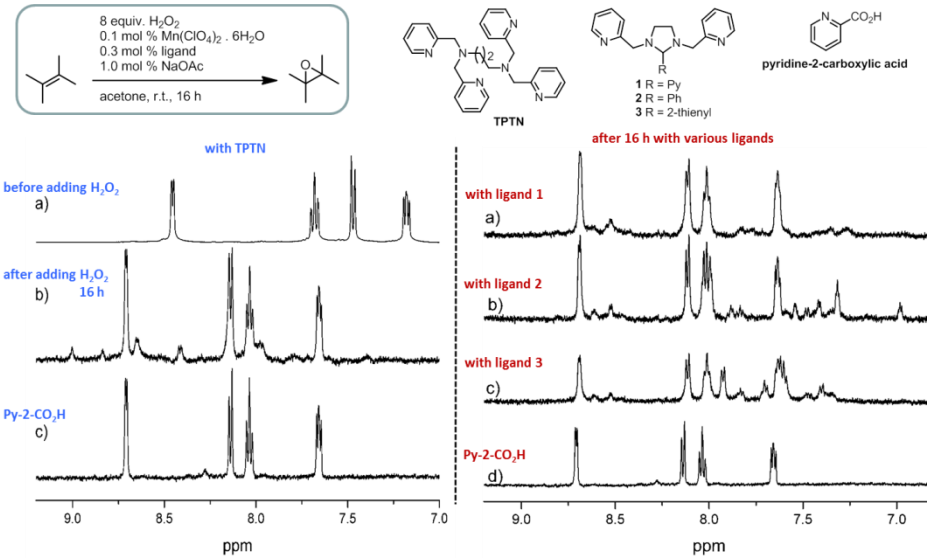
Subsequently, it was confirmed that PCA was the active ligand in this system, and neither its further oxidation product, pyridine-*N*-oxide-2-carboxylic acid nor pyridine-carboxylic acids in which the 6 position was substituted showed substrate conversion. Indeed, the ligand degradation product obtained in all cases with the TPTEN and aminal based ligands was confirmed by ^{1}H NMR spectroscopy to be pyridine-2-carboxylic acid (PCA) under standard reaction conditions (scheme 5).



Scheme 5. Degradation of TPEN (and aminal based ligands) under reaction conditions that leads formation of PCA and hence alkene oxidation to epoxide and *cis*-diol.

1.3.2 Oxidative ligand degradation and origin of reactivity

The observation of PCA as a degradation product after the reactions were complete, does not a priori mean that PCA is a ligand to the active catalyst.



Scheme 6. The decomposition of pyridyl containing ligands to PCA under standard reaction conditions was confirmed by ^{1}H-NMR spectroscopy. Reproduced from ref 65. Copyright RSC (2010).

That PCA was involved was further confirmed by comparison of the conversion and especially product distributions obtained using PCA with that obtained using ligand 2. For three distinct substrates, cyclooctene, diethyl fumarate and diethyl maleate, similar conversion and identical product distributions (diol vs epoxide products) were obtained. Notably, however, for reactions using PCA, the lag period was much shorter and H_2O_2 decomposition was not apparent, enabling a reduction in the H_2O_2 used from 8 to 2 equivalents with respect to substrate without a decrease in substrate oxidation (conversion). It should be emphasized that the system, even with PCA used as ligand, showed activity only in ketone based solvents (namely acetone and butanone).

The discovery that oxidative ligand degradation could occur so readily under reaction conditions is perhaps unsurprising given the vulnerability of the benzylic positions especially to oxidation. However, the fact that a ligand degradation product could provide such high turnover numbers and frequencies was unprecedented and has a major impact

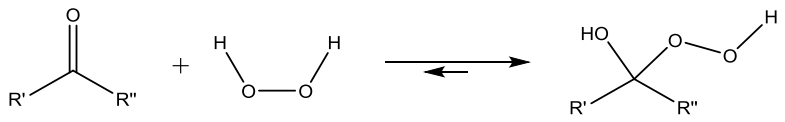
on both strategies taken towards ligand design in this area of catalysis and especially in understanding structure activity relations.

Although efforts to develop design rules for oxidation with the TPEN/aminal ligand class lead to the realization that the active catalyst was in fact a combination of PCA and Mn(II), several design roles with regard to other reaction components became apparent, not least the requirement for a ketone based solvent (acetone or 2-butanone) to be used. For instance, the oxidation of alkenes was not observed in acetonitrile or ^{t}BuOH/H_2O even with the use of PCA. Furthermore, the addition of several equivalents, with respect to Mn(II), of a base was necessary, although the actual base used had no influence on the outcome of the reaction (*e.g.*, NaOAc, NaOH or Na_2CO_3).

The discovery of the role of the pyridyl based ligands prompted us to develop an efficient catalytic method for the catalytic *syn*-dihydroxylation of electron poor alkenes. The system was insensitive to the nature of base used with, amongst others, NaOAc, $NaHCO_3$, or NaOH, providing comparable results, confirming that its role was not as a ligand although it was necessary that at least 1 equiv. with respect to PCA was added, indicating that its role was simply to deprotonate PCA and enable catalyst formation. Notably, although conversion was not observed if the base was omitted or acid added (*e.g.*, acetic acid) prior to addition of H_2O_2, addition of acid after addition of H_2O_2 only resulted in a decrease in reaction rate and moderately reduced conversion. The role of both acids and bases in the reaction will be discussed below.

1.3.3 Solvent dependence of the Mn/PCA catalyzed reaction

Though acetone was the solvent of choice for the system, this showed to work equally well in 2-butanone, proving useful for the oxidation of less polar substrates. The essential lack of activity in any other solvent used hinted, as observed before, that a ketone based solvent is necessary for the catalysis to take place, and that the solvent itself plays a key role in the catalysis as already proposed by Que and coworkers.[69] Indeed, the equilibrium between ketones and H_2O_2 is well established, and when hydrogen peroxide is added to acetone or 2-butanone, the equilibrium lies towards the formation of the adduct (scheme 7).



Scheme 7. Equilibrium between ketone and hydrogen peroxide.

Some tolerance was showed: for example using 10% acetone in acetonitrile leads to 20% conversion, while employing substoichiometric amounts of CF_3COCH_3 notably lead to 90% conversion, with ^{19}F-NMR indicating formation of different species from the starting haloketone, though the use of acetone or butanedione is preferable for reasons of cost and environmental friendliness. The presence of water is effective in reducing hazards associated with the use of acetone as a solvent in combination with H_2O_2.

1.4 Application of the Mn/PCA/Ketone catalyst system in oxidation catalysis

The discovery that PCA is the ligand present during the oxidation of alkenes with H_2O_2 and a wide range of manganese complexes, had the positive result that an in situ prepared catalyst protocol for selective oxidations was developed. Even though the system is not ligand free, as in the case of the system developed by Burgess *et al*. (scheme 3),[48] PCA is a readily available compound and the in situ preparation of the catalyst, ambient reaction conditions and fast reaction rates achievable make this system easily applicable. The catalyst system developed, which is prepared *in situ* by dissolution of $Mn(ClO_4)_2$ and PCA in a ketone containing solvent followed by addition of the substrate and NaOAc, could achieve up to 1000 turnovers in the *syn*-dihydroxylation of diethyl fumarate with only 1.5 equiv. of H_2O_2, yielding *d/l*-diethyl tartrate as sole product. Further oxidation of the vicinal diols formed was not observed, even where excess of H_2O_2 was used. In the case of electron rich alkenes such as cyclooctene, the catalyst system provided for good to excellent conversions and yields of the epoxide products, with equally high TONs. Efforts to optimize reaction conditions and especially product distributions (epoxide vs *syn*-diol ratio) proved of limited success. Although the outcome of the reaction in terms of product distribution was essentially solely dependent on the substrate, variation in reaction conditions allowed for improvements in conversion (vide infra). In general, a 1:6:10 ratio of a Mn^{II} salt, PCA, and NaOAc with 1.5 to 2 equivalents of H_2O_2 provided good conversion and yield of the diol or epoxide product for most substrates, with only α,β-unsaturated esters and, curiously {since its stereoisomer was converted efficiently}, diethyl maleate showing poor conversion.

Although the method developed initially for the *cis*-dihydroxylation of the electron poor alkenes also showed moderate to good activities and selectivities towards the epoxidation of electron rich alkenes, the system presented two important disadvantages. The first was the need for a ketone to be used as (co)solvent, presumed to be due to the formation of an adduct with H_2O_2, which either reduced the steady state [H_2O_2] or to actively played a role in the catalytic cycle. The second was that of potential explosion risk in the use acetone with H_2O_2, especially for larger scale reactions. Initial efforts to find alternatives led to the identification of 1,1,1-trifluoroacetone which could be used at 5 v/v % in other solvents. The cost of reagent, the generation of fluorinated waste and its aggressive nature prompted further studies screening reactivity with diethylfumarate and cyclooctene, which led to the identification of butanedione, a widely used flavor ingredient and product of fermentation, as a suitable ketone to be used at (sub)stoichiometric levels.

The use of butanedione allowed for a dramatic widening of the solvent scope which enabled access to less polar substrates with acetonitrile proving the most convenient solvent both in terms of reaction rate and solubility. Furthermore the reaction rates and the turnover frequencies obtained with butanedione were dramatically improved with respect to reactions carried out in acetone or butanone enabling a several order of magnitude reduction in catalyst loading (to 600 nM in Mn(II)!), at room temperature. The protocol earlier discovered for the *cis*-dihydroxylation of electron poor alkenes was

therefore implemented with butanedione, leading to a system that acetonitrile (or alcohols) as solvent, a Mn/PCA based system, NaOAc as a base and butanedione as co-solvent. Under these conditions the catalytic nature of the role of the ketone was demonstrated and the importance of reversible and fast formation of adducts with H_2O_2. From a mechanistic perspective the absence of allylic oxidation, in all the substrates examined, together with retention of configuration at chiral centers of enantiopure protected allylic alcohols indicate that a selective oxidant (active species) is involved.

1.4.1 Epoxidation of electron rich alkenes and *cis*-dihydroxylation of α,β-unsaturated carbonyl compounds

A wide range of electron rich alkenes were subjected to catalytic oxidation with the Mn(II)/PCA system and in all cases the corresponding epoxide was the major product obtained; although significant amounts (10-15%) of *syn*-diol were formed also. Indeed in contrast to the electron deficient substrates, the *syn*-diol products underwent further oxidation to the corresponding acyloin and ultimately C-C bond cleavage products. The tendency to form diol products reduces to some extent the selectivity of the system, however, less so than with alternative catalyzed approaches such as with $RuCl_3/NaIO_4$, Ru^{III}-tmtacn (where tmtacn = *N,N',N''*-trimethyl-1,4,7-triazacyclononane, figure 3) and to a lesser extent for the Mn-tmtacn catalyst systems.

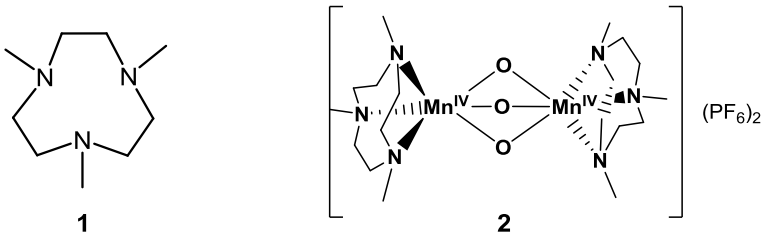
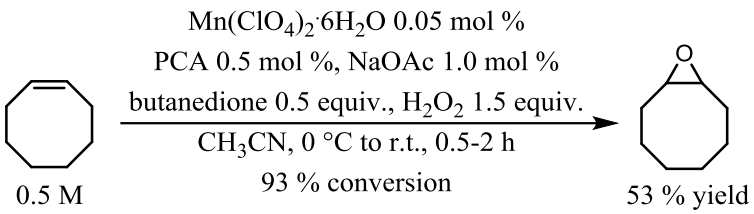


Figure 3. Tmtacn ligand (1) and a dinuclear Mn-tmtacn commonly used in oxidation catalysis, first reported by Hage *et al.*[49]

Asymmetric internal α-β unsaturated alkenes show the lowest conversions and selectivity and secondary oxidation products are likely to be formed, *e.g.*, oxalate monoester, by carbon carbon bond cleavage through further oxidation of the diol products. The apparent correlation between electron deficiency of the alkene substrate and *cis*-diol/epoxide ratio (*e.g.*, the *cis*-diol/epoxide ratio obtained for *cis*-cyclooctene and ethyl crotonate are, respectively, 1:6 and 1:2) indicates that the outcome is substrate controlled and is in line with trends observed by Que and coworkers[69] for an Fe^{II} polypyridyl based catalyst.

1.4.2 Epoxidation of electron rich alkenes: optimal conditions and substrate scope

Initial screenings using cyclooctene as model substrate, showed that conversion was achieved, albeit with only a 53 % yield of epoxide; the remainder was a mixture of *cis*-diol and α-hydroxy ketone products.



Scheme 8. Initial screening in the oxidation of cyclooctene with Mn/PCA system as reported by Dong *et al*.[45]

An increase in butanedione led to a decrease in conversion and selectivity towards the epoxide, while decreasing the catalyst loading to 0.01 mol % (Mn(II)) resulted in higher turnover numbers (9500) and 80 % yield of the desired epoxide product within 15 min at room temperature. These conditions could be applied generally to a wide range of alkenes such as α-pinene, with similar conversions and yields of epoxides. Although trisubsituted linear alkenes provided high yields of the corresponding epoxide products, 1-octene underwent only 44% conversion, primarily due to solubility issues. In general, internal di-, tri- and tetra-substituted alkene proved more reactive and showed full conversion with an epoxide yield ranging from 70 % to 83 %.

Similarly aromatic alkenes, including styrene, were oxidized to the corresponding epoxides in high conversions and yields, even though phenantrene showed only 50 % conversion. The optimized conditions found for the cyclooctene were found to be generally good for many substrates, though, for example, 1-octene and phenantrene showed poor conversion (50%), which was not improved by variation in the concentration of butanedione, catalyst or H_2O_2. However, as will be discussed later, a mechanistic aspect of the reaction, that the reaction rate is zero order in substrate, means that reducing the substrate concentration from 0.5 to 0.25 M, while keeping all other concentrations constant gave 90 and 85 % conversion, respectively.

Regioselectivity is relatively good in non-conjugated dienes: a series of substrates with progressively dissimilar double bonds showed that epoxidation of the more substituted double bond was preferred. In the case of limonene, selective epoxidation of the internal double bond, is observed while with citral only the isolated alkene is oxidized and the α-β-unsaturated double bond and aldehyde are untouched. From the point of view of application, chemoselectivity is an important challenge. The Mn/PCA system shows good to high tolerance for compounds bearing oxidation sensitive moieties, such as alcohols and aldehydes: in general, primary alcohols and aldehydes proved stable under reaction conditions, *e.g.*, *N*-phenylcarbonyl-1,2-dihydroquinoline-2-carbonitrile, whose corresponding epoxide was obtained in 65 % isolated yield. Amides and nitrile moieties were stable under those conditions also. Scaling up of the reaction to multigram levels (*e.g.*, 9 g of stilbene) was achieved without significant differences in product distribution being observed.

The oxidation of acid and/or base sensitive alkenes or of alkenes for which the epoxide product is particularly susceptible to ring opening, as in the case of α-pinene and styrene,

was achieved in high yields and selectivities with the Mn/PCA method and highlighting the mildness of the reaction conditions. Furthermore, hydrolytically sensitive acetyl and tert-butoxycarbonyl (BOC) protected compounds tolerate the reaction conditions well. The stereochemical outcome of the reactions and especially the retention of configuration in E,Z-alkenes is of importance for applications in total *syn*theses. The terpenoids 2- and 3-carene, and N-phenylcarbonyl-1,2-dihydroquinoline-2-carbonitrile, yield only products as single diastereoisomers. The retention of stereochemistry observed in the epoxidation of allylic alcohols makes this system of general applicability for selective epoxidation of complex alkenes.

1.4.3 Epoxidation of electron rich alkenes: limitations

Although good to excellent conversions can be achieved in the epoxidation of many electron rich alkenes, a key limitation is encountered with α-β-unsaturated carbonyl compounds, which showed both poor selectivity and conversion with the major product often being the *syn*-diol. In addition conjugated dienes show modest regioselectivity compared to isolated alkenes such as cyclooctene and as expected, given the use of H_2O_2, silyl-based protecting groups are too unstable under reaction conditions to be recovered.

1.4.4 *syn*-Dihydroxylation of electron poor alkenes

The catalyst system (Mn/PCA/acetone) proved equally effective in the selective *cis*-dihydroxylation of mono-, di-, tri- and tetra-substituted electron deficient alkenes with good to excellent conversions obtained and exclusively the *syn*-diol product (table 1).[46]

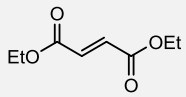
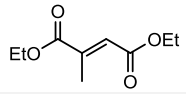
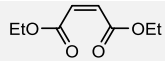
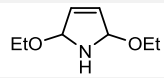
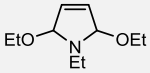
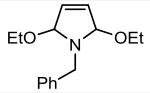
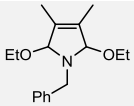
Substrate	Conversion %[a]	Isolated yield %
	100 (> 95 %)[b]	91 (95)[b]
	> 95	88
	63	47[c]
	100	98
	100	> 95
	100	91
	100	75

Table 1. *Syn*-Dihydroxylation of alkenes with H_2O_2 catalyzed by $Mn^{II}(ClO_4)_2$/PCA/NaOAc in acetone. [a]Determined by Raman and ^1H NMR spectroscopy. [b]In 2-butanone. [c]25% recovered starting material.[65]

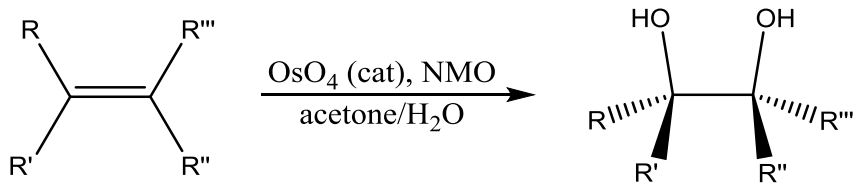
As mentioned above, diethyl maleate showed surprisingly low conversion (63%) after optmization of reaction conditions. The origin of the lack of reactivity could be due to product inhibition, *i.e.* sequestration of Mn(II) by meso-tartrate, however, a competition

experiment with diethyl fumarate showed that the latter underwent 90% conversion in contrast to only 20% conversion for the former substrate. Furthermore the present of either *meso* or *d/l*-diethyl tartrate had no effect on conversion of diethylfurmate. These data indicate that product inhibition is not responsible for the lower reactivity.

Although the catalyst system delivers *syn*-diols for electron deficient alkenes only, fortuitously this class of substrate has proven to be a major challenge to contemporary methods and hence an important gap is now filled. The present method widens the substrate scope for *syn*-dihydroxylation of alkenes using 1st row transition metals and H_2O_2, and is complementary to the Mn-tmtacn developed in our group.[45,46,47] Subsequent studies lead to the identification of butanedione, which could be used sub-stoichiometrically and hence allowed for a large expansion of the solvent scope of the reaction. Importantly however, this innovation allowed for a dramatic reduction in reaction time and, with some modifications of the conditions (*i.e.* 1.5 equiv. of butanedione instead of 0.5 equiv.) optimized for epoxidation of electron rich alkenes, full selectivity and conversion could be achieved at ambient conditions within ca. 30 min. A notable point of mechanistic interest is that increasing catalyst loading (to 0.05 mol% Mn) resulted in a decrease in maximum conversion.

1.4.5 *syn*-Dihydroxylation of electron poor alkenes: comparison with other methods

The classic approaches to *syn*-dihydroxylation of alkenes are perhaps those methods based on MnO_4^-, OsO_4 (Upjohn process, Scheme 9)[70,71,72] and $RuO_4/NaIO_3$, which although often effective, suffer from poor atom economy, toxicity and selectivity. The Mn/PCA system leads to alkene epoxidation in most cases and hence is not a viable competitor to these systems. Nevertheless the high selectivity and activity shown in the oxidation of electron deficient alkenes sets it apart as it is these very substrates that have proven to be the most challenging for contemporary oxidation chemistry. The system uses acetone or 2-butanone as solvents, and presents a complementary substrate scope to the Mn/tmtacn based catalysts reported by de Boer *et al.*, which uses H_2O_2 as terminal oxidant also.



Scheme 9. Upjohn process for *cis*-dihydroxylation.

The Upjohn process, which uses *N*-methyl-morpholine as terminal oxidant to regenerate the OsO_4^{2-}, was subsequently modified by Warren and coworkers,[71] recently, following the Sharpless protocol, which uses catalytic OsO_4 and potassium ferrocyanide as terminal oxidant. This modification provided the desired *cis*-diols using the "ligand acceleration effect" generated by the two achiral cinchona alkaloid units (*i.e.* quinuclidine) tethered via a heterocyclic spacer, especially in the case of more substituted alkenes. However,

despite this modification, only electron rich alkenes with specific substitution patterns are converted efficiently, especially stilbene based derivatives. Indeed, of relevance to the Mn/PCA system, electron deficient alkenes show little reactivity with the modified Upjohn protocol.

A widely used alternative to osmium was described first by Sharpless and coworkers[23,24,25,26,27,28,29,31,32] using catalytic RuO_4 and $NaIO_4$ as terminal oxidant. In addition to its use in *syn*-dihydroxylation, its tendency to oxidize the diol product further has been exploited in developing methods for C-C bond cleavage of primary alcohols and diols. The increased overoxidation by RuO_4 is expected as it has a higher oxidation potential that does the isoelectronic OsO_4. Shing's group revisited this protocol more recently developing the first Ru catalyzed *syn*-dihydroxylation of alkenes,[73,74,75] also known as "fast dihydroxylation", with products obtained in good yield with reaction times of 30 s to 30 min, which helped overcome (outrun) the slower oxidation of diols, especially water soluble diols by periodate. The substrate scope is somewhat limited with unencumbered α,β-unsaturated cyclohexene and cyclopentene performing well, while yields and selectivity range from moderate to poor with acyclic and cyclic hindered alkenes (2 and 3-carene). Remarkably, substrates with electron-withdrawing groups conjugated with or adjacent to the C=C double bond were converted with better yields. Moreover, in contrast to the analogous OsO_4 mediated process, this protocol shows better selectivities with *trans*-alkenes than with *cis*-alkenes.

Plietker[38,39,40,41,42,43,44] performed an extensive study of the catalyzed oxidation of alkenes with *in situ* generated Ru oxide (from $RuCl_3$). This system is versatile and can achieve dihydroxylation or ketohydroxylation of alkenes, depending on the terminal oxidant used ($NaIO_4$ or Oxone, respectively), or selective monooxidation over vicinal diols. Notably, although the system was based on the report of Shing and coworkers, a significative increase in reaction rates was achieved by addition of a Brönsted acid. The rate acceleration was ascribed to an increase in the rate of hydrolysis of the five membered ruthenate ester intermediate, which is the rate determining step. The slowness of this step is also the origin of the reduction in selectivity due to the formation of aldehydic byproducts. Addition of sulfuric acid (up to 0.2 equiv. w.r.t. substrate) led to improved conversion without affecting the selectivity and allowed for a reduction in catalyst loading 0.5 mol %. A drawback of the use of acid is the increase in the rate of competing side products, *e.g.*, aldehydes. Notably, functional groups such as allylic halides, esters and amides, are tolerated and triple bonds do not undergo oxidation.

$KMnO_4$ is the textbook reagent for *cis*-dihydroxylation, despite that further oxidation of the diols formed to acyloins and C-C bond cleavage leads to often quite low yields especially at pH < 9. The high pH conditions required place a natural limit to the substrate scope that can be accessed, nevertheless, homogeneous stoichiometric *cis*-dihydroxylation with permanganate is usually selective and shows a wide substrate scope.[76,77] It is typically employed in reactions where OsO_4 dihydroxylation is unsuccessful. In particular, permanganate dihydroxylation is effective with α,β-unsaturated substrates, as exemplified in the *syn*thesis of (±)proto-quercitol (obtaining the

cis-diol from a substituted cyclohexene) by Salamci *et al*.,[78] a key precursor of furanyl progesterone by Katzenellenbogen *et al.*,[79] and the oxidation of oxazines to pyrrolizidinones by Reissig *et al*.[80] Soldatenkov *et al*.[81,82] have shown that azines can be converted to their corresponding diols as well as the dihydroxylation of several partially dehydrogenated heterocyclic compounds through the Wagner method (aqueous potassium permanganate).

Heterogeneous approaches using a phase transfer catalyst for the oxidation of alkenes have been reported by Ogino[83] and Mochizuki,[84] using pulverized $KMnO_4$ in dichloromethane with benzyltrimethylammonium chloride, to yield the corresponding diols in good yields. This approach was utilized by Rivera *et al*.[85] in the *syn*thesis of brassinosteroid, yielding the required *syn*-diol in good yield.

A variety of simple and hindered cyclohexene derivatives were dihydroxylated with tetradecylammonium permanganate by Hazra *et al*.,[86] using a biphasic solvent mixture (^tBuOH:CH_2Cl_2:H_2O, 50:10:1.25 by volume). Chandrasekaran and coworkers [87,88] have also used the $KMnO_4$-18-crown-6-CH_2Cl_2 system or, cetyltrimetylammonium potassium permanganate. Asymmetric phase transfer catalysts, together with potassium permanganate, were reported by Brown and coworkers[89] in 2002, using a chiral dicationic *bis*-guanidinium complex, which was used by Wang and coworkers,[90] for the asymmetric oxidation and ketohydroxylation of acrylates, respectively. A common challenge encountered in this phase transfer approach, however, is the use of basic media that promote epoxide ring opening.

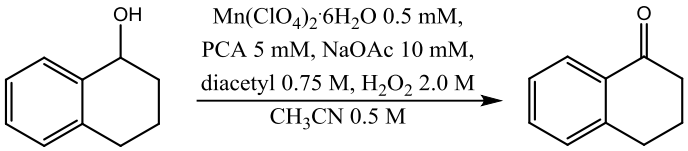
Homogenous conditions for the catalytic epoxidation of alkenes are simpler by comparison with biphasic approaches. Perhaps one of the more studied systems is based on manganese complexes of the tmtacn ligands. Several groups including de Vos,[53,54,56,58] Berkessel,[51] Lindsay Smith,[91] and Feringa and coworkers[92] demonstrated that varying solvent and co-catalyst has a profound effect on the activity of this family of catalysts in the epoxidation of alkenes.[64] de Vos[93] and later Feringa[94,95] and coworkers reported significant amounts of dihydroxylation of alkenes with a hetereogenized system and with addition of aldehydes, respectively. De Boer *et al*.[92,94,95] showed that the unusual reactivity was due to the presence of carboxylic acids, which acted ligands directing the selectivity between epoxide and diol products.

1.4.6 Alcohol oxidation and C-H oxidation with Mn/PCA and H_2O_2

In the absence of alkenes, the Mn(II)/PCA/ketone system shows significant activity towards C-H and alcohol oxidation.[47] High yields and selectivities in the oxidation of secondary alcohols were achieved in contrast to primary alcohols which showed negligible reactivity. Furthermore, C-H oxidations at benzylic positions are preferred over oxidation at other positions. Notably, however, the catalyst loading needed to be increased to achieve good conversions. The selectivity of the oxidation of secondary aliphatic and aromatic alcohols in the presence of primary alcohols was demonstrated in a series of competition experiments with an equimolar mixture of 1- and 2-penylethanol. 75 % conversion to acetophenone with little conversion of the 2-phenylethanol confirmed

that the catalyst is selective. Similarly in the case where secondary and primary aliphatic alcohols are present on the same molecule, oxidation of the secondary proceeded preferentially. The preference for oxidation of alcohols over C-H oxidation leads to good to excellent selectivity in the oxidation of cycloalkanes to monoketones. The absence of Baeyer-Villiger oxidation in these reactions was notable and indicates that the reactive manganese species is the same as that engaging in alkene oxidation or at the least that the activated species involved in both cases have electrophilic character.

The selectivity between aryl alcohols and benzylic positions was explored through the oxidation of 1,2,3,4-tetrahydro-1-naphthol, which underwent oxidation only at the alcohol moiety: confirming the tendency for secondary aryl alcohols to react more readily that benzylic moieties even in the presence of excess oxidant (scheme 10).



Scheme 10. Selective oxidation of 1,2,3,4-tetrahydro-1-naphthol as reported by Dong *et al*.[47]

Notably even if the alcohol is converted to an ether, it will still undergo oxidation, albeit at a lower rate, indicating the possibility of direct oxidation of protected benzylic alcohols. Overall the lack of reactivity towards primary alcohols makes the system complementary to primary alcohol selective copper/TEMPO-based catalysts.

1.4.7 Mechanistic aspects of the Mn/PCA/Ketone system

Several mechanistic studies of the Mn/PCA/Ketone system have been reported both with acetone as solvent and with butanedione as a cocatalyst in other solvents. The reaction, although carried out from an *in situ* prepared catalysts is remarkably complex, with all components essential to reactivity, *i.e.* Mn(II) salt, base, ketone, solvent, and PCA. Curiously, however, one could say that the substrate does not have to be present since in the absence of a substrate, *e.g.*, alkene, the ketone is oxidized. Systematic analysis of the reaction components has shed some light on the mechanism, albeit that the structure of the active oxidant (manganese complex) remains elusive. The earliest studies focused on the role of solvent (ketone) and of the base during the development of the protocol for the dihydroxylations of the electron deficient alkenes.[46] The identification of ketones as being an active participant in the reaction through the formation of hydroxyhydroperoxy adducts has proven key to understanding the effects of other components such as acids (vide infra).

The dependence of the reaction on catalyst (*i.e.* Mn(II) and PCA) concentration is remarkably complex. The typical catalyst concentration ([Mn(II)]) used is 50-250 μM (0.01-0.05 mol%). Decreasing the concentration of Mn(II) to 5 μM (0.001 mol %) had little effect on yield (71 % - 74 %) with conversion dropping to 30% only with 0.5 μM (0.0001 mol %) of Mn, although this still represents a TON of 300000 with respect to Mn(II). The reaction rate decreases with catalyst concentration in an apparently linear

manner. Curiously, increasing the concentration of Mn(II) to >0.5 mM results in a rapid decrease in conversion.[45] The required concentration of PCA is dependent on the concentration of Mn(II) used, and must be present in 3-fold excess at least. Below that ratio, the activity decreases dramatically. However, the concentration of PCA has relatively little effect thereafter. As shown in recent studies of the Mn/PCA system,[96] in all cases a lag phase of (15 to 25 minutes) prior to the onset of substrate conversion is observed, the duration of which is catalyst loading dependent (higher loading → shorter lag-time). As with PCA, the amount of base added must be in a slight excess with respect to PCA and indeed the use of sodium pyridine-carboxylate eliminates the need for a base.

1.4.8 Role of the ketone

The central role played by the ketone in the reaction is remarkable and appears to center around the formation of a ketone-H_2O_2 adduct that can interact directly with the catalyst, without which activity is not observed. The absence of conversion observed in acetonitrile without a ketone, especially, confirms that an intermediate of the type observed in Payne oxidation[97] (peroximidic acid yielding epoxide and acetamide upon reaction with an alkene) is not involved.

Importantly, the ketone acts catalytically and with 0.01 mol% Mn(II) (50 μM) also complete conversion is often achieved with only 0.5 equiv. of butanedione w.r.t. the substrate are used. Analysis by UV/vis and Raman spectroscopy confirmed that butanedione reacts within a few seconds of addition of a small excess of H_2O_2 manifested in the decrease in intensity and blue shift in both the carbonyl stretch (1722 cm^{-1}) and the absorption band at 417 nm. The essentially complete loss in those bands of butanedione even with a 1:1 ratio supports that the formation of a monohydroperoxo acetal species is essentially complete. Indeed signals from the 2-hydroxy-2-hydroperoxobutanone appear commitment. The importance of this species is manifest in the fact that the reaction shows a zero order dependence on [H_2O_2] where it is in excess w.r.t. butanedione and its catalytic role is clear as when 1 equiv. of H_2O_2 is used w.r.t. the substrate, a 66% recovery in butanedione is observed once all H_2O_2 has been consumed. Nevertheless it is clear that butanedione is oxidized to acetic acid during the reaction also, confirmed through ^{13}C NMR spectroscopy.

1.4.9 Effect of carboxylic acids

In the first reports on the Mn/PCA/acetone system, it was noted that the addition of acetic acid slowed or even halted the reaction despite that acetic acid was formed during the reaction by oxidation of acetone. In the cases where butanedione was employed acetic acid addition resulted in elimination of the lag phase (during which acetic aside was actually formed in situ). However, addition of acetic acid had no other effect in terms of maximum TOF and conversion. The presence of acetic acid does not affect the butanedione/H_2O_2 equilibrium significantly. However, the role of acid in the reaction was not clear even though it is essential for reactivity. Nevertheless the presence of acids with different pK_as could affects reaction rate and conversion, in any of several ways including 1) loss of diacetyl and reduced activity, 2) the effect on the H_2O_2/butanedione

equilibrium, pushed towards reagent as nucleophilicity of H_2O_2 is reduced, and 3) destabilization of a putative Mn/PCA complex.

Several other acids were found to eliminate the lag phase also, however, their effect was found to be dependent on their *p*K_a. Strong acids stop conversion due to disturbance of the shifting the H_2O_2/butanedione – adduct equilibrium to the left reducing the concentration of the terminal oxidant (the adduct) dramatically. Acids with a pK_a less than that (of the carboxylate moiety) of picolinic acid (pKa_1 = 1.07 (CO_2H/CO_2^-) and pKa_2 = 5.25 (PyH^+/Py)),[98] retard the reaction but have only a minor effect on the H_2O_2/butanedione – adduct equilibrium, indicating that protonation of PCA results in a reduction of be deprotonated in order to form the complex with manganese. This observation supports the rationalization for the role of base in the reaction by the studies conducted in the base.

1.4.10 Potential intermediacy of peracids and dioxiranes in the Mn/PCA system

A key question that needed to be addressed in the development of the Mn/PCA/Ketone system was the potential involvement of well-established oxidants such as peracids and dioxiranes.

The formation of acetic acid from butanedione during the reaction raises the possibility that peracids are formed *in situ* under reaction conditions. The oxidation of alkenes such as diethylfumarate and cyclooctene does not occur in the absence of any one reaction component, *i.e.* Mn(II) salt, PCA, butanedione, H_2O_2 etc. Addition of PAA (peracetic acid which contains H_2O_2 and acetic acid) in place of H_2O_2 leads to an increase in conversion of cyclooctene, even in the absence of butanedione. However, the oxidation of diethylfumarate did not proceed with in the presence of peracetic acid. The orgin of this difference in effect is due to the propensity of cyclooctene to undergo oxidation with PAA (chart 1)[45] as noted recently also by Stack *et al*.[99] Hence, there is no evidence that *in situ* formation of peracetic acid occurs under the reaction conditions employed.

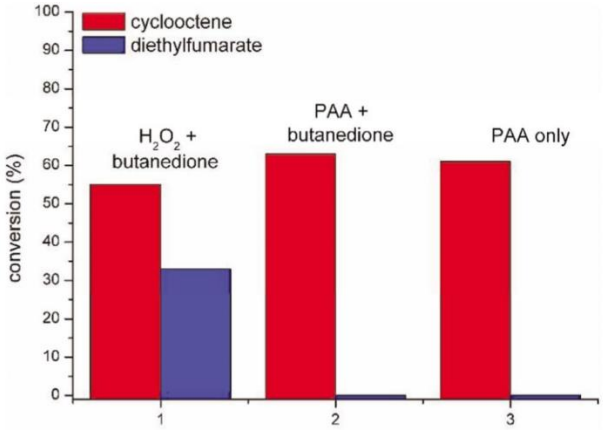
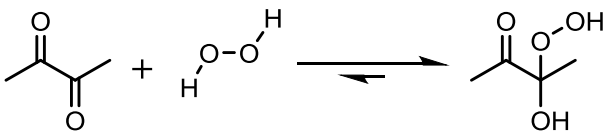


Chart 1. Oxidation of cyclooctene (red) and of diethylfumarate (blue) with peracetic acid in the presence and absence of butanedione under otherwise standard reaction conditions. Reproduced from ref 45. Copyright ACS (2016).

Dioxiranes, originally discovered by Murray,[100,101,102,103] have seen extensive use,[104,105,106,107,108] to the extent that dimethyldioxirane (DMDO) is considered the standard reagent for alkene epoxidation, although its use can be hazardous. The formation of such species is plausible in the Mn/PCA/ketone catalyst system, however, it should be noted that dioxarines are prepared, either separately or (more generally) *in situ*, by oxidation of ketones with peracids and more typically Oxone. The need for a strong oxidant in DMDO reactions, and the significant formation of peracetic acid and absence of Baeyer-Villiger oxidation products under the typical Mn/PCA reaction conditions, precludes the participation of dioxiranes in the catalytic cycle of the Mn/PCA/ketone system. Importantly, the reaction rates achieved with dioxiranes are not sufficiently fast compared with those achieved by the Mn/PCA system (< 5 min for 10000 turnovers) for them to be considered kinetically competent. Furthermore, differences in substrate scope for epoxidation by DMDO, especially the reactivity towards α,β-unsaturated compounds which are converted to the corresponding epoxide cleanly, while the Mn/PCA system tends towards *syn*-diol formation, if it reacts at all. Furthermore epoxidation performed with DMDO proceeds stereospecifically, with retention of configuration, in contrast to that observed with the Mn/PCA system where the degree of retention of configuration for *cis*- and *trans*-2-heptene was relatively low.

1.4.11 Proposed mechanism for the oxidation of substrates by Mn/PCA

The reaction of ketones with hydrogen peroxide is well known, and in the case of butanedione the formation of a hydroxy-hydroperoxy ketone was confirmed with a large equilibrium constant (Scheme 11).[45]



Scheme 11 Equilibrium between H_2O_2 and butanedione and their gem-hydroxy-hydroperoxy adduct.

The involvement of this species directly in the catalytic cycle is supported by the greater reactivity shown with butanedione and trifluoroacetone, compared to acetone or butanone and can be rationalized on the basis of the electrophilicity of the various ketones. It is important to note that this species does not react directly with substrate but instead with the catalyst to form, presumably, a high valent manganese complex, as shown in reactions without Mn(II) or PCA. The observed substrate control of selectively (between epoxide and *syn*-diol) and the relatively broad solvent scope, that also includes protic and aprotic polar solvents, suggests that the mechanism is largely the same for both processes: the incomplete retention of configuration in epoxidation contrasts with the constant selectivity towards the *syn*-diol product suggests a stepwise mechanism in the former for which rotation around the C-C bond is competitive.

1.4.12 Future opportunities

The versatility of the Mn/PCA/ketone system in regard to temperature, solvent etc., and especially the observation of certain over-oxidation products such as the oxidation of electron rich 1,2-diols opens up many opportunities for a wider application of the method. In particular, the use of the reaction as a key step in obtaining acyloins and in C=C bond cleavage as an alternative to ozonolysis and the exploration of unusual solvent systems for polymer modification. The zero order dependence on substrate and H_2O_2 opens up possibilities for the use of flow chemistry, especially for large scale reactions.

1.5 Overview of the thesis

In this thesis, the Mn/PCA/Ketone oxidation system is applied to a broader scope of reactions and further efforts to understand the chemistry involved are made. This catalyst system has proven to be quite adaptable to several oxidative conversions including alkene oxidation, C-H activation and alcohol oxidations, providing often relatively clean reactions with good to excellent efficiency in terminal oxidant (H_2O_2). In this thesis, these efforts will be built upon with the key aim not only to expand the scope of the catalysts system's repertoire of oxidative transformations but also to expand the range of conditions in which it can be applied to tackle challenging substrates, in particular to exploit the reactions selectivity to enable clean access to more extensively oxidized alkenes. The use of Raman spectroscopy proved of central importance in this study, as it makes it possible to follow the concentration of the most significant components of the catalytic system (butanedione, H_2O_2 and the hydroperoxo adduct) and importantly, of the majority of the substrates/products. The rapid and accurate reaction monitoring it allows is shown to enable facile optimization of reaction conditions and elucidation of mechanistic aspects.

In chapter 2 efforts towards the use of this and other oxidation catalysts to isolate 2-carene, or more specifically its oxidation products, from mixtures of 2- and 3-carene are described. The C=C bond cleavage products of the (much more) expensive 2-carene (obtainable from 3-carene through thermal base catalyzed isomerization) are potentially valuable *syn*thons but are notoriously troublesome to isolate from the oxidation products

of 3-carene. The goal, however, was not primarily to obtain a specific product but instead to explore the opportunities that selective oxidations could present in circumventing problems encountered in the separation of isomeric mixtures in multistep reactions. The use of two catalytic oxidation systems (Mn-tmtacn and Mn/PCA) combined with various spectroscopy techniques including Raman spectroscopy to study kinetic oxidative attrition and ^{1}H-NMR for the one-pot cleavage of epoxides (explored further in chapter 3) is considered.

In chapter 3 the development of an alternative to ozonolysis for the cleavage of C=C bonds through the use of a one-pot multistep process is described. The method is based on oxidation of alkenes with the Mn/PCA system to either their epoxide or *syn*-diol products followed by rapid oxidation with 1-2 equiv. $NaIO_4$, with intermediate epoxide ring opening to the diol forms where necessary using catalytic aqueous $Fe(III)(ClO_4)_3$. Overall reaction times ranged from 30 min to 4 h depending on substrate and the reactions are carried out under ambient conditions. A drawback of the method is that acetone is the most preferred solvent (in particular for the ring-opening step) which presents a safety hazard due to the use of H_2O_2. However, it is shown that this drawback can be overcome by applying flow chemistry techniques.

The high degree of functionalization of α-hydroxy ketones makes them valuable *syn*thons, however their sensitivity to oxidation has made their preparation challenging, especially through direct oxidation of the corresponding diols. However, the ease with which *vic*-diols can be accessed from alkenes either directly or indirectly makes this route highly attractive. In chapter 4, the ability of the Mn/PCA system to engage in alcohol oxidation is built upon in the oxidation to vicinal diols to α-hydroxy ketones.

Although most of the studies to date on the Mn/PCA catalyst system have focused on the use of acetonitrile and acetone, this catalyst system shows remarkable solvent scope ranging from highly polar to relatively apolar solvents. The only requirement is that a ketone is present and that the reaction is homogeneous. In chapter 5, this flexibility in solvent scope is exploited in the epoxidation of alkene subunits in EPDM (ethylene propylene diene monomer, M-class, rubber) polymers using a nearly 1:1 mixture of cyclohexane and cyclohexanone. EPDM polymers are elastomers whose use is quite widespread; this class (M) of elastomers has a saturated chain of the polymethylene type. The reactivity of the alkene units in the polymers (containing variously substituted alkene moieties) reflects that observed for analogous low molecular weight compounds. This extension of the method opens up possibilities for post *syn*thetic modification of apolar polymers especially towards crosslinking strategies.

In chapter 6 attention is turned to answering mechanistic questions that arise in the application of the Mn/PCA catalyst system. Kinetic analysis with Raman spectroscopy is shown to be invaluable in understanding the apparent order of reaction components, especially substrates and butanedione, the rate at which the equilibrium between butanedione and H_2O_2 is established and hence the role of acid and base, and above all the various reasons why in many cases conversion ceases suddenly in this reaction.

1.6 References

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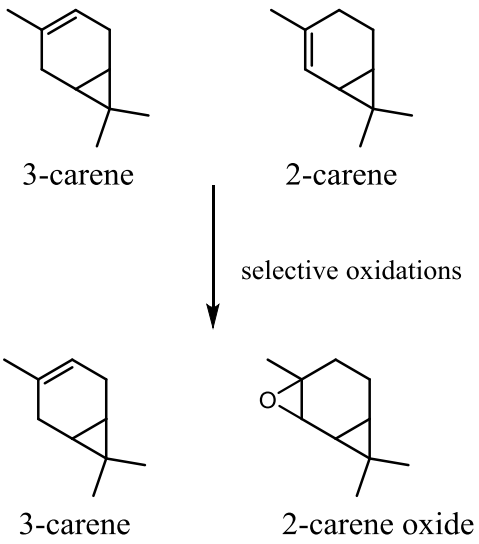
Chapter 2

Towards attritional oxidation of 2- and 3-carene

Abstract. 2-carene is the precursor of a useful aldehyde synthon and is often used on a large scale, however, it is much less readily available than its thermodynamically more stable isomer 3-carene. Furthermore, it is with notable exceptions obtained as mixture with 3-carene and the separation of the oxidation products of 2/3-carene mixtures is usually laborious and expensive. An alternative approach to obtain 2-carene or any of its oxidation products economically is to begin with readily obtainable mixtures of 2/3-carene and use selective oxidation reactions to allow for facile separation of the mixture through divergence. In this chapter several approach to tackling this challenge are described and although the methods are not per se effective the challenge itself is shown to contribute to the kindling of ideas worked out in the following chapters in this thesis



2.1 Introduction

The growth in interest in efficient synthetic approaches to produce enantio-enriched biologically active compounds, which find application as pharmaceuticals, agrochemicals, flavors and fragrances, etc., is reflected in an increasing need of stereo and enantio-rich (pure) precursors. The ready accessibility to a particular 'synthon', i.e. a key compound, in an economic way can generate considerable savings to the overall cost of a synthetic procedure, or even open up completely new synthetic routes.

Within the family of terpenes, a staple of the flavor and fragrance industry[1], 3-carene and 2-carene are widely used. 3-carene is a more readily available bioresource than 2-carene and hence is considerably cheaper. It has a sweet and pungent odor and is a component of turpentine (up to 42 %) together with the terpenes α- and β-pinene and to a lesser extent camphene, dipentene, and terpinolene, and in sweet orange essence. It is also used for the enhancement of other essential oils. In contrast, the isomer 2-carene, which is more reactive due to the proximity of the cyclopropyl moiety to the double bond,[2] is less stable and less widely available, especially when separate from 3-carene.[3] The difference in the reactivity of the two isomers will be exploited in the present study.

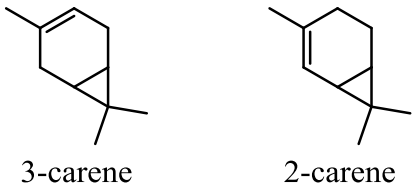
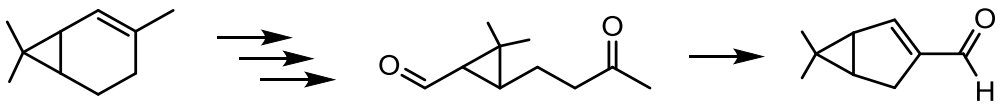


Figure 1: the regioisomers 3- and 2-carene

Ironically, 2-carene shows much wider application as a synthon[4] (see scheme 1), for example in the production of menthol, than 3-carene; unfortunately though, its use is hampered by its scarce availability and, therefore, cost. The fraction of 2-carene in carene oil does not exceed 5–7%, and, as will be discussed, the separation of the isomers is extremely laborious, given their similar chemical and physical properties;[5] indeed it is more convenient to extract 2-carene from sources other than turpentine such as lavender.[6,7]



Scheme 1. Oxidation of 2-carene to the aldol condensation product.

Isomerization of the inexpensive 3-carene is an attractive approach to tackle this problem, as already demonstrated by Macaev et al.[8]: between the several isomerization sequences they reported from previous studies, it is important to underline that the generic isomerization of 3-carene by strong bases at high temperatures leads to a ~ 40:60 equilibrium mixture of 2- and 3-carene, as this process is thermodynamically controlled and the bicyclic system is more stable when the cyclopropyl condensed ring is not in the

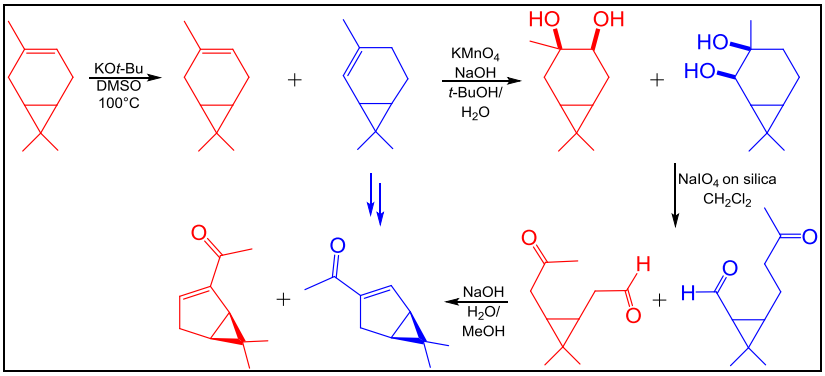
allylic position, due to the increase in ring strain it causes.[9] This aspect is nevertheless exploited in the present chapter.

However, since 2-carene is only a precursor of the compound that can be used as synthon, which is prepared by a formal C=C bond cleavage on the 2-carene and a subsequent aldol condensation (see scheme 1), we thought it could be feasible to carry several oxidation steps using an isomeric mixture and to separate the mixture at a later stage, when the properties of the products would differ in a more substantially.

In this chapter a series of approaches to obtain pure 2-carene derivatives, starting from pure 3-carene, is described. The first step makes use of the known thermal approach to obtaining mixtures of 2- and 3-carene.[8] Subsequently an attritional approach is taken to obtain a mixture of compounds that can be separated more easily. Ideally, the selective oxidation of 3-carene would allow for the mole fraction of 2-carene to be increased beyond the azeotropic point. The first approach taken was to epoxidize 3-carene in presence of 2-carene using a Mn-tmtacn based catalyst (see chapter 1). However, although some attrition in favor of the desired regioisomer was obtained, it was not sufficient to reach beyond the azeotropic ratio. Nevertheless, this approach required a method for inline analysis of a biphasic reaction mixture, and prompted the use of in-line Raman spectroscopy, using a capillary to discriminate between the solvent and the substrate layers. The second approach followed was to carry the mixture of regioisomers through several oxidation steps and then separate the products making use of a kinetic attrition (with only the oxidation product of 2-carene consumed). The attrition was successful, but the final product could not be recovered in isolated amounts.

Overall, although the primary goal was not met in the regard to isolating the oxidation products of 2-carene from mixtures of 2- and 3-carene, the lessons learned and innovations that were made prompted the development of several approaches to selective oxidations, in particular the use of $NaIO_4$ to perform a one-pot dihydroxylation/C-C bond cleavage of alkenes, which is the subject of chapter 3.

As discussed above, 3-carene can be isomerized to 2-carene with the use of a strong base, an aprotic solvent and high temperatures: this conditions lead to an equilibrium in which the 3-carene:2-carene ratio is ca. 60:40,[8] due to the greater thermodynamic stability of the 3-carene. This reaction was exploited in earlier studies,[10] where all the steps including *cis*-dihydroxylation, C-C bond cleavage and further aldol condensation were performed on the mixture of carenes, and the resulting products separated through laborious column chromatography. The 2/3-carene mixture is subjected to permanganate *cis*-dihydroxylation, and the resulting diols cleaved with $NaIO_4$ to the corresponding keto-aldehydes; in the last synthetic step, the products undergo aldol condensation to give the corresponding bicyclic five membered ring products, which are ultimately separated by column chromatography (scheme 2).



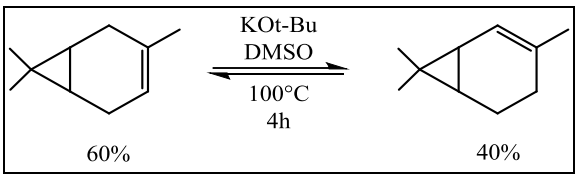
Scheme 2. Isomerization and oxidative steps performed on 3-carene to achieve the desired product of 2-carene oxidation.

Our goal was thus to develop an approach to achieve separation between the careen isomers or any of their products, trying to avoid a chromatographic step, to reduce drastically the cost of the process. An alternative approach taken was kinetic attrition during any of the successive oxidation steps: ideally reaction of 3-carene (or one of its products) selectively in the presence of 2-carene or any of its equivalent products.

2.2 Results

2.2.1 First attempt: separation of isomers through (reduced pressure) distillation

The isomerization of 3-carene to 2-carene is performed using potassium *tert*-butoxide in DMSO at 100 °C, providing a ca. 60:40 mixture of the isomers, with no significant by-products. Normal and reduced pressure distillation were carried out on the crude product provided some enrichment of the molar fraction of 2-carene: albeit the azeotrope composition was 47:53 = 2-carene:3-carene, and hence the fraction of 2-carene could not be increased further by distillation.



Scheme 3. 3-carene isomerization to 2-carene.

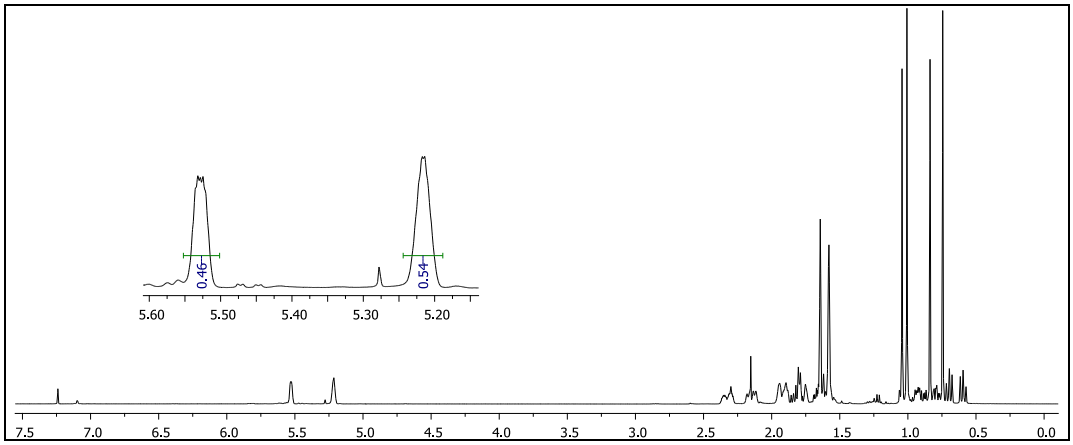


Figure 2. ^{1}H-NMR spectrum of the carene mixture.

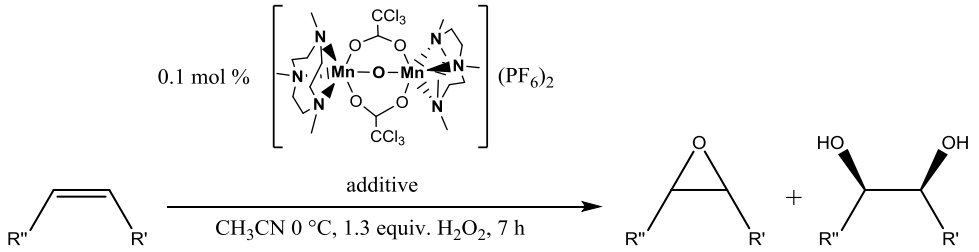
Notwithstanding this, it proved an excellent method for the purification of the crude of the reaction, both to remove solvent (DMSO) and other impurities which were not apparent by ^{1}H-NMR spectroscopy but lead to a brown coloration of the solution.

2.2.2 Kinetic attrition

The challenge of obtaining 2-carene from mixtures of 2- and 3-carene through attrition was attempted using catalytic oxidations. In the first attempt, the Mn-tmtacn based catalyst is employed, followed by the use of the Mn/PCA catalyst system discussed in chapter 1. The goal is to oxidation sufficient amounts of 3-carene to get over the azeotropic point to enable distillation to be used for further enrichment of 2-carene.

Oxidation of mixtures of 2- and 3-carene with Mn-tmtacn

Previous works from De Boer et al.[111213] showed a convenient catalytic method for oxidation of alkenes, using a dinuclear trimethyl-triazacyclononane (tmtacn) manganese catalyst, a carboxylic acid as co-catalyst and hydrogen peroxide as terminal oxidant (scheme 4).



Scheme 4. Oxidation of Alkenes with the method reported by de Boer et al in ref. 5,6,7.

This catalyst system is tunable by using different carboxylic acids; it was demonstrated that, depending on the catalyst tuned, the specificity of the system towards the alkene has, as a preferred outcome, either *cis*-diols or epoxides.[11] The role of the carboxylic acid is primarily to bridge the two manganese(III) ions and, depending on its nature, epoxidation or *cis*-dihydroxylation of alkenes is preferred. We envisioned that it could be possible to realize kinetic attrition between 2- and 3-carene, given that the relatively bulky catalyst would be able to discriminate between the regioisomers and epoxidize, either one of the

two preferentially. Indeed, introducing such kind of transformation would already result in drastic changes to physical properties such as polarity and boiling point, therefore opening a new range of possibilities and techniques to perform separations. Several carboxylic acids were tested, including salicylic, trichloroacetic, dichlorobenzoic, ascorbic and oxalic (with sodium oxalate to form a buffer) acids. A priori, it is not possible to predict the reactivity and selectivity with a particular acid with respect to 2- and 3-carene. Monitoring of the reaction by Raman spectroscopy allowed the conversion to be determined in real time (figure 2).

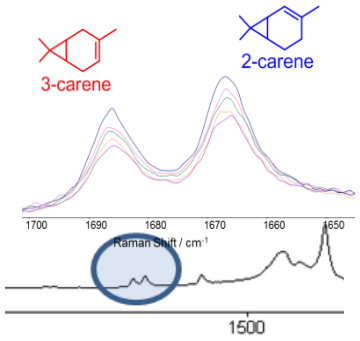


Figure 3. Raman spectra of 2- and 3-carene.

The oxidation of the 2- and 3-carene mixture was carried out using conditions developed earlier by de Boer et al.[12] When salicylic acid was used as co-catalyst, 2-carene was consumed more rapidly than 3-carene, while with dichlorobenzoic, ascorbic acid or oxalate buffer selectivity was not observed. In contrast with trichloroacetic acid, 3-carene was oxidized preferentially and the 2-carene:3-carene ratio could be shifted from 47:53 to 56:44 in the unreacted alkenes. Though a shift in the preferred direction, it was insufficient to be useful with respect to the azeotropic point.

During the screening of co-catalysts an issue arose with regard to analysis, especially due to the limited solubility of the carenes in the reaction media (acetonitrile/water). This limitation, however, could be used to good effect as it allowed for the concentration of 2- and 3-carene in the acetonitrile layer to be maintained at a pseudo steady state, albeit that the light scattering that results is not ideal to identify the optimum point at which the reaction should be stopped. Analysis of both phases in real time was challenging but a combination of Raman microscopy and phase separation in capillaries allowed for the composition in each phase to be determined relatively rapidly (figure 3).

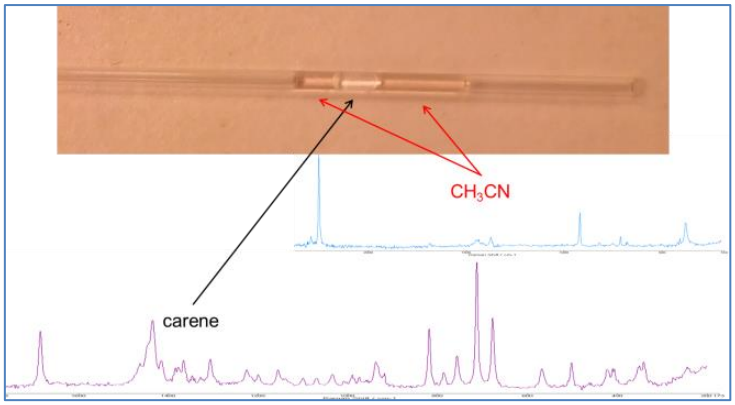


Figure 4. Raman spectra of different phases split within a capillary.

In this way, on-line analysis of the reaction could be carried out and the results indicated that increasing the substrate present, and thereby forcing a biphasic situation, improved to a certain extent the outcome of the reaction. The goal was to move past the 2-,3-carene ratio threshold needed to enable azeotropic purification of 2-carene. Despite the positive results obtained, sufficient attrition of 3-carene was not achieved to overcome the azeotropic threshold. This, together with the poor reproducibility of the reactions (that take place at the interface between the two layers), the detection limits at low concentrations (at which the reaction proceeds) and the need to the monitor the reaction off-line prompted us to search for an alternative approach.

Importantly, we showed that in cases where there is a substantial difference in solubility, phase separation of the substrate from the rest of the reaction mixture can be used to increase the selectivity, not due to the intrinsic properties of the catalyst, but rather due to mass transport phenomena.

2.2.3 Separation after oxidation

The second approach was to perform the separation at a later stage, but nevertheless avoiding the need for demanding separation methods, including column chromatography; the mixture of 2- and 3-carene was submitted to several oxidation steps, until one of those would show selectivity of one over the other.

In previous studies,[10] the cis-diols obtained from permanganate oxidation of alkenes could be cleaved, using $NaIO_4$, to their respective keto-aldehyde products. $NaIO_4$ is the standard reagent for the cleavage of vicinal diols, but it has also been reported to cleave epoxide C-C bonds also,[14] through diol intermediates, as is also confirmed further in chapter 3. As oxidation to the desired 2-carene product is carried out via the diol, we envisioned that submitting the epoxide to cleavage could, in principle, selectively oxidize that epoxide which showed greater susceptibility to ring opening.

The epoxidation of the the mixture of carenes using the Mn/PCA based catalyst[15] was preferred in this case as it was already show to be efficient for both 2- and 3-carene with H_2O_2 as terminal oxidant, as well as secondary alcohols to ketones. These transformations are selective and achieved in good to excellent yields, sometimes with slight deviations

from the standard conditions with variation in the amount of terminal oxidant or of the substrate. ^{1}H-NMR spectroscopic analysis of the reaction mixture with 2- and 3-carene, showed quantitative conversion of the carenes to the corresponding epoxides; unfortunately however, aqueous workup resulted in loss of a large part of the 2-carene epoxide (see figure 4); a similar result was obtained when the mixture was purified by short path vacuum distilation. In both cases the loses are ascribed to the intrinsic reactivity of the 2-carene epoxide.

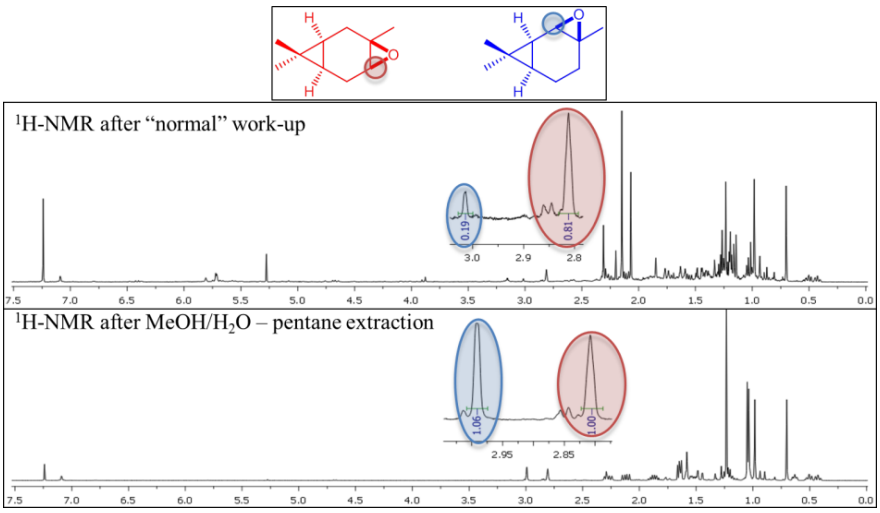
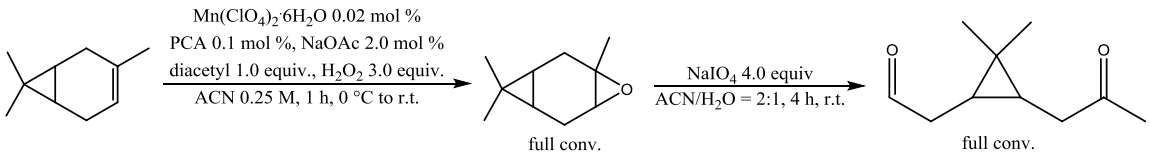


Figure 5. ^{1}H NMR analysis shows a change in the 2-: 3-carene ratio after workup.

Modification of the workup procedure that would not lead to loss of 2-carene, resulted in methanol being used in place of water. However, to reduce the miscibility of methanol with pentane or heptane, 10 % water by volume was added to the methanol layer. This simple extraction allowed for more or less full retention of the ratio of products obtained from the reaction mixture: thus the instability of 2-carene oxide prompted us to explore how this difference in reactivity could be explored to achieve separation.

2.2.4 Use of $NaIO_4$ to cleave epoxides

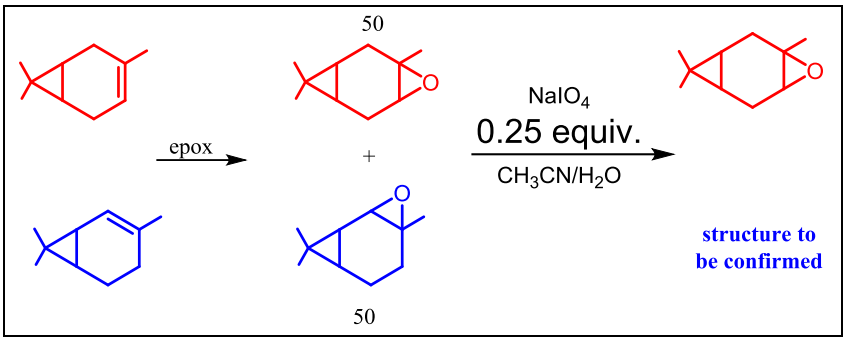
Preliminary studies on the 3-carene epoxide showed that it underwent cleavage in presence of 4.0 equiv. $NaIO_4$ (2.0 equiv. led to a 57 % conversion of the epoxide) and a 2:1 solvent mixture of CH_3CN and H_2O.



Scheme 5. two-step one-pot oxidation of 3-carene to the equivalent product of ozonolysis.

Further experiments confirmed that both 3-carene and 2-carene oxides can react to give the corresponding scission products. Interestingly though, when a substoichiometric amount of the oxidant is added, 2-carene epoxide is oxidized preferentially even in the presence of 3-carene epoxide, which is left untouched at the end of the reaction, as

confirmed by ^{1}H-NMR analysis. Although conditions in which 2-carene was unreacted and 3-carene consumed would be the most preferred, provided the scission product of 2-carene oxide would be desirable then this approach is worth pursuing since the chemical and physical properties of the product and 3-carene epoxide would be greatly different, thus allowing for a simple separation techniques. At this point, it is finally possible to discriminate between the oxidation products of 2- and 3-carene, though it is unfortunately not clear whether the product of 2-carene epoxide is the expected scission product. As it is not possible to recognize the typical aldehyde peak after workup (this product was already reported to be unstable.



Scheme 6: 2-carene kinetical attrition performed over the carene oxides mixture.

Though the product of oxidation of 2-carene epoxide has not been identified yet, it is clear that 3-carene epoxide is left while 2-carene epoxide is consumed. The approach, in principle, works, though it is not possible to isolate the desired product or confirm its structure either. C-C bond cleavage was also attempted on 2-carene epoxide alone, in CH_3CN/H_2O: the desired product was not observed by ^{1}H-NMR analysis of the reaction mixture after workup. In this case the workup procedure was innocent as direct analysis of the reaction mixture using CD_3CN/D_2O did not show the desired product either.

2.3 Conclusions

Even though our aims to separate 2- and 3-carene using a kinetic resolution, and to play on differences in the reactivity of their oxidation products, has not succeeded in the sense that chemistry does not go the desired way, the efforts made in this study open up two projects, of which one has been exploited, and the other is of potential interest for the future:

- use of the Mn-tmtacn in a biphasic reaction, with possible and interesting further applications;
- use of the $NaIO_4$ to perform a one-pot dihydroxylation/C-C bond cleavage over alkenes, elaborated on in chapter 3.

The difference in reactivity of related substrates with the use of Mn-tmtacn and Mn/PCA is, in principle, a powerful tool for achieving high selectivity over multiple steps, but it is essential to be able to obtain spectral analysis in real time; an aspect in which Raman spectroscopy is particularly well suited. The use of biphasic reaction conditions although

generally avoided can allow for mass transport phenomena to be exploited to achieve desired selectivity.

2.4 Experimental

All reagents were of commercial grade and were used as received unless stated otherwise. Hydrogen peroxide was used as received (Acros Chemicals) as a 50 wt % solution in water; note that the grade of H_2O_2 employed can affect the outcome of the reaction, as some sources are stabilized using sequestrants. ^{1}H NMR (400.0 MHz) and ^{13}C NMR (100.59 MHz) spectra were recorded on a Varian Avance 400. Chemical shifts are relative to the following: ^{1}H NMR, $CDCl_3$ (7.26 ppm) and CD_3CN (1.94 ppm); ^{13}C NMR, $CDCl_3$ (77 ppm) and CD_3CN (118 ppm). Reaction monitoring with Raman spectroscopy involved monitoring of the intensity of the C=C and C=O stretching bands between 1550 and 1800 cm^{-1} (e.g., at 1724 cm^{-1} for butanedione), between 600 and 900 cm^{-1} relating to the C=C and C=O bending modes (682 cm^{-1} for butanedione), and the O−O stretching mode of H_2O_2 at 870 cm^{-1}. Raman spectra at 785 nm were recorded using a PerkinElmer Raman Station and at 532 nm using a custom-made Raman spectrometer; a 532 nm DPSS laser (25 mW, Cobolt Lasers) was fiber-coupled to a low-cost Raman probe (Inphotonics) and the collected scattering feed into a Shamrock163 spectrograph (500 nm blaze, 1200 l/mm grating, Andor Technology) and dispersed onto a Newton EMCCD (Andor Tehcnology) operated in conventional CCD mode.

Caution! The drying or concentration of solutions that potentially contain H_2O_2 should be avoided. Prior to drying or concentrating, the presence of H_2O_2 should be tested for using peroxide test strips followed by neutralization on solid $NaHSO_3$ or another suitable reducing agent. When working with H_2O_2, suitable protective safeguards should be in place at all times due to the risk of explosion.

Caution! Butanedione has been linked with lung disease upon prolonged exposure to its vapors. It should be handled in a properly ventilated fume hood, and exposure to vapors should be avoided.

Typical procedure for 3-carene isomerization to 2-carene 3-carene (400 mmol, 54.5 g, 63 mL) was dissolved in DMSO (200 mL) and KOt-Bu (400 mmol, 44.9 g) was added; the resulting mixture was heated at 100 °C with stirring for 4 h. After cooling to r.t., H_2O (40 mL) is added carefully, followed by pentane (80 mL). The two bottom layers were extracted with pentane (3 x 300 mL) and the combined organic layers were washed with H_2O (200 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. This mixture was purified by short path distillation. Spectroscopic data agree with those found in literature.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (s, 1H, 2-carene, 46 %), 5.23 (s, 1H, 3-carene), 2.35 (m, 1H, 3-carene), 2.16 (m, 1H, 3-carene), 1.99 – 1.89 (m, 1H, 3-carene), 1.98 – 1.88 (m, 1H, 2-carene), 1.87 – 1.78 (m, 1H, 2-carene), 1.83 – 1.74 (m, 1H, 3-carene), 1.72 – 1.53 (m, 2H, 2-carene), 1.66 (s, 3H, 2-carene), 1.60 (s, 3H, 3-carene), 1.06 (s, 3H, 2-carene), 1.03 (s, 3H, 3-carene), 0.98 – 0.92 (m, 1H, 2-carene), 0.86 (s, 3H, 2-

carene), 0.76 (s, 3H, 3-carene), 0.84 – 0.78 (m, 1H, 2-carene), 0.74 – 0.68 (m, 1H, 3-carene), 0.64 – 0.58 (m, 1H, 3-carene).

Typical Procedure for Catalytic Oxidations with Mn/TMTACN A stock solution containing $[Mn_2O_3(Me_3\text{-}TACN)_2](PF_6)_2 \cdot H_2O$ (24.2 mg, 0.03 mmol), carboxylic acid (0.03 mmol) and H_2O_2 (50 % wt in water, 86 µL) in CH_3CN (10 mL) was prepared at room temperature and stirred for 20 min. The mixture of 2- and 3-carene (1 mmol) was added to this solution (0.330 mL) together with CH_3CN (0.660 mL). H_2O_2 (50 % wt in water, 43 µL, 0.75 mmol) was added via syringe pump (30 µL/h) and the mixture stirred for 16 h at r.t. Subsequently, sat. aq. $NaHCO_3$ (7 mL) was added to the mixture and the aqueous layer extracted with CH_2Cl_2 (3 x 7 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo, providing the product mixture.

Typical Procedure for Catalytic Oxidations with Mn/PCA 2- and 3-carene mixture (1 mmol) was added to a 1.0 mL solution containing $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 1.0 mL solution PCA (12.3 mg in 10 mL of solvent) in acetonitrile (or acetone) to give a final concentration of the substrate of 0.25 M. 33.4 µL NaOAc (aqueous, 0.6 M), 87 µL butanedione (0.5 mmol) and acetonitrile (or acetone) were added to give a final volume of 4 mL and a final substrate concentration of 0.25 M. The solution was stirred in an ice/water bath before addition of 170 µL (3.0 mmol) H_2O_2 (50 wt %). Conversion was verified by ^1H NMR by dilution of a part of the reaction mixture in CD_3CN or by directly diluting the sample in $CDCl_3$ (when acetone is used). Reaction mixture is added a 9:1 mixture of MeOH/water (10 mL) and extracted with Pentane (3 x 10 mL); the pentane layers are gathered, dried over anhydrous $MgSO_4$ and the solvent evaporated (not to full vacuum) in vacuo to yield the crude of reaction. Spectroscopic data agree with those found in literature.[15,16] ^1H NMR (400 MHz, $CDCl_3$) δ 3.01 (s, 1H, 2-carene), 2.83 (s, 1H, 3-carene), 2.29 (ddd, J = 16.5, 9.1, 1.9 Hz, 1H, 3-carene), 2.14 (ddd, J = 16.2, 9.1, 0.9 Hz, 1H, 3-carene), 1.95 – 1.84 (m, 2H, 2-carene), 1.70 – 1.64 (m, 2H, 2-carene), 1.63 (dt, J = 16.5, 2.3 Hz, 1H, 3-carene), 1.56 – 1.50 (m, 1H, 2-carene), 1.48 (dd, J = 16.2, 2.3 Hz, 1H, 3-carene), 1.26 (s, 3H, 2-carene), 1.25 (s, 3H, 3-carene), 1.07 (s, 3H, 2-carene), 1.06 (s, 3H, 2-carene), 1.00 (s, 3H, 3-carene), 0.72 (s, 3H, 3-carene), 0.68 – 0.62 (m, 1H, 2-carene), 0.48 (dtd, J = 31.7, 9.1, 2.4 Hz, 2H, 3-carene).

Typical Procedure for $NaIO_4$ mediated ring opening of the epoxide(s) 1.0 equiv. of $NaIO_4$ (213.89 g/mol) was added to the reaction mixture; the reaction mixture was monitored off-line by ^1H NMR spectroscopy (a small sample of reaction was shaken with 1 ml brine and 1 ml $CDCl_3$, and the organic layer used to record the NMR spectrum). Product was isolated by addition of brine (10 mL) and extraction with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous), and filtered, and the dichloromethane removed in vacuo.

2 step epoxidation/C-C bond cleavage over 3-carene 1.0 mmol of 3-carene was added to a 1.0 ml solution containing $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 ml solvent) and 1.0 ml solution PCA (12.3 mg in 10 ml of solvent) in acetonitrile; 33.4 µl NaOAc (aqueous, 0.6 M) and 87.0 µl butanedione (0.5 mmol) were added to give a final volume of 4 mL and a

concentration of the substrate of 0.25 M. The solution was stirred in an ice/water bath before addition of 170 µl (3.0 mmol) H_2O_2 (50 wt %). Conversion was verified by ^1H NMR by dilution of a part of the reaction mixture in CD_3CN. After epoxidation was complete, 2.0 mL of H_2O and 4.0 mmol of $NaIO_4$ were added, and the resulting mixture was stirred for 5 h. The reaction mixture was monitored off-line by ^1H NMR spectroscopy (a small sample of reaction was shaken with 1 ml brine and 1 ml $CDCl_3$, and the organic layer used to record the NMR spectrum). Product was isolated by addition of brine (10 mL) and extraction with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous), and filtered, and the CH_2Cl_2 removed in vacuo yielding the crude containing the expected scission product as main product. ^1H NMR agrees with data found in literature.[17] ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, J = 1.8 Hz, 1H), 2.36 (d, J = 6.8 Hz, 2H), 2.32 (dd, J = 1.8 Hz, J = 7.0 Hz, 2H), 2.17 (s, 3H), 1.13 (s, 3H), 0.98 (m, 2H), 0.92 (s, 3H).

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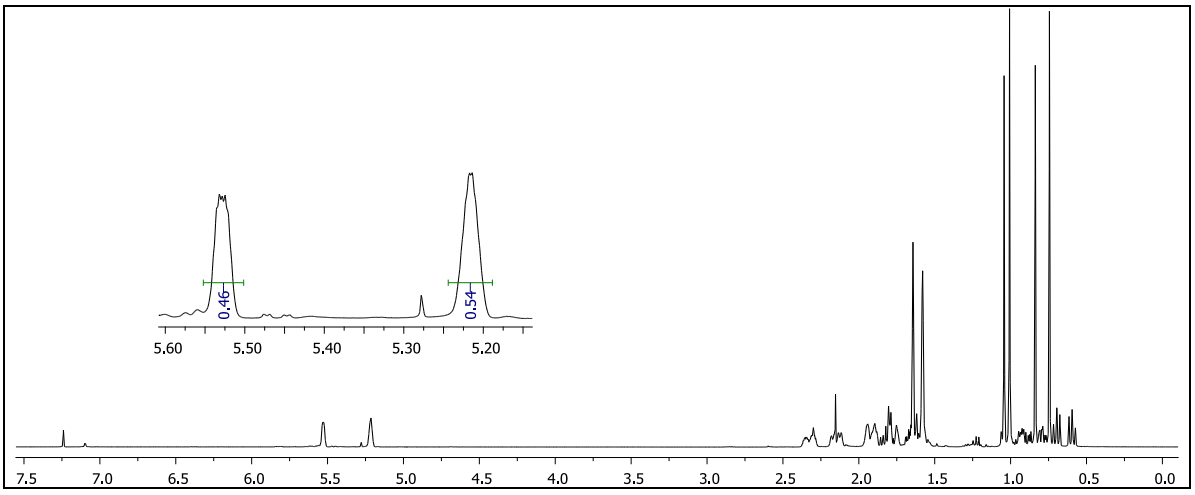
2.6 Supplementary information

Isomerization of 3-carene to 2-carene

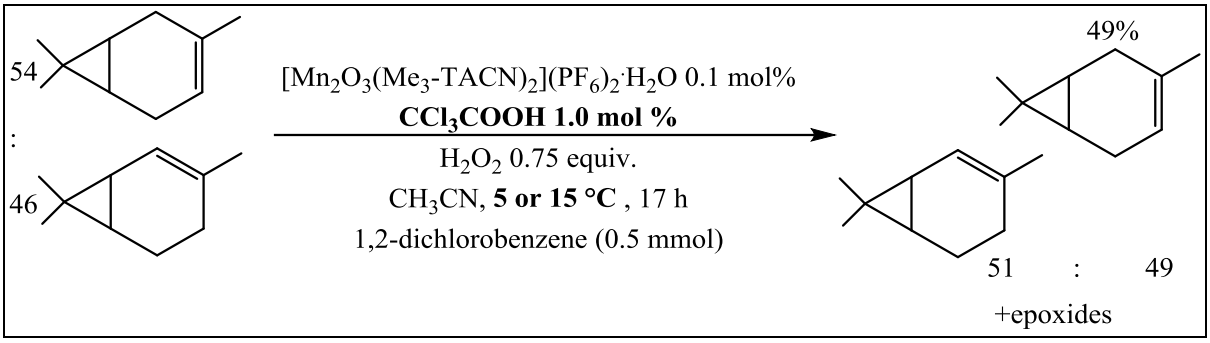
63 ml of 3-carene (136.23 g/mol, 400 mmol, 54.49 g, 0.864 g/ml) were dissolved in 200 ml of DMSO to which 44.88 g of KOt-Bu (112.21 g/mol, 400 mmol) were added. The mixture was heated to 100 °C with stirring for 4 h. The solution was cooled to room temperature and H_2O (40 ml) added, followed by pentane (80 ml). The aqueous layers were extracted with pentane (3 x 150 ml) and the combined organic layers washed with d.d. H_2O (3 x 100 ml), dried over anhydrous $MgSO_4$ and concentrated in vacuo (≈ 100 mbar). The 3-carene/2-carene ratio was 54/46. This mixture was purified by short path distillation.



Screening of carboxylic acids for kinetic attrition by oxidation with $[Mn_2O_3(Me_3\text{-}TACN)_2](PF_6)_2$.

A stock solution* in CH_3CN (10 ml) was prepared containing $[Mn_2O_3(Me_3\text{-}TACN)_2](PF_6)_2 \cdot 6H_2O$ (24.2 mg, 0.03 mol), the respective carboxylic acid (0.3 mmol) and H_2O_2 (50% in water, 86 µl). Entry A: trichloroacetic Acid, B: 2,6-dichlorobenzoic acid, C: oxalic acid sodium oxalate and D: ascorbic acid The mixture was stirred for 20 min, after which 0.330 ml of this solution (1 µmol $[Mn_2O_3(Me_3\text{-}TACN)_2](PF_6)_2 \cdot 6H_2O$, 0.1 mol %, 10 µmol carboxylic acid, 1.0 mol %) was added to the substrate (a 54/46 mixture of 3- and 2-carene, 1 mmol) in CH_3CN (0.66 ml). H_2O_2 (50% wt in water, 43 µl, 0.75 equiv.) was added via syringe pump (30 µl/h) and the mixture was stirred for 16 h at room temperature. Saturated aqueous $NaHCO_3$ (7 ml) and CH_2Cl_2 (7 ml) were added and the aqueous layer extracted CH_2Cl_2 (3 x 7 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo, yielding the product.

Kinetic attrition (oxidation) on 2/3-carene mixtures monitored in situ by Raman spectroscopy and ex-situ by ^{1}H NMR spectroscopy



0.330 ml of the stock catalyst solution* (1 µmol $[Mn_2O_3(Me_3\text{-}TACN)_2](PF_6)_2.{}_6H_2O$, 0.1 mol %, 10 µmol carboxylic acid,1.0 mol %) was added to a solution of the substrate (1 mmol) in CH_3CN (0.66 ml). 1,2-dichlorobenzene (0.057 ml, 0.5 mmol, 0.0735 g) was added as internal standard. H_2O_2 (50% wt in water, 43 µl, 0.75 equiv.) was added via syringe pump (rate 10 µl/h) at either 5 or 15 ^oC and after addition of H_2O_2 was complete, the mixture was stirred for 16 h at room temperature. Reaction progress was monitored by Raman spectroscopy at ten min intervals. The mixture was added to saturated aqueous $NaHCO_3$ (7 ml) and CH_2Cl_2 (7 ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 7 ml) and the combined organic layers dried over anhydrous $MgSO_4$ and concentrated in vacuo, yielding the product.

It is noted that during the reaction the solubility of the substrate was not always complete. As conversion proceeded the phase separation decreased to yield ultimately a homogeneous mixture. Increasing the temperature to 15°C increased solubility. In both cases ^{1}H NMR spectroscopy indicated 60% conversion with a 2-c/3-c ratio of 54/46. Since conversion ceased after 5 h and addition, after 6.5 h, of 0.830 mg (0.1 mol %) of $[Mn_2O_3(Me_3\text{-}TACN)_2](PF_6)_2.{}_6H_2O$ to continue conversion. After 21 h the mixture was worked up as above. Raman spectroscopy indicated that after 16 h, 3-carene was consumed completely with only a minor amount of 2-carene remaining which was also consumed after 17 h. Carrying out the reaction at room temperature and with an increased rate of H_2O_2 addition showed erratic results with in one case a 2-c/3-c ratio of 65/35 for a crude conversion of 50% that was not reproducible. The effect of the internal standard on solubility was notable. Reactions carried out under identical conditions in the absence of 1,2-dichlorobenzene showed erratic results ascribed to increased demixing.

Oxidation under biphasic conditions

The reaction under biphasic conditions was carried out as described above, however, 10 mmol of substrate was added in place of 1 mmol resulting in phase separation and H_2O_2 (50% wt in water, 0.53 equiv.) was added over 3 h via syringe pump (rate 100 µl/h) with vigorous stirring. In this case only minor conversion was observed. Neither addition of

butyronitrile (1 mL) nor reducing the amount of substrate to 2 mmol had an effect on the outcome of the reaction.

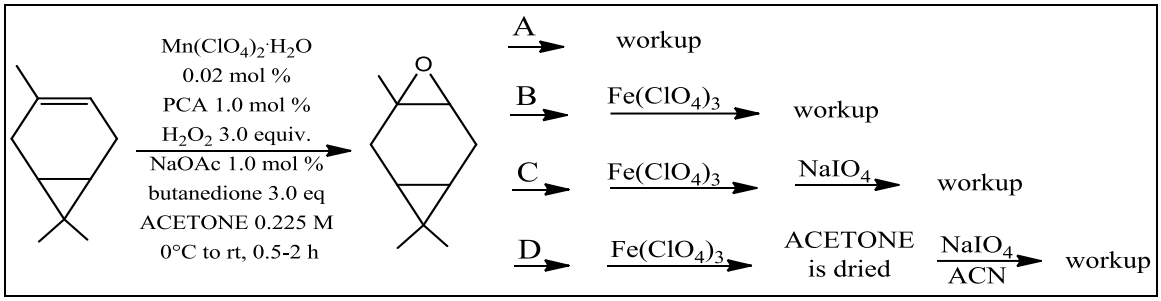
Oxidation of 3-carene and 2-/3-carene mixtures with Mn/PCA

Epoxidation of 3-carene trial with Mn/PCA

Two 10 ml stock solutions in solvent of $Mn(ClO_4)_2 \cdot 6H_2O$ (0.72 mg) and of PCA (12.3 mg) were prepared. 0.5 ml each of stock solution were mixed followed by addition of 1 mmol of 3-carene (0.158 ml, d = 0.864 g/ml), 43.5 µl of butanedione (0.5 equiv.), 16.7 µl NaOAc (0.5 mol %) and 780 µl solvent, (final volume 2 ml). The mixture was cooled in ice water and H_2O_2 added dropwise (50% by volume, 86 µl, 1.5 equiv.). After 2 h, $CDCl_3$ and brine (10 ml of both) are added to the solution, and the layers separated. The organic layer was extracted again with brine (2 x 10 ml), and dried over anhydrous $MgSO_4$, and solvent removed in vacuo to yield the crude product.

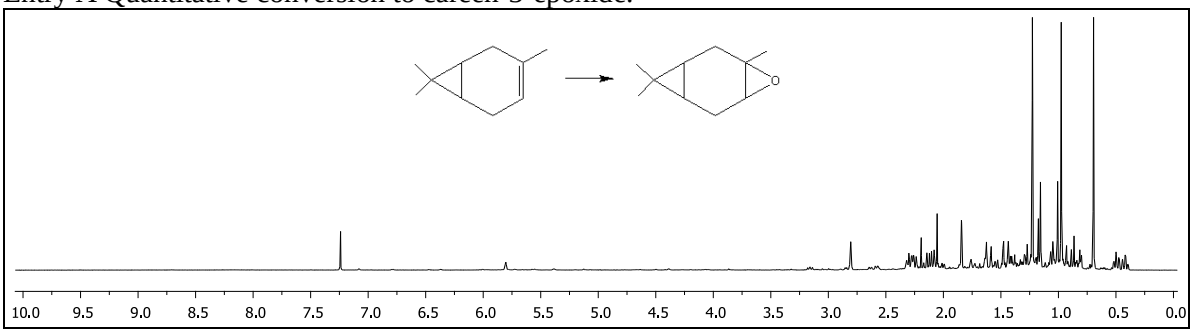
Under these conditions, in acetone 50% conversion to the epoxide product was observed whereas near full conversion to the epoxide was observed in acetonitrile**.** Substitution of 50% of the substrate with solvent resulted in both cases in quantitative formation of the epoxide.

One pot 3-carene epoxidation/ring opening in acetone

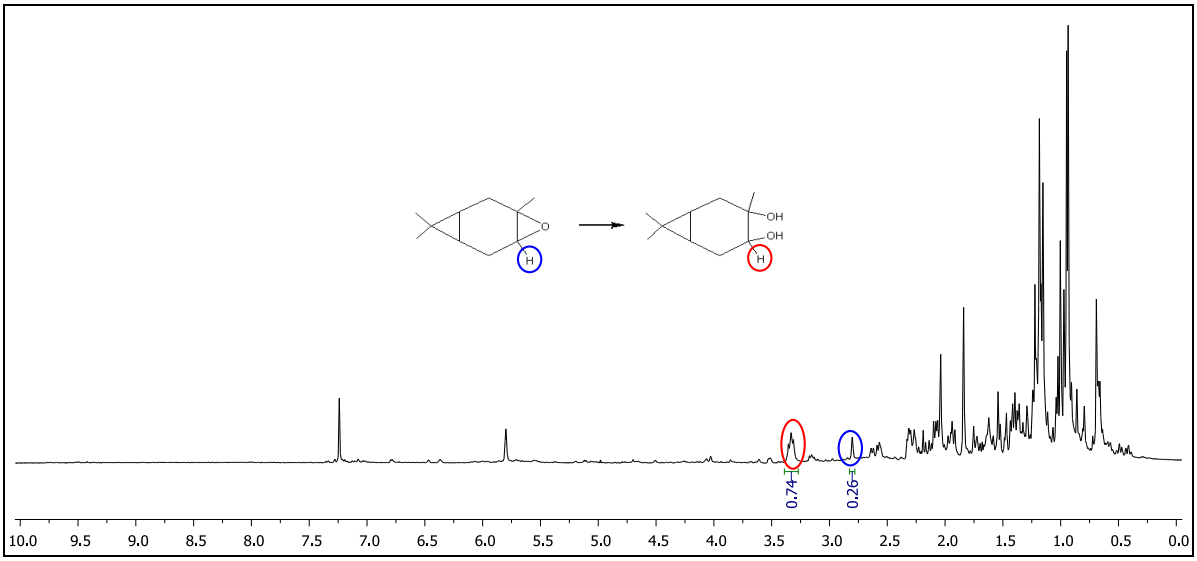


The epoxidation was carried out as described above with 0.5 mmol of 3-carene in place of 1 mmol. Entry A was worked up after the first step as above; 0.01 mol % $Fe(ClO_4)$ were added directly after epoxidation in the case of entries B, C and D. In the case of entry C $NaIO_4$ (2 eq, 214 mg) was added directly while for Entry D solvent was removed in vacuo and acetonitrile added with $NaIO_4$ (2 eq, 214 mg). Entries B, C and D were worked up as follows: 15 ml of H_2O were added and the reaction extracted with dichloromethane. The combined organic layers are washed with water and brine; the product dried over Na_2SO_4 (anhyd.), filtered, and the dichloromethane removed in vacuo.

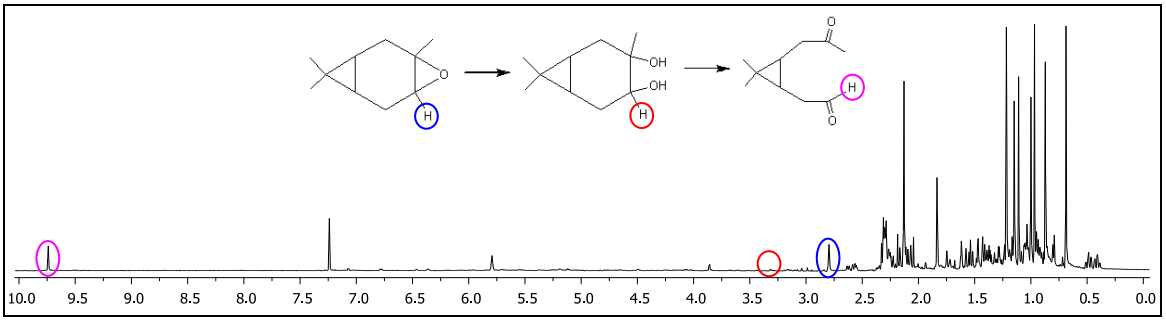
Entry A Quantitative conversion to careen-3-epoxide.



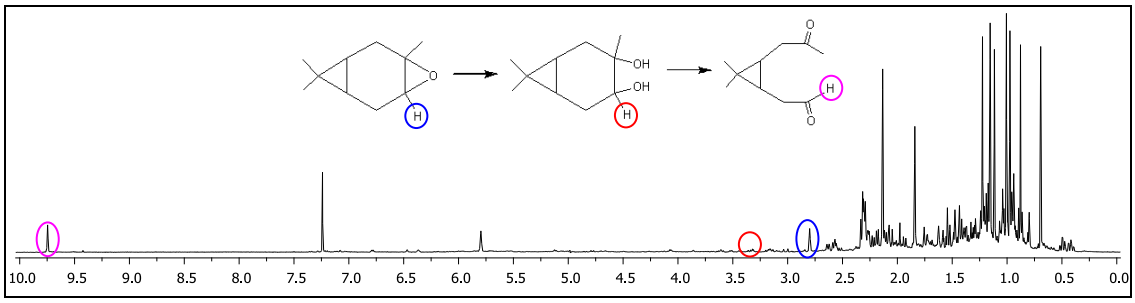
Entry B Partial (74 %) conversion of the epoxide to the corresponding diol, (signals at δ 2.6 ppm and 3.3 ppm).



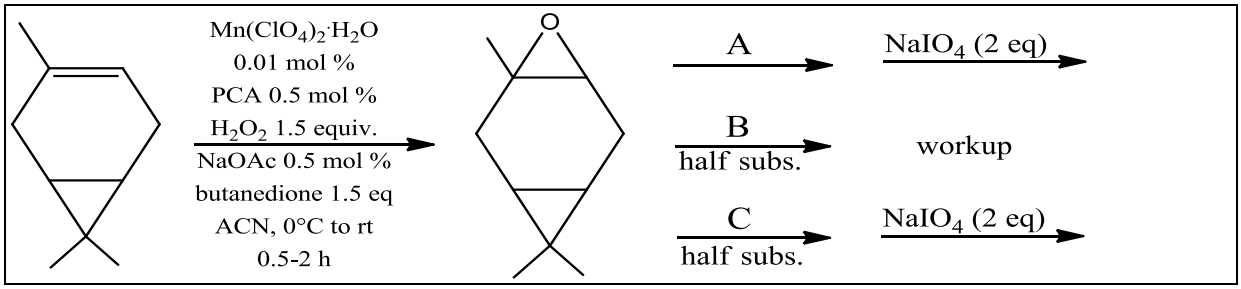
Entry C shows formation of aldehyde; the absence of diol and residual epoxide.



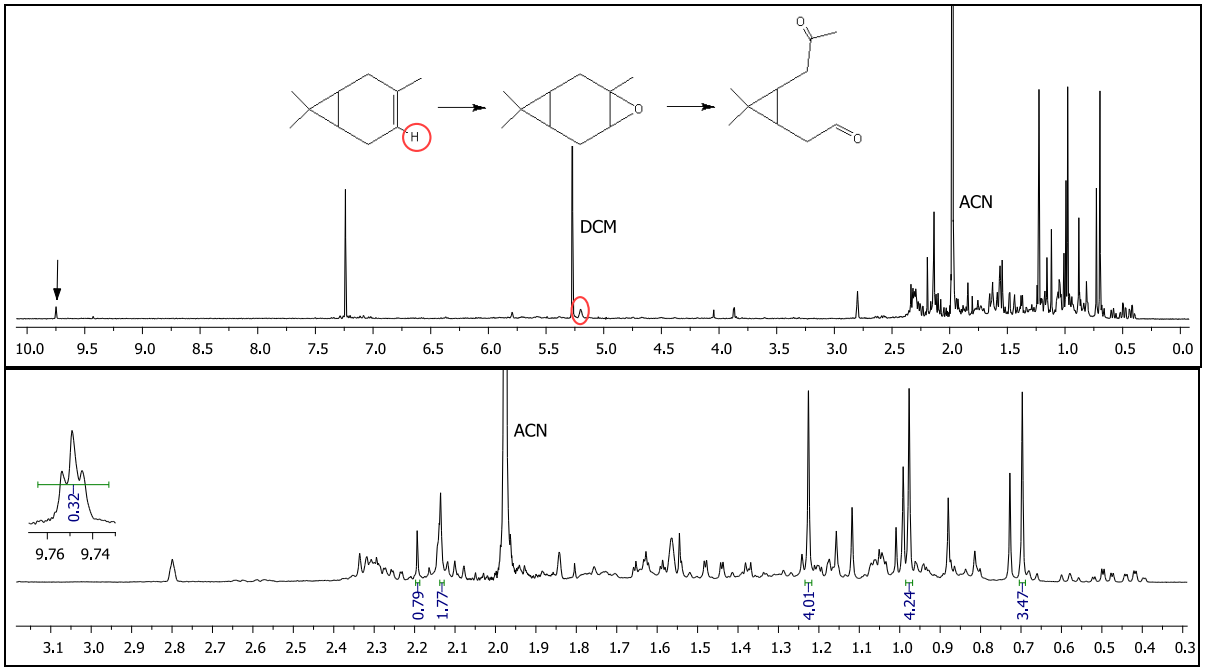
Entry D shows a similar result as for entry C.



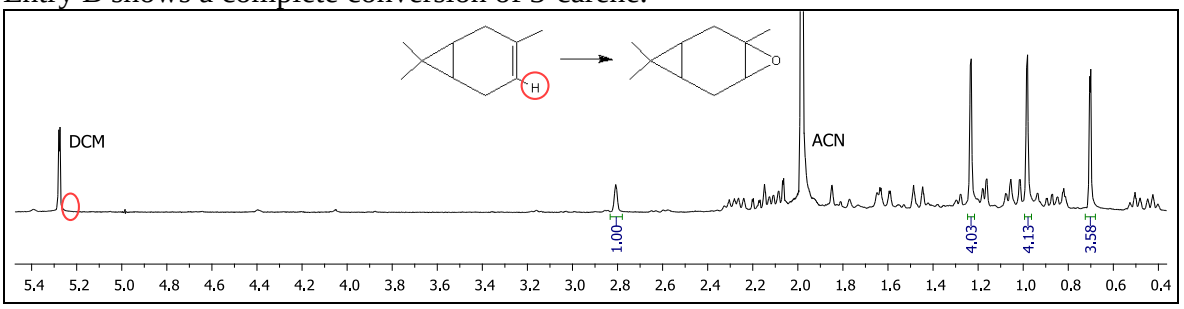
One pot 3-carene epoxidation/C-C bond cleavage in CH_3CN



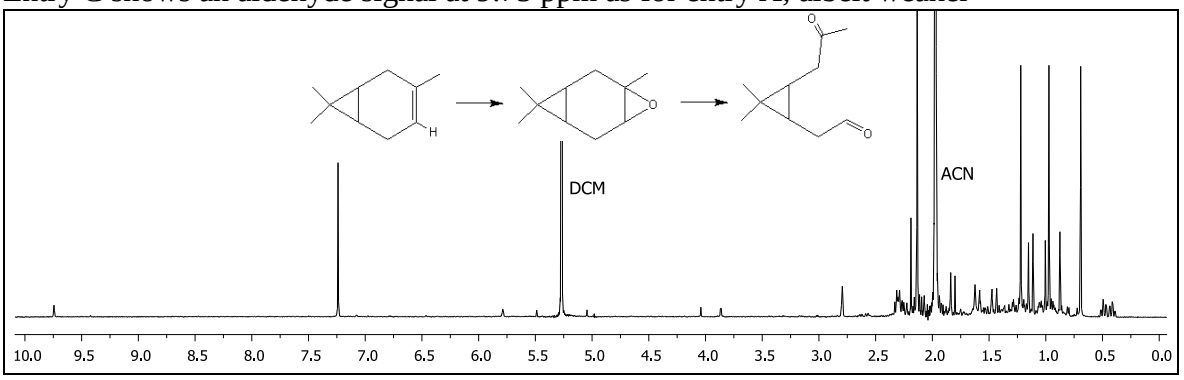
Reactions were carried out as described above, except: that in entry B and C with 0.5 mmol of 3-carene was added. For entries A and C, $NaIO_4$ (2 eq., respectively 42 mg and 21 mg) was added after epoxidation was complete to determine whether the epoxide underwent C-C bond cleavage directly. Raman spectra were recorded at each step. Work up was as described above. Entry A shows an aldehyde signal at 9.75 ppm, and signals at 2.13 δ and 2.19 δ, whose area ratio was 3:2.



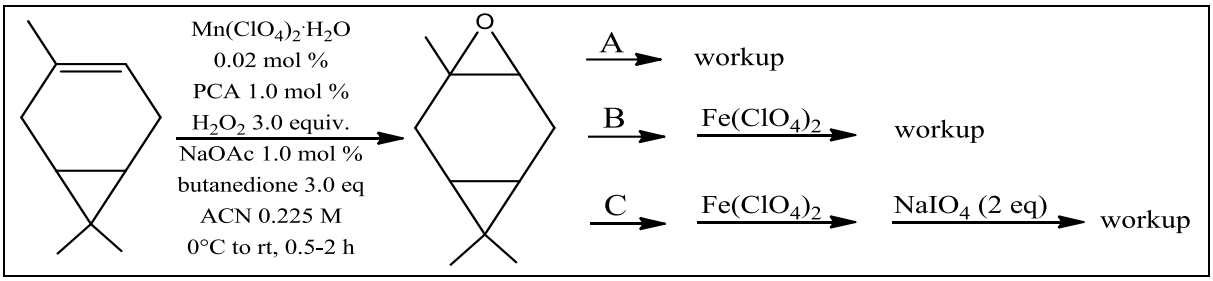
Entry B shows a complete conversion of 3-carene.



Entry C shows an aldehyde signal at 9.75 ppm as for entry A, albeit weaker

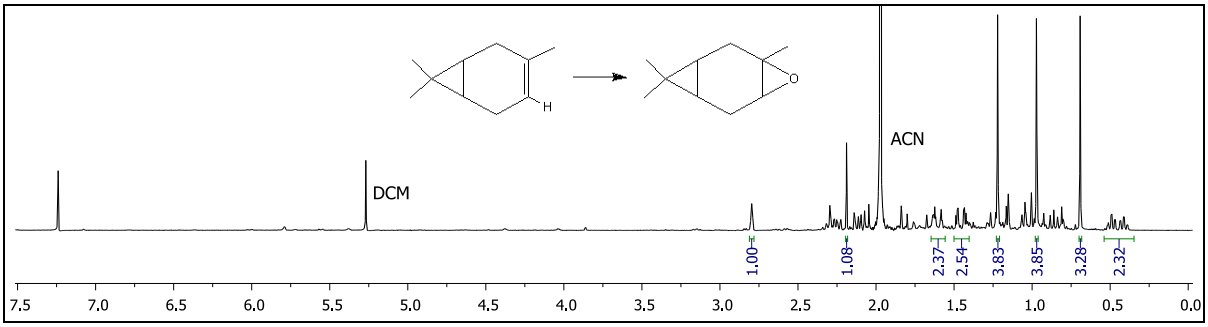


One pot 3-carene epoxidation/ring opening/ C-C bond cleavage in CH_3CN

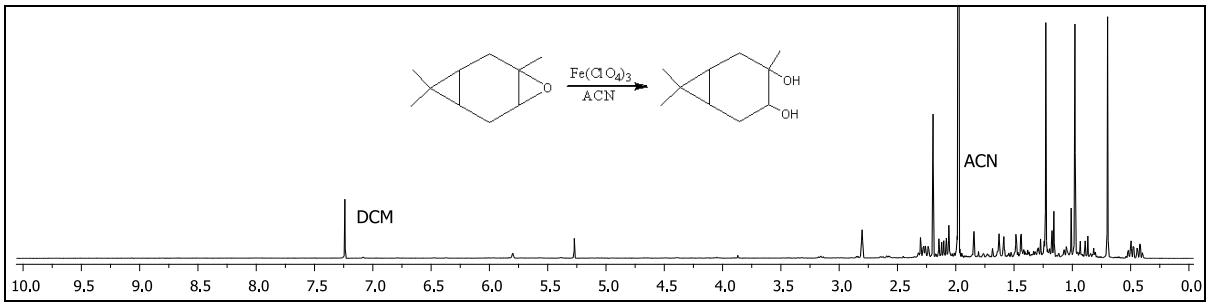


As for epoxidation/cleavage reactions except that in $Fe(ClO_4)_2$ (0.01 %, 3.54 mg) was added after epoxidation in the case of entries B and C.

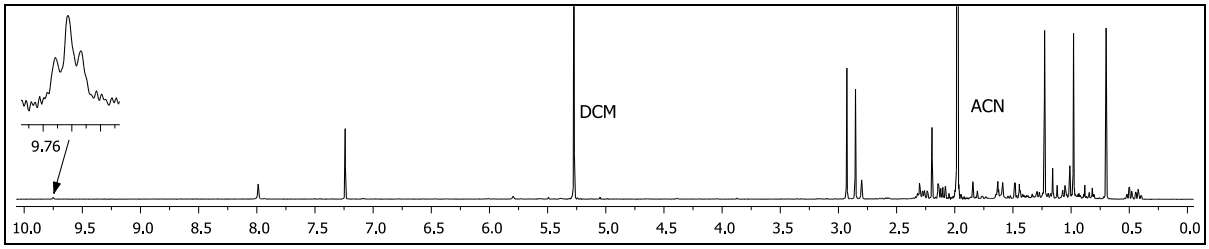
Entry A shows, as expected, full conversion to the epoxide.



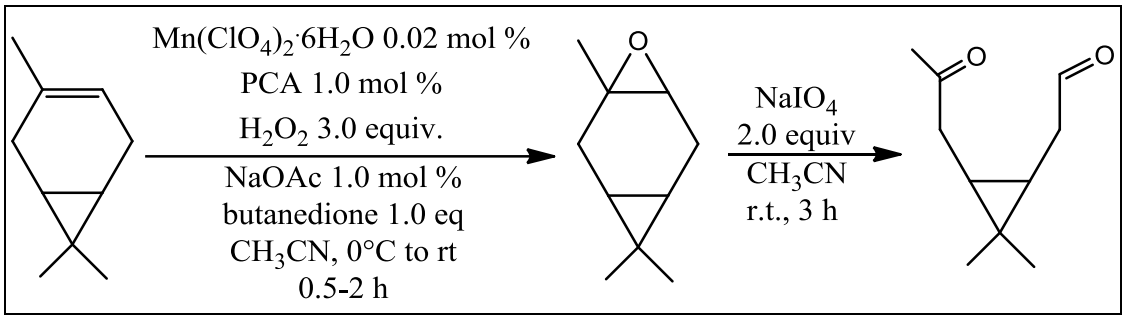
Entry B shows that epoxide ring opening did not occur in CH_3CN



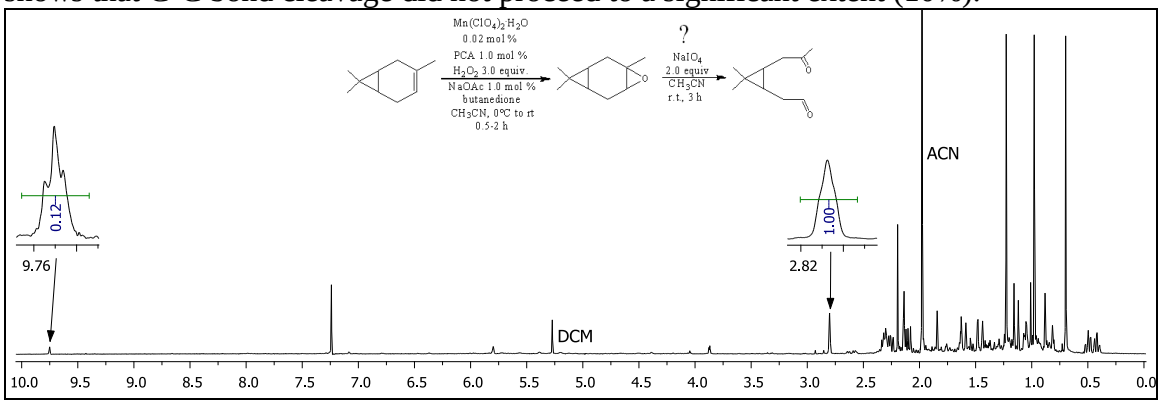
Entry C shows some aldehyde formation however epoxide ring opening/oxidation was not significant



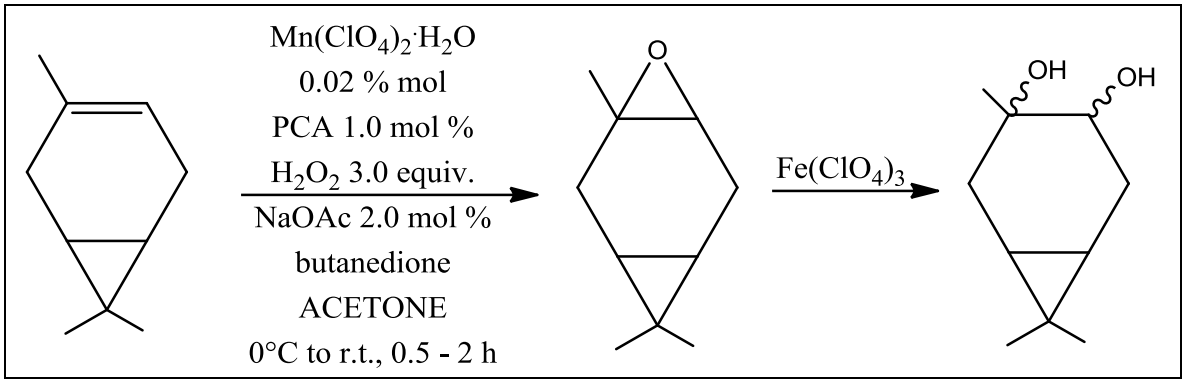
One pot 3-carene epoxidation/C-C bond cleavage in CH_3CN



Catalysis was carried out as described above. The ^{1}H-NMR spectrum of the final product shows that C-C bond cleavage did not proceed to a significant extent (10%).

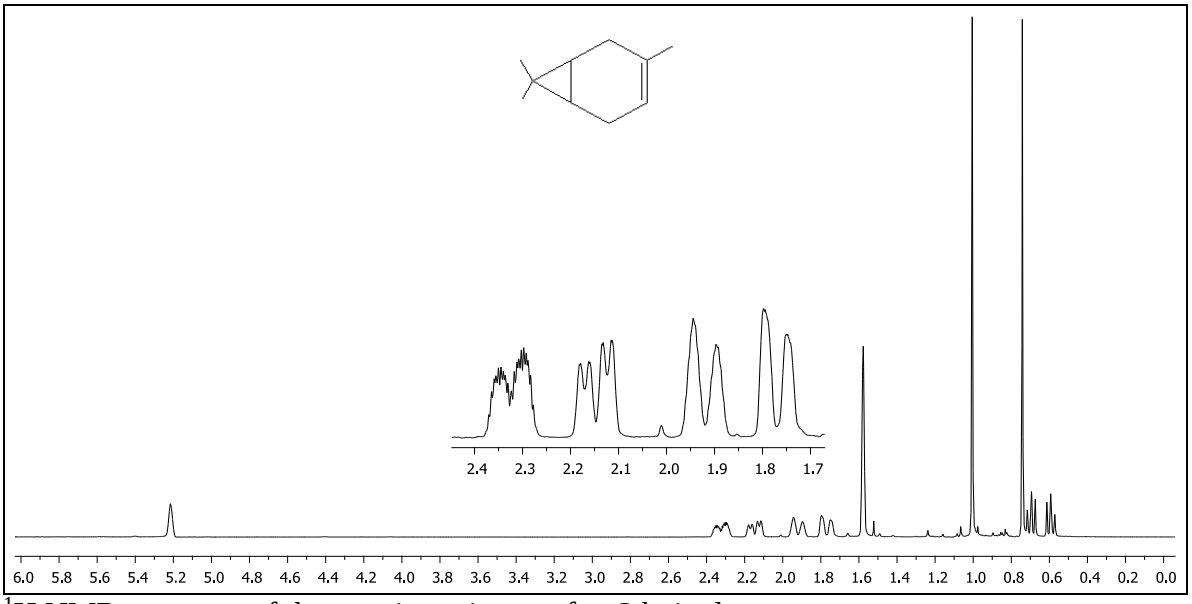


One pot 3-carene epoxidation/ring opening

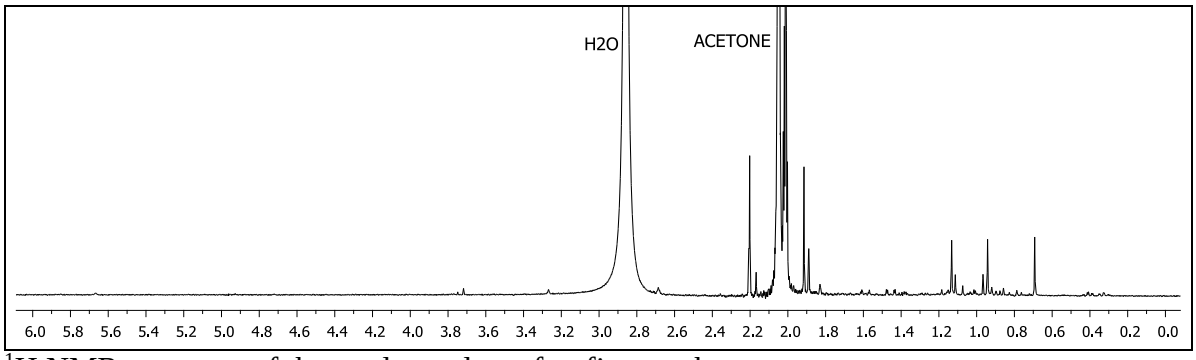


As described above. After 3 h, 3.54 mg $Fe(ClO_4)_3$ was added to the reaction mixture and after stirring overnight was worked up. 10 ml of H_2O and 10 ml of CH_2Cl_2 were added to the reaction mixture. The aqueous layer was extracted (2 x 5 ml) with dichloromethane and the combined organic phases dried over anhydrous $MgSO_4$ and filtered; solvent was evaporated in vacuo). Pentane (about 5 ml) was added and this inhomogeneous mixture which was sonicated for several minutes, followed by decantation to yield the carene-3-diol as the main product.

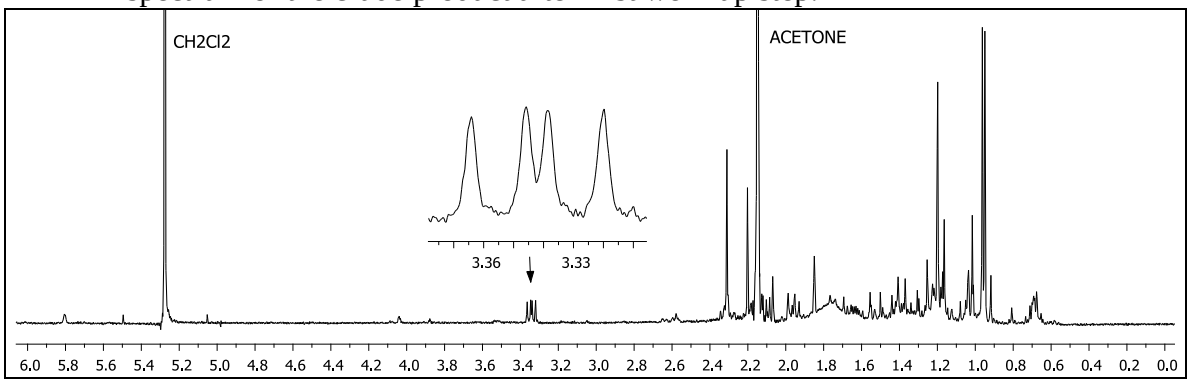
^{1}H NMR spectrum of **3-carene**:



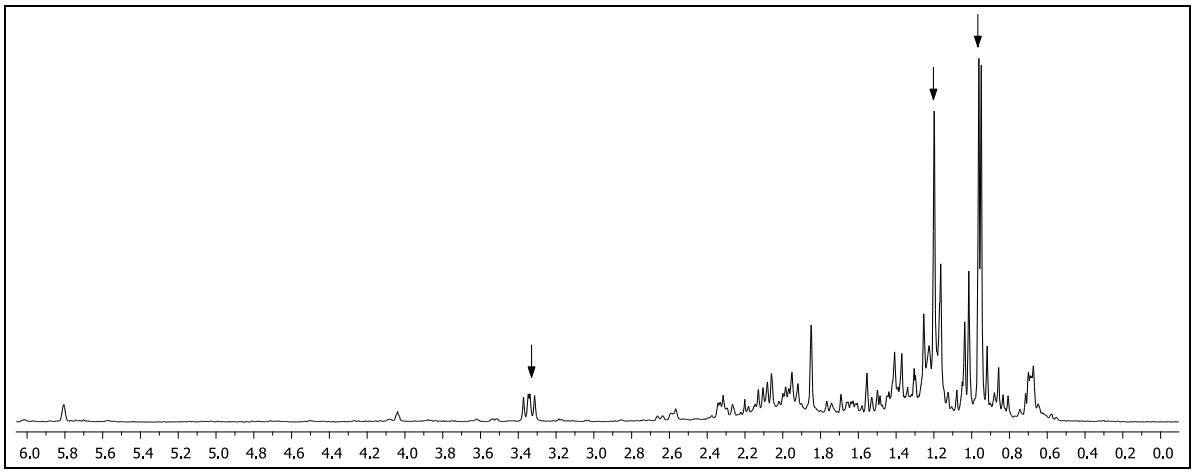
^{1}H NMR spectrum of the reaction mixture after 2 h, in d-acetone:



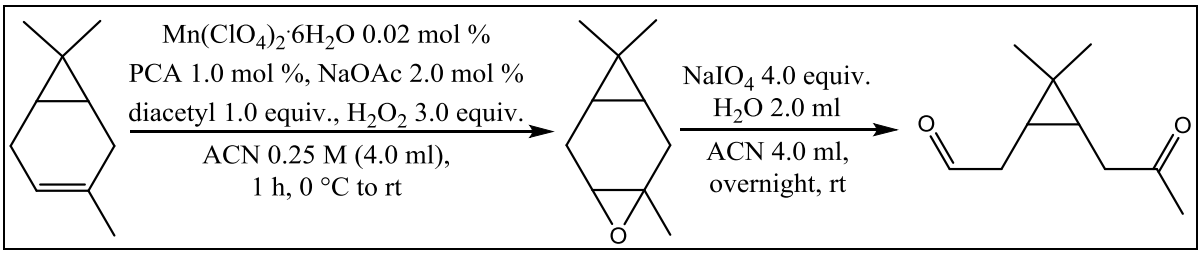
^{1}H NMR spectrum of the crude product after first work up step.



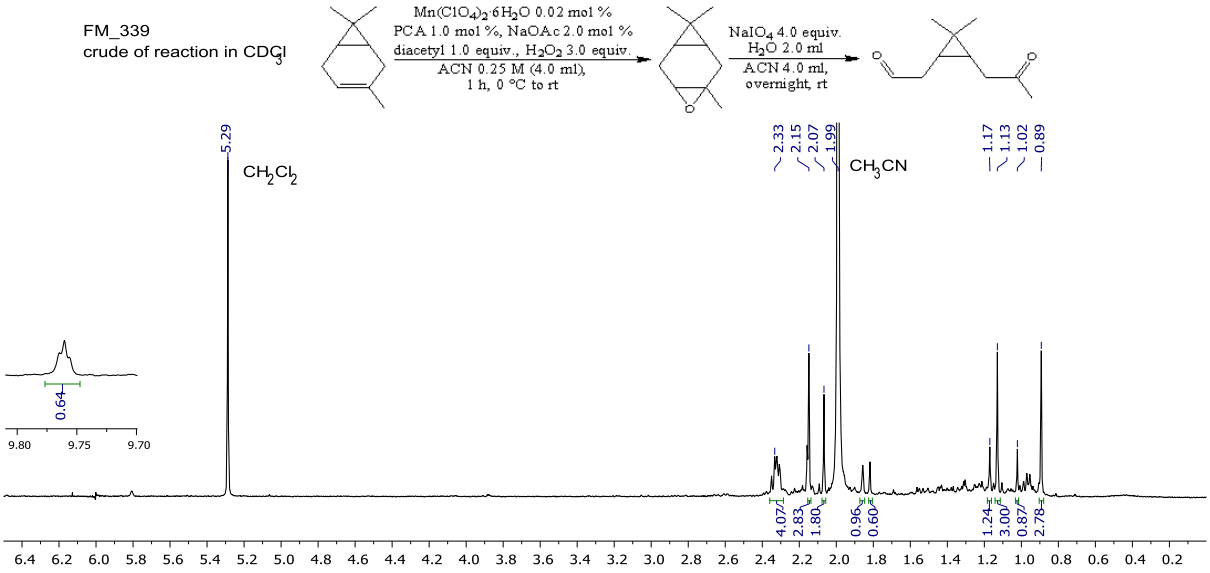
^{1}H NMR spectrum in $CDCl_3$ of the pale yellow liquid obtained from pentane:



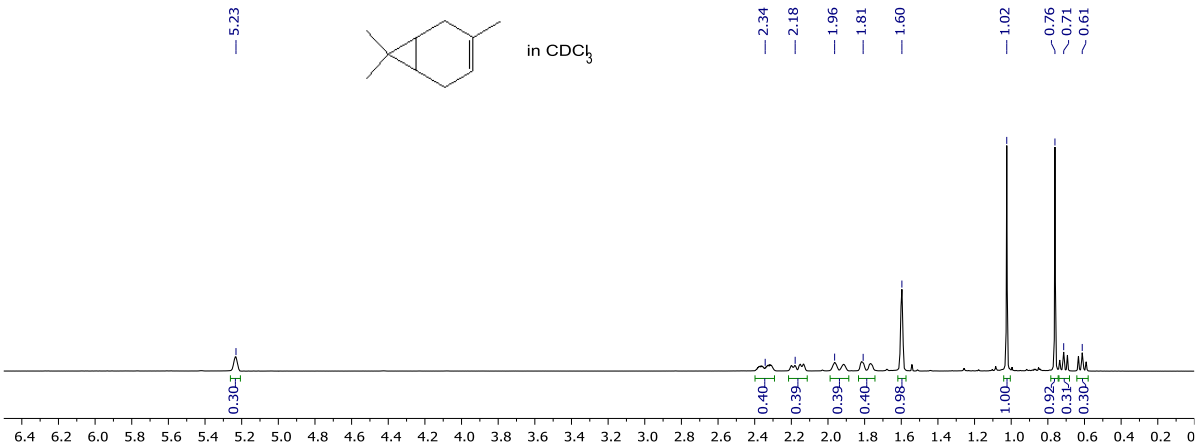
One pot two steps 3-carene epoxidation/C-C bond cleavage in ACN



As described above. After 1 h, 856 mg (4.0 mmol) $NaIO_4$ and 2.0 ml H_2O were added to the reaction mixture and after stirring overnight was worked up. 40 ml of H_2O and 40 ml of CH_2Cl_2 were added to the reaction mixture. The aqueous layer was dried over anhydrous $MgSO_4$ and filtered; solvent was evaporated in vacuo) to yield the carene-3-diol as the main product.

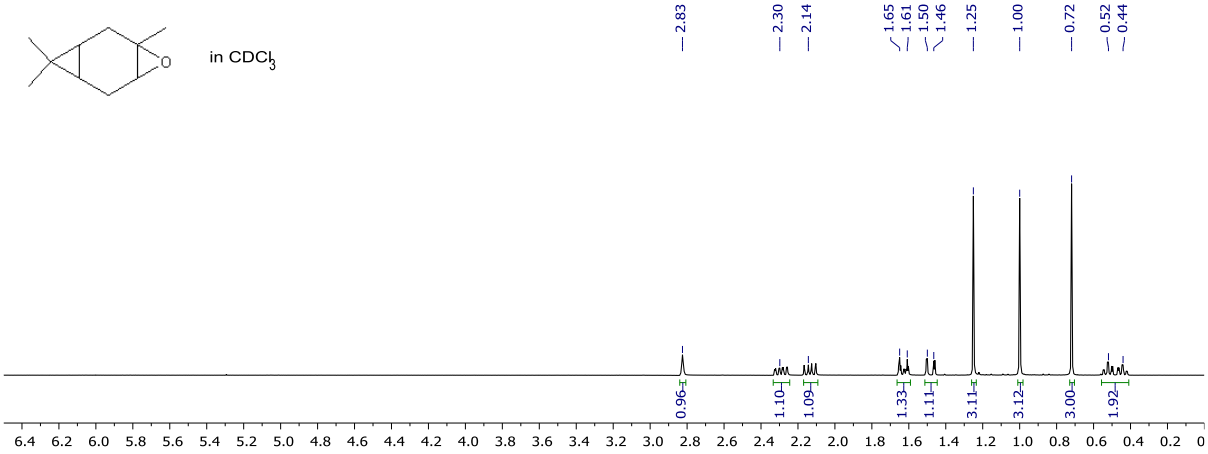


^1H NMR spectrum of the crude product after work up; 3-carene and 3-carene oxide are both not present, to testify the full conversion achieved in both steps.



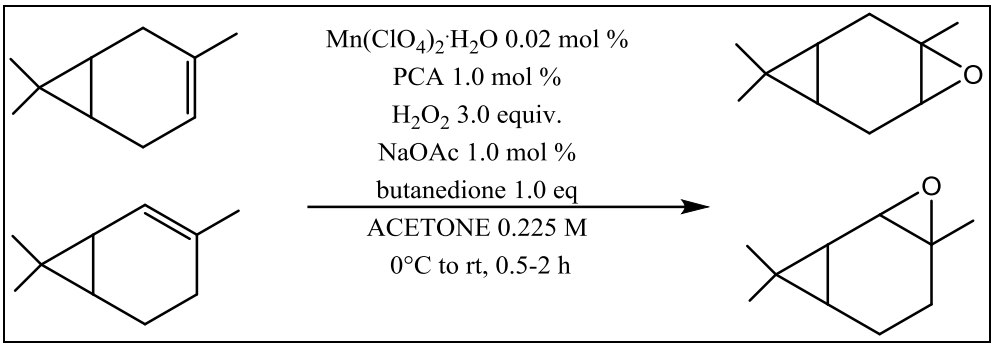
^{1}H NMR spectrum of the 3-carene for comparison.

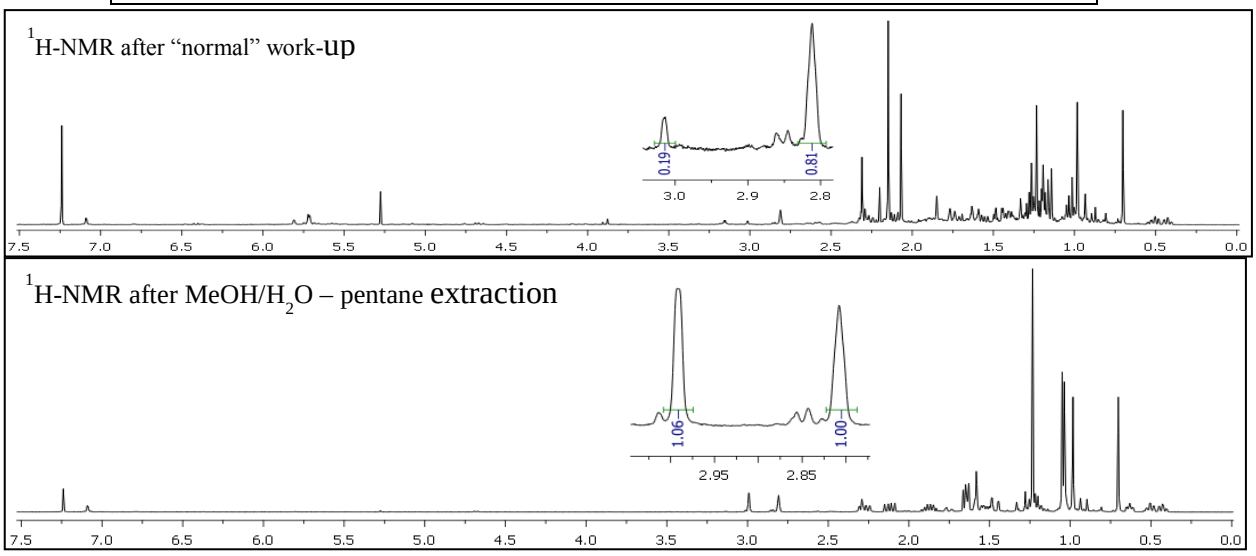
^{1}H NMR spectrum of the 3-carene oxide for comparison.



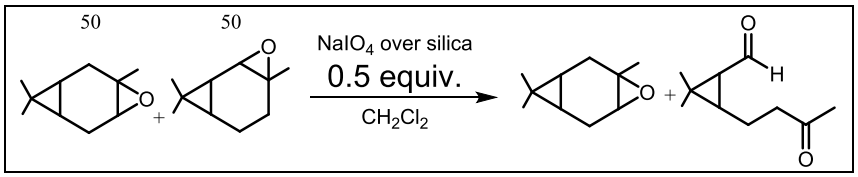
Isolation of product of oxidation of 2-/3-carene mixtures

Although oxidation of mixtures of 2-/3-carene proceeded in an identical manner to those of 3-carene alone, the instability of the 2-carene products required modification of the work up procedure in which MeOH with 10% water was used to wash the crude reaction mixture in place of water and brine..



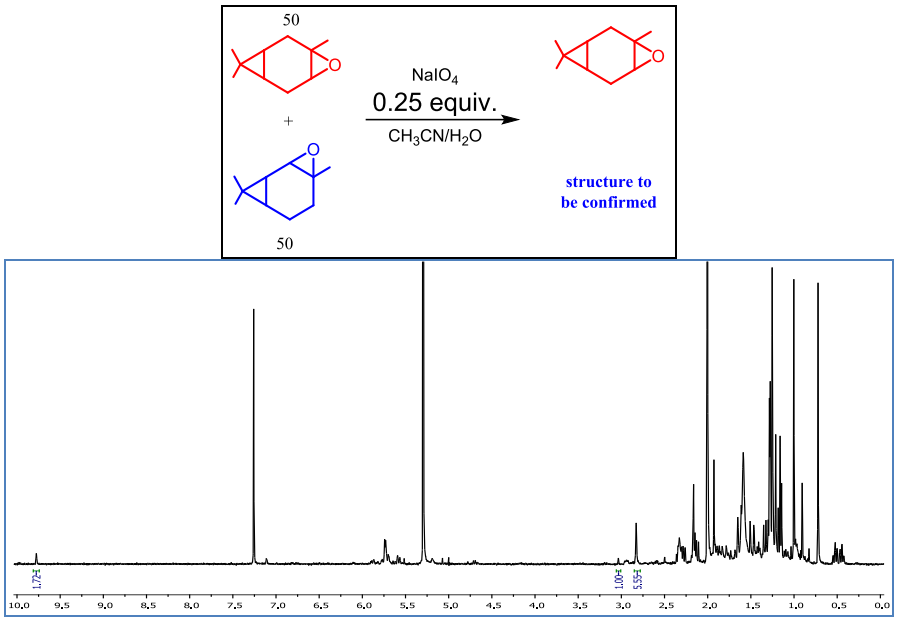


Selective ring opening of the 2-carene epoxide



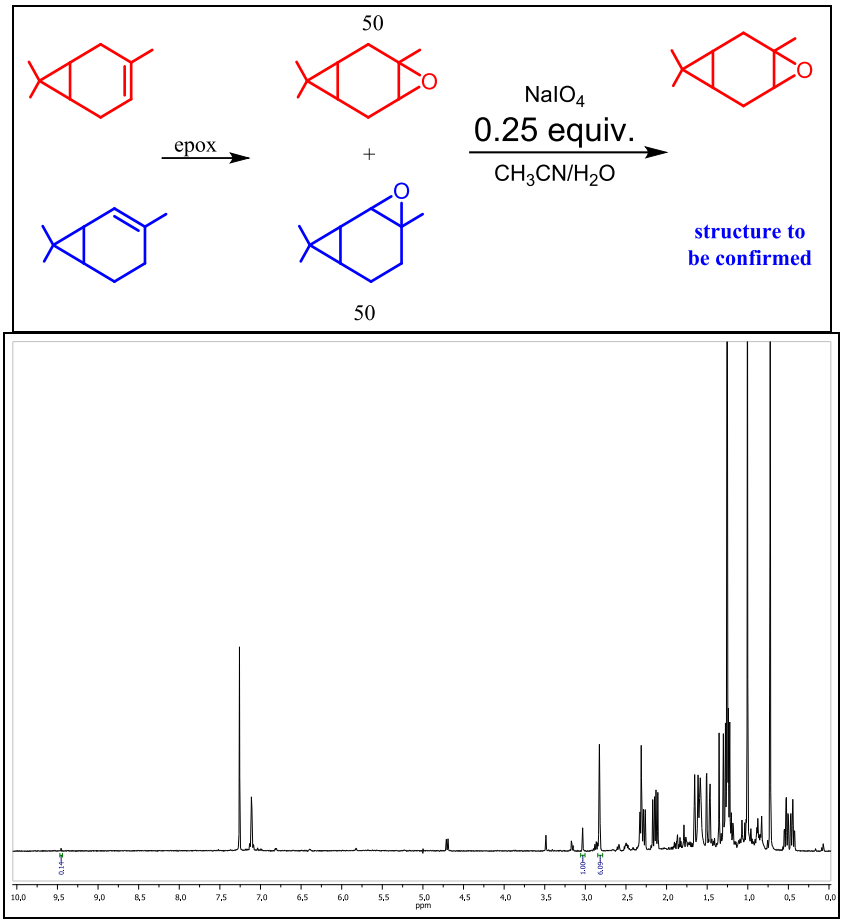
Sodium periodate was dissolved in a minimum of H_2O at 80°C and added to SiO_2 with vigorous manual shaking until all the water was absorbed. The epoxide mixture in dichloromethane was added and stirred overnight. Silica was removed by filtration and washed with chloroform. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. ^1H NMR spectral analysis indicated a preference for oxidation of 2-carene over 3-carene. For practical reasons the same procedure which employs periodate and acetonitrile/water as solvent was use.

Selective ring opening and oxidation of 2-carene epoxide



The 1:1 mixture of 2- and 3-carene epoxide (52 mg, 0.33mmol) were added to 0.33 ml CH_3CN, 0.33 ml H_2O_2 and $NaIO_4$ (35.5 mg, 0,166 mmol). The reaction mixture was stirred for 2 days after which 10 ml of H_2O and 10 ml of CH_2Cl_2 were added, the aqueous layer extracted (2 x 5 ml) with dichloromethane and the organic layers combined and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo.

One pot epoxidation/ring opening of 2-/3-carene mixtures

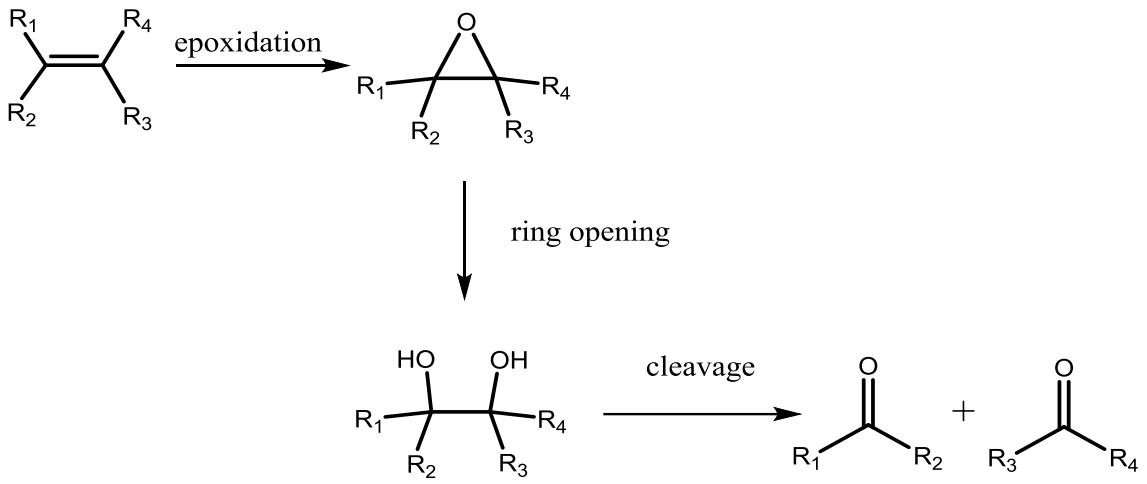


The epoxidation was carried out as described above to full conversion. After epoxidation, $NaIO_4$ (53.5 mg, 0.25 equiv.) and H_2O (4 ml) were added and reaction stirred overnight. 100 ml H_2O and 100 ml CH_2Cl_2 are then added, the aqueous layer was extracted (2 x 5 ml) with dichloromethane and the organic layers combined, dried with anhydrous $MgSO_4$ and the solvent removed in vacuo. The 2-carene epoxide was almost completely converted.

Chapter 3

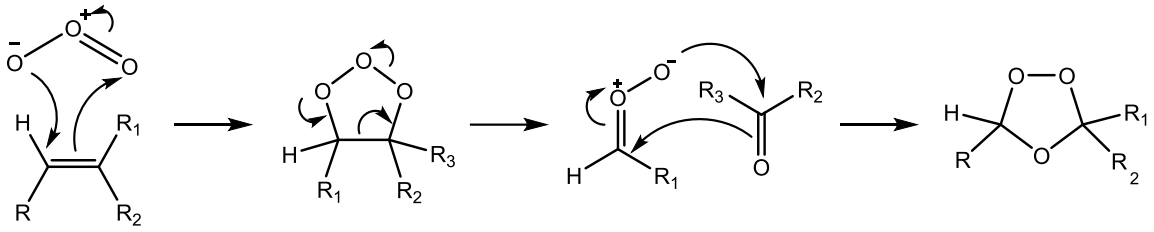
Oxidative cleavage of alkene C=C bonds: an alternative to ozonolysis

Abstract. A novel, multi-step, one-pot method for the cleavage of C=C double bond of alkenes, that is an alternative to ozonolysis, is reported in this chapter. The first step is the epoxidation/*cis*-dihydroxylation of alkenes using a method developed previously in our group, which determines the selectivity of the overall process. This step is followed by an Fe(III) assisted ring opening of the epoxide (where necessary) to a 1,2-diol. The cleavage of the diol with sodium periodate allows actual carbon-carbon bond cleavage, which is the final step, to be done with little sensitivity to unreactive alkenes and other functional groups; the mild conditions (r.t.) used in all three steps make this a viable general alternative to ozonolysis.



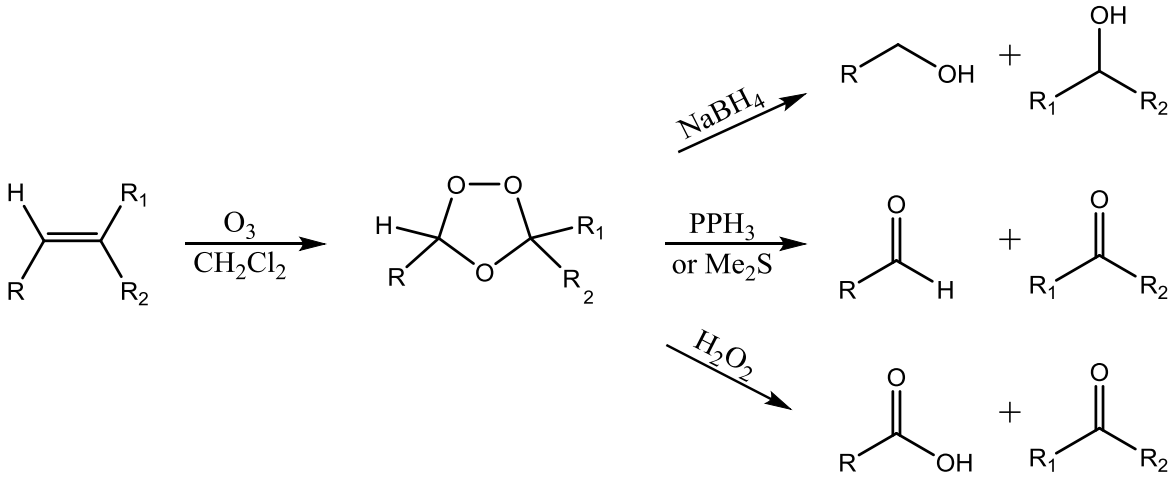
3.1 Introduction

The cleavage of C=C bonds to yield (di)carbonyl compounds (ketones and aldehydes) is a key reaction in synthetic organic chemistry and especially in medicinal chemistry.[1] Ozonolysis is seen perhaps as the method of first resort, to introduce oxygen functionalities through alkene cleavage. Indeed ozonolysis is highly versatile in synthesis as it can provide access to products with varying degrees of oxidation depending on the workup that follows the formation of the trioxolane intermediate, as was confirmed by Criege[2] first and Berger[3] later on.



Scheme 1: Crieege's proposed mechanism for the formation of the stable trioxolane intermediate, passing through the 1-3 dipolar cycloaddition (step 1) to give the molozonide and its rearrangement.[1]

For instance carbonyl (ketones and aldehydes) products are obtained after treatment with reducing agent such as zinc/acetic acid, (bi)sulfite, iodide and dimethyl sulfide, whereas alcohols are obtained after workup with lithium aluminum hydride or sodium borohydride.[4] Dimethyl sulfide is generally preferred when the carbonyl products are desired as it can be removed through evaporation[5] and the reaction is the least exothermic, albeit that it still requires careful control.

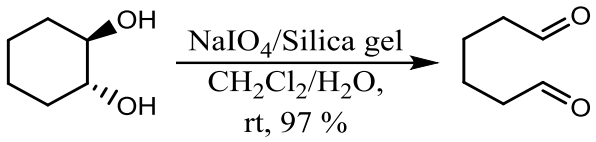


Scheme 2. Ozonolysis products depending on the work-up performed.[4]

Ozonolysis of alkenes is often impractical, however, as it requires potentially hazardous *in situ* generation of O_3 (and a generator) and presents safety issues since low molecular weight ozonides and peroxides are often formed as reactive intermediates, especially where concentration is performed prior to workup. The scaling up of these reactions is therefore difficult to realize and needs careful assessment of the energetics of the reaction. A further issue is that these reactions often require low temperatures, typically from – 78 to 0 °C [6,7,8,9]

and functional group tolerance is low, e.g., ozone reacts with alkynes to yield carboxylic acids. Continuous flow approaches have led to the mitigation of some of these issues and has seen continued interest in recent years.[10]

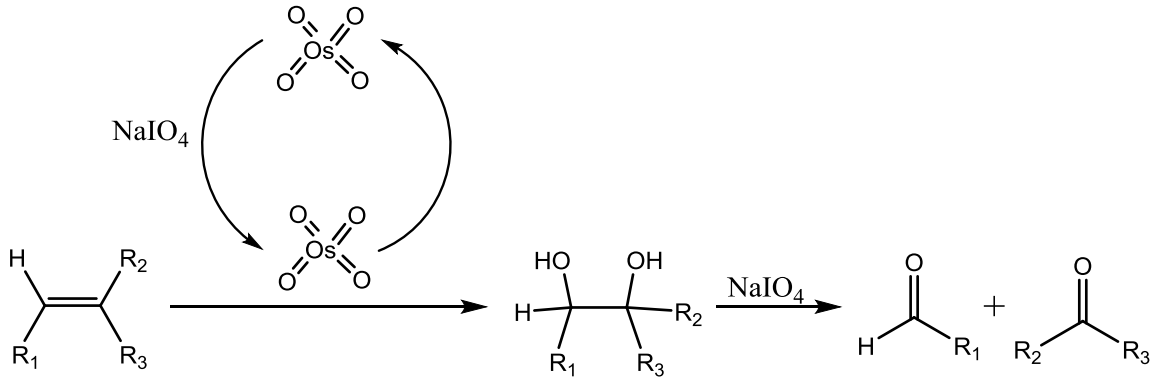
The oxidative cleavage of an alkene is, nevertheless, a multistep reaction and indeed an alternative, stepwise approach to the overall oxidation of alkenes to carbonyl compounds can provide for better selectivity, as it allows for greater control over each step. Several methods are available to provide diols, which can be oxidized readily with sodium periodate, periodic acid and lead tetraacetate to yield the scission products; $NaIO_4$ is the reagent of choice for the scission of the C-C bonds of vicinal diols, which is usually performed with a 1:1 stoichiometry, with high selectivities and typically full conversion.[11,12] These oxidants are in fact preferred over direct treatment with ozone, dichromate [13] or permanganate in the cleavage of the C-C bonds of diols.[14,15,16]



Scheme 3. Diol C-C bond cleavage reported by Sudalai et al.[12]

The search for approaches to C=C bond cleavage that provide better atom economy and selectivity has led to the development of one pot methods[17] that use $RuCl_3 \cdot H_2O$ or OsO_4 for vicinal dihydroxylation in combination with oxidants such as Oxone, NaOCl and $NaIO_4$, exploiting the ability of the periodate ion, in particular, to cleave diols.[18,19,20]

In 1956, Lemieux and Johnson reported a method for C=C bond cleavage of an olefin with OsO_4 as catalyst to form the diol intermediate and $NaIO_4$ as terminal oxidant to cleave the diol formed (and regenerate the osmium tetroxide); [18,21,22,23,24,25] despite the cost and toxicity of osmium tetroxide, the subsequent literature testifies to the interest this approach has received.

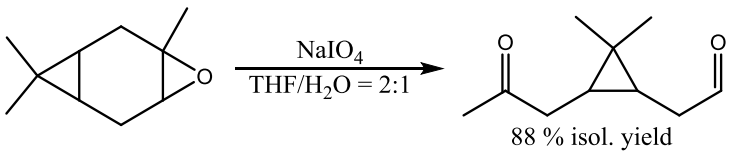


Scheme 4. The Lemieux-Johnson reaction.[21]

The method reported by Noyori et al.[26,27] for the epoxidation of alkenes with OsO_4 and $NaIO_4$ has also been adapted to C=C bond cleavage. $RuCl_3$ has been used in combination

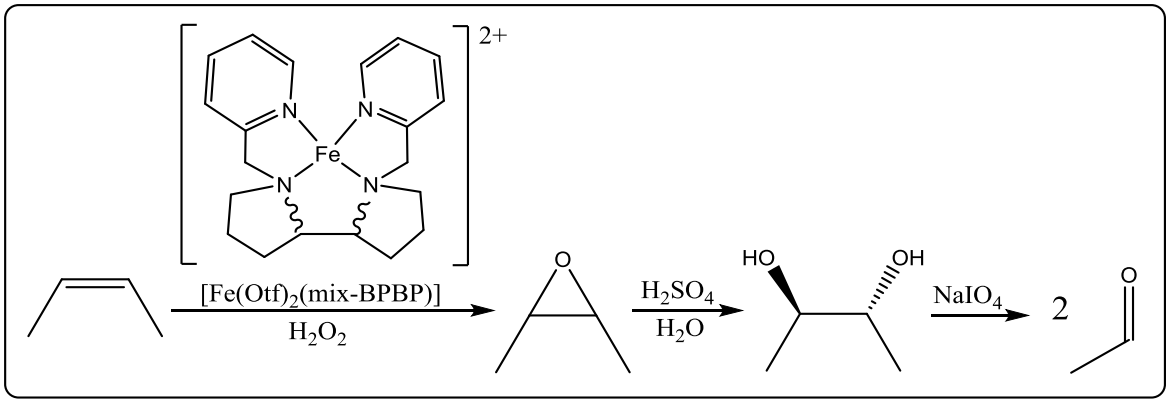
with $NaIO_4$ or Oxone, using various solvent combinations, to give the same transformations.[28,29]

In efforts to reduce the reliance on second and third row transition metal based catalysts, Binder et al.[30] demonstrated the possibility to cleave epoxides directly to carbonyl compounds with aqueous $NaIO_4$ at room temperature in a 2:1 mixture of CH_3CN (or THF) and H_2O; subsequently Ochiai [31] and Lai [32] demonstrated the presence of epoxide intermediates in the multi-step one-pot cleavage of alkenes with Iodosyl benzene and manganese porphyrin catalyst.



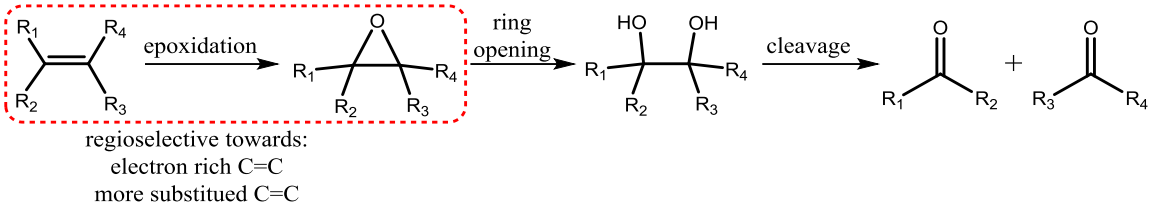
Scheme 5. Epoxide C-C bond cleavage on the 3-carene oxide as reported by Binder et al.[30]

The drive for sustainable chemical syntheses has focused efforts towards catalytic methods employing preferably first row transition metal based complexes and highly efficient terminal oxidants, e.g., H_2O_2. Klein Gebbink et al.[33] recently reported a one-pot three step epoxidation-dihydroxylation-cleavage, which is equivalent to the process achieved with ozone. While the first step is achieved through an iron based catalyst and H_2O_2 as terminal oxidant, the second ring opening step is achieved with sulfuric acid; finally, the diol is cleaved with stoichiometric $NaIO_4$ to give the corresponding (di)carbonyl compounds in good to excellent yields (43 % to 99 %) and selectivities (scheme 1).



Scheme 6. 3-step epoxidation-ring opening-cleavage strategy developed by Klein Gebbink et al.[33]

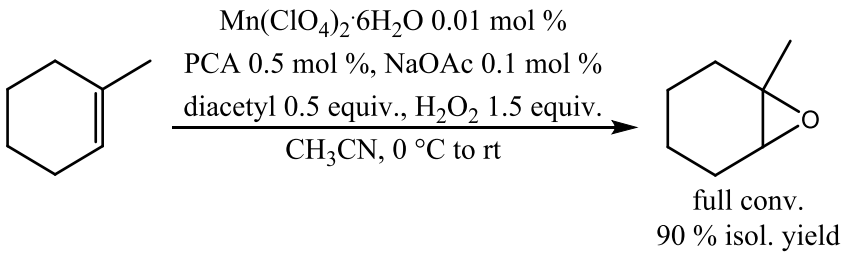
A limitation of this approach is that electron poor alkenes show poor yields and acid sensitive compounds may not be stable to the sulfuric acid mediated ring opening conditions. Nevertheless, the introduction of the epoxidation step opens up opportunities in regard to the regio- and chemo-selectivity of the system, as the catalyzed epoxidation allows for discrimination between distinct C=C double bonds (scheme 2).



Scheme 7. Role of the epoxidation in the determination of overall regioselectivity.

The stepwise approach faces three main challenges; 1) generating the epoxide, 2) selective ring open to the diol and 3) selective oxidation of the diol. Furthermore, compatibility between the reagents and products formed in each step is essential to achieve the reaction in a "one-pot" fashion. Importantly, in the stepwise approach the selectivity towards the C=C bonds to be oxidized is governed by the epoxidation step, and hence a multistep oxidation protocol allows regioselectivity between several alkene motifs to be achieved. A further point with regard to selectivity lies at the ring opening step, which has been largely neglected to date.

A one-pot multi-step oxidative cleavage of alkenes can therefore be a safer, cheaper and more practical approach than ozonolysis with the challenge of achieving compatibility between steps and selectivity. Over the last decade, our group has developed a flexible oxidation system based on a Mn(II) salt, a simple ligand (2-picolinic acid PCA), (sub)stoichiometric butanedione as a co-catalyst and H_2O_2 as terminal oxidant.[34] This system is able to transform electron rich and electron poor alkenes to the corresponding epoxides and diols, respectively, in high yields and selectivities and with high turnover frequencies (up to 40 s^{-1}) and numbers (up to 300 000).

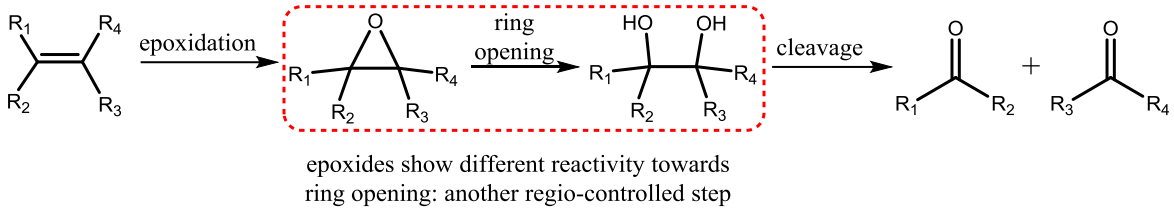


Scheme 8. Oxidation of methylcyclohexene reported by Saisaha et al.[41]

In this chapter, we report a general practical method based on this catalytic system together with periodate based diol cleavage to introduce carbonyl moieties, or to yield doubly oxygen functionalization starting from cyclic alkenes.

A two/three step one-pot C=C bond cleavage reaction is carried out by an *in situ* Mn/PCA catalyzed epoxidation/*cis*-dihydroxylation with H_2O_2 as terminal oxidant for the cis-dihydroxylation/epoxidation; the diol obtained with electron poor alkenes and by the $Fe(ClO_4)_3$ mediated hydrolysis of the epoxides are thus cleaved with stoichiometric $NaIO_4$, yielding the corresponding (di)carbonyl compounds in high yields and selectivity. Moreover, the regio- and chemo-selectivity of the double bonds is explored through the oxidation of compounds bearing multiple C=C bonds.

Importantly, we are able to control the regioselectivity through the ring opening step also, as different epoxides show markedly different reactivity towards the conditions used for ring opening with iron(III) perchlorate or direct oxidation with $NaIO_4$.

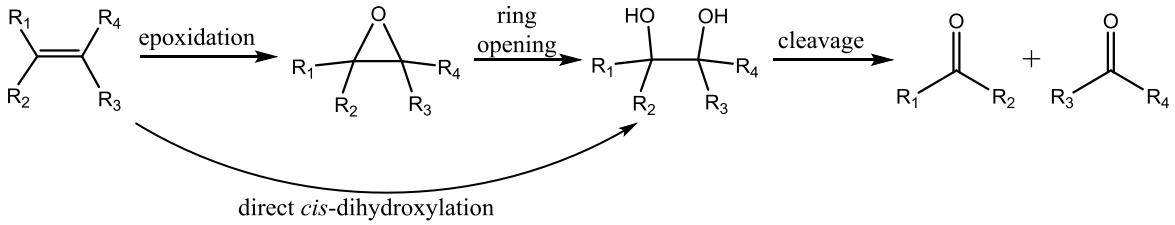


Scheme 9. Alternative approach to control the regioselectivity of C-C bond cleavage through epoxide ring opening.

In the case of electron poor alkenes, diols are obtained directly upon oxidation with the Mn(II)/PCA system and we show that they can be cleaved upon addition of water and $NaIO_4$, and using acetonitrile as solvent. Achieving the necessary compatibility of the steps has a consequence for the choice of acetonitrile as solvent for the epoxidation, as iron(III) perchlorate catalyzed ring opening does not take place in this solvent, presumably due to the formation of $[Fe(CH_3CN)_6]^{2+}$; hard acids can be used, as shown earlier by Klein Gebbink et al.,[33] but this presents a limitation in terms of substrate scope and selectivity, as substrates that are hard acid sensitive may not survive the reaction conditions. Indeed, earlier we demonstrated[34] that even the use of silica to ring open α-pinene oxide *in situ* yielded campholenic acid upon gentle heating. In the present study, the use a silica/$NaIO_4$ mixture for an *in situ* ring opening/cleavage of the 3-carene oxide proceeded in the same manner as $NaIO_4$ mediated C-C bond cleavage of the corresponding diol reported earlier.[33] This compound however was stable despite that α-pinene underwent rearrangement under these conditions. Ring opening with hard acids such as H_2SO_4 or etherate BF_3 was considered but discarded, as milder reaction conditions and thus broader functional group tolerance was desired. Furthermore, the later reagent limits the use of a one-pot strategy as further oxidation with $NaIO_4$ requires addition of water which would not be compatible with diethyl ether.

The flexibility of the Mn(II)/PCA system in terms of solvent, however, opens up opportunities to achieve the ring opening step in acetone, under sufficiently mild conditions to circumvent the sensitivity limitations of hard acid conditions.

In chapter 4, we will show the feasibility of a one pot epoxidation-ring opening of the alkenes, using $Fe(ClO_4)_3$ after the epoxidation step, with acetone as solvent. This approach however raises safety issues with regard to the use of acetone and H_2O_2, however, these can be eliminated in large scale reactions (over 50 g), using flow chemistry, which we show allows us to take advantage of the ring opening of epoxides with an Fe(III) catalyst in a one-pot procedure.

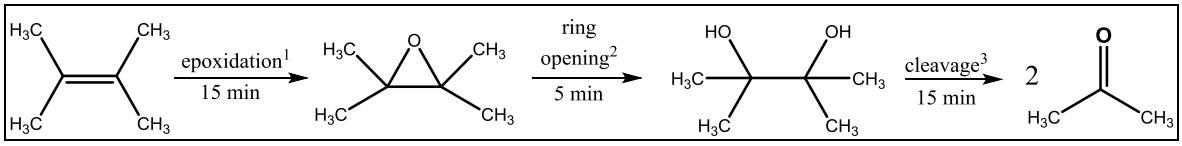


Scheme 10. One-pot multi-step bond cleavage methodology applied in the present study.

3.2 Results and discussion

The one-pot 3 steps procedure used is based on the conditions reported earlier for alkene oxidation.[34] Three classes of alkenes are examined (linear, cyclic and benzylic). Ring opening was achieved by addition of $Fe(ClO_4)_3$ and water after the oxidation of the alkene in acetone was complete, as determined by in line Raman and off line ^1H NMR spectroscopic analysis.

The efficiency of the methodology was confirmed through the epoxidation of 2,3-dimethyl-2-butene in $(CD_3)_2CO$ (scheme 11), followed by immediate ring opening to the corresponding diol with $Fe(ClO_4)_3$ and subsequent cleavage to acetone with 1.0 equiv. of $NaIO_4$ with full conversion and excellent selectivity for the expected product (acetone), verified by comparison with a solution of acetone in $(CD_3)_2CO$. The epoxidation, ring opening and subsequent periodate oxidation is achieved in an overall reaction time of 1 h.

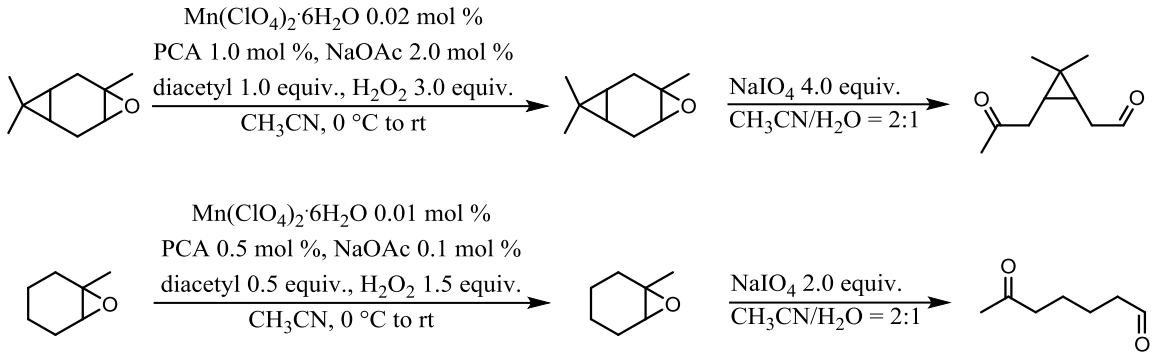


Scheme 11. One-pot three step methodology used in the oxidation of the tetramethyl ethylene.

1) $Mn(ClO_4)_2.6H_2O$ 0.01 mol %, PCA 0.5 mol %, NaOAc 1.0 mol %, butanedione 0.5 equiv., H_2O_2 1.5 equiv., acetone, 0.5 M substrate, r.t., 15 min; 2) $Fe(ClO_4)_3$ 0.1 mol %, acetone/H_2O (2:1, v/v), r.t., 5 min; 3) $NaIO_4$ 1 equiv., acetone/H_2O (2:1, v/v), r.t., 5 min.

As discussed above, C-C bond cleavage can be achieved directly with epoxides using $NaIO_4$:[31] in principle by-passing the ring opening step by addition of water and $NaIO_4$ to the epoxide containing reaction mixture. With cyclic alkenes, *e.g.*, 3-carene, methylcyclohexene and α-pinene, epoxidation under standard conditions (or with half the standard amount of starting material) gave full conversion. Addition of water (½ by volume w.r.t. the reaction mixture) and $NaIO_4$ to the reaction mixture was carried out in an attempt to perform the C-C bond cleavage directly with the epoxide (omission of water resulted in no conversion of the 3-carene oxide). Epoxidation of α- and β-pinene gave several byproducts besides the desired products, as reported earlier by Binder[30] and in our previos work,[34] while 3-carene and methylcyclohexene gave only the desired scission product. Notably, 4.0 and 2.0 equivalents of $NaIO_4$ and longer reaction times (ca. 4 h) were required when the crude of reactions containing epoxide were diluted with water (by 50 v/v %), which resulted in full conversion of the epoxide (with 2.0 equiv. of $NAIO_4$ 57 % conversion 3-carene to its epoxide was observed). Furthermore, the latter reaction mixture turned into

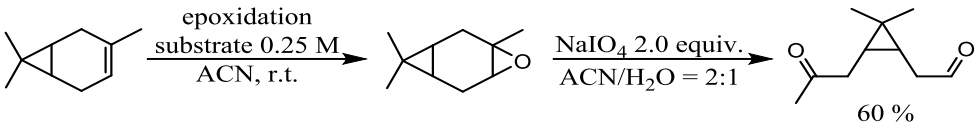
an inhomogeneous suspension when $NaIO_4$ was added, precluding in line reaction monitoring. In the case of the 3-carene, the cyclopropyl ring was unaffected during both the epoxidation and the subsequent ring opening reactions (scheme 12).



Scheme 12. One-pot two-step oxidation of 3-carene and methyl cyclohexene oxides to the corresponding scission products.

When a 1:1 mixture of acetonitrile and water was used, 3-carene epoxide was converted cleanly to the desired cleavage product with only 1.0 or 2.0 equivalents of $NaIO_4$, with 75% and full conversion reached, respectively, possibly due to the increased solubility of $NaIO_4$.

Addition of 2 equiv. $NaIO_4$ and 50 % water (w.r.t. the initial volume) to a reaction mixture containing the 3-carene epoxide, 60 % of the epoxide was converted to the desired product, indicating that the acetic acid formed from butanedione during the epoxidation step is highly advantageous in regard to the subsequent periodate oxidation (scheme 13).



Scheme 13. One-pot two-step epoxidation and C-C bond cleavage of 3-carene.

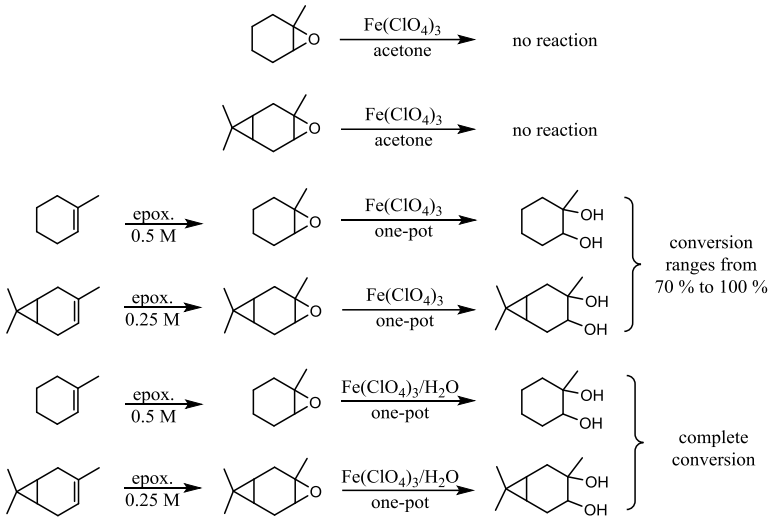
In the examples described thus far, the epoxidation step takes place under mildly acid (acetic acid) conditions, and the addition of periodate and water does not result in rapid nucleophilic attack on the epoxide (i.e. ring opening).

3.2.1 Ring opening with $Fe(ClO_4)_3$

Iron(III) salts were considered as a possible alternative to hard acids to achieve epoxide ring opening, as they have been shown earlier to catalyze the ring opening of epoxides in the presence of various nucleophiles under solvolytic conditions;[35,36,37,38] in particular $Fe(ClO_4)_3$ has been used in catalyzing epoxide ring opening in alcohols.[39,40] As the last step of the cleavage reaction uses periodate in water, addition of aqueous $Fe(ClO_4)_3$ to perform ring opening, and subsequent addition of $NaIO_4$ was considered as a possibly mild methodology.

Addition of aqueous $Fe(ClO_4)_3$ to 3-carene and methylcyclohexene epoxides in acetone, however, resulted in only a limited extent of ring opening (scheme 14). By contrast, addition of aqueous $Fe(ClO_4)_3$ to reaction mixtures containing the 3-carene and

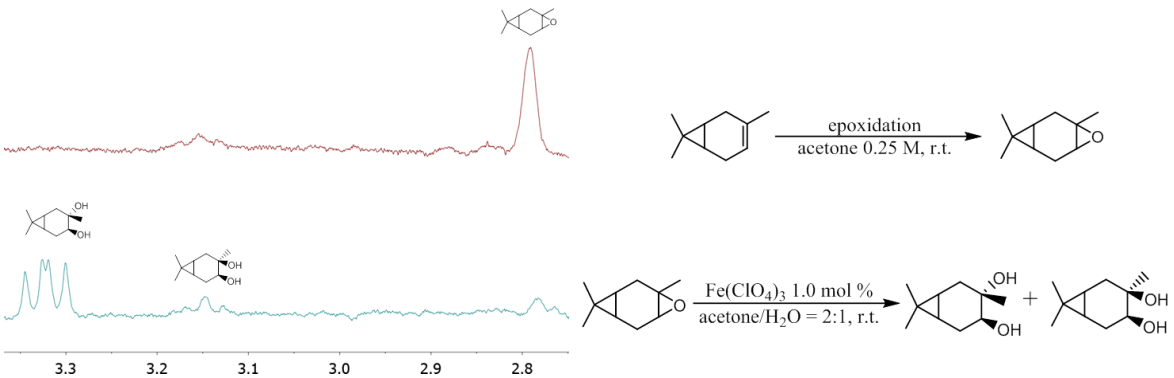
methylcyclohexene epoxides, formed by epoxidation of the corresponding alkenes, typically yielded good to full conversion to the diol products (overnight). Indeed addition of aqueous $Fe(ClO_4)_3$ lead to full conversion to the corresponding diols (*trans*- : *cis*- ratio ranges from 4:1 to 3:2 for the methylcyclohexene) overnight.



Scheme 14. Summary of ring opening reactions described in the text.

The last step ($NaIO_4$ mediated C-C bond cleavage) requires addition of water[30] (i.e. addition of $NaIO_4$ alone to mixture solution of 3-carene oxide in acetone results in only 20% conversion) and a 2:1 acetone:water mixture was found to be optimal for ring opening and the further C-C bond cleavage.

^{1}H-NMR spectroscopy shows the conversion of epoxides to diols (scheme 15 and figure 3), with the loss of epoxide concomitant with the formation of *trans*-diol occurring within 3 h. The *cis*-diol present originates from the oxidation of the alkene in which minor amounts of syn-dihydroxylation takes place also.



Scheme 15. ^{1}H-NMR spectrum of the reaction mixture following epoxidation (red) and ring opening reactions (blue).

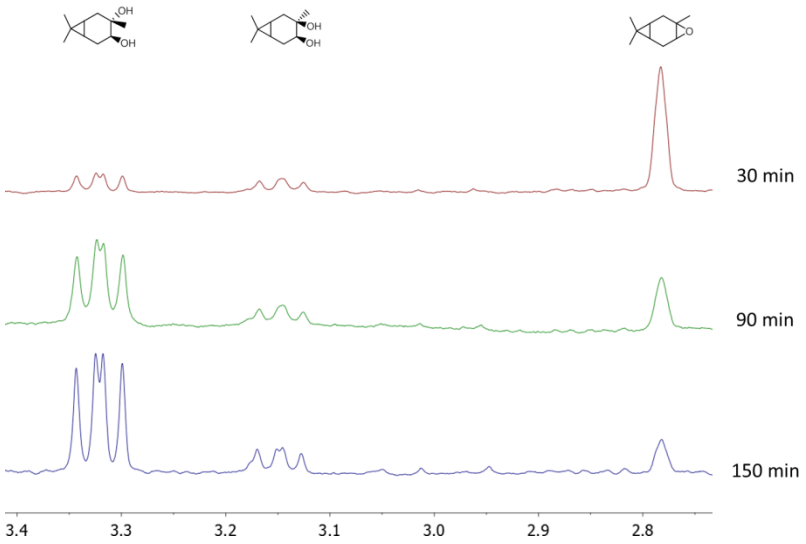
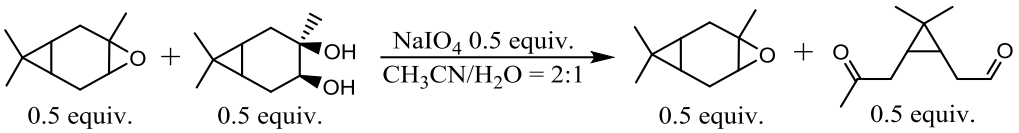


Figure 1. ^{1}H NMR spectrum of 3-carene oxide during Fe(II) catalyzed ring opening.

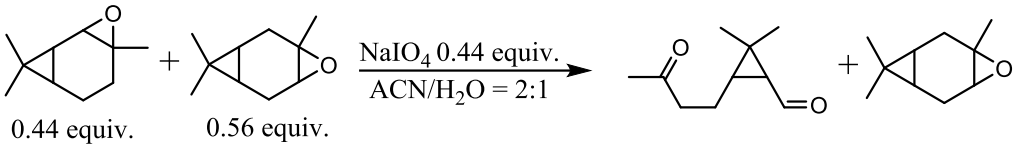
The use of iron perchlorate, other than providing excellent selectivity in ring opening of the epoxide under mild conditions, provides broad functional group tolerance also, which is ideal as an intermediate step as it is compatible with conditions used in epoxidation and subsequent C-C bond cleavage with periodate.

Ring opening of the epoxides occurs slowly under reaction conditions and limits the rate of periodate oxidation and hence increases the opportunity for competing reactions to reduce overall selectivity. The rate determining step of the direct cleavage of epoxides was expected to be the ring opening of the epoxide; indeed, the corresponding diols reacted much more quickly and with (nearly) stoichiometric amounts of periodate, as demonstrated by a competition reaction performed between 3-carene -oxide and its -diol (scheme 16). This competition reaction also indicates that unwanted diol formed during epoxidation can be removed by increasing its polarity through selective oxidation with periodate.



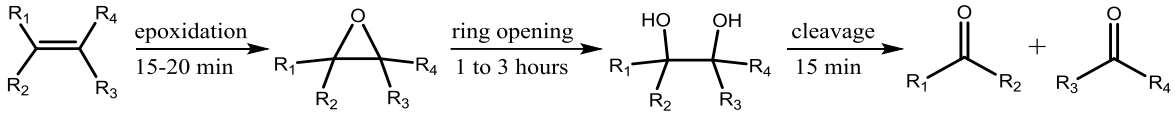
Scheme 16. Selective oxidation of the 3-carene diol in the presence of the 3-carene oxide.

Furthermore, direct oxidation of the epoxides can be used to achieve selectivity where one epoxide is more susceptible to ring opening than another, as exemplified in the kinetic attrition of a mixture of 2- and 3-carene epoxides. Although the expected oxidation product of 2-carene oxide is not obtained due to subsequent degradation, the 3-carene oxide is left relatively untouched (scheme 17). The selectivity in the case of 2- and 3-carene confirms that $NaIO_4$ does not react directly with epoxides.



Scheme 17. Selective oxidation of the 2-carene oxide in the presence of the 3-carene oxide; the product of oxidation of 2-carene was not been confirmed.

A further point that supports that ring opening of epoxides precedes periodate oxidation is that oxidation of the corresponding diols is complete within ca. 15 min, in contrast to ring opening which typically takes ca. 3 h for aliphatic substrates under the present conditions. Overall the reaction takes less than 5 h to the scission products starting from the alkene (scheme 18).



Scheme 18. One pot, three step conversion of aliphatic alkenes to C=C cleavage products.

Although providing for facile epoxide ring opening with Fe(III) salts, the use of acetone in combination with H_2O_2, raises a safety issue, due to the possible formation of explosive organic peroxides. Although the Mn(II)/PCA system has been shown to be safe for small scale reactions;[34] for larger scale reactions, the use of an in-flow epoxidation-ring opening system for the oxidation of the alkenes is preferred. The epoxidation step was performed in-flow using a syringe pump and mixer: the substrate and the reagents, in one syringe, were mixed continuously in small volumes with a solution of hydrogen peroxide. Over and above the fact that this method is intrinsically safe, the reaction is indeed slightly cleaner than when performed in batch. The organic layer was collected and aqueous $Fe(II)(ClO_4)_2$ were added (figure 4). The resulting mixture yielded the corresponding diol quantitatively, and subsequent addition of sodium periodate achieved bond cleavage. Using this approach, styrene was converted to benzaldehyde (vide infra) at 5 mmol scale smoothly also.

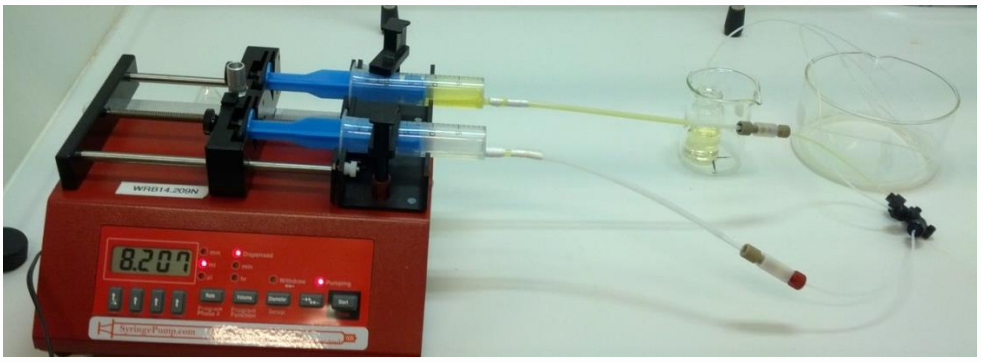
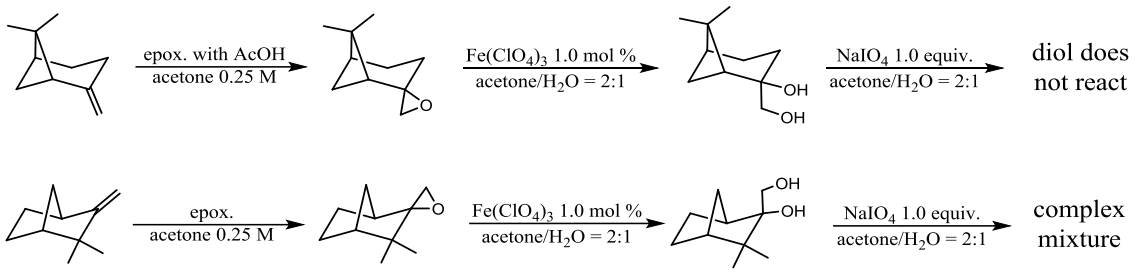


Figure 2. Continuous flow arrangement for the epoxidation of alkenes.

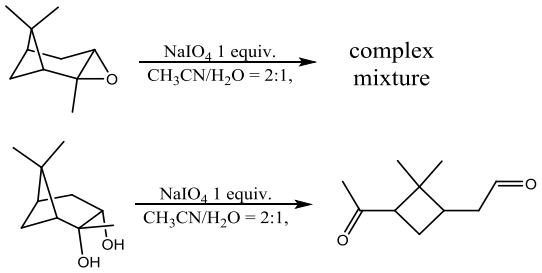
3.2.2. Oxidation of aliphatic substrates

Epoxidation and direct scission of 1-methylcyclohexene with only 2.0 equivalents of $NaIO_4$ in CH_3CN/H_2O yielded the scission product quantitatively, as shown in scheme 12. In contrast, β-pinene and camphene required three steps epoxidation - ring opening – cleavage, however, in both cases, although the corresponding epoxides and diol were obtained after the 1st and 2nd steps, respectively, the β-pinene diol unexpectedly did not seem to react further. Camphene gave a complex mixture of product, which is ascribed to rearrangements, as observed by Binder et al.[30] earlier for α- and β-pinene epoxides.



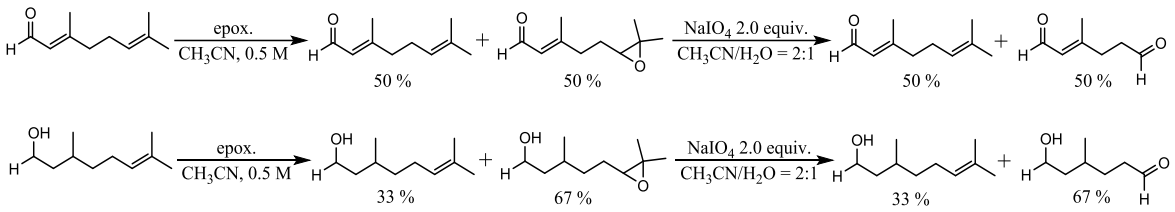
Scheme 19. 3-step one-pot oxidation over β-pinene (up) and camphene (bottom).

Although oxidation of α-pinene oxide with $NaIO_4$ in acetonitrile/water (2:1 v/v) resulted in a complex mixture of products, oxidation of (1R,2R,3S,5R)-(−)-pinanediol and (1S,2S,3R,5S)-(+)-pinanediol under the same conditions yielded the expected aldehyde (scheme 20), with little evidence of the rearrangements observed under the conditions of Binder et al.[30] These data highlight that ring opening of the epoxide to diols is likely the limiting factor in the cleavage step.



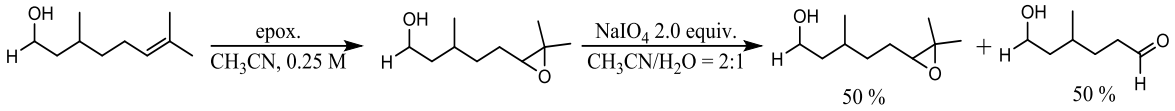
Scheme 20. $NaIO_4$ mediated cleavage attempt over α-pinene oxide (up) α-pinene diol.

Partial epoxidation of both citral and citronellol was carried out to assess the selectivity of the subsequent reaction steps. Oxidation with 2.0 equiv. of $NaIO_4$ (with 50 % water by volume) resulted in selective conversion of the epoxide to the desired aldehyde, with the remaining starting material recovered fully (scheme 21). These data confirm that neither terminal alcohols, trisubstituted, nor α,β-unsaturated alkenes are sensitive to the cleavage conditions of the final step. Furthermore, it demonstrates that the double bond selectivity in the epoxidation step can be used to control the overall selectivity of C=C bond cleavage.



Scheme 21. One-pot two step C=C bond cleavage of citral and citronellol.

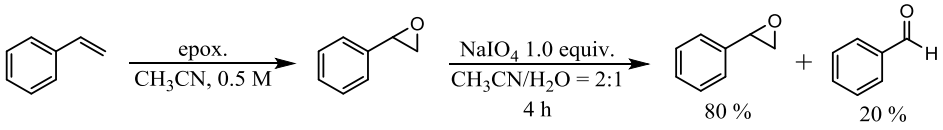
With 0.25 M instead of 0.5 M citronellol, full conversion to the epoxide was observed with 50% conversion to the cleavage product after the 2nd step (scheme 22).



Scheme 22. Oxidation of citronellol (0.25 M) under otherwise identical conditions as used in scheme 19.

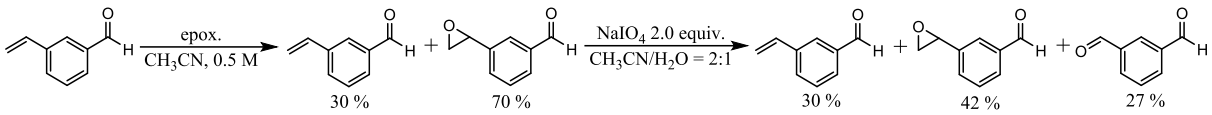
3.2.3. Oxidation of benzylic substrates

The reactivity of aryl-alkenes is often distinctly different to aliphatic alkenes, especially in regard to the stability of their epoxide products. Oxidation of styrene with H_2O_2 followed by periodate oxidation (i.e. under the one pot 3-step conditions that proved successful with 3-carene, section 3.2) provided the desired product in 4 h. Reaction monitoring (of the first two steps in line through Raman spectroscopy and the third step off line by ^{1}H NMR spectroscopy) was used to determine when full conversion at each step was achieved. In contrast, oxidation of styrene to styrene oxide followed by direct addition of periodate in water resulted in only 20% conversion. It is notable however that the diol and α-hydroxy ketone byproducts formed in the first step were absent after this step, confirming that epoxides show limited susceptibility to (nucleophilic) ring opening under the conditions used for diol C-C bond cleavage (scheme 23).



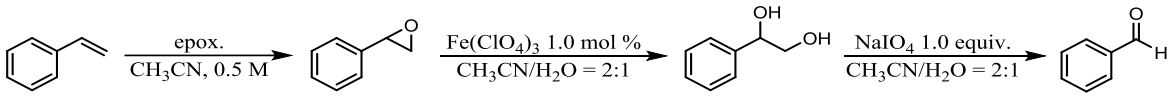
Scheme 23. Two step cleavage of styrene oxide.

Similar results were obtained with 3-vinyl benzaldehyde. In a one-pot 2-step reaction (i.e. without deliberate ring opening of the epoxide product) partial oxidation of the alkene and subsequently partial oxidation of the epoxide to 1,3-benzene-dialdehyde was observed. Importantly, the aldehyde functionality was preserved in both steps and the unreacted alkene was unaffected by the periodate oxidation (scheme 22).



Scheme 24. Partial conversion of the 3-vinyl benzaldehyde to its epoxide and subsequently dialdehyde.

Reaction optimization (scheme 24) was achieved smoothly via Lewis catalyzed ring opening of the epoxide, that was complete within only 15 min (determined by in situ reaction monitoring by Raman spectroscopy, figure 3) and was followed by oxidative C-C bond cleavage with periodate/water over 1 h. the surprisingly short time requested for the Lewis acid catalyzed ring-opening of the styrene oxide opened an easy pathway for the C-C bond cleavage of aromatic substrates and new possibilities for the chemoselectivity of the system. Moreover, the reaction time for cleavage was substantially shorter (1 h vs 1 day) than observed for direct oxidation of the epoxide.



Scheme 25. 3 step one pot oxidation of styrene.

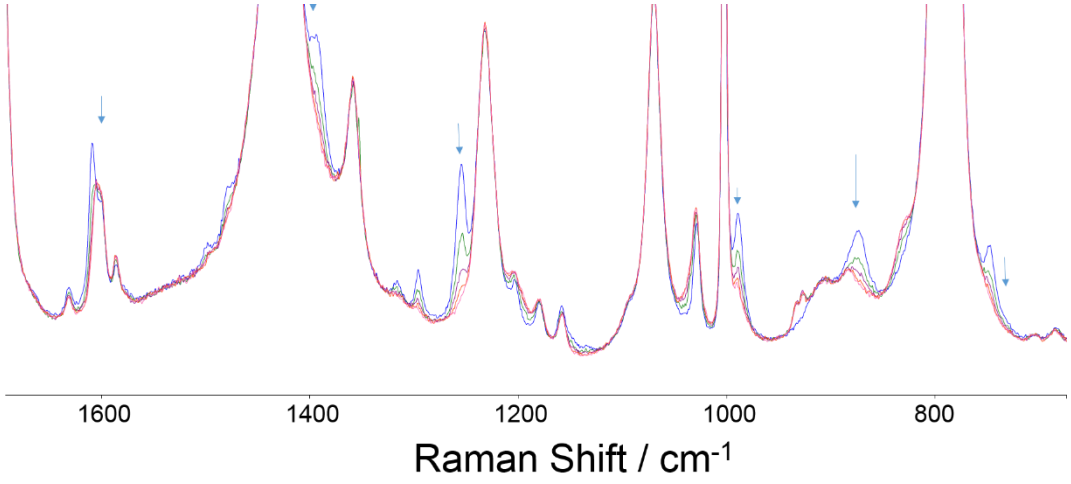
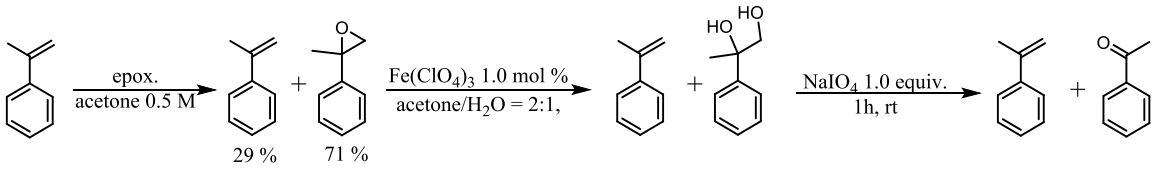


Figure 3. In-line monitoring of the ring opening of styrene oxide by Raman spectroscopy (spectra at 4 min intervals). Initial spectrum in blue, final spectrum in red.

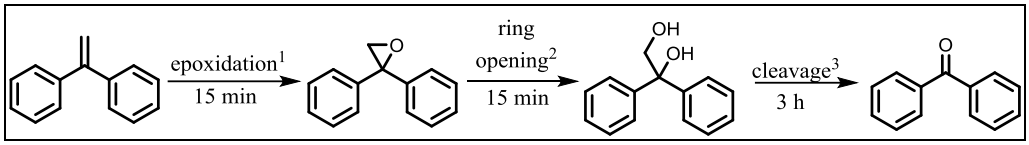
This difference in the reactivity of epoxides and diols towards periodate can also be useful to remove diol and α-hydroxy ketone byproducts from an epoxide (vide supra),[34] or to cleave diols in the presence of epoxides and even of epoxides with significant differences in stability, as already shown above with 2- and 3-carene epoxides. The difference between an aliphatic and a benzylic substrate in terms of reactivity was expected to be more pronounced.

α-Methyl styrene was converted to acetophenone under the same reaction conditions as used for styrene and isolation by column chromatography in 65 % yield, with an overall reaction time of 2 h, for the three steps. It is important to note that the epoxidation step proceeded with 71 % conversion, indicating that the subsequent two steps were essentially quantitative and selective towards formation of the desired product. Also, the selectivity of the ring-opening and C-C cleavage steps are remarkable (scheme 26).



Scheme 26. 3 step one-pot C=C bond cleavage of α-Methyl styrene.

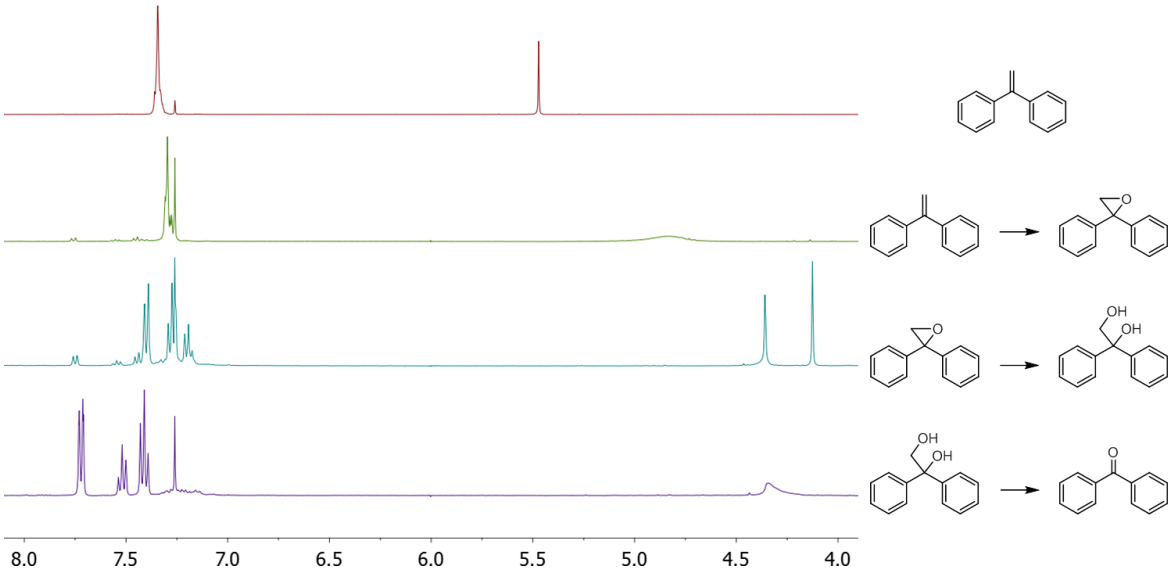
The low conversion in the epoxidation step for diphenyl ethylene (scheme 27) was overcome by a reduction of the amount of starting material to 0.25 M and addition of acetic acid to eliminate the lag phase.[41]



Scheme 27. 3 step one-pot C=C bond cleavage of diphenyl ethylene.

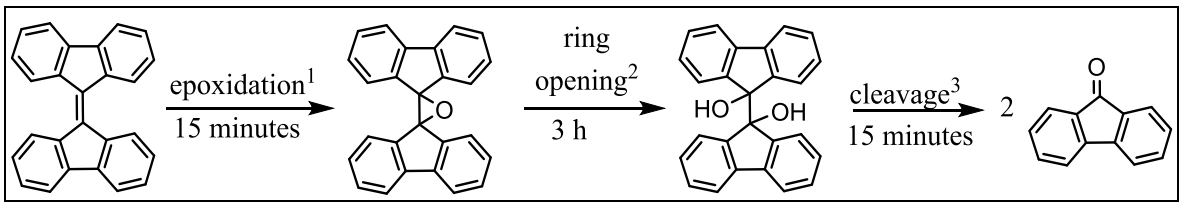
1) $Mn(ClO_4)_2.6H_2O$ 0.02 mol %, PCA 1.0 mol %, NaOAc 2.0 mol %, butanedione 1.0 equiv., H_2O_2 3.0 equiv., acetone, substrate 0.25 M, r.t., 15 min; 2) $Fe(ClO_4)_3$ 0.1 mol %, acetone/H_2O (2:1 v/v), r.t., 5 min; 3) $NaIO_4$ 1.2 equiv., acetone/H_2O (2:1, v/v), r.t., 3h.

Subsequent ring opening was rapid (<1 h), while the C-C bond cleavage step was complete even with only a slight excess of $NaIO_4$ (3 h). A basic workup yielded the desired product in almost quantitative yield and high selectivity (scheme 28).



Scheme 28. ^{1}H-NMR spectra of 1,1-diphenyl-ethene, after epoxidation, ring opening and cleavage reactions, (respectively).

Although it shows low solubility, bisfluorene (scheme 29) could be oxidized under the same conditions, albeit with an 8-fold decrease in substrate concentration. Although other solvent (combinations) could be used for the epoxidation to increase solubility, this option was less convenient as it would limit ring opening of the epoxide using $Fe(ClO_4)_3$. Reaction progress was readily apparent by the change in color from bright red to yellow. Addition of aqueous $Fe(ClO_4)_3$ changed the solution to a light pink, which turned to light brown at the end of the ring opening reaction. Addition of 1.0 equiv. $NaIO_4$ resulted in C-C bond cleavage with the ketone as main product; however, in contrast to other substrates, the selectivity was lower, with other oxidation products, e.g., Baeyer-Villiger, observed.

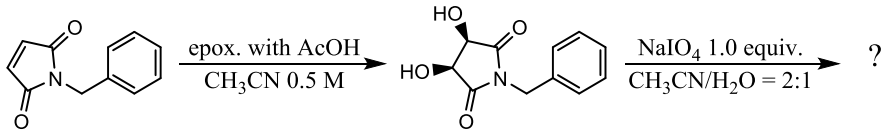


Scheme 29. 3 step one-pot C=C bond cleavage of bisfluorene.

1) $Mn(ClO_4)_2.6H_2O$ 0.08 mol %, PCA 4.0 mol %, NaOAc 8.0 mol %, butanedione 4.0 equiv., H_2O_2 12.0 equiv., acetone 0.625 M, r.t., 15 min; 2) $Fe(ClO_4)_3$ 0.1 mol %, acetone/H_2O=2:1, r.t., 5 min; 3) $NaIO_4$ 1.2 equiv., acetone/H_2O=2:1, r.t., 3 h

3.2.4 C=C bond cleavage of electron poor alkenes

The selectivity of the Mn/PCA system is substrate dependent on substrate, with epoxidation observed for electron rich alkenes and electron deficient alkenes yielding the corresponding (syn)vicinal diols directly. *N*-benzylmaleimide (scheme 30) was oxidized to the diol under conditions[34] reported earlier, and the diol subsequently cleaved to full conversion with periodate, although isolation of product was not achieved.



Scheme 30: C=C bond cleavage attempt over the N-benzyl maleimide.

Isolation of the highly electrophilic (diketo)dialdehyde formed was not achieved.

3.3. Conclusion and future perspectives

In this chapter, an alternative protocol to ozonolysis is described, which overcomes several of the limitations faced using ozonolysis for C=C bond cleavage. Importantly, all steps are carried under ambient conditions with off-the-shelf reagents and the approach provides for useful selectivity both between double bonds and with regard to other functional group. For instance the lack of reactivity of alkynes, primary alcohols and aldehydes reported earlier for the Mn/PCA system opens up application of the C=C bond cleavage approach to these substrates. The selectivity of the present method comes from both the first oxidation step: the Mn/PCA based epoxidation/syn-dihydroxylation is both selective and specific towards the differently electron rich double bonds over α,β-unsaturated double bonds; and the epoxide ring opening step. The C-C bond cleavage can be performed directly on the epoxide with between 2 and 7 equiv. of periodate, however, if the epoxidation is carried out in acetone, facile ring opening to the diol with $Fe(ClO_4)_3$ proceeds relatively quickly (depending on substrate) and can be followed by cleavage with only on equiv. of $NaIO_4$, with overall reaction times of less than 4 h. For electron deficient alkenes, which form syn-diols directly upon Mn/PCA oxidation in acetonitrile reaction times are reduced further to about 30 min. Importantly, all reactions were performed at room temperature in the presence of water and air in contrast to the "classic" ozonolysis conditions (e.g., -78 °C) and avoids the formation of potentially hazardous intermediates such as trioxolane intermediates.

3.4 Experimental

All reagents were of commercial grade and were used as received unless stated otherwise. Hydrogen peroxide was used as received (Acros Chemicals) as a 50 wt % solution in water; note that the grade of H_2O_2 employed can affect the outcome of the reaction, as some sources are stabilized using sequestrants. ^{1}H NMR (400.0 MHz) and ^{13}C NMR (100.59 MHz) spectra were recorded on a Varian Avance 400. Chemical shifts are relative to the following: ^{1}H NMR, $CDCl_3$ (7.26 ppm) and CD_3CN (1.94 ppm); ^{13}C NMR, $CDCl_3$ (77 ppm) and CD_3CN (118 ppm).

Caution! The drying or concentration of solutions that potentially contain H_2O_2 should be avoided. Prior to drying or concentrating, the presence of H_2O_2 should be tested for using peroxide test strips followed by neutralization on solid $NaHSO_3$ or another suitable reducing agent. When working with H_2O_2, suitable protective safeguards should be in place at all times due to the risk of explosion.

Caution! Butanedione has been linked with lung disease upon prolonged exposure to its vapors. It should be handled in a properly ventilated fume hood, and exposure to vapors should be avoided.

1,2-Dichlorobenzene, which has a negligible effect on the reaction, was employed as internal standard for Raman and ^{1}H NMR spectroscopy. Reaction monitoring with Raman spectroscopy focused primarily on the intensity of the C=C and C=O stretching bands between 1550 and 1800 cm^{-1} (e.g., at 1650 cm^{-1} for cyclooctene and 1724 cm^{-1} for butanedione), between 600 and 900 cm^{-1} relating to the C=C and C=O bending modes (682 cm^{-1} for butanedione and 701 cm^{-1} for cyclooctene), and the O−O stretching mode of H_2O_2 at 870 cm^{-1}. UV/vis absorption spectra were recorded in 1 or 10 mm path length cuvettes on a AnalytikJena Specord 600 instrument. Raman spectra at 785 nm were recorded using a PerkinElmer Raman Station and at 532 nm using a custom-made Raman spectrometer; a 532 nm DPSS laser (25 mW, Cobolt Lasers) was fiber-coupled to a low-cost Raman probe (Inphotonics) and the collected scattering feed into a Shamrock163 spectrograph (500 nm blaze, 1200 l/mm grating, Andor Technology) and dispersed onto a Newton EMCCD (Andor Tehcnology) operated in conventional CCD mode.

Typical procedure for catalytic oxidations and characterization of products (Scheme 11). The substrate (1 mmol) was added to a 0.5 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 0.5 mL solution PCA (12.3 mg in 10 mL of solvent) in acetonitrile or acetone. 16.7 µL NaOAc (aqueous, 0.6 M), 43.5 µL butanedione (0.5 mmol), acetic acid (0.2 mmoL, 0.011 mL) and acetonitrile/acetone (depending on the amount of substrate used) were added to give a final volume of 2 mL and a final concentration of the substrate of 0.5 M (for less reactive substrates the amount of starting material is reduced by half to give a final concentration of 0.25 M). The solution was stirred in an ice/water bath before addition of 85 µL (1.5 mmol) H_2O_2 (50 wt %). Conversion was verified by ^{1}H NMR by dilution of a part of the reaction mixture in CD_3CN or by directly diluting the sample in $CDCl_3$.

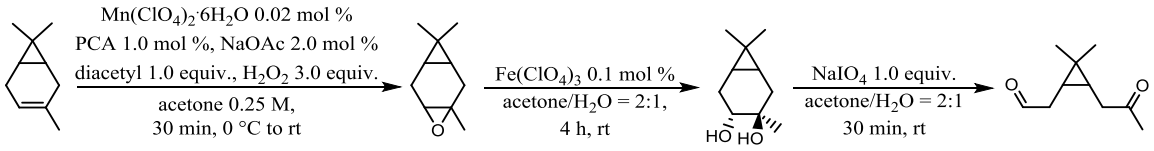
One pot epoxide ring opening (Scheme 11). When epoxidation (in acetone) was complete, $Fe(ClO_4)_3$ was added (3.54 mg, 1.0 mol %) with water (half the volume of the reaction mixture); the reaction was monitored either directly by Raman spectroscopy or indirectly by ^{1}H NMR spectroscopy (a small sample of reaction was shaken with 1 mL brine and 1 mL $CDCl_3$, and the organic layer was used to record the NMR spectrum).

Diol and epoxide C-C bond cleavage (Scheme 11). 1.0 (2.0 to 4.0) equiv. of $NaIO_4$ (213.89 g/mol) was added (with 50 v/v % of water) to the reaction mixture containing the diol (epoxide). The reaction was monitored indirectly by ^{1}H NMR spectroscopy (a sample was shaken with 1 mL brine and 1 mL $CDCl_3$, and the organic layer was used to record the ^{1}H NMR spectrum). Product was isolated by addition of brine (10 mL) and extraction with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous), and filtered, and the dichloromethane was removed in vacuo.

Procedure for oxidation of styrene in flow

5 mmol scale oxidation of styrene to benzaldehyde was carried out as follows: two acetone solutions, each with a final volume of 6.180 mL, were prepared, one containing substrate and catalyst, the other containing H_2O_2. The former solution contained styrene (5.0 mmol, 520.75 mg, 0.574 mL), $Mn(ClO_4)_2$ (0.18 mg) and PCA (3.075 mg), aqueous 0.6 M NaOAC (0.083 mL), butanedione (0.217 mL), water (0.25 mL) to prevent precipitation of sodium acetate, and acetic acid (1.0 mmol, 0.057 mL). Solution two was composed by 5.76 mL of acetone and 0.425 mL of H_2O_2 50 % wt. The first step was performed over 40 min (residence time) in flow, with quantitative yield of the corresponding epoxide (verified by both Raman and ^{1}H-NMR spectroscopy). The resulting epoxide was collected followed by addition of aqueous iron(III) perchlorate (17.7 mg in 5.0 mL) and after stirring for ca. 15 min, the ring opening was verified by both Raman and ^{1}H-NMR spectroscopy; subsequently solid $NaIO_4$ (1 equiv., 1.070 g) was added to cleave the diol to the desired aldehyde.

One-pot three-step oxidation of 3-carene to 2-(2,2-dimethyl-3-(2-oxopropyl)cyclopropyl)acetaldehyde

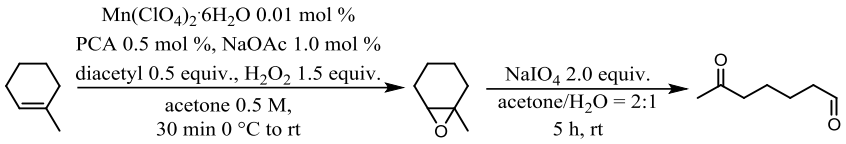


The substrate (2.5 mmol) was added to a 2.5 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 2.5 mL solution PCA (12.3 mg in 10 mL of solvent) in acetone. 84 µL NaOAc (aqueous, 0.6 M), 218 µL butanedione (2.5 mmol) and acetone were added to give a final volume of 10 mL and a final concentration of the substrate of 0.25 M. The solution was stirred in an ice/water bath before addition of 425 µL (7.5 mmol) H_2O_2 (50 wt %). Conversion was verified by ^{1}H NMR by dilution of a part of the reaction mixture in CD_3CN or by directly diluting the sample in $CDCl_3$.

After 30 min, $Fe(ClO_4)_3$ was added (8.85 mg, 1.0 mol %) with 5.0 mL water; the reaction was monitored indirectly by ^{1}H NMR spectroscopy (a small sample of reaction was shaken with 1 mL brine and 1 mL $CDCl_3$, and the organic layer was used to record the NMR spectrum).

1.0 equiv. (535 mg) of $NaIO_4$ (213.89 g/mol) was added to the reaction mixture containing the diol. The reaction was monitored indirectly by ^{1}H NMR spectroscopy (a sample was shaken with 1 mL brine and 1 mL $CDCl_3$, and the organic layer was used to record the ^{1}H NMR spectrum). Product isolation involved addition of brine (50 mL) and extraction with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous) and filtered, and the dichloromethane was removed in vacuo, yielding the crude containing the desired scission product as the major one. ^{1}H NMR spectral data is in agreement with literature values.[42] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, J = 1.8 Hz, 1H), 2.36 (d, J = 6.8 Hz, 2H), 2.32 (dd, J = 1.8 Hz, J = 7.0 Hz, 2H), 2.17 (s, 3H), 1.13 (s, 3H), 0.98 (m, 2H), 0.92 (s, 3H).

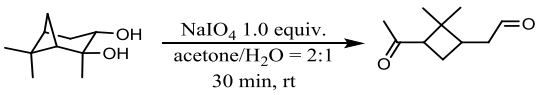
One-pot two-step oxidation of methylcyclohexene to 1,6-hexanedial



The substrate (2.0 mmol) was added to a 1.0 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 1.0 mL solution PCA (12.3 mg in 10 mL of solvent) in acetonitrile. 33 µL NaOAc (aqueous, 0.6 M), 87 µL butanedione (2.5 mmol) and acetonitrile were added to give a final volume of 10 mL and a final concentration of the substrate of 0.5 M. The solution was stirred in an ice/water bath before addition of 85 µL (1.5 mmol) H_2O_2 (50 wt %). Conversion was verified by ^{1}H NMR by dilution of a part of the reaction mixture in CD_3CN or by directly diluting the sample in $CDCl_3$.

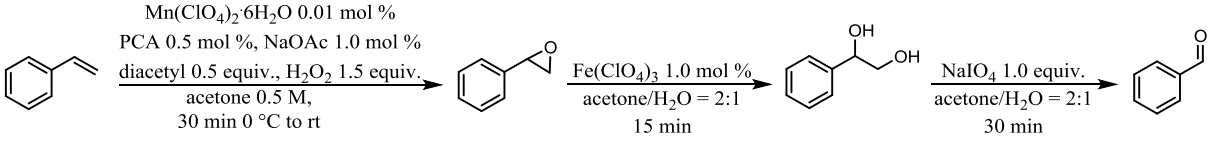
After 30 min, reaction mixture was added 2.0 equiv. (856 mg, 4.0 mmol) of $NaIO_4$ (213.89 g/mol) and 2 mL of water. The reaction was monitored indirectly by ^{1}H NMR spectroscopy (a small sample of reaction was shaken with 1 mL brine and 1 mL $CDCl_3$, and the organic layer was used to record the NMR spectrum). Product isolation involved addition of brine (50 mL) and extraction with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous) and filtered, and the dichloromethane was removed in vacuo, yielding the crude containing the desired scission product as the major one. ^{1}H NMR spectral data is in agreement with literature values.[43] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, 1H), 2.47 – 2.40 (m, 4 H), 2.15 (s, 3H), 1.54 – 1.64 (m, 4 H).

Oxidation of Pinanediol to (3-acetyl-2,2-dimethylcyclobutyl)acetaldehyde



The substrate (0.5 mmol) was dissolved in 2.0 mL in acetonitrile. 0.5 mmol (107 mg) $NaIO_4$ (213.89 g/mol) and 1 mL of water were also added; the resulting mixture was stirred for 30 min. The reaction was monitored indirectly by ^{1}H NMR spectroscopy (a small sample of reaction was shaken with 1 ml brine and 1 ml $CDCl_3$, showing that the reaction mixture contained the desired scission product as the major one. ^{1}H NMR spectral data is in agreement with literature values.[32] ^{1}H NMR (400 MHz, CD_3CN) δ 9.70 (m, 1H), 2.96 (m, 1H), 2.50–2.40 (m, 3H), 1.99 (s, 3H), 1.95 – 1.93 (m, 2H), 1.29 (s, 3H), 0.80 (s, 3H).

One-pot 3 step oxidation of styrene to benzaldehyde



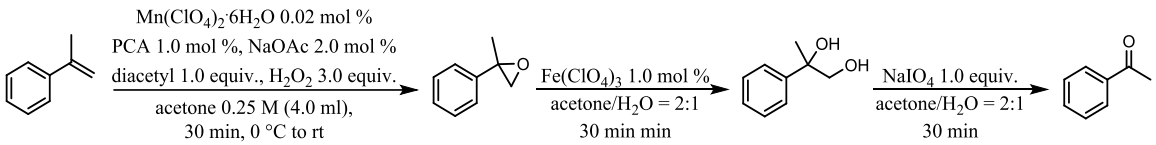
The substrate (5.0 mmol) was added to a 2.5 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 2.5 mL solution PCA (12.3 mg in 10 mL of solvent) in acetonitrile. 83 µL

NaOAc (aqueous, 0.6 M), 217 µL butanedione (2.5 mmol), 0.067 µL acetic acid (1.0 mmol) and acetone were added to give a final volume of 10 mL and a final concentration of the substrate of 0. 5 M. The solution was stirred in an ice/water bath before addition of 425 µL (7.5 mmol) H_2O_2 (50 wt %). Conversion was verified by ^{1}H NMR by directly diluting the sample in $CDCl_3$.

After 30 min, $Fe(ClO_4)_3$ was added (17.7 mg, 1.0 mol %) with 5.0 mL water; the reaction was monitored indirectly by ^{1}H NMR spectroscopy (a small sample of reaction was shaken with 1 mL brine and 1 mL $CDCl_3$, and the organic layer was used to record the NMR spectrum).

After 15 min, 1.0 equiv. (1070 mg, 5.0 mmol) of $NaIO_4$ (213.89 g/mol) was added to the reaction mixture. The reaction was monitored indirectly by ^{1}H NMR spectroscopy (a small sample of reaction was shaken with 1 mL brine and 1 mL $CDCl_3$, and the organic layer was used to record the NMR spectrum). Product isolation involved addition of brine (50 mL) and extraction with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous) and filtered, and the Et_2O was removed in vacuo, yielding the crude containing the desired scission product as the major one. ^{1}H NMR spectral data is in agreement with commercially available samples (Sigma Aldrich). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.89 (d, J = 7.1 Hz, 2H), 7.67 – 7.60 (m, 1H), 7.54 (dd, J = 8.2, 6.9 Hz, 2H).

One-pot three-step oxidation of α–methyl styrene to acetophenone[44]



The substrate (2.5 mmol) was added to a 2.5 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 2.5 mL solution PCA (12.3 mg in 10 mL of solvent) in acetone. 84 µL NaOAc (aqueous, 0.6 M), 218 µL butanedione (2.5 mmol) and acetone were added to give a final volume of 10 mL and a final concentration of the substrate of 0.25 M. The solution was stirred in an ice/water bath before addition of 425 µl (7.5 mmol) H_2O_2 (50 wt %). Conversion was verified by ^{1}H NMR by dilution of a part of the reaction mixture in CD_3CN or by directly diluting the sample in $CDCl_3$.

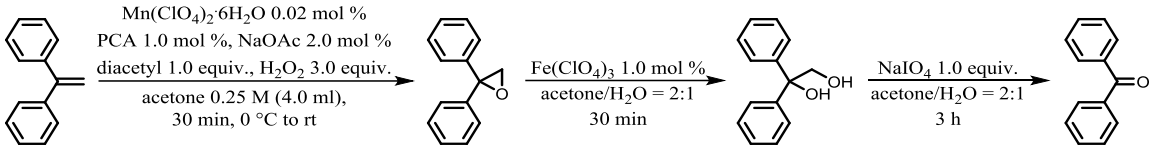
After 30 min, $Fe(ClO_4)_3$ was added (8.85 mg, 1.0 mol %) with 5.0 mL water; the reaction was monitored indirectly by ^{1}H NMR spectroscopy (a small sample of reaction was shaken with 1 mL brine and 1 mL $CDCl_3$, and the organic layer was used to record the ^{1}H NMR spectrum).

Reaction mixture containing the diol was added 1.0 equiv. (535 mg, 2.5 mmol) of $NaIO_4$ (213.89 g/mol). The reaction was monitored indirectly by ^{1}H NMR spectroscopy (a small sample of reaction was shaken with 1 mL brine and 1 mL $CDCl_3$, and the organic layer was used to record the NMR spectrum). Product isolation involved addition of brine (50 mL) and extraction with dichloromethane (3 x 50 mL). The combined organic layers were

washed with brine and, once gathered, with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 (anhydrous), and filtered, and the dichloromethane was removed in vacuo.

Crude of reaction is purified by column chromatography with Silica gel and eluted with a Pentane:Et_2O = 9:1 mixture, to yield the pure product, as a colorless liquid, in 65 % yield. Spectroscopic data is in agreement with commercially available samples (Sigma Aldrich). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.91 (m, 2H), 7.60−7.50 (m, 1H), 7.50−7.40 (m, 2H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ = 198.1, 137.0, 133.0, 128.5, 128.2, 26.5.

One-pot three-step oxidation of diphenyl ethylene to benzophenone

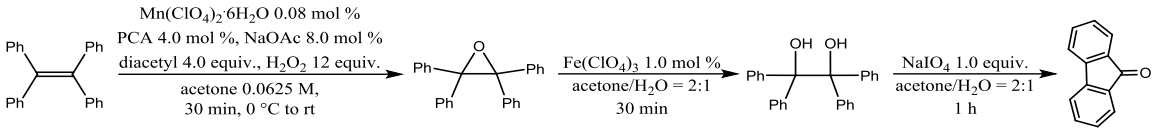


The substrate (5.0 mmol) was added to a 5 mL solution $Mn(ClO_4)_2·6H_2O$ (7.2 mg in 100 mL solvent) and 5 mL solution PCA (12.3 mg in 10 mL of solvent) in acetonitrile. 167 µL NaOAc (aqueous, 0.6 M), 430 µL butanedione (2.5 mmol), 114 µL acetic acid (2.0 mmol) and acetone were added to give a final volume of 20 mL and a final concentration of the substrate of 0.25 M. The solution was stirred in an ice/water bath before addition of 850 µL (15 mmol) H_2O_2 (50 wt %). Conversion was verified by ^{1}H NMR by directly diluting the sample in $CDCl_3$.

After 15 min, $Fe(ClO_4)_3$ was added (17.7 mg, 1.0 mol %) with 10 mL water; the reaction was monitored indirectly by ^{1}H NMR spectroscopy (a small sample of reaction was shaken with 1 ml brine and 1 ml $CDCl_3$, and the organic layer was used to record the NMR spectrum).

After 15 min, reaction mixture was added 1.0 equiv. (1070 mg, 5.0 mmol) of $NaIO_4$ (213.89 g/mol). The reaction was monitored indirectly by ^{1}H NMR spectroscopy (a small sample of reaction was shaken with 1 mL brine and 1 mL $CDCl_3$, and the organic layer was used to record the NMR spectrum). Product isolation involved addition of brine (100 mL) and extraction with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous) and filtered, and the dichloromethane was removed in vacuo, yielding the crude containing the desired scission product as the major product. Spectroscopic data is in agreement with commercially available samples (Sigma Aldrich).. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 4H), 7.63 – 7.56 (m, 2H), 7.49 (dd, J = 8.3, 7.0 Hz, 4H).

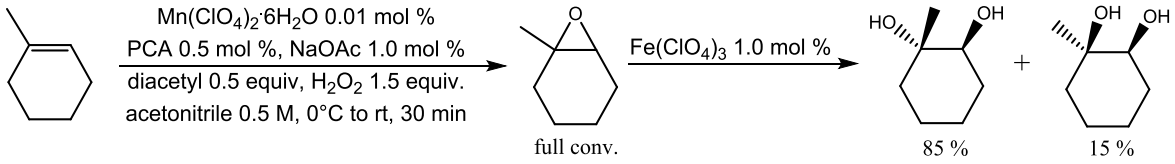
One-pot three-step oxidation of bisfluorene to 9-fluorenone



The substrate (0.25 mmol) was added to a 1.0 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 1.0 mL solution PCA (12.3 mg in 10 mL of solvent) in acetonitrile. 33 µL NaOAc (aqueous, 0.6 M), 87 µL butanedione (2.5 mmol), 22 µL acetic acid (0.5 mmol) and acetone were added to give a final volume of 4 mL and a final concentration of the substrate of 0.0625 M. The solution was stirred in an ice/water bath before addition of 85 µL (1.5 mmol) H_2O_2 (50 wt %). Given the low concentration, conversion was verified by color changing (from glossy red to yellowish giving the loss of extensive conjugation). After 30 min, $Fe(ClO_4)_3$ was added (0.885 mg, 1.0 mol %) with 2 mL water.

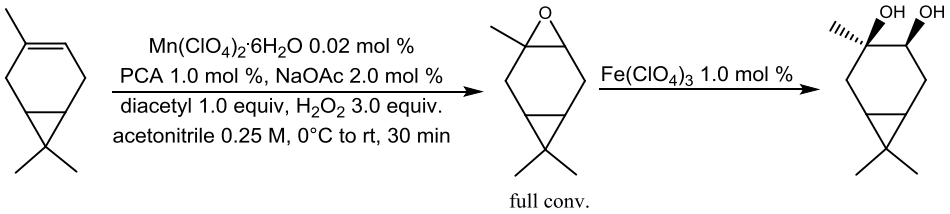
After a further 30 min, reaction mixture was added 1.0 equiv. (53.5 mg, 0.25 mmol) of $NaIO_4$ (213.89 g/mol). The reaction was stirred for 4 h. Product isolation involved addition of brine (10 mL) and extraction with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous) and filtered, and the dichloromethane was removed in vacuo, yielding the crude containing the desired scission product as the major one. Spectral data are in agreement with literature values.[45] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.4 Hz, 2H), 7.52 – 7.47 (m, 4H), 7.30 (td, J = 7.2, 1.9 Hz, 2H).

(1S,2S)-1-methylcyclohexane-1,2-diol



The substrate (20 mmol, 1.923 g) was added to a 10 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 10 mL solution PCA (12.3 mg in 10 mL of solvent) in acetonitrile. 336 µL NaOAc (aqueous, 0.6 M), 872 µL butanedione (2.5 mmol) and acetonitrile were added to give a final volume of 40 mL and a final concentration of the substrate of 0.5 M. was submitted to the same conditions listed above for reaction of less reactive alkenes (half substrate w.r.t. standard conditions). After epoxidation was complete (30 min), $Fe(ClO_4)_3$ (1.0 mol %) was added and reaction was stirred overnight. The mixture was then added 200 mL saturated aqueous NaCl and 200 mL CH_2Cl_2, and layers were separated; aqueous layer was extracted again (2 x 200 mL CH_2Cl_2) and the gathered organic layers are gathered and dried over anhydrous $MgSO_4$; solvent is evaporated in vacuo to yield the crude of reaction, which is purified through column chromatography (Silica, EtOAc : CH_2Cl_2 = 4:6, then improving the EtOAc ratio) yielding the pure compound in 35 % yield. Spectroscopic data agree with those found in literature.[46] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (m, 1H), 1.88 – 1.62 (m, 4H), 1.23 – 1.39 (m, 4H), 1.18 (s, 3H).

(3R,4S)-3,7,7-trimethylbicyclo[4.1.0]heptane-3,4-diol

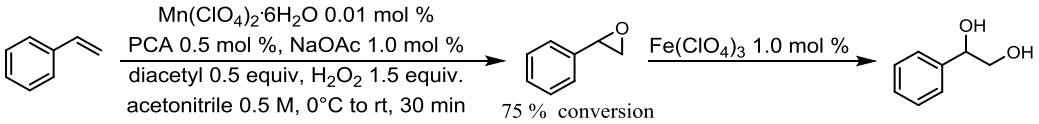


full conv.

The substrate 5.0 mmol (681 mg) was added to a 5 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 5 mL solution PCA (12.3 mg in 10 mL of solvent) in acetone. 170 µL NaOAc (aqueous, 0.6 M), 440 µL butanedione (5.0 mmol) and acetone were added to give a final volume of 20 mL and a final concentration of the substrate of 0.25 M. After epoxidation was complete (30 min) $Fe(ClO_4)_3$ (1.0 mol %) was added and reaction was stirred overnight. The mixture was then added 200 mL saturated aqueous NaCl and 200 mL CH_2Cl_2, and layers were separated; aqueous layer was extracted again (2 x 200 mL CH_2Cl_2) and the gathered organic layers are gathered and dried over anhydrous $MgSO_4$; solvent is evaporated in vacuo to yield the crude of reaction, purified by column chromatography (Silica, Pentane : Et_2O = 1:1, in gradient of Et_2O) to afford the product in 30 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (dd, 1H), 2.11 (dd, 1H), 1.97 (dd, 1H), 1.70 – 1.56 (m, 3H), 1.26 – 1.19 (m, 1H), 1.22 (d, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.75 – 0.67 (m, 2H).

Crude of reaction is purified by column chromatography (Silica, Pentane : Et_2O = 1:1, in gradient of Et_2O) to afford the product in 30 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (dd, 1H), 2.11 (dd, 1H), 1.97 (dd, 1H), 1.70 – 1.56 (m, 3H), 1.26 – 1.19 (m, 1H), 1.22 (d, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.75 – 0.67 (m, 2H).

1-phenyl-1,2-ethandiol



75 % conversion

Substrate 10 mmol (1.042 g) was added to a 5 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 5 mL solution PCA (12.3 mg in 10 mL of solvent) in acetone. 170 µL NaOAc (aqueous, 0.6 M), 440 µL butanedione (5.0 mmol) and acetone were added to give a final volume of 20 mL and a final concentration of the substrate of 0.5 M. After epoxidation was complete (30 min) $Fe(ClO_4)_3$ (1.0 mol %) was added and reaction was stirred overnight. The mixture was then added 100 mL saturated aqueous NaCl and 200 mL CH_2Cl_2, and layers were separated; aqueous layer was extracted again (2 x 100 mL CH_2Cl_2) and the gathered organic layers are gathered and dried over anhydrous $MgSO_4$; solvent is evaporated in vacuo to yield the crude of reaction, which is purified through column chromatography (Silica, CH_2Cl_2 : Et_2O = 8:2, then improving the Et_2O ratio) yielding the pure compound in 38 % yield. Spectroscopic data agree with those of the commercially available compound purchased from Sigma Aldrich. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.82 (dd, 1H), 3.76 (dd, 1H), 3.66 (dd, 1H), 2.45 (bs, 1H), 2.05 (bs, 1H).

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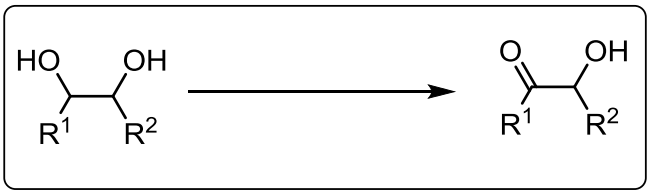
Chapter 4

Oxidation of vicinal diols to α-hydroxy ketones with H_2O_2 and a simple manganese catalyst

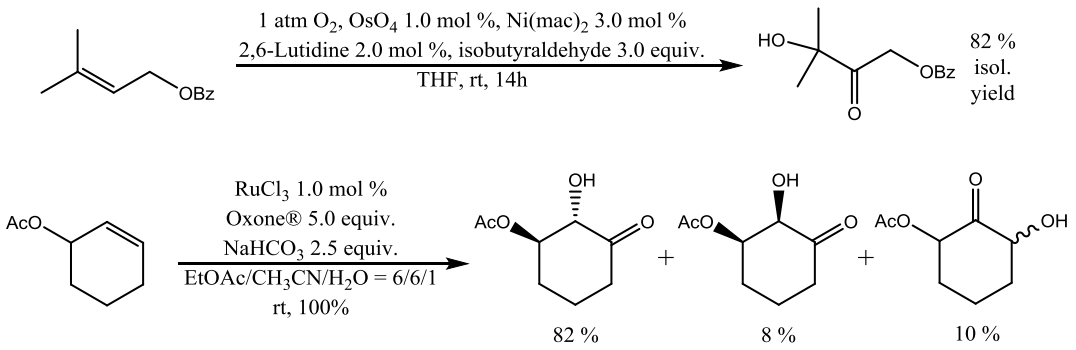
Abstract. Although α-hydroxy ketones are valuable synthons in organic chemistry, their synthesis is not always readily achievable. In this chapter, we show that the Mn/PCA based catalytic system discussed in chapter 1, is effective in achieving selective oxidation of epoxides and diols to their corresponding α-hydroxy ketones. Notably the epoxides and diols are, as reported earlier, obtained from the corresponding alkene via the same oxidation method.



4.1 Introduction

Acyloin building blocks are ubiquitous structural motifs in both biologically active natural products and drugs, and represent highly versatile synthons. Despite their proven value, only a limited number of general approaches to their synthesis are available, which include the well-known acyloin condensation,[1] for which catalytic versions, employing, *e.g.*, lanthanum,[2] titanium,[3] or Cs_2CO_3 with *N*-heterocyclic carbenes, have appeared recently providing access to various regioisomers[4] and enolate oxidation[5] (a two-step procedure, consisting of enolate generation followed by oxidation of the enol double bond, typically with *m*-CPBA) providing for non-stereoselective C-O bond formation. Catalysts with cyclic guanidine ligands[6] based on palladium have been used in the racemic transition-metal-catalyzed direct α-hydroxylation of ketones[7,8] and polymeric $\{[Cu(bpy)(BF_4)_2(H_2O)_2](bpy)\}_n$ (bpy = 4,4′-bipyridine) catalysts have been employed for the direct α-oxygenation of ketones with molecular oxygen.[9] The requirement for pre-enolization of the substrates limits the scope of these latter approaches, however. The metal free radical ketooxygenation of alkenes using hydroxamic acids followed by H_2 hydrogenation, was reported recently by Schmidt and Alexanian.[10]

Ketohydroxylation of olefins and monooxidation of vicinal diols[11,12] represent an important alternative approach, with the earliest examples making use of stoichiometric $KMnO_4$ [13] or NaOCl[14] under mildly acidic conditions. Mukaiyama *et al.* reported the first catalytic version, combining a catalytic OsO_4 and a Ni(II) complex to oxidize allylic ethers and terminal alkenes directly to α-hydroxy ketones.[15,16] Recently, Plietker has employed catalytic RuO_4 (from $RuCl_3$ with Oxone™) in the ketohydroxylation of olefins (scheme 1) and monooxidation of vicinal diols.[17]

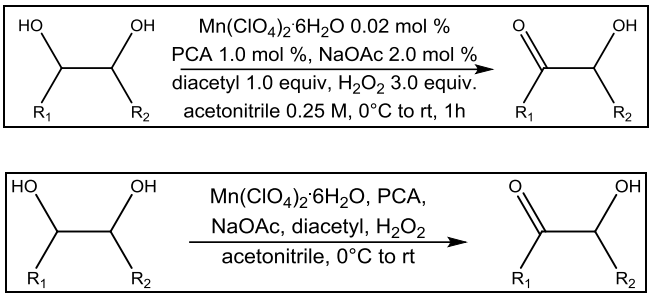


Scheme 1. (up) Catalytic oxidation of allylic ethers to α-hydroxy ketones reported by Mukaiyama[15] (bottom) "Ketohydroxylation" of olefins as reported by Plietker.[17]

The same transformation via a boronic acid catalyzed protocol, in water, employing dibromoisocyanuric acid (DBI) as a terminal oxidant or via electrochemical oxidation[18] has been reported recently also.

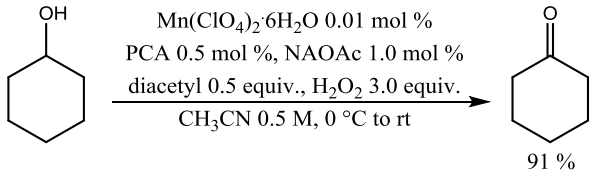
The challenge therefore is to access α-hydroxy ketones from 1,2-diols and alkenes using environmentally benign atom efficient oxidants (*e.g.*, H_2O_2) and non-toxic catalysts.

In this chapter, a catalytic method is described for the preparation of acyloins and benzoins employing an *in situ* prepared manganese catalyst and H_2O_2 as terminal oxidant, to achieve good to excellent selective monooxidation of vicinal diols. This method shows limited further oxidation (*e.g.*, to diketone products, Baeyer-Villiger oxidation and C-C bond cleavage) and good selectivity.



Scheme 2. Oxidation of 1,2,-diols to α-hydroxy-ketones described in this chapter

The catalyst employed comprises of a Mn(II) salt and pyridine-2-carboxylic acid (Scheme 2), which was previously reported by our group to catalyse the oxidation of olefins to epoxides and *cis*-diols,[19] and more recently for the oxidation of secondary alcohols to ketones (chapter 1).[20] This methodology employs the atom-economic oxidant H_2O_2 and shows excellent solvent scope, including alcohols and acetone, as well as, acetonitrile, under essentially pH neutral conditions. The substrate scope of this catalytic system prompted us to investigate its application to the selective monooxidation of diols to α-hydroxy ketones (scheme 3).



Scheme 3. Oxidation of cyclohexanol to cyclohexene as reported by Dong et al.[20]

We show here that for a broad range of 1,2-diols selective conversion to the corresponding α-hydroxy ketone product can be achieved with limited overoxidation under ambient conditions and with reaction times of less than 30 min. Furthermore we show that in the case of cyclic diols, *trans*-1,2-diols are more reactive than their *cis*-isomers which, together with the absence of significant overoxidation, points to the involvement of a highly selective active oxidant.

4.2 Results and Discussion

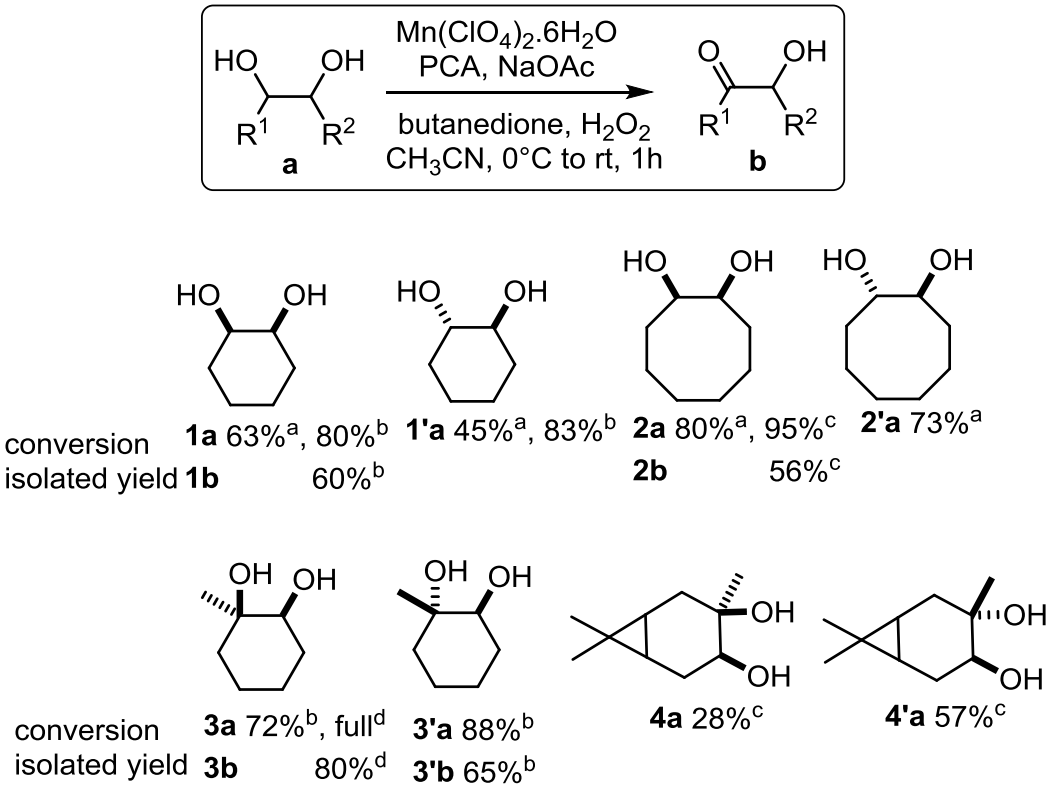
Cyclic and linear diols, as well as benzylic substrates, were submitted to the oxidative conditions described in Scheme 1, with good to excellent selectivity and conversion even without specific optimization of the reactions conditions. The catalyst was prepared *in situ* by mixing $Mn(ClO_4)_2{\cdot}6H_2O$, PCA and a base (NaOAc) in acetonitrile with (sub)stoichiometric butanedione with respect to the substrate. Our earlier studies revealed

that the role played by the ketone, either as a solvent (acetone) or additive in alcohols or acetonitrile, was to form a hydroperoxy adduct with H_2O_2, which in turn reacted with the catalyst to form the active oxidant. In the present study, butanedione was selected due to its availability, low cost and the reaction rates achieved with it in earlier studies (i.e. < 30 min).[19c,20] As observed earlier in the oxidation of alkenes and alcohols with this system, addition of H_2O_2, the terminal oxidant, to the reaction mixture resulted in all cases in a rapid change from yellow to colourless due to the formation of a hydroperoxy hydroxy ketone.[19c]

Oxidation of cyclic diols.

The oxidation of cyclic vicinal diols was examined with particular attention paid to the relative rate of reaction of *cis*- and *trans*-diols and also, the effect of ring size on conversion and selectivity.

Conditions optimized earlier for the oxidation of alkenes[19c] were applied initially to *cis*-1,2-cyclohexandiol (scheme 4). The reaction proceeds smoothly to the α-hydroxy ketone albeit with 63 % conversion using 1.5 equiv. of H_2O_2. Nearly full conversion is achieved with addition of 3 eq. hydrogen peroxide, albeit with minor amounts (5 %) of further oxidation products (*e.g.*, aldehyde due to C-C bond cleavage). Similar results were obtained with its stereoisomer *trans*-1,2-cyclohexandiol, again with 3.0 eq. H_2O_2 providing higher conversion.



Scheme 4. Oxidation of cyclic 1,2-diols to acyloin.

[a] 0.5 M substrate, 0.01 mol % $Mn(ClO_4)_2 \cdot 6H_2O$, 0.5 mol% PCA, 1.0 mol% NaOAc, 0.5 equiv. butanedione, 0.75 M H_2O_2 in acetonitrile; [b] 0.5 M substrate, 0.01 mol% $Mn(ClO_4)_2 \cdot 6H2O$, 0.5 mol% PCA, 1.0 mol % NaOAc, 0.5 M butanedione, 1.5 M H_2O_2 in acetonitrile; [c] 0.25 M substrate, 0.02 mol % $Mn(ClO_4)_2 \cdot 6H_2O$, 1.0 mol % PCA, 2.0 mol % NaOAc, 1.0 M butanedione, 0.75 M H_2O_2 in acetonitrile; followed by submission of the crude product obtained to condition '[c]'.

Cis- and *trans*-cyclooctanediols (scheme 4, entry 2) are converted to the corresponding α-hydroxy-ketones as major products, with minor amounts of di-ketones obtained also. Conversion and selectivity is increased by a reduction in the amount of substrate used, with the α-hydroxy ketone obtain in 56 % yield after column chromatography. Nevertheless, mass loss was noted in the crude yields and analysis with 1,2-dichlorobenzene as internal standard ^{1}H-NMR spectroscopy indicated full conversion, but integrals of product and internal standard confirmed an unexplained mass loss.

With *cis*- and *trans*-methyl-cyclohexane-diol (scheme 4, entries 3), which present only one secondary alcohol moiety, 72 % and 88 % conversion, respectively, was observed with 3.0 eq. H_2O_2.

The α-hydroxyketone products were obtained in 80 and 65 % isolated yield of the α-hydroxy ketone, respectively, after aqueous workup which helps getting rid of the diol starting material: *trans*-methyl-cyclohexane-diol indeed does not undergo full oxidation in the reported conditions (scheme 4, entry 3'a), but it is not present in the crude. The absence of side products indicate that cationic or radical intermediates are not formed, and demonstrates the mildness of the reaction conditions especially in comparison to methods that employ Oxone, NaOCl or $KMnO_4$ as terminal oxidant. When this reaction is carried on 10 mmol scale, a 55 % isolated yield of the product after column chromatography is achieved.

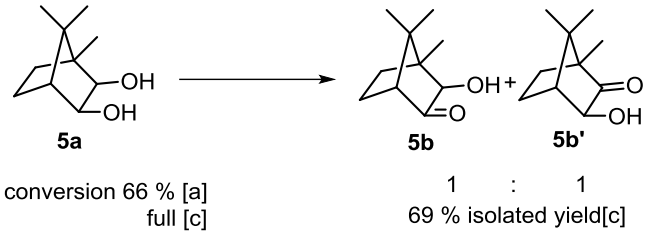
The more reactive *trans*-diol was isolated after workup (under non-optimized reaction conditions, entry [b]) in 65 % yield. The *cis* isomer was isolated in 80 % yield, after resubmission of the crude product to the same reaction conditions (entry [d]) (particular care must be taken during evaporation of the solvent).

A notable difference between the reactivity of *cis*- and *trans*-3-carene-diol (scheme 4, entry 4) was observed under standard conditions with 28% and 57% conversion to the desired α-hydroxyketone, respectively. Importantly, for both substrates the formation of byproducts was negligible. The selectivity achieved is remarkable considering that cyclopropyl moiety remains unreacted).

In the case of cyclopentane-1,2-diols, conversion to α-hydroxy ketones is observed for both *cis*- and *trans*-diol (with the latter being more reactive), albeit with poor selectivity and multiple byproducts as observed earlier by Plietker[17b] also. The increased tendency towards further oxidation for both cyclooctane-1,2-diol and cyclopentane-1,2-diol compared with their homologues, the cyclohexane-1,2-diols, indicates that ring strain

plays an important role in determining the ease with which subsequent oxidation of the initial α-hydroxyketone product occurs.

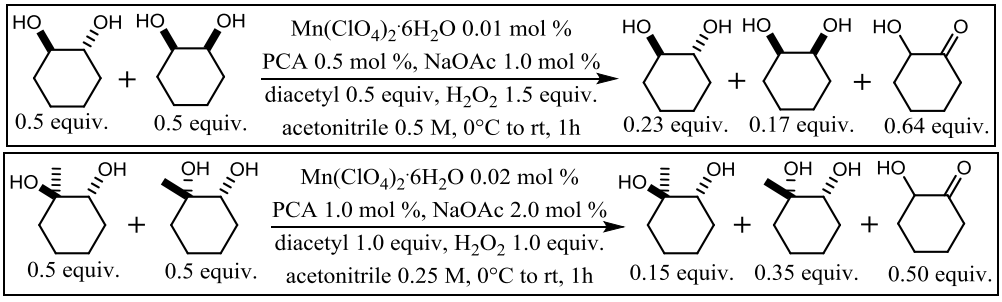
Camphene diol (scheme 5) was converted (66%) to a 1:1 mixture of regioisomers of α-hydroxy ketones with 1.5 equiv. of H_2O_2, without significant further oxidation. Notably, full conversion was observed, with retention of high selectivity w.r.t. the overoxidation products, when the substrate concentration was decreased by half. The two regioisomers were obtained in 69% isolated yield, after column chromatography.



Scheme 5. Oxidation of camphene diol.

Reaction conditions: [a] 0.5 M substrate, 0.01 mol % Mn(ClO4)2·6H2O, 0.5 mol % PCA, 1.0 mol % NaOAc, 0.25 M butanedione, 1.5 M H_2O_2 in acetonitrile. [c] 0.25 M substrate (0.5 mmol), 0.02 mol % $Mn(ClO_4)_2{\cdot}6H_2O$, 1.0 mol % PCA, 2.0 mol % NaOAc, 0.5 mmol butanedione, 3.0 mmol H_2O_2 in acetonitrile.

Competition reactions between *cis*- and *trans*-1,2-cyclohexandiol (Scheme 6) demonstrate that the former undergoes oxidation more readily than the latter. Similarly, oxidation of a mixture of *cis*- and *trans*-methylcyclohexane-1,2-diol (10 : 9.5 initial ratio, by ^{1}H-NMR spectroscopy) showed higher conversion (final substrate ratio 10 : 4.4) for the *trans*-isomer. These data indicate that oxidation of axial C-H bonds occurs more readily than at equatorial C-H bonds.

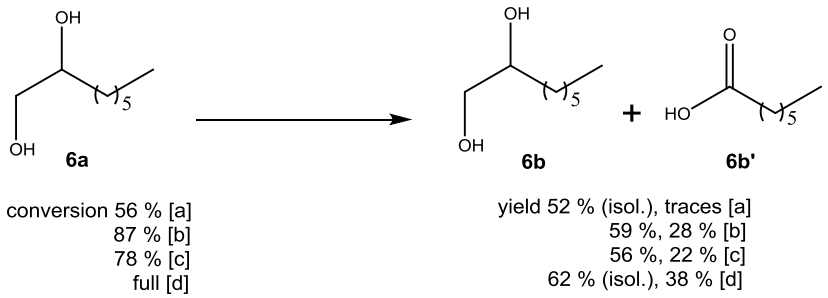


Scheme 6. Competition between *syn*- and *anti*-diols under oxidation conditions with 0.5 mmol of each diol in both cases.

Oxidation of linear aliphatic diols.

Whereas ring strain is an important factor for cyclic vicinal diols, for terminal linear diols selectivity between primary and secondary alcohol oxidation is of concern. Previously, we demonstrated[20] that the present catalytic system shows a strong preference for secondary and especially benzylic, alcohol oxidation and hence it was anticipated that a

preference for formation of 1-α-hydroxy-2-ketones would be observed for linear aliphatic 1,2-diols.

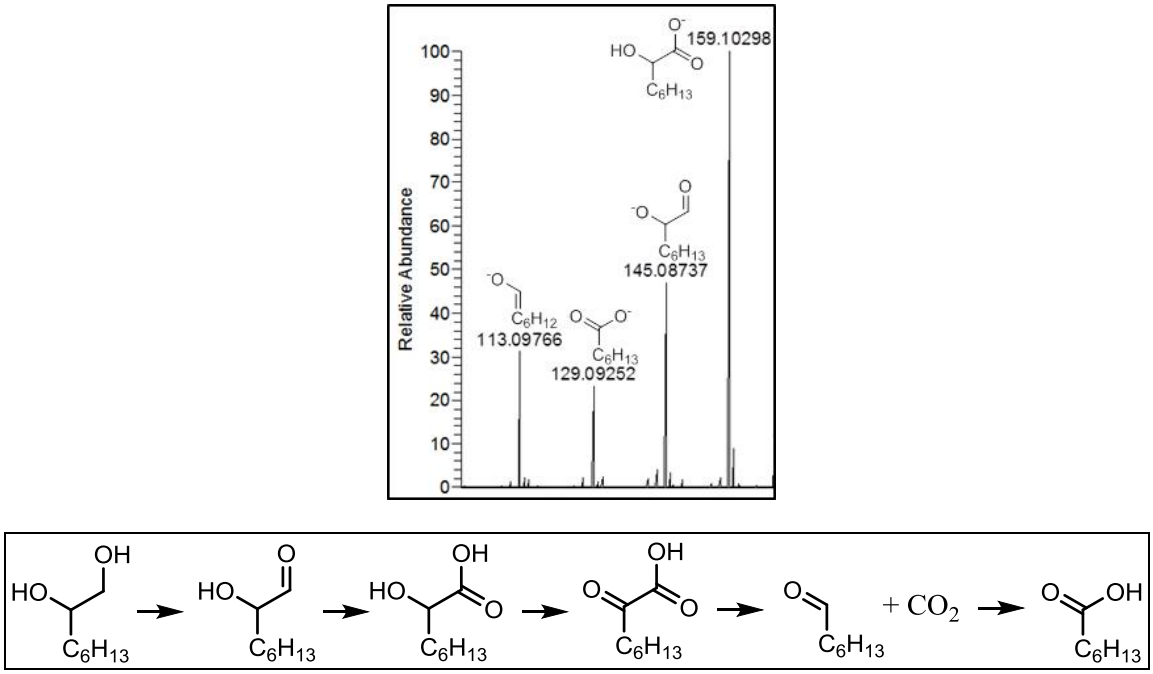


Scheme 7. Oxidation of octane-1,2-diol.

Reaction conditions: [a] 0.5 M substrate (1 mmol), 0.01 mol% $Mn(ClO_4)_2 \cdot 6H_2O$, 0.5 mol % PCA, 1.0 mol % NaOAc, 0.5 mmol butanedione, 1.5 mmol H_2O_2 in acetonitrile. [b] 0.5 M substrate (1 mmol), 0.01 mol % $Mn(ClO_4)_2 \cdot 6H_2O$, 0.5 mol % PCA, 1.0 mol% NaOAc, 0.5 mmol butanedione, 3.0 mmol H_2O_2 in acetonitrile. [c] 0.25 M substrate (0.5 mmol), 0.02 mol% $Mn(ClO_4)_2 \cdot 6H_2O$, 1.0 mol% PCA, 2.0 mol % NaOAc, 1.0 mmol butanedione, 3.0 mmol H_2O_2 in acetonitrile. [d] substrate submitted to conditions [c] and the resulting crude product again to conditions [c].

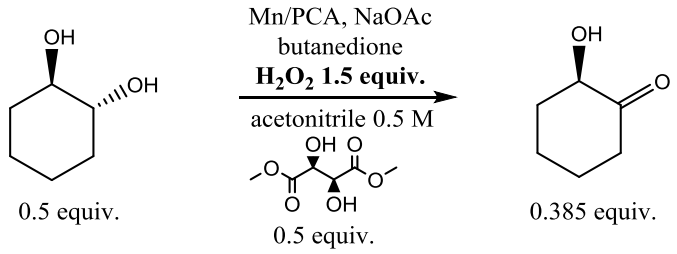
56 % conversion of 1,2-octanediol (scheme 7) was observed under standard conditions with a 52% isolated yield of the corresponding α-hydroxyketone after column chromatography. 87% conversion could be achieved with 3.0 eq of H_2O_2 albeit with formation of heptanoic acid together with other overoxidation products, as confirmed by negative mode ESI mass spectrometry (*vide infra*). Notably although the conversion improved when the initial amount of substrate is decreased by 50%, with all other reagent concentrations unchanged, an increase in the proportion of heptanoic acid formed was observed. As this is the only significant byproduct observed, the reaction mixture was resubmitted to the same reaction conditions in order to achieve full conversion of the starting material, and thus isolate the α-hydroxy ketone product after basic workup in 62 % yield.

The formation of heptanoic acid from 1,2-octandiol involves C-C bond cleavage. ESI-MS (negative mode, scheme 8) analysis of the reaction mixture, provided evidence of discrete amounts of other overoxidation products also, which clarifies the reaction pathway to heptanoic acid (129 m/z). The signals at 145 m/z and 143 m/z pertain to the starting material and α-hydroxyketone, respectively. The signal at 159 m/z indicates that the primary alcohol is susceptible to oxidation also leading to the formation of the α-hydroxy-octanoic acid. The signals 157 and 113 m/z correspond to the α-keto-octanoic acid and its decarboxylation product, respectively. Notably hexanoic acid is not observed confirming that C-C bond cleavage takes place between the 1^e and 2^e carbon only.



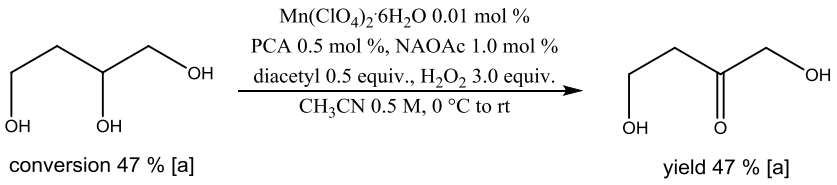
Scheme 8. ESI mass spectrum of oxidation reaction of 1,2-octandiol and interpretation of the oxidative pathway to carboxylic acid.

As expected, based on the excellent selectivity observed earlier[19c] in the *cis*-dihydroxylation of diethylfumarate, the product dimethyl-tartrate shows very low conversion. That this substrate is essentially unreactive under reaction conditions but does not itself inhibit the catalyst is confirmed by the concurrent oxidation with *trans*-1,2-cyclohexandiol (scheme 9), which underwent 77% conversion in the presence of dimethylmaleate.



Scheme 9. Oxidation of *trans*-cyclohexandiol in presence of diethylfumarate.

Oxidation of butane-1,2,4-triol (scheme 10) under standard reaction conditions enabled the selectivity between both primary and secondary alcohols, and between 1,2 and 1,3 diols to be acertained. 50% conversion was observed with formation of the α-hydroxyketone as the sole product. Comparable result was obtained when a 1:1 mixture of CH_3CN and MeOH was used as solvent.

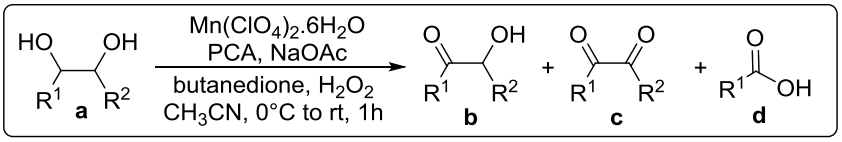


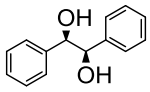
Scheme 10. Oxidation of butane-1,2,4-triol.

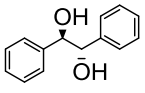
0.5 M substrate (1 mmol), 0.01 mol % $Mn(ClO_4)_2 \cdot 6H_2O$, 0.5 mol % PCA, 1.0 mol% NaOAc, 0.5 mmol butanedione, 3.0 mmol H_2O_2 in 1:1 CH_3CN.

Oxidation of aryl diols.

Both (R,R)-(+)-hydrobenzoin and *meso*-hydrobenzoin underwent 48 and 62% conversion under standard conditions with 1.5 eq. of H_2O_2, which increased to 75 % and full conversion (respectively) with 3.0 eq. of H_2O_2. In contrast to aliphatic diols, for aromatic diols selective oxidation is challenging as they show a strong tendency to undergo further oxidation and C-C bond cleavage to yield the corresponding benzoic acid products, which was observed to increase concomitant with increased substrate conversion. Hydrobenzoin(s) were indeed chosen to test the selectivity of the system, given their tendency to easily yield the corresponding diketone and C-C bond cleavage to acid.[21] It should be noted that the optimization of the conversion and selectivity by decreasing the concentration of substrate while keep other reagents concentration still worked as expected for the (R,R)-(+)-hydrobenzoin (scheme 11, entries 7 [a], 7 [b] and 7 [c]) while for *meso*-hydrobenzoin (scheme 11, entries 7') in which only doubling the amount of hydrogen peroxide (scheme 11, entry 7' [a]) lead to a result comparable to that obtained when half amount of substrate is used (scheme 11, entry 7' [c]), but that can be ascribed to the major reactivity of this substrate. Use of this condition lead to an isolated yield of 72 % of α-hydroxy ketone product, both on 5 mmol (1.070 g) or 15 mmol (3.210 g). Importantly, the acidic impurity is removed by basic work-up, while the diketone byproduct (yellow powder) is easily removed by the crude of reaction by dissolution in either CH_2Cl_2 or Et_2O. The low amount of benzoic acid is remarkable considering the propensity of benzoin to undergo oxidative carbon carbon bond cleavage.







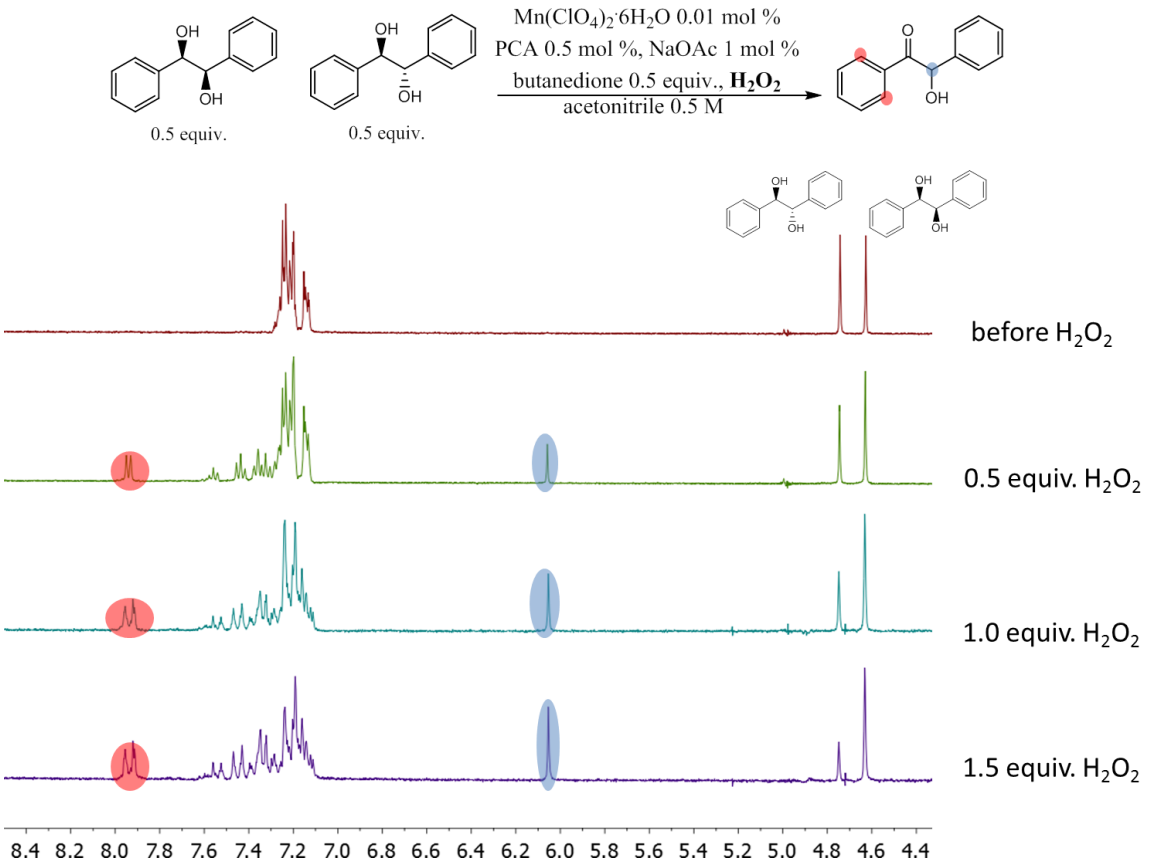
conversion	**7a** 48% [a], 75% [b], 73% [c]	**7'a** 62% [a], full [b], full [c]
yield	**7b** 43% [a], 67% [b], 68% [c]	**7'b** 59% [a], 78 % [b], 74% [c], isol. 72 %[c]
yield	**7c** 5% [a], 6% [b], 4% [c]	**7'c** 3% [a], 20% [b], 24% [c]
yield	**7d** 0% [a], 2% [b], 1% [c]	**7'd** 0% [a], 2% [b], 2% [c]

Scheme 11. Oxidation of (R,R)-(+)-hydrobenzoin and *meso*-hydrobenzoin.

Reaction conditions: [a] 0.5 M substrate (1 mmol), 0.01 mol % $Mn(ClO_4)_2 \cdot 6H_2O$, 0.5 mol % PCA, 1.0 mol % NaOAc, 0.5 mmol butanedione and 1.5 mmol H_2O_2 in acetonitrile. [b] 0.5 M substrate (1 mmol), 0.01 mol % $Mn(ClO_4)_2 \cdot 6H_2O$, 0.5 mol % PCA, 1.0 mol % NaOAc, 0.5 mol butanedione, 3.0 mmol H_2O_2 in acetonitrile. [c] 0.25 M substrate (0.5 mmol), 0.02 mol % $Mn(ClO_4)_2 \cdot 6H_2O$, 1.0 mol % PCA, 2.0 mol % NaOAc, 1.0 mmol butanedione, 3.0 mmol H_2O_2 in acetonitrile. [d] Substrate submitted to condition [c] and the resulting crude product to condition [c].

Knowledge of the reaction kinetics allows optimization of the reaction conditions. The reaction is zero order w.r.t. the substrate, and only proceeds for a limited time (typically ca. 20 min).[19c] The effective terminal oxidant is the hydroperoxy abduct formed by the addition of H_2O_2 to butanedione, which forms within 10 s. The butanedione itself can undergo oxidation to acetic acid and, hence, provided that the substrate is more susceptible to oxidation that butanedione, but the primary oxidation product is less susceptible, the conversion can be increased by reducing the initial concentration of substrate. Furthermore, the lag phase observed earlier is observed for the present substrates also, and is eliminated by addition of acetic acid (typically 0.05-0.2 equivalents w.r.t. the substrate).

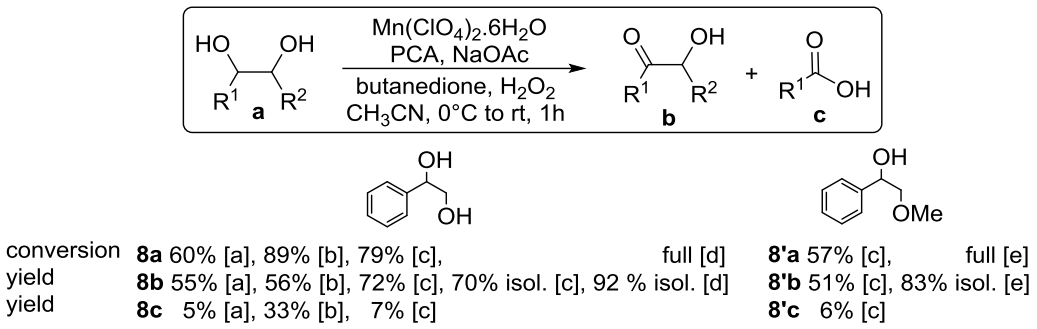
As for cyclic aliphatic diols, (R,R)-(+)-hydrobenzoin was found to be more reactive than *meso*-hydrobenzoin. The difference in reactivity of the substrates was explored through competition experiments, using a limited amount of hydrogen peroxide under otherwise standard conditions (scheme 12). It is evident that, since nearly equal amount of the two substrates were present, the *meso*-hydroxybenzoin is formed from the the diastereomer (R,R)-(+)-hydrobenzoin, in agreement with data obtained when oxidation of each substrate is carried out separately, scheme 11. These data further support the conclusion the active oxidant is selective.



Scheme 12. Competition experiment in the oxidation of (R,R)-(+)-hydrobenzoin and *meso*-hydrobenzoin.

Under standard conditions (scheme 13) 1-phenyl-1,2-ethanediol underwent 60 % conversion, with 50 % yield of α-hydroxyketone (oxidation at the secondary alcohol) and 5% of benzoic acid, and aldehyde was not detected, indicating that the 1,2 diol moiety undergoes C-C bond cleavage more easily than oxidation of the primary alcohol to aldehyde, in contrast to linear terminal diols (entry 6). Increasing the concentration of H_2O_2 (scheme 13, entry 8 [b]) resulted in significantly increased formation of benzoic acid, whereas reducing the initial amount of substrate by 50% w.r.t. standard conditions (scheme 13, entry 8 [c]) both conversion and selectivity improved substantially with, after column chromatography, 70 % isolated yield. However, as discussed above, resubmission of the crude product to the same reaction conditions (but with only 10% of oxidant, entry 8 [d]), made use of the selectivity of the system to achieve full conversion. The acid formed was easily separable through a basic workup, which yielded the pure product in 92 % yield.

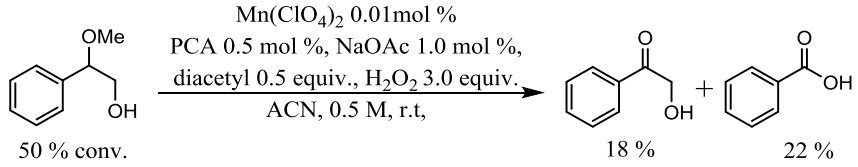
With 2-methoxy-1-phenylethan-1-ol good selectivity was achieved despite low conversion, even with conditions [c]. Again full conversion was achieved by submitting the crude of reaction to the same reaction conditions (entry [e]) followed by a basic workup to remove the acid, yielding the product in 83 % yield.



Scheme 13. Oxidation of benzylic diols.

Reaction conditions: [a] 0.5 M substrate (1 mmol), 0.01 mol % $Mn(ClO_4)_2 \cdot 6H_2O$, 0.5 mol % PCA, 1.0 mol % NaOAc, 0.5 mmol butanedione and 1.5 mmol H_2O_2 in acetonitrile. [b] 0.5 M substrate (1 mmol), 0.01 mol % $Mn(ClO_4)_2 \cdot 6H_2O$, 0.5 mol % PCA, 1.0 mol % NaOAc, 0.5 mol butanedione, 3.0 mmol H_2O_2 in acetonitrile. [c] 0.25 M substrate (0.5 mmol), 0.02 mol % $Mn(ClO_4)_2 \cdot 6H_2O$, 1.0 mol % PCA, 2.0 mol % NaOAc, 1.0 mmol butanedione, 3.0 mmol H_2O_2 in acetonitrile. [d] Substrate submitted to condition [c] and the resulting crude product to condition [c] with 10 mol % H_2O_2. [e] Substrate submitted to condition '[c]' and the resulting crude to condition '[c]'.

2-Methoxy-2-phenylethanol was less reactive (around 50 % conversion, scheme 14), yielding two major products beside the starting material: benzoic acid and α-hydroxyketone in a roughly 2:1 ratio (determined by ^{1}H-NMR analysis). This result shows that, even though it is protected, benzylic carbon is more prone to undergo oxidation than the terminal carbon, confirming the conclusions reached in regard to selectivity between benzylic and terminal carbons of 1-phenyl-1,2-ethanediol.



Scheme 14. Oxidation of 2-Methoxy-2-phenylethanol.

4.3 Conclusions

In this chapter a new catalytic method for the selective oxidation of 1,2-diols to α-hydroxyketones is described, which, to the best of our knowledge, is the first reported method that employs a 1st row transition metal catalyst with H_2O_2 as terminal oxidant. Although good selectivity is achieved in many cases, for several challenging substrates, selectivity, still has room for improvement to reduce further the extent of overoxidation.

4.4 Experimental

All reagents were of commercial grade and were used as received unless stated otherwise. Hydrogen peroxide was used as received (Acros Chemicals) as a 50 wt % solution in water; note that the grade of H_2O_2 employed can affect the outcome of the reaction, as some sources are stabilized using sequestrants. ^{1}H NMR (400.0 MHz) and ^{13}C NMR

(100.59 MHz) spectra were recorded on a Varian Avance 400. Chemical shifts are relative to the following: ^{1}H NMR, $CDCl_3$ (7.26 ppm) and CD_3CN (1.94 ppm); ^{13}C NMR, $CDCl_3$ (77 ppm) and CD_3CN (118 ppm).

Caution! The drying or concentration of solutions that potentially contain H_2O_2 should be avoided. Prior to drying or concentrating, the presence of H_2O_2 should be tested for using peroxide test strips followed by neutralization on solid $NaHSO_3$ or another suitable reducing agent. When working with H_2O_2, suitable protective safeguards should be in place at all times due to the risk of explosion.

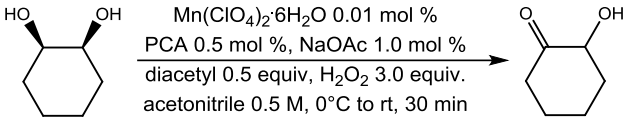
Caution! Butanedione has been linked with lung disease upon prolonged exposure to its vapors. It should be handled in a properly ventilated fume hood, and exposure to vapors should be avoided.

Typical Procedure for Catalytic Oxidations Described in Scheme 4. The substrate (1 mmol) was added to a solution containing $Mn(ClO_4)_2 \cdot 6H_2O$ and PCA in acetonitrile. NaOAc (aqueous, 0.6 M), butanedione (0.5 mmol), acetic acid (0.2 mmol, 0.011 ml) and acetonitrile/acetone (amount depending on that of the substrate) were added to give a final volume of 2 mL and a final concentration of the substrate of 0.5 M (for less reactive substrate the amount of starting material is divided by half to give a final concentration of 0.25 M). The solution was stirred in an ice/water bath before addition of H_2O_2 (50 wt %). Conversion was verified by ^{1}H NMR by dilution of a part of the reaction mixture in CD_3CN or by directly diluting the sample in $CDCl_3$ (when acetone is the solvent). Product isolation involved addition of brine (10 mL) and extraction with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous), and filtered, and the dichloromethane was removed in vacuo. Substrates prone to give C-C bond cleavage (1,2-octandiol and 1-phenyl-1,2-ethanediol) were purified by reaching full conversion and removing the acid impurities with a basic workup. In the case of hydrobenzoin(s), the overoxidation diketone product is selectively removed, after CH_2Cl_2 is evaporated, by washing the resulting powder with small amounts of Et_2O (a yellow byproduct is removed).

1,2-Dichlorobenzene, which has a negligible effect on the reaction, was employed as internal standard for Raman and ^{1}H NMR spectroscopy. Reaction monitoring with Raman spectroscopy focused primarily on the intensity of the C=C and C=O stretching bands between 1550 and 1800 cm^{-1} (e.g., at 1724 cm^{-1} for butanedione), between 600 and 900 cm^{-1} relating to the C=C and C=O bending modes (682 cm^{-1} for butanedione), and the O−O stretching mode of H_2O_2 at 870 cm^{-1}.

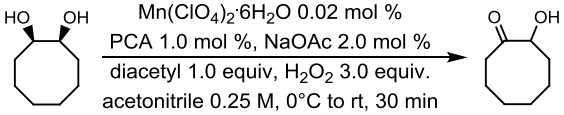
Characterization of isolated compounds

2-hydroxycyclohexan-1-one



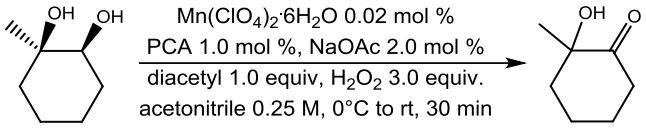
The substrate (1 mmol) was added to a 0.5 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 0.5 mL solution PCA (12.3 mg in 10 mL of solvent) in acetonitrile. 16.7 µL NaOAc (aqueous, 0.6 M) and 43.5 µL butanedione (0.5 mmol) were added to give a final volume of 2 mL and a final concentration of the substrate of 0.5 M. Reaction mixture is cooled in an ice bath and H_2O_2 (170 µL, 3.0 mmol) is added dropwise while stirring. Reaction is allowed to reach rt. Conversion was verified by ^{1}H NMR by dilution of a part of the reaction mixture in CD_3CN and after 30 min reaction was added 10 mL CH_3Cl and 10 mL saturated aqueous NaCl. Layers are separated and the aqueous one is extracted with CH_3Cl (2 x 10 mL); gathered organic layers are dried over anhydrous $MgSO_4$ and filtered, and the solvent is evaporated in vacuo. Crude of reaction is purified through column chromatography (Silica gel, Pentane : Et_2O = 8:2) to give an isolated yield of 65 % (82 mg). Spectroscopic data agree with those found in literature.[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (ddd, J = 12.5, 6.9, 1.3 Hz, 1 H), 3.25 (br s, 1 H,), 2.61 − 2.31 (m, 3 H); 2.17 − 2.07 (m, 1 H), 1.95 − 1.85 (m, 1 H), 1.81 − 1.43 (3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.4, 75.3, 39.5, 36.7, 27.6, 23.4.

2-hydroxycyclooctan-1-one



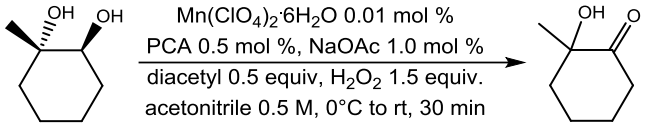
The substrate (1 mmol) was added to a 1.0 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 1.0 mL solution PCA (12.3 mg in 10 mL of solvent) in acetonitrile. 16.7 µL NaOAc (aqueous, 0.6 M) and 43.5 µL butanedione (0.5 mmol) were added to give a final volume of 2 mL and a final concentration of the substrate of 0.25 M. Reaction mixture is cooled in an ice bath and H_2O_2 (170 µL, 3.0 mmol) is added dropwise while stirring. Reaction is allowed to reach rt. Conversion was verified by ^{1}H NMR by dilution of a part of the reaction mixture in CD_3CN and after 30 min reaction was added 20 mL CH_3Cl and 20 mL saturated aqueous NaCl. Layers are separated and the aqueous one is extracted with CH_3Cl (2 x 20 mL); gathered organic layers are dried over anhydrous $MgSO_4$ and filtered, and the solvent is evaporated in vacuo. Crude of reaction is purified through column chromatography (Silica gel, Pentane : Et_2O = 8:2) to give an isolated yield of 56 % (82 mg). Spectroscopic data agree with those found in literature.[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (d, J = 6.4 Hz, 1 H), 3.72 (br s, 1 H), 2.71 (td, J = 12.2, 3.8 Hz, 1 H), 2.44 − 2.29 (m, 2 H), 2.08 − 1.91 (m, 2 H), 1.87 − 1.62 (m, 4 H), 1.45 − 1.32 (m, 2 H), 0.98 − 0.84 (m, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 217.4, 76.2, 37.3, 29.2, 28.7, 25.5, 24.5, 22.1.

2-hydroxy-2-methylcyclohexan-1-one



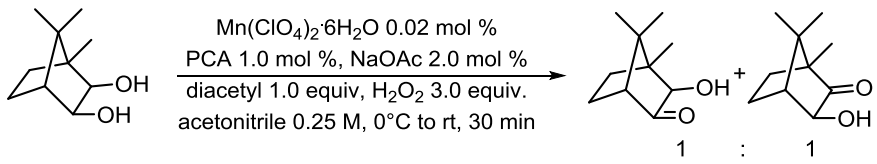
Substrate is submitted to the same reaction conditions as 2-hydroxycyclooctan-1-one. Crude of reaction is then resubmitted to the same reaction conditions to reach full conversion to the product. Product (80 % yield) is the main component of the crude, while amount of byproducts is negligible. Spectroscopic data agree with those found in literature.[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.0 (BS, 1H), 2.43 – 2.60 (m, 2H), 1.55 – 2.17 (m, 8H), 1.40 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 214.5, 76.6, 42.2, 37.9, 28.0, 25.5, 23.2.

2-hydroxy-2-methylcyclohexan-1-one



The substrate (1 mmol) was added to a 0.5 mL solution $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 mL solvent) and 0.5 mL solution PCA (12.3 mg in 10 mL of solvent) in acetonitrile. 16.7 µL NaOAc (aqueous, 0.6 M) and 43.5 µL butanedione (0.5 mmol) were added to give a final volume of 2 mL and a final concentration of the substrate of 0.5 M. Reaction mixture is cooled in an ice bath and H_2O_2 (85 µL, 1.5 mmol) is added dropwise while stirring. Reaction is allowed to reach rt. Conversion was verified by ^{1}H NMR by dilution of a part of the reaction mixture in CD_3CN and after 30 min reaction was added 10 mL CH_3Cl and 10 mL saturated aqueous NaCl. Layers are separated and the aqueous one is extracted with CH_3Cl (2 x 10 mL); gathered organic layers are dried over anhydrous $MgSO_4$ and filtered, and the solvent is evaporated in vacuo. Product (65 % yield) is the main component of the crude, while amount of byproducts is negligible. Spectroscopic data agree with those found in literature.[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 – 2.60 (m, 2H), 1.55 – 2.17 (m, 8H), 1.40 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 214.5, 76.6, 42.2, 37.9, 28.0, 25.5, 23.2.

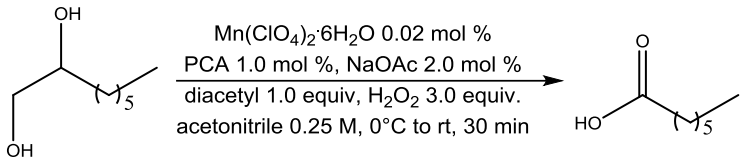
2-hydroxy-bornan-3-one and 3-hydroxy-bornan-2-one



Substrate was submitted to the same reaction conditions of 2-hydroxycyclooctan-1-one. Crude of reaction was purified by column chromatography (Silica, Pentane : Et_2O = 7:3) yielding the product in a 1:1 mixture of regioisomers in 69 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 1H), 3.53 (s, 1H), 1.64 (br, 2H), 2.17 (d, J = 1.0, 1H), 2.09 (d, 1H),

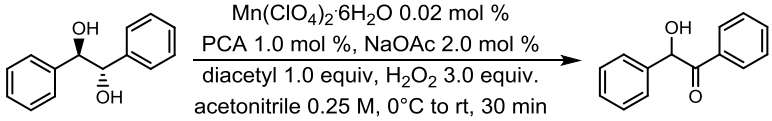
2.05 - 1.80 (m, 4H), 1.66 (td, 1 H), 1.48 – 1.35 (m, 5H), 1.04 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H) ; ^{13}C NMR (400 MHz, $CDCl_3$) δ 220.2, 218.8, 79.7, 77.6, 58.8, 57.2, 49.4, 46.9, 34.1, 28.7, 25.4, 21.3, 20.5, 20.3, 19.0, 10.4, 9.2.

1-hydroxyoctan-2-one



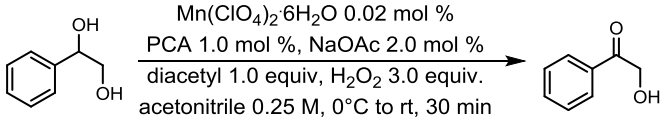
Substrate is submitted to the same reaction conditions as 2-hydroxycyclooctan-1-one. Crude of reaction is then resubmitted to the same reaction conditions to reach full conversion to the product. The only heptanoic acid byproduct present in the mixture is eliminated via basic workup, yielding the pure product in 62 % yield. Spectroscopic data agree with those found in literature.[18] ^{1}H-NMR (400 MHz, CDCl3) δ 4.23 (s, 2 H), 3.14 (br. s, 1 H), 2.40 (t, J = 7.45 Hz, 2 H), 1.50 − 1.65 (m, 2 H), 1.20 − 1.35 (m, 6 H), 0.90 − 0.80 (m, 3 H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 209.9, 68.1, 38.4, 31.4, 28.8, 23.7, 22.4, 13.0.

phenyl benzoate



Substrate was submitted to the same reaction conditions of 2-hydroxycyclooctan-1-one and also in 5 mmol (1.070 g) or 15 mmol (3.210 g) scale. The benzoic acid byproduct present in the resulting is eliminated via basic workup, yielding a mixed white (product) and yellow (diketone byproduct) powder. The diketone is eliminated by washing the powder with either CH_2Cl_2 or Et_2O thanks to its major solubility, yielding the pure product in 72 % yield. Spectroscopic data are compared with available commercial product purchased from Sigma Aldrich. ^{1}H-NMR (400 MHz, CDCl3) δ 7.91(m, 2H), 7.52 (m, 1H), 7.40 (m, 2H), 7.35 – 7.30 (m, 5H), 5.95 (d, J = 6.3 Hz, 1H), 4.55 (d, J = 6.3 Hz, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ 198.9, 139.0, 133.8, 133.5, 129.1, 129.1, 128.6, 128.5, 127.7, 76.2.

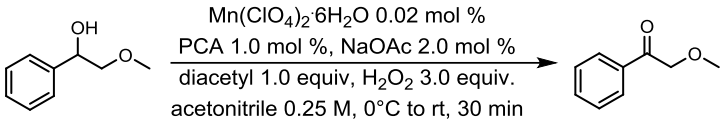
1-phenylethane-1,2-diol



Substrate was submitted to the same reaction conditions of 2-hydroxycyclooctan-1-one on a 2.0 mmol scale; the resulting crude was then submitted to the same reaction conditions

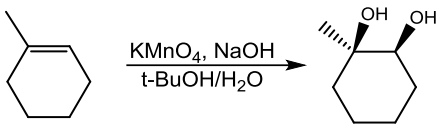
but employing only 10 % of H_2O_2. The only significant benzoic acid byproduct present in the resulting is eliminated via basic workup, yielding the product in 92 % yield. Spectroscopic data agree with those found in literature.[18] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.4, 2H), 7.65 − 7.60 (m, 1 H), 7.53 − 7.48 (m, 2 H), 4.89 (s, 2 H), 3.53 (bs, 1 H). ^{13}C-NMR (400 MHz, $CDCl_3$) δ 198.4, 134.3, 133.3, 128.9, 127.8, 65.46.

2-methoxy-1-phenylethan-1-one



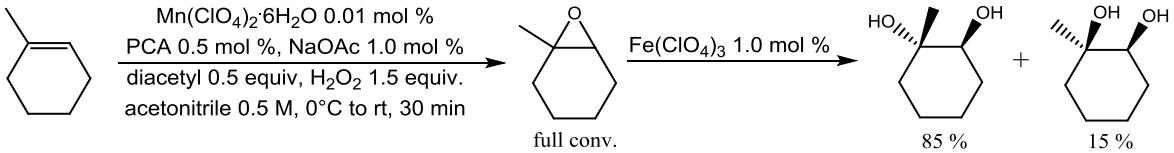
Substrate was submitted to the same reaction conditions of 2-hydroxycyclooctan-1-one an on a 15 mmol (3.2 g) scale; the resulting crude was submitted to the same reaction conditions. The only significant benzoic acid byproduct present in the resulting is eliminated via basic workup, yielding the product in 83 % yield. Spectroscopic data agree with those found in literature.[24] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 4.71 (s, 2H), 3.50 (s, 3H).

(1R,2S)-1-methylcyclohexane-1,2-diol



Substrate (20 mmol, 1923 g) was dissolved in a mixture of *t*-BuOH/H_2O = 4.1 : 1.6 (mL) and cooled to 0 °C. Previously, 4.4 g $KMnO_4$ and 735 mg NaOH were dissolved in 80 mL H_2O; 6.8 ml of this solution were added, dropwise, to the substrate containing solution: the resulting mixture was stirred at 0 °C for at least 15 min. Reaction mixture was filtered through a glass filter (por 3) and the filtrate was saturated with NaCl; an oil could separate, in which case had to be collected. Aqueous layer is extracted with $CHCl_3$ (3 x 10 mL); oil and organic layers are gathered and washed with H_2O (2 x 20 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude of reaction is purified by column chromatography (Silica, EtOAc : CH_2Cl_2 = 4:6, then improving the EtOAc ratio) yielding the pure compound in 58 % yield. Spectroscopic data agree with those found in literature.[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (m, 1H), 1.90 - 1.20 (br, 10H), 1.28 (s, 3H).

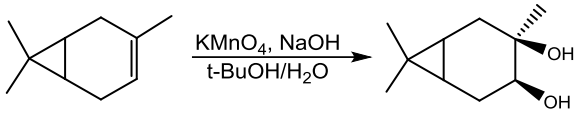
(1S,2S)-1-methylcyclohexane-1,2-diol



The substrate (20 mmol, 1.923 g) was submitted to the same conditions listed above for 2-hydroxy-2-methylcyclohexan-1-one. After epoxidation was complete (30 min) 1.0 mol % $Fe(ClO_4)_3$ was added and reaction was stirred overnight. The mixture was then added

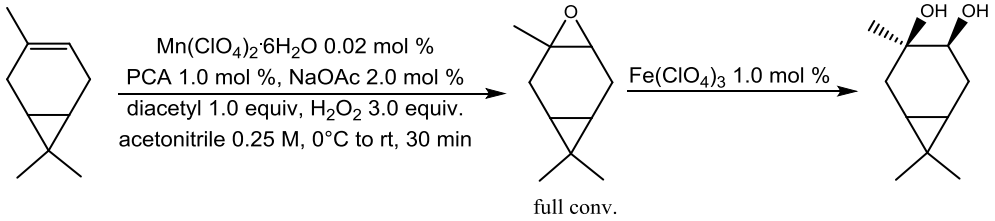
200 mL NaCl saturated aqueous and 200 mL CH_2Cl_2, and layers were separated; aqueous layer was extracted again (2 x 200 mL CH_2Cl_2) and the gathered organic layers are gathered and dried over anhydrous $MgSO_4$; solvent is evaporated in vacuo to yield the crude of reaction, which is purified through column chromatography (Silica, EtOAc : CH_2Cl_2 = 4:6, then improving the EtOAc ratio) yielding the pure compound in 35 % yield. Spectroscopic data agree with those found in literature.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (m, 1H), 1.88 – 1.62 (m, 4H), 1.23 – 1.39 (m, 4H), 1.18 (s, 3H).

(3R,4S)-3,7,7-trimethylbicyclo[4.1.0]heptane-3,4-diol



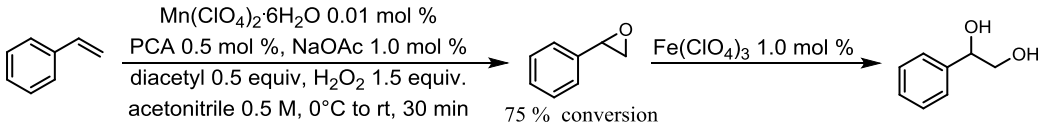
Substrate is submitted to the same reaction conditions as (1R,2S)-1-methylcyclohexane-1,2-diol to yield the product in 53 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (m, 1H), 2.18 – 1.98 (m, 2H), 1.80 – 1.58 (m, 3H), 1.30 – 1.16 (m, 1 H), 1.20 (s, 3H), 1.00 (s, 3H), 0.88 – 0.79 (m 1H), 0.89 (s, 3H), 0.63 (td, 1H).

(3R,4S)-3,7,7-trimethylbicyclo[4.1.0]heptane-3,4-diol



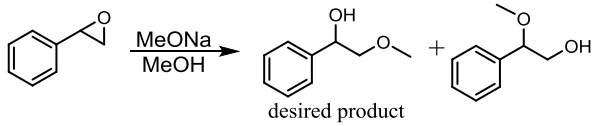
The substrate was submitted to the same reaction conditions of 2-hydroxy-2-methylcyclohexan-1-one but on a 5.0 mmol (681 mg) scale. The mixture was then added 200 mL saturated aqueous saturated aqueous NaCl and 200 mL CH_2Cl_2, and layers were separated; aqueous layer was extracted again (2 x 200 mL CH_2Cl_2) and the gathered organic layers are gathered and dried over anhydrous $MgSO_4$; solvent is evaporated in vacuo to yield the crude of reaction, purified by column chromatography (Silica, Pentane : Et_2O = 1:1, in gradient of Et_2O) to afford the product in 30 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (dd, 1H), 2.11 (dd, 1H), 1.97 (dd, 1H), 1.70 – 1.56 (m, 3H), 1.26 – 1.19 (m, 1H), 1.22 (d, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.75 – 0.67 (m, 2H).

1-phenyl-1,2-ethandiol



Substrate was submitted to the same reaction conditions of 2-hydroxy-2-methylcyclohexan-1-one on a 10 mmol (1.042 g) scale. After epoxidation was complete (30 min) 1.0 mol % $Fe(ClO_4)_3$ was added and reaction was stirred overnight. The mixture was then added 100 mL saturated aqueous NaCl. and 200 mL CH_2Cl_2, and layers were separated; aqueous layer was extracted again (2 x 100 mL CH_2Cl_2) and the gathered

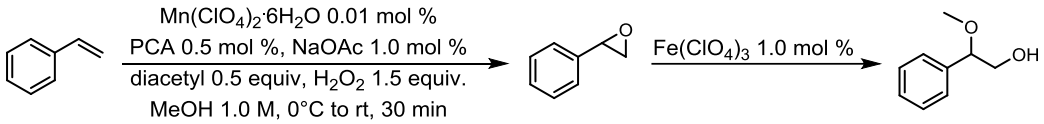
organic layers are gathered and dried over anhydrous $MgSO_4$; solvent is evaporated in vacuo to yield the crude of reaction, which is purified through column chromatography (Silica, CH_2Cl_2 : Et_2O = 8:2, then improving the Et_2O ratio) yielding the pure compound in 38 % yield. Spectroscopic data agree with those of the commercially available compound purchased from Sigma Aldrich. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.82 (dd, 1H), 3.76 (dd, 1H), 3.66 (dd, 1H), 2.45 (bs, 1H), 2.05 (bs, 1H).



2-methoxy-1-phenylethan-1-ol

Crude of reaction containing styrene epoxide (10 mmol substrate, oxidized in 0.25 M conc.)[19c] is added 813 mg NaOH and 10 mL ethanol and stirred overnight. The mixture was then added 100 mL saturated aqueous NaCl and 200 mL CH_2Cl_2, and layers were separated; aqueous layer was extracted again (2 x 100 mL CH_2Cl_2) and the gathered organic layers are gathered and dried over anhydrous $MgSO_4$; solvent is evaporated in vacuo to yield the crude of reaction, which is purified through column chromatography (Silica, CH_2Cl_2 : Et_2O = 95:5, then improving the Et_2O ratio), yielding the desired product in 20 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 5H), 4.89 (dd, 1H), 3.55 (dd, 1H), 3.47 – 3.41 (m, 1H), 3.44 (s, 3H), 2.51 (bs, 1H).

2-methoxy-2-phenylethan-1-ol



Substrate was submitted to the same reaction conditions of 1-phenyl-1,2-ethandiol on a 10 mmol (1.042 g) scale, but solvent is methanol in this case and substrate concentration is 1.0 M. After epoxidation was complete (30 min) 1.0 mol % $Fe(ClO_4)_3$ was added and reaction was stirred overnight. The mixture was then added 100 mL saturated aqueous NaCl and 200 mL CH_2Cl_2, and layers were separated; aqueous layer was extracted again (2 x 100 mL CH_2Cl_2) and the gathered organic layers are gathered and dried over anhydrous $MgSO_4$; solvent is evaporated in vacuo to yield the crude of reaction, which is purified through column chromatography (Silica, CH_2Cl_2 : Et_2O = 8:2, then improving the Et_2O ratio) yielding the pure compound in 30 % yield. Spectroscopic data agree with those found in literature.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.38 (m, 5H), 4.31 (dd, 1H), 3.72 – 3.58 (m, 2H), 3.31 (s, 3H), 2.35 (bs, 1H).

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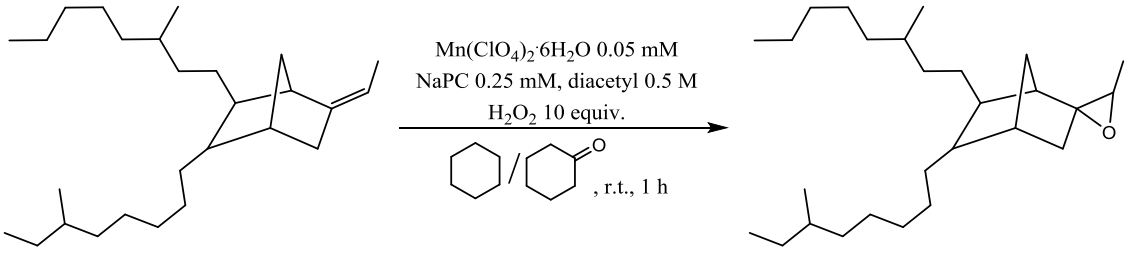
Chapter 5

Manganese-catalyzed epoxidation of ethylene/propylene/diene rubber with hydrogen peroxide.

Abstract. A versatile catalytic methodology for the epoxidation of EPDM polymers with H_2O_2 using an in-situ formed Mn-based catalyst is described. The catalyst system was earlier shown to be effective in the efficient oxidation of electron-rich alkenes to epoxides in polar solvents, such as acetone, acetonitrile and ethanol. These solvents are unsuitable for the epoxidation of the residual unsaturation in EPDM polymer, due to the latter's insolubility. The versatility of the Mn catalyst system in regard to solvent was exploited to overcome this by using solvent mixtures based on cyclohexane and cyclohexanone, enabling the control of the extent of epoxidation with reaction times of less than 1 h at room temperature. The mild conditions employed avoid gelation and polymer degradation, which have been observed with previously described methods for the epoxidation of EPDM polymers. Furthermore the method opens opportunities for further functionalization steps in a one pot procedure and facile polymer isolation by addition of a non-solvent.



5.1 Introduction

Rubbers and elastomers are typically soft, flexible, high-molecular weight polymers with little or no crystallinity and a glass transition temperature below their application temperature.[1] Although soluble in certain solvents, they are typically processed in a melt, which allows mixing with (reinforcing) fillers, plasticizers, curatives and other additives, as well as extrusion and compression/injection molding into the desired shapes. Rubbers are used without crosslinking to toughen brittle, semi-crystalline thermoplastics,[2] such as polypropylene (PP) and engineering polyamides (PA-6 and PA-6.6) and polyesters (PET and PBT). The crosslinking of rubbers, however, provides the elasticity, high strength and solvent resistance needed in applications such as tires, seals, tubes, and valves, etc.[3] Sulphur vulcanization of rubber is most commonly used and results in excellent mechanic and dynamic performance, but with somewhat poor heat ageing resistance. In contrast, peroxide curing of rubber results in excellent heat ageing resistance, but cannot be performed in hot-air tunnels and is viewed as less versatile and more expensive compared to sulfur vulcanization.

The high degree of unsaturation in commodity rubbers, *i.e.* natural rubber (NR), butadiene rubber (BR) and styrene/butadiene rubber (SBR), facilitates fast and efficient sulfur vulcanization. A drawback of unsaturation, however, is that it increases the polymer's susceptibility to damage by oxygen, ozone and heat. Ethylene/propylene/diene rubber (EPDM), which has a fully saturated backbone, has relatively low levels of unsaturation in the side groups, providing excellent resistance to damage from oxygen, ozone, heat and UV light. EPDM rubber has a high resistance against polar solvents. Hence, EPDM is applied widely in automotive seals, window gaskets, roof sheeting, thermoplastic vulcanisates, tubes, and hoses. However, EPDM performs poorly in contact with apolar solvents (e.g., petrol and oil). Furthermore, it shows poor adhesion to polar materials, both on a macroscopic (co-extrusion with polar polymers such as polyamides and polyesters) and on a microscopic level (composites with inorganic fillers and blends with polar polymers).

Optimizing polymer performance for specific applications can be achieved through the introduction of new functionalities, either by addition of new co-monomers during polymerization or by post-reactor modification of commodity polymers. The latter approach is technically and economically highly interesting as it allows for greater versatility in tuning polymer properties. Chemical modification of polymers is performed either in solution, in a latex (NR), in the melt (reactive extrusion) or only on the surface of a polymer substrate. Epoxide-containing rubbers are produced on a commercial scale via co-polymerization and post-reactor modification. For example, ter-polymerization of ethylene, methyl acrylate and glycidyl methacrylate (GMA) yields elastomers with an epoxide function, which are used as impact modifier of engineering polyesters, such as PBT. Carboxylic acid end groups of PBT react at the interface with the rubber epoxy groups, resulting in graft copolymers that act as compatibilizer for the PBT/rubber blend. Terpolymerization of ethylene, vinyl acetate and GMA yields elastomers with an epoxide function, which enables a new way of crosslinking with dicarboxylic acids with some

benefits over peroxide curing. Up to 50% epoxidation of the alkene moieties in NR results in modification of its bulk properties, especially oil resistance and gas permeability, and can potentially provide better roll resistance and wet grip in car tires.

Epoxidation of the alkene motifs present in EPDM polymers provides a versatile handle for both modification of the polymer properties and their further functionalization. Epoxidized EPDMs are of interest as impact modifiers for engineering polyesters and polyamides and opens opportunities for crosslinking with diacids and protected diamines to achieve the same high-temperature performance as peroxide crosslinking.

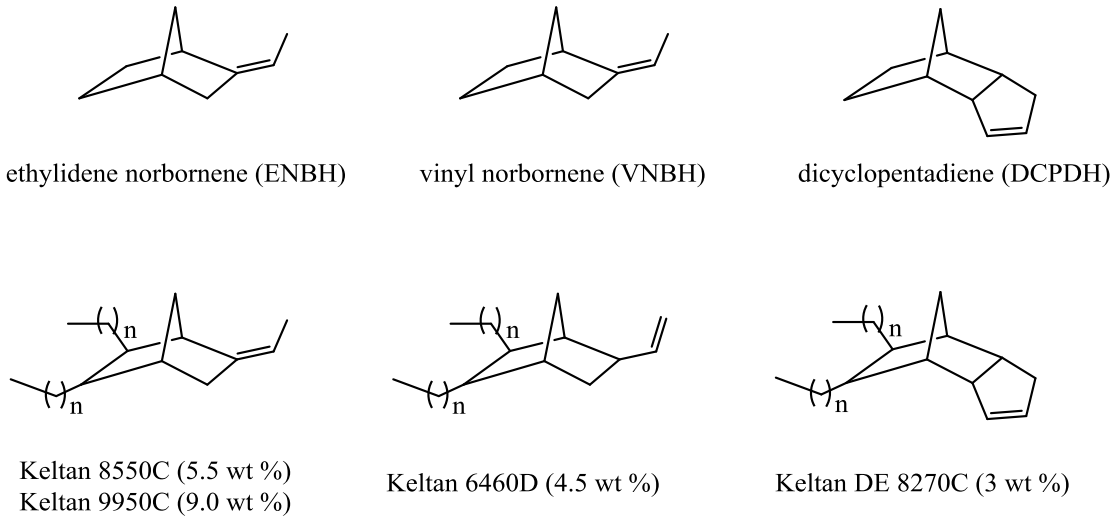


Figure 1. EPDM polymers bearing mono-, di-, and tri-substituted alkene moieties and their small molecule analogs evaluated for post-polymerization epoxidation. The % double bonds by mass is indicated in parentheses.

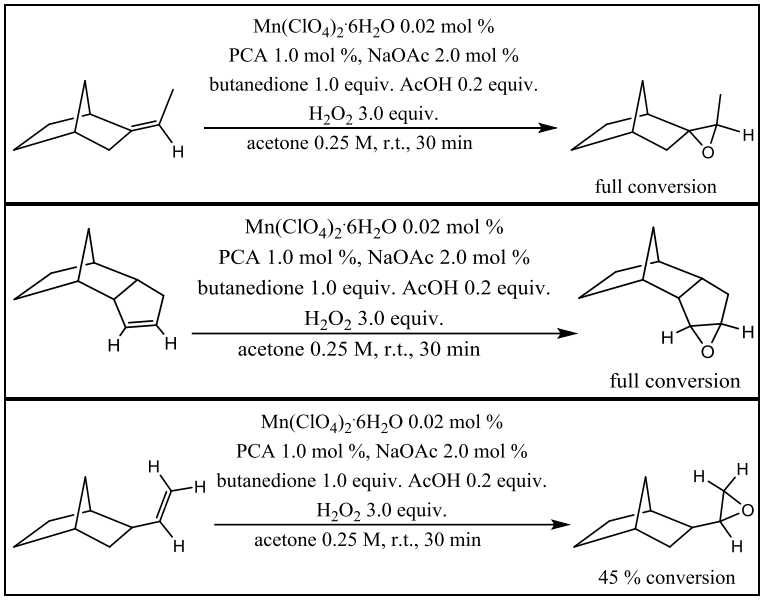
Epoxidation using peroxy acids, used directly (*e.g.*, perbenzoic acids) or formed *in situ* (performic acid), has been described earlier. The in situ generation of performic acid is the more commonly used approach as it shows reduced formation of byproducts as the extent of polymer epoxidation increases. Indeed, the stability of the epoxidized polymers depends on the amount of acid and hydrogen peroxide (H_2O_2) present, *e.g.*, due to epoxide ring-opening to a diol which subsequently reacts with other epoxide groups resulting in solvent gelation. Recently, t-butyl hydroperoxide has been applied together with MoO_3 catalysts (at as low as 0.065 M) to avoid the use of acidic conditions and realize nearly complete epoxidation of the alkene moieties in EPDM within 8 h at 90 ^oC. First row transition metal catalysts (*e.g.*, Mn(II)), that are environmentally benign and can be removed easily together with atom economic oxidants such as H_2O_2 at low temperatures, would be highly preferable to the use of stoichiometric organic peroxides. However, solvent compatibility in the case of EPDM polymers is a major challenge and the use of, for example, phase transfer catalysts is undesirable both for environmental reasons and in controlling polymer properties.

In this chapter, the relatively simple catalyst system, in terms of preparation, described in earlier chapters to epoxidize alkenes and other substrates cleanly and effectively, can also

be applied to the epoxidation of EPDM polymers. The catalyst system explored in our previous study[4] is formed *in situ* from a Mn(II) salt, pyridine-2-carboxylic acid (PCA), and a ketone such as butanedione (BD), a base, such as NaOAc, and acetic acid which, together with H_2O_2 as terminal oxidant, can epoxidize a wide range of electron-rich alkenes with high turnover numbers and selectivities.[5] In this system, the butanedione forms an adduct with H_2O_2, which subsequently reacts with the manganese catalyst to generative the active oxidant. The addition small amount of base added serves to form the catalytically active manganese complex and the butanedione/H_2O_2 adduct. Acetic acid is required for conversion to proceed and although it is formed in situ upon oxidation of butanedione, its addition prior to addition of H_2O_2 eliminates a notable lag phase.[6] We demonstrate that the wide solvent scope of this catalyst system allows for the epoxidation of a range of EPDM polymers with good control over conversion and, importantly, under sufficiently mild conditions to avoid formation crosslinks (and hence gels). The epoxidized polymers are isolated by precipitation with a non-solvent. The method described provides an excellent alternative to the use of stoichiometric organic peroxides described earlier.

5.2 Results and discussion

Initial studies focused on the application of conditions developed earlier[5] for the oxidation of model alkene compounds representative of the functional units found in EPDMs (Figure 1). Of interest is both the relative susceptibility of the various alkene motifs to epoxidation as well as the characterization of the spectral changes expected, which will enable a comparison with spectral changes observed for the polymers (*vide infra*). Based on earlier observations[5] it was expected that higher conversions would be obtained for ENBH and DCPDH than for VNBH, which bears a terminal alkene unit. Indeed, for ENBH and DCPDH full conversion to the epoxide was observed. Direct analysis with ^{1}H-NMR spectroscopy shows complete conversion for ENBH with the disappearance of the alkene ^{1}H signals and the appearance of signals at ca. 3.0 ppm, indicative of formation of a mixture of exo and endo epoxides. For DCPDH, although less substituted, also full conversion was achieved but with only one epoxide product observed. For VNBH, the terminal alkene motif was expected to show lower conversion under standard conditions,[6] and indeed was only ca. 50 %.



Scheme 1. Epoxidation of ENBH, DCPDH, and VNBH as model compounds for the functional groups present in EPDM polymers, using conditions applied earlier in the oxidation of simple alkenes.

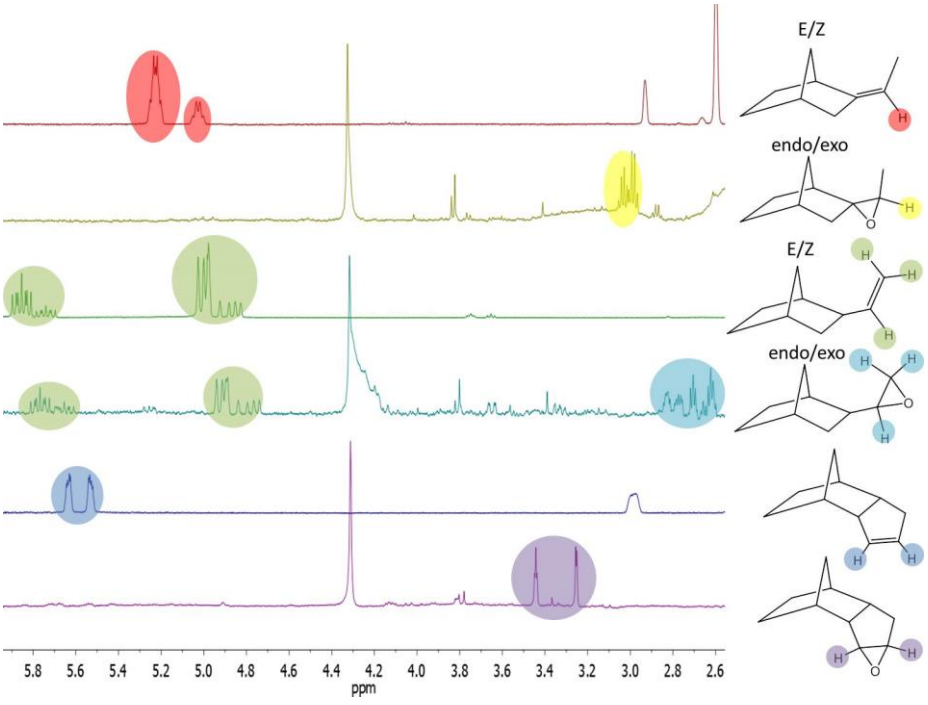


Figure 2. ^{1}H-NMR spectra of model compounds before and after epoxidation (see Scheme 1 for conditions).

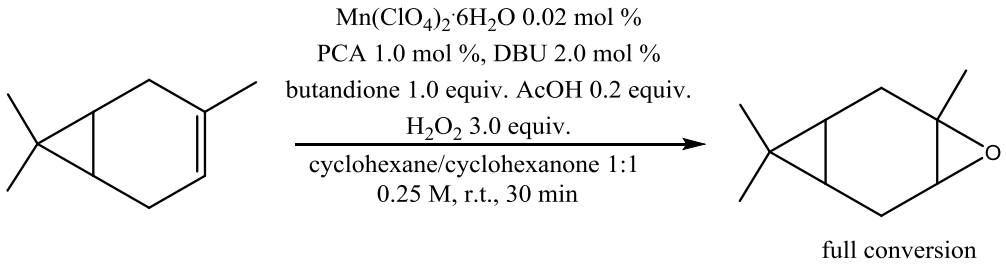
The potential of the Mn/PCA/H_2O_2 oxidation system in the epoxidation of EPDM polymers was evaluated using three polymers bearing either mono-, di- and tri-substituted alkenes. Attempts to epoxidize the EPDM polymers under the same conditions as the model compounds showed no conversion, ascribed to the insolubility of the polymers in the reaction solvent (acetone). The insolubility of EPDM in polar solvents renders the in-

situ prepared catalysts system based on Mn(II)/PCA ineffective in the epoxidation of the alkene motifs present in the polymer.

In contrast to low molecular weight alkenes, discussed above, for very high molecular weight, apolar polymers such as EPDM, apolar solvents are required for dissolution (*e.g.*, alkanes or aromates). Indeed methods available for the oxidation of EPDM with perbenzoic acids utilize toluene as solvent. Fortuitously, the Mn(II)/PCA catalyst system has a broad solvent scope, which presents opportunities to achieve conditions compatible with both polymer dissolution and catalyst operation. The basic requirements for the present catalytic system are that i) it should be homogenous {hence the solvent should be sufficiently polar to solubilize the catalyst (Mn(II)/PCA), a base such as sodium acetate}, and ii) prevent phase separation upon addition of aqueous H_2O_2. Furthermore, as noted above, a ketone (preferably BD) is required to form a hydroxyl-hydroperoxy intermediate. Therefore the need for an apolar solvent to solubilize the polymer must be balanced with the need for a polar solvent for the catalyst and the oxidant.

It was envisioned that a reaction medium largely composed of two structurally related solvents (one polar and one apolar) could be effective in both solubilizing the catalyst components and the EPDM polymers. Cyclohexane and cyclohexanone are commonly used, relatively non-toxic solvents and cost effective. Importantly, we have shown earlier[7] that both solvents are not susceptible to oxidation (*e.g.*, hydroxylation, Baeyer-Villiger) by the catalyst system.

Under essentially standard reaction conditions but with a mixture of cyclohexane and cyclohexanone in place of acetone, relatively low conversion was observed for the model compounds (VNBH, DCPDH and ENBH). Although the reaction mixture appeared homogenous it is suspected that the base, aqueous NaOAc, precipitated upon addition to the reaction mixture. The possibility of using a less polar base, *i.e.* 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), was tested in the oxidation of 3-carene. Under these conditions full conversion to the corresponding epoxide observed.



Scheme 2. Epoxidation of 3-carene and EPDM with DBU as base in place of sodium acetate.

The higher diene content in 9% ENB-EPDM allows for the conversion to be determined by ^{1}H NMR spectroscopy. The ^{1}H-NMR spectrum is dominated by the aliphatic signals of the polymer backbone, however the alkene ^{1}H signals are well resolved and show the presence of the two regioisomers of the alkenyl moiety in ca. 55:45 ratio and is similar to the spectrum of the model compound ENBH. Under reaction conditions similar to those

applied to 3-carene, the residual unsaturation in 9% ENB-EPDM and 4.5% ENB-EPDM underwent ca. 45% and almost quantitative conversion, respectively, to the epoxide with 27 and 46 equivalents (with respect to the moles of double bonds present) of H_2O_2, as determined by FTIR spectroscopy. The products were obtained by precipitation from the reaction mixture upon addition of acetone. A five-fold increase in the concentration of both the catalyst components and H_2O_2 lead to only a minor increase in conversion (60%) for 9%ENB-EPDM. In contrast even with increased amounts of H_2O_2, the conversion achieved for the 3%VNB-EPDM polymer, which bears a terminal alkene moiety, is negligible, which is unexpected but nevertheless consistent with the lower reactivity of the catalyst system towards terminal alkenes.

The use of DBU, despite the good conversion observed with 9%ENB-EPDM, is not ideal as it can be difficult to remove from the product in contrast to NaOAc. Furthermore the formation of AcOH occurs during the reaction (by oxidation of BD) and indeed its presence is essential for significant conversion. More polar conditions are preferred and, hence, the solubility of EPDM polymers over a range of conditions was examined. 100 mg of polymer was found to be soluble even with an increased ratio of cyclohexanone to cyclohexane (14.2 ml to 15 ml), allowing for the catalyst loading to be increased. Furthermore, sodium pyridine-2-carboxylate was used in place of pyridine-2-carboxylic acid/NaOAc. With this reaction medium the absolute catalyst concentrations were the same as those used for the epoxidation of the model compounds (Scheme 1). Under these conditions 9%ENB-EPDM showed 30% conversion of its alkene moieties with only 10 equivalents of H_2O_2. Addition of AcOH resulted in an increase in conversion to 60% in 1 h at room temperature.

In the ^{1}H-NMR spectrum it is possible to see how the peaks of the double bond almost completely disappear upon oxidation, and the pattern already seen in the model compound arise (multiplicity is not possible to see anymore due to slow relaxation in the polymer). The same conditions were applied to the related 4.5%ENB-EPDM polymer, which has a lower content of the alkene moiety. In this case full conversion to epoxide was already expected, but required an increased amount of H_2O_2 in order to achieve good conversion.

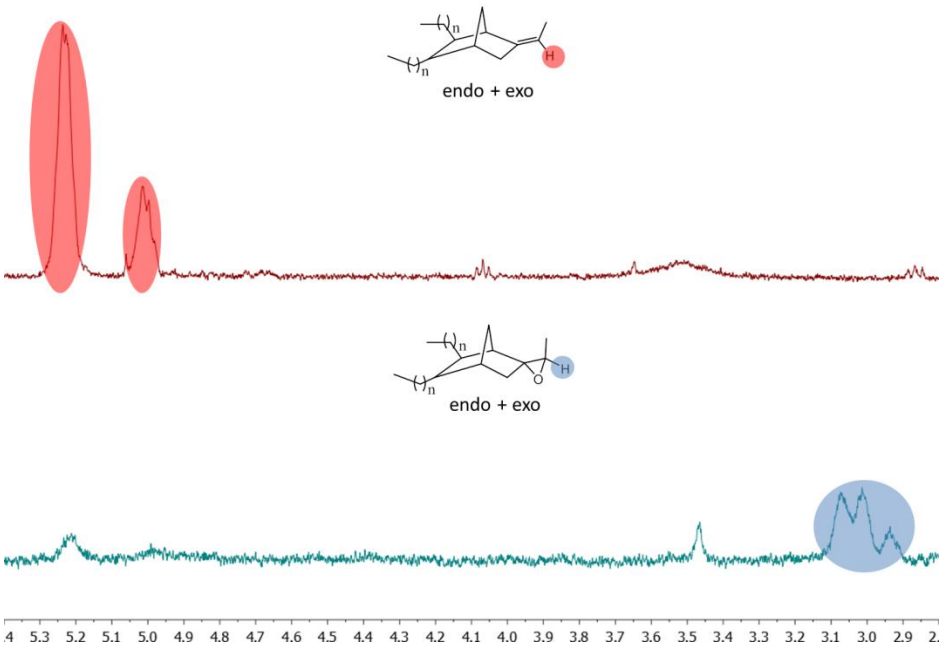


Figure 3. ^{1}H-NMR spectrum of the reaction mixture containing EPDM polymer K9950C before (above) and after (below) oxidation. Conditions: 100 mg of polymer in cyclohexane (15 mL) $Mn(ClO_4)_2 \cdot 6H_2O$ (1.08 mg), sodium picolinate (21.75 mg), butanedione (0.653mL) and acetic acid (3.0 mmol, 0.171 mL) in cyclohexanone (14.2 mL), with a single addition of H_2O_2 50 % (0.043 mL).

Notably, under the conditions used for EPDM polymer epoxidation, none of the model alkene compounds undergo epoxidation. This underlines the primary requirement that the reaction mixture must be homogeneous in order for epoxidation to occur. The tunability of the reaction conditions, especially in regard to the solvent, means that for particular substrates (polymer or otherwise), the solvent conditions can be adapted readily to achieve homogeneity and avoids the need for phase transfer catalysts and surfactants. Furthermore, many organic compounds such as 1,2-dichlorobenzne and 1,2-dichloroethane (used as internal standards for analysis) and toluene are tolerated by the catalyst system increasing opportunities for establishing suitable solvents systems for particular polymers.

5.3 Conclusions

In this study we have demonstrated that the epoxidation of alkene bearing EPDM polymers can be achieved under mild conditions (room temperature) and with short reaction times (< 1 h) using a simple in-situ prepared catalyst system and H_2O_2 as terminal oxidant. The reaction conditions can be modified easily to balance the need for the catalyst system to operate in a homogenous polar environment and the limited solubility of the polymer through the use of a solvent combination. The solubility of the catalyst components in polar solvents allows for the facile recovery of the epoxidized EPDM product by precipitation in acetone. The present system avoids the use of heavy

metal catalysts and peracids/alkylperoxides and is sufficiently mild to limit or avoid completely the ring opening of the epoxide functional groups, introduced during the reaction, and, hence, unintended polymer crosslinking. Furthermore, the difference in reactivity between the mono-, di-, and tri-substituted alkenes opens opportunities towards the selective epoxidation of specific double bonds in mixed polymers.

5.4 Experimental

All reagents were of commercial grade and were used as received unless stated otherwise. Hydrogen peroxide was used as received (Acros Chemicals) as a 50 wt % solution in water; note that the grade of H_2O_2 employed can affect the outcome of the reaction, as some sources are stabilized using sequestrants. Keltan 8550C, 9950C, 6460D and DE8270C DE were kindly supplied by ARLANXEO. Performance Elastomers ^{1}H NMR (400.0 MHz) and ^{13}C NMR (100.59 MHz) spectra were recorded on a Varian Avance 400. Chemical shifts are relative to the following: ^{1}H NMR, $CDCl_3$ (7.26 ppm) and CD_3CN (1.94 ppm); ^{13}C NMR, $CDCl_3$ (77 ppm) and CD_3CN (118 ppm). Raman spectra at 785 nm were recorded using a PerkinElmer Raman Station and at 532 nm using a custom-made Raman spectrometer; a 532 nm DPSS laser (25 mW, Cobolt Lasers) was fiber-coupled to a low-cost Raman probe (Inphotonics) and the collected scattering feed into a Shamrock163 spectrograph (500 nm blaze, 1200 l/mm grating, Andor Technology) and dispersed onto a Newton EMCCD (Andor Technology) operated in conventional CCD mode.

Caution! The drying or concentration of solutions that potentially contain H_2O_2 should be avoided. Prior to drying or concentrating, the presence of H_2O_2 should be tested for using peroxide test strips followed by neutralization on solid $NaHSO_3$ or another suitable reducing agent. When working with H_2O_2, suitable protective safeguards should be in place at all times due to the risk of explosion.

Caution! Butanedione has been linked with lung disease upon prolonged exposure to its vapors. It should be handled in a properly ventilated fume hood, and exposure to vapors should be avoided.

Typical Procedure for Catalytic Oxidations (see Scheme 1 for the model compounds). The substrate (1 mmol) was added to a solution containing $Mn(ClO_4)_2 \cdot 6H_2O$ and PCA in acetonitrile to give a final concentration of the substrate of 0.25 M. NaOAc (aqueous, 0.6 M), butanedione (0.5 mmol) and acetic acid (0.2 mmol, 0.011 ml) were added to give a final volume of 4 mL. The solution was stirred in an ice/water bath before addition of H_2O_2 (50 wt %). Conversion was verified by ^{1}H NMR by dilution of a part of the reaction mixture in CD_3CN or by directly diluting the sample in $CDCl_3$.

Typical Procedure for Catalytic Oxidations of Polymers See figure 4. K9950C and K8550C polymers (100 mg) were dissolved in cyclohexane (15 ml) overnight while stirring. Cyclohexanone solutions (1.5 ml each) containing $Mn(ClO_4)_2 \cdot 6H_2O$ (7.2 mg in 100 ml) and sodium picolinate (145 mg in 100 ml), butanedione (0.5 mmol) and acetic

acid (3.0 mmol, 0.171 ml) were added to give a final volume of 30 mL. The resulting mixture was stirred for ca. 5 min before H_2O_2 (50 %) was added, and reaction continued for 1 h, after which solvent was partially evaporated in vacuo to ca. 15 ml. The residue was poured into an excess of acetone (around 60 ml) to precipitate the polymer, which was recovered, washed with acetone and dried before a ^{1}H-NMR spectrum was recorded in $CDCl_3$. For other polymers, a 10 times greater amount of catalyst and H_2O_2 (50 %) was used.

EPDM was submitted to similar reaction conditions: 30 ml of cyclohexane to solubilize the polymers (50 mg) and 1.5 ml of cyclohexanone to solubilize the $Mn(ClO_4)_2$ and the pyridine-2-carboxylic acid is replaced by the organic base DBU. The polymer was dissolved in cyclohexanone (100 mg / 15 ml) overnight; $Mn(ClO_4)_2.6H_20$ (7.2 mg) and NaPCA (36.25 mg) were dissolved in 10 ml of cyclohexanone. Once homogeneous, the Mn(II) salt solution (1.5 ml) and Na PCA solution (6 ml) were added to the substrate containing solution. Butanedione (0.653 ml, 7.25 mmol), acetic acid (0.171 ml, 3 mmol) and cyclohexanone were added to reach a final volume of 30 ml. the resulting mixture was stirred for ca. 5 min. before H_2O_2 (50 %) was added, and reaction continued for 1 h, after which solvent is partially evaporated in vacuo to about 15 ml. The residue is then poured in an excess of acetone (around 60 ml) to precipitate the polymer out of the solution. This is further washed with acetone and dried before a ^{1}H-NMR spectrum is recorded.

5.1 References

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Chapter 6

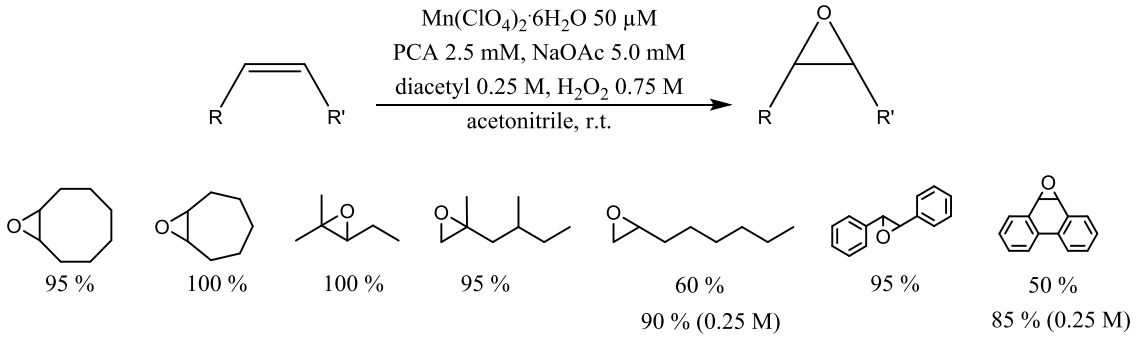
Mechanistic considerations in Mn(II)/pyridine-2-carboxylic acid catalysed oxidations with H_2O_2

Abstract. In this chapter, mechanistic insights of the Mn(II)/PCA system are explored. A general overview over the fast equilibrium between butanedione and hydrogen peroxide to form the hydroxo-peroxo adduct is given, as well as its dependence on the temperature. The influence of substrate concentration is explored, and the pseudo zero order of reaction w.r.t. substrate and oxidant is investigated further. A critical explanation of factors that govern the conversion and selectivity is given, together with the tools for a fine tuning of the reaction itself.

6.1 Introduction

The oxidation of alkenes, alcohols and diols with H_2O_2 catalysed by manganese and pyridine-2-carboxylic acid shows several aspects that can be regarded as unusual, not least the zero order dependence on substrate and H_2O_2 concentration. The reaction is characterized by a time dependence which involves an initial lag phase that has been identified as due to the formation of acetic acid, followed by a period in which rate of conversion is constant, and after a specific time (which is highly repeatable for the same reaction conditions) the conversion of substrate stops. The addition of acetic acid (typically 0.1 M) either before or immediately after addition of H_2O_2 eliminates the lag phase and conversion of the substrate starts immediately; though, conversion and rates are not affected by acetic acid, whose role in the reaction remains unclear, although its presence is essential for the reaction to begin.

The lack of the dependence of the duration of the reaction (i.e. the time over which conversion proceeds) on substrate type (alkene, alcohol etc.) indicates that a common active oxidant is involved.[1] The essentially zero order dependence of the reaction rate on substrate concentration has been made use of to achieve higher (usually full) conversion for those substrates that did not undergo complete oxidation under reactions conditions typically used for alkene oxidation by simply reducing the concentration of the substrate while keeping concentration of all other components the same (scheme 1).[1]



Scheme 1. Conversions and yields obtained for the epoxidation of electron-rich alkenes using reaction conditions optimized for cyclooctene at 0.5 M and at 0.25 M substrate.

Perhaps, the most notable aspect however is that conversion ceases in many cases before substrate conversion is complete. The time after addition of oxidant at which conversion ceases is expected to depend on catalyst concentration, competitive oxidation of butanedione or PCA (both of which are essential for activity to be observed) and the amount of H_2O_2 present. In the case of ketone solvents, such as acetone and butanone, the limiting factor appears to be the oxidation of PCA to its corresponding *N*-oxide,[1] However, in cases where substoichiometric amounts of ketones are used, such as butanedione, the competing oxidation of the ketone provides a natural limit to conversion.[1] The expectation is that for different substrates the reaction time will vary, except when the substrate is less easily oxidisable than butanedione itself. In those cases where substrate is more susceptible of oxidation than butanedione, then the reaction

duration will always depend on the rate of which butanedione is consumed. Reasons for the cessation of activity are explored for various substrates: the postulated competitive oxidation of PCA to PCA N-oxide as an important deactivation channel was only partially to be responsible of cessation of activity.

As already seen in chapter 3, practical issues arise with the use of acetone at larger scales: the Mn(II)/PCA system was tailored to the use of acetonitrile as solvent, but the solvent scope also includes alcohols, in which case the yields and selectivities are only slightly lower. Importantly, it works equally well in acetone, as already demonstrated in chapters 2, 3 and 4; the use of this solvent is particularly useful in order to perform a two-step one-pot epoxidation-ring opening of the alkenes, using $Fe(ClO_4)_3$ as Lewis acid. Unfortunately, despite the near stoichiometric amounts of oxidants used, the combination with the organic solvents poses safety issues, especially in the case of bigger scale reactions, which therefore require an accurate assessment of the energetics and of the correlated risks. Also, the homogeneity of the reaction mixture is important, especially when hydrogen peroxide is added, as phase separation with starting materials could lead to overoxidation of the product and therefore diminished selectivity.

In this chapter several mechanistic aspects are explored with a focus on understanding the factors which limit reactivity. Furthermore the challenges faced in up-scaling of the reaction, especially in regard to the use of acetone as solvent are addressed. Raman spectroscopy is used extensively for in-line reaction monitoring as in earlier studies[1,2,3] of the Mn(II)/PCA.

6.2 Results and discussion

6.2.1 Dependence of reaction rate on substrate type and concentration

Although the formation of acetic acid from butanedione is clearly an essential prerequisite for the oxidation of alkenes and alcohols to proceed (i.e. it is the origin of the lag period observed), addition of acetic acid prior to H_2O_2 does not have a significant effect on maximum reaction rate or conversion (see figure 1).[1]

As apparent from figure 1, addition of acetic acid does not affect on the overall conversion nor on the maximum rate of conversion (the two curves are parallel in their linear part, representing the maximum rate of conversion), but it does eliminate the lag phase, making kinetic analysis and comparison between different concentrations of reactants possible.

Several substrates were submitted to oxidation, at varying concentrations to verify the (apparent) order of the reaction: styrene, benzylic alcohol and 3-carene showed similar trends: the maximum reaction rate showed no dependence on the concentration of the substrate. In the case of styrene (figure 2), whose optimum concentration for complete conversion is ca. 0.5 M, conversion reaches ca. 60 % when the concentration is 1.0 M and full conversion with 0.2 M styrene.

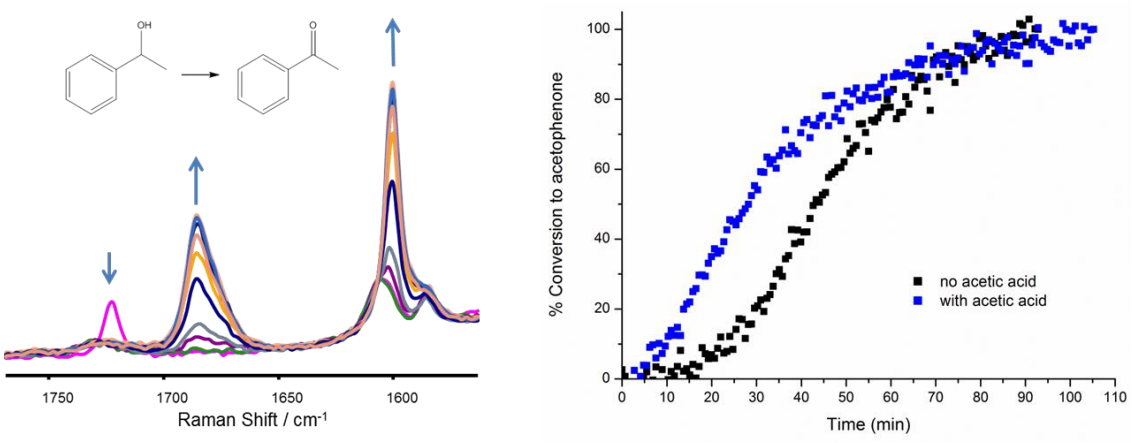


Figure 1. (left) Raman spectra recorded during the oxidation of styrene and, (right) elimination of the lag phase by addition of acetic acid. Conditions: $Mn(ClO_4)_2{\cdot}6H_2O$ 50 µM, PCA 2.5 mM, NaOAc 5.0 mM, diacetyl 0.25 M, AcOH 0.1M (blue dot), H_2O_2 0.75 M, acetonitrile 0.5 M, r.t.

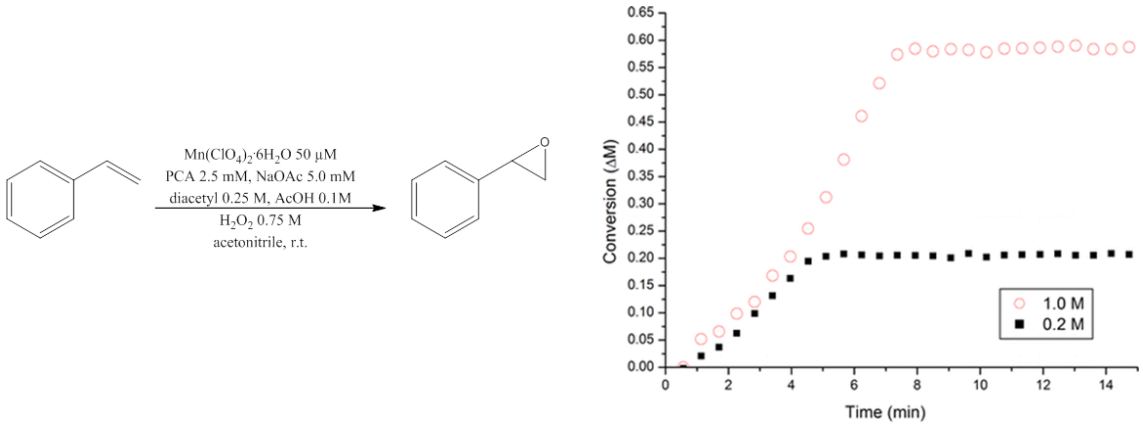


Figure 2. Comparison between epoxidation of styrene at 1.0 M and 0.2 M concentrations.

Importantly, the reaction rate is independent of the concentration. Moreover, as already demonstrated in chapter 4, selectivity is practically unaffected when substrate concentration is decreased. The same comparison with different concentrations of styrene over the rate of reaction has been explored using ethanol as solvent which shows that although slower as already reported,[1] the reaction proceeded at the same rate.

6.2.2. Butanedione oxidation

It must be noted that the observed reaction rate is the sum of the oxidation of butanedione as well as of the substrate: in previous studies it was noted that the diketone is indeed consumed in a competitive reaction with the substrate.[2] Experiments in which increasing amounts of H_2O_2 were added revealed that butanedione recovers one the oxidant is consumed however the extent of recovery is inversely proportional to the amount of oxidant added.

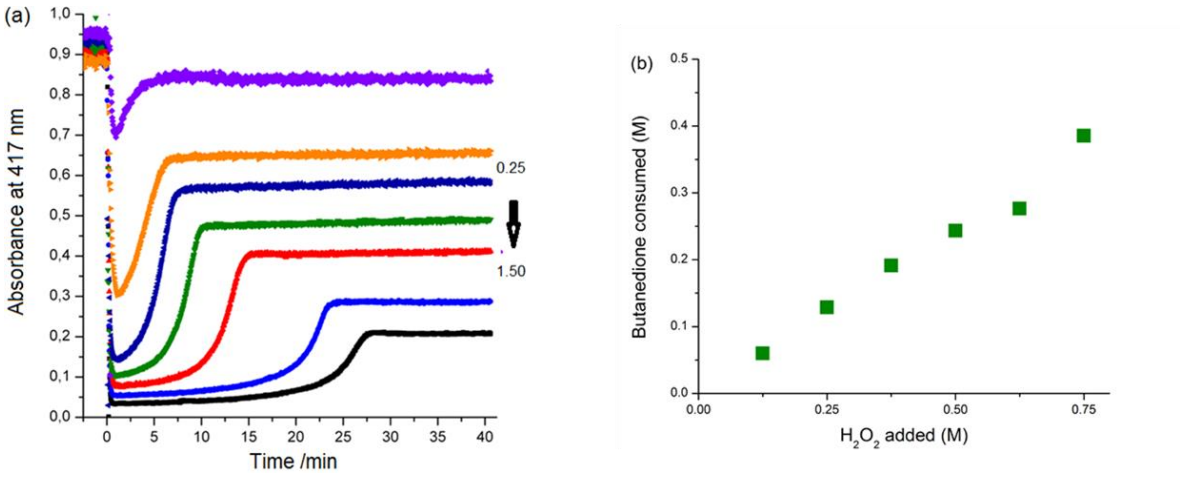


Figure 3. (a) Change in absorbance of butanedione at 417 nm over time after addition of H_2O_2 at t = 0 min (0.125–0.875 M; 0.25, 0.50, 0.75, 1.00, 1.25, 1.35, and 1.50 equiv with respect to cyclooctene), with 0.05 mM Mn $(ClO_4)_2$, 0.5 M cyclooctene, 5 mM NaOAc, 0.25 M butanedione, and 2.5 mM PCA in acetonitrile. (b) Dependence of butanedione consumed on amount of H_2O_2 added. Data reproduced with permission from ref 2. Copyright ACS 2012.

Although butanedione is oxidized, the rate of oxidation is lower than for the substrates. This is confirmed by addition of less H_2O_2 than butanedione, where the lag phase is reduced despite the minor amount of oxidant present: if $[H_2O_2]$:[butanedione] < 2 (under these conditions a discrete amount of "free" butanedione is able to undergo oxidation to acetic acid), the lag phase observed prior to the onset of oxidation of cyclooctene was absent, and it increased with the initial concentration of H_2O_2. Shortly after addition of H_2O_2, the loss in conjugation by formation of 3-hydroxy-3-hydroperoxybutanone results in a concomitant loss of the absorbance of butanedione at 417 nm (Figure 3). It must be pointed out that the lag phase cannot be ascribed to the formation of this adduct, as it forms within several seconds after addition of H_2O_2. The absorption band of butanedione does not recover further after 30 min; the amount of butanedione consumed is approximately linearly dependent on the amount of peroxide added; this shows how the amount of oxidant added directly affects the extent of oxidation and the time taken for this to occur is dependent. Butanedione is oxidized at a constant rate during the course of reaction, in an analogous way as substrates are (figure 4).

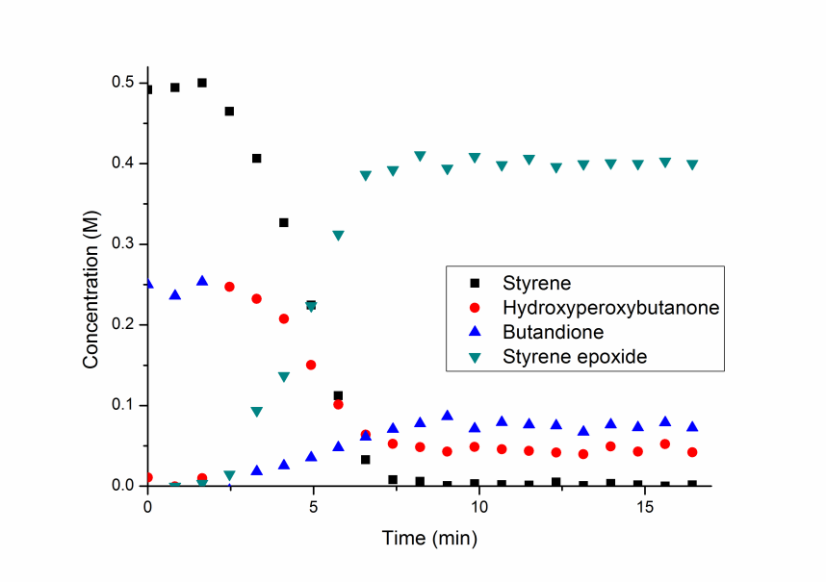


Figure 4. Change in concentration of styrene (substrate, 0.5 M), styrene oxide (product), butanedione and hydroxyl-hydroxperoxybutanone over time after addition of H_2O_2; with acetic acid (0.1 M), [Mn^{II}] 0.05 mM, 5 mM NaOAc, 0.25 M butanedione, 0.25 mM PCA in acetonitrile. A single addition of 1.5 equiv. of H_2O_2 w.r.t. substrate was made at t = 2.5 min. From ref 1. Copyright ACS 2016.

As briefly mentioned, the observed rate is given by both the oxidation rate of butanedione and that one of the substrate: $k_{obs} = k_{BuDi} + k_{sub}$. The rate of oxidation of the diketone therefore represents the lower limit of the overall observed rate, no matter how low the substrate concentration is. It is important to underline, at this point, that the reaction is not zero order w.r.t. butanedione, as evident in the oxidation of styrene with "std" alkene oxidation conditions (see figure 5) and this should affect the observed rate as well.

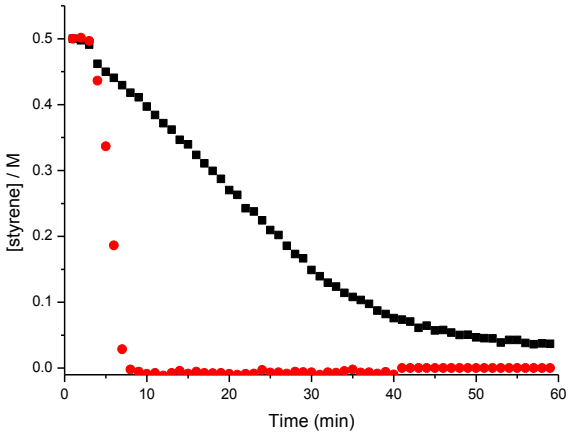


Figure 5. Effect of [butanedione] on the oxidation of styrene; conditions: (substrate 0.5 M), acetic acid (0.1 M), [Mn^{II}] 0.05 mM, 5 mM NaOAc, 0.125 (black squares) or 0.5 M (red circles) butanedione, 0.25 mM PCA in acetonitrile.

Styrene and 3-carene were submitted to competition experiments in order to clarify if the system shows selectivity w.r.t. different substrates. When a 10 to 1 ratio of 3-carene and styrene were oxidized, selectivity between towards styrene was observed (see figure 6).

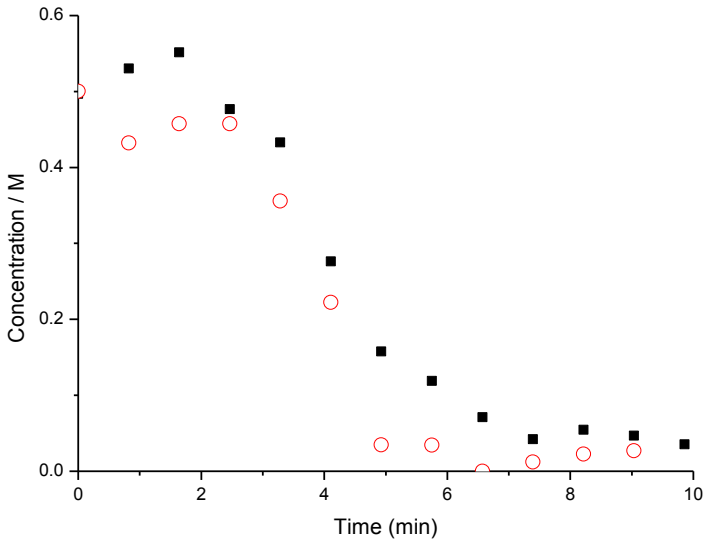
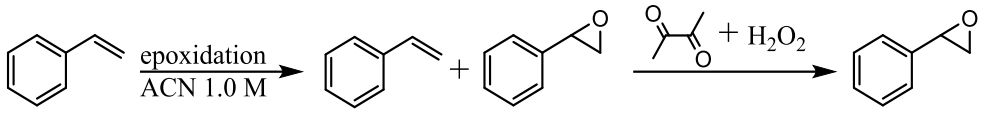


Figure 6. Change in concentration of styrene (substrate, 0.05 M, black squares; conc. by 10) and 3-carene (0.5 M, open red circles) over time after addition of H_2O_2; with acetic acid (0.1 M), [Mn(II)] 0.05 mM, 5 mM NaOAc, 0.25 M butanedione, 0.25 mM PCA in acetonitrile. A single addition of 1.5 equiv. of H_2O_2 w.r.t. substrate was made at t = 2.5 min. Reproduced from ref 1. Copyright ACS (2016).

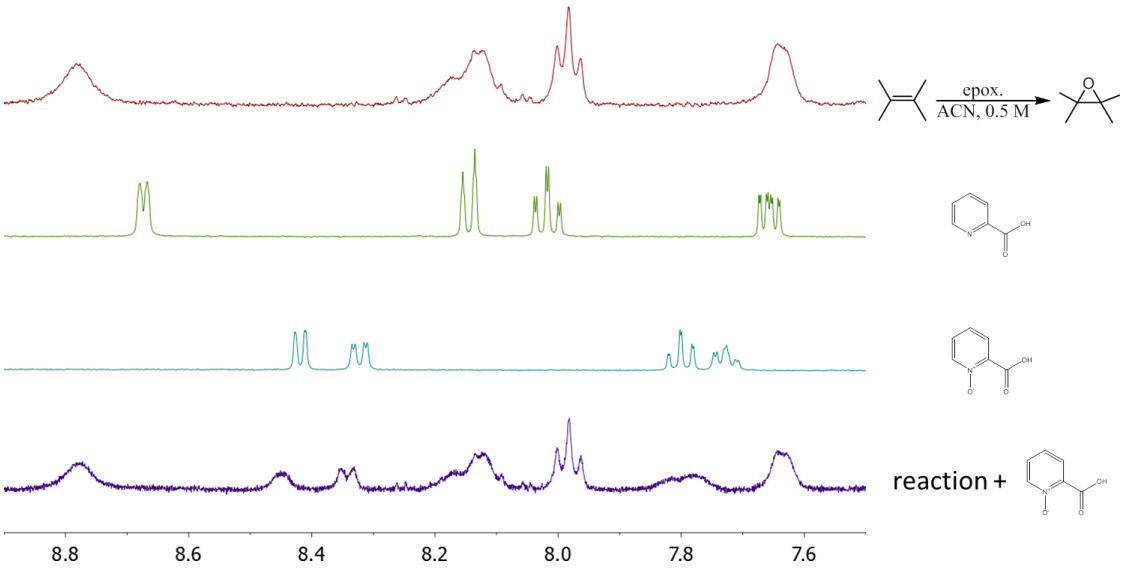
6.2.3. Investigation over the cessation of conversion

The oxidation reactions performed with the Mn(II)/PCA catalyst show a common dependence on the time. After a lag-phase at the start, that can vary depending on the substrate and on the catalyst loading (but it is also hardly reproducible) the reaction rate quickly increases to its maximum and keeps constant for a certain amount of time, after which rapidly decreases to zero. Several hypotheses why the reaction to stop can be made; data on the Mn/PCA ratio indicates that oxidation of the PCA to the corresponding N-oxide could lead to a cessation of the catalytic activity, as when PCA was replaced by the corresponding N-oxide as ligand no catalytic activity was observed.[4] Futhermore two trivial reasons that can be responsible for the reaction to stop are that the butanedione or the H_2O_2 is consumed. As the reaction proceeds, substrate is converted, H_2O_2 is consumed and there is an increasing amount of butanedione although it is also being consumed; when butanedione is fully consumed the reaction stops. Styrene (in excess, 1.0 M) was submitted to the otherwise standard reaction conditions, with acetic acid to eliminate the lag phase. Conversion stops ca. 35 minutes after addition of H_2O_2. Addition of PCA results in negligible additional conversion, however conversion continues upon addition of butanedione and H_2O_2 (see scheme 2).



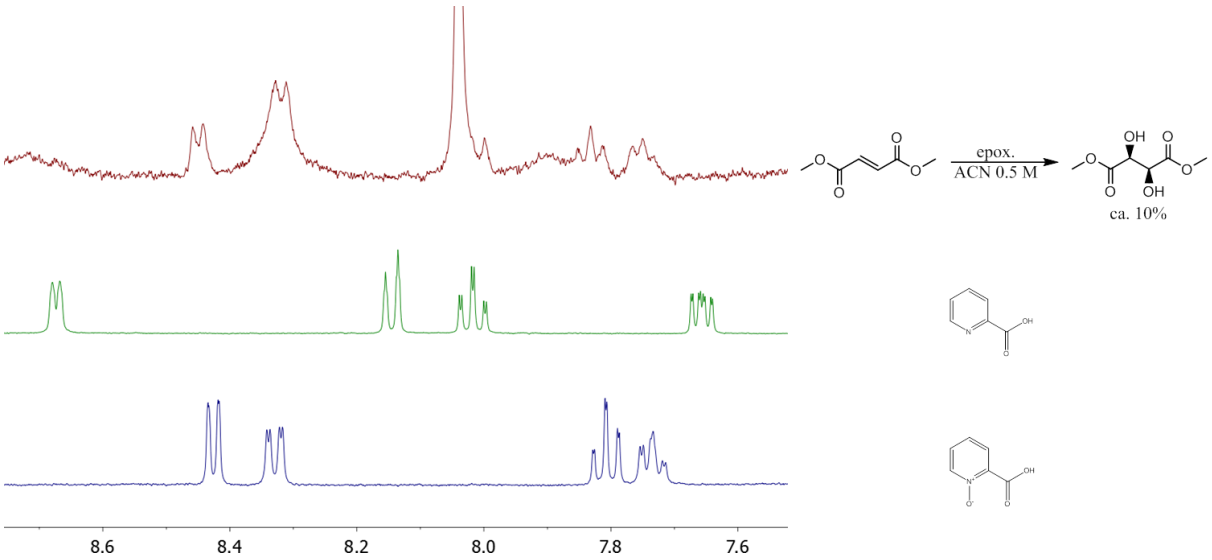
Scheme 2. Oxidation of styrene (1.0 M) present in excess followed by continuation of the reaction by addition of butanedione and H_2O_2.

A large scale (10 mmol, 0.5 M) reaction with tetramethyl ethylene proceeded with full conversion to the corresponding epoxide, was removed in vacuo together with solvent and butanedione. The ^{1}H-NMR spectrum of the residue in CD_3CN shows that PCA was not oxidized during the reaction (confirmed by spiking the sample with PCA N-oxide, scheme 3).



Scheme 3. ^{1}H-NMR comparison of 1) residue of reaction, 2) PCA, 3) PCA N-oxide and 4) reaction with added PCA N-oxide.

Though, styrene and tetramethyl ethylene are substrates which undergo complete at a 0.5 M concentrations, dimethyl maleate shows negligible reactivity (ca. 10%) under standard reaction conditions for the oxidation of alkenes. Though maleate is not volatile, and neither is the corresponding diol, there spectral features do not overlap with those of PCA (from 7.6 p.p.m. to 8.7 p.p.m.). Concentration of the reaction mixture and dilution in CD_3CN indicated that PCA underwent oxidation to PCA N-oxide (scheme 4).



Scheme 4. ^{1}H-NMR comparison of 1) residue of reaction, 2) PCA, 3) PCA N-oxide.

In contrast to that observed with styrene, only PCA N-oxide was observed after the reaction. If formation of PCA-N-oxide occurs during the reaction then the loss of PCA would have a sudden and dramatic effect on reaction rate as seen in Figure 7. Reaction monitoring by Raman spectroscopy, revealed that even though butanedione and H_2O_2 were still present, catalytic conversion halted after a short period, and hence were still present during work-up. Therefore the observation of PCA-N-oxide by ^{1}H NMR spectroscopy does not confirm that it was formed during the reaction itself. This would imply of course that an oxidation product of the maleate would be responsible for inhibition however a candidate for such a species has not yet been identified. Nevertheless, it has been noted earlier[1] that salicylic acid was able to reduce the reaction rate, possibly due to sequestering of the manganese present.

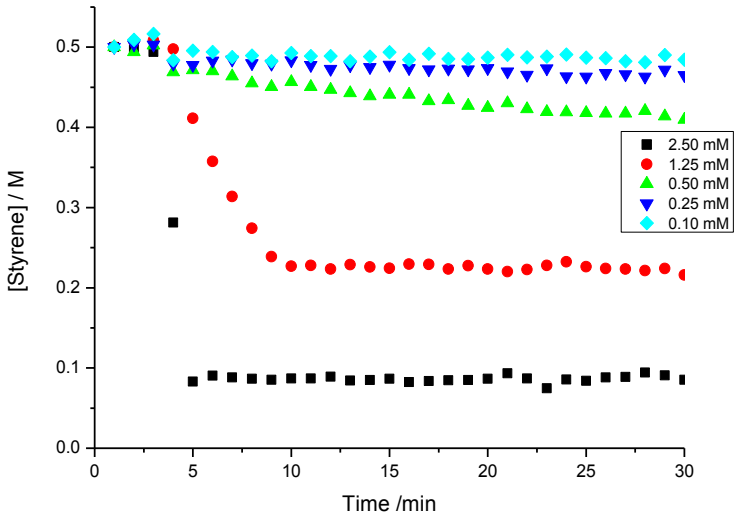
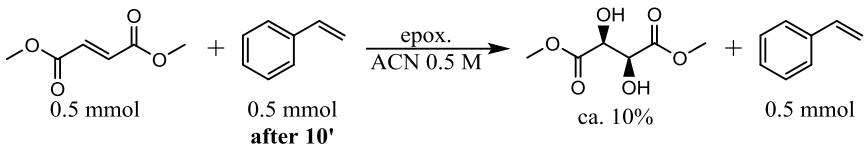


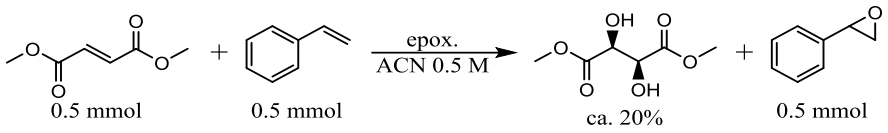
Figure 7. Effect of [PCA] in the oxidation of styrene; conditions: (substrate 0.5 M), acetic acid (0.1 M), [Mn(II)] 0.05 mM, 5 mM NaOAc, 0.25 M butanedione in acetonitrile.

A competition experiment between maleate and styrene (scheme 5) was conducted in which styrene was added 10 min after addition of H_2O_2. In this case styrene did not undergo conversion confirming that catalytic activity was already halted.



Scheme 5. Competition between dimethyl maleate and styrene (added 10 min after H_2O_2).

By contrast, when styrene is added before H_2O_2 (scheme 6), full conversion was observed, confirming that maleate itself is not an inhibitor. Furthermore increased conversion of maleate was observed indicating that the presence of styrene 'protected' PCA from oxidation.



Scheme 6. Competition between dimethyl maleate and styrene (added before H_2O_2).

Figure 8 summarizes the changes in concentration of styrene when it is added (a) before addition of H_2O_2 or (b) after addition of H_2O_2.

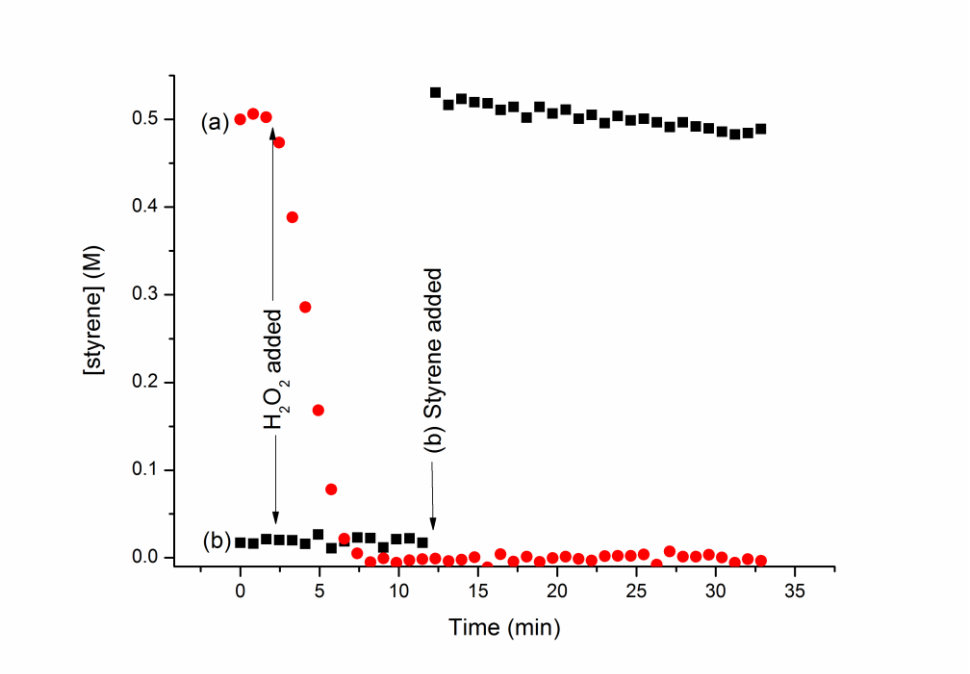
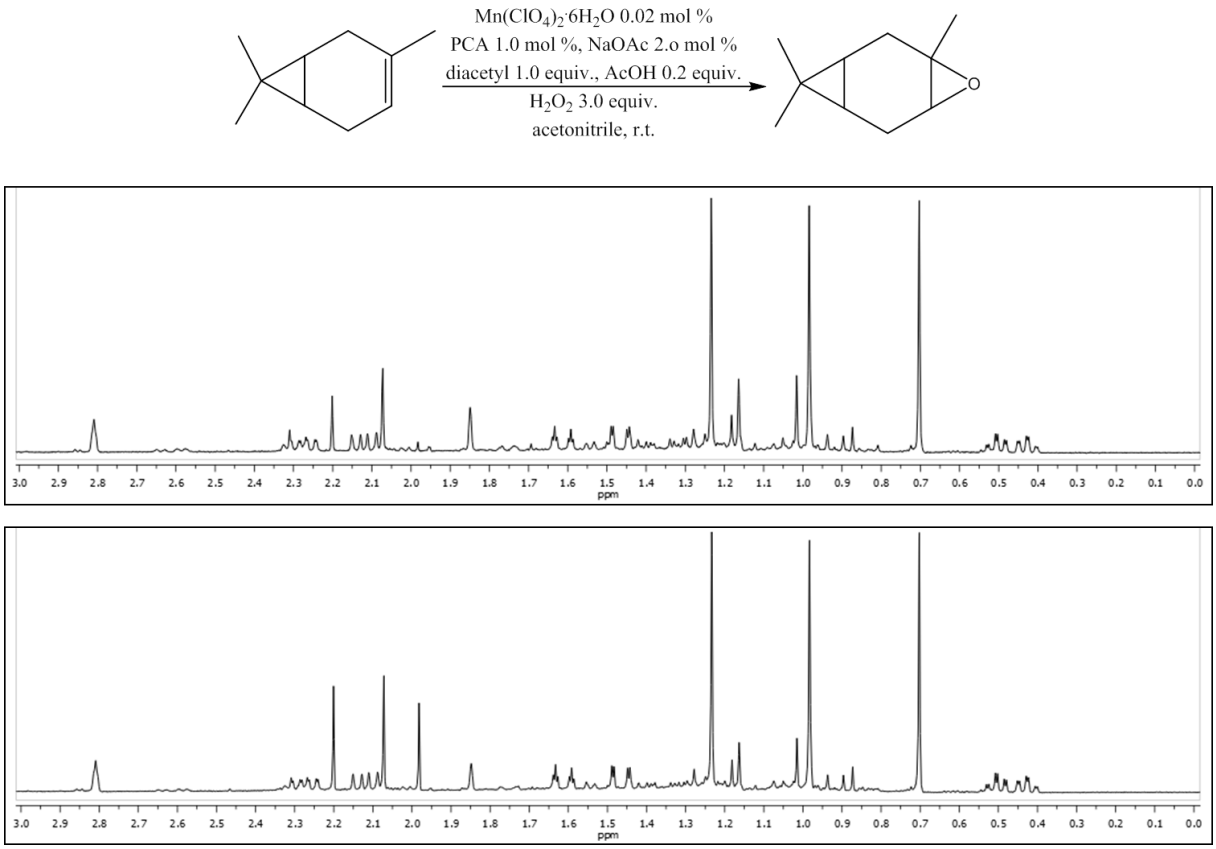


Figure 8. Change in concentration of styrene (0.5 M) with time. Styrene was added before (a) or after (b) addition of H_2O_2 to a solution containing with diethylmaleate (0.5 M), 2.5 mM PCA, 0.5 mM NaOAc, 0.5 M cyclooctene, 0.1 M AcOH, and 0.05 mM MnII in acetonitrile. A single addition of 1.5 equiv of H_2O_2 was made at t = 2.5 min. Reproduced from ref 1. Copyright ACS (2016)

It should be noted that maleate shows low reactivity in several other oxidative systems.[5] The reaction of the catalyst with butanedione at the start is limited by the fact that most of the butanedione is in the hydroxy-peroxy form and free butanedione is present at very low concentrations. Hence given the poor reactivity of maleate oxidation of PCA becomes competitive and once the concentration of PCA drops below twice that of Mn(II) the reaction ceases. However, in the absence of maleate, i.e. with no substrate present, it has been shown that butanedione undergoes near complete oxidation.

6.2.4. Upscaling and the application of flow chemistry to the oxidation of 3-carene

When large scale reactions had to be performed (5 to 10 mmols) the issue of safety arose with the use of acetone and H_2O_2, as already discussed in chapter 2. Beside this, batch addition of H_2O_2 will lead to inhomogeneous distribution of H_2O_2, and increasing the reaction temp in regions of high H_2O_2 concentration will result in consumption of the butanedione more rapidly. Furthermore, the heat of the reaction could shift the equilibrium in favour of butanedione and H_2O_2, increasing the rate of its oxidation and therefore reducing the maximum conversions that can be achieved. Batch reaction is faster than in flow, but conversion of substrate is less. We therefore envisioned that flow chemistry could suit these reactions, given that excellent mixing and avoidance of safety issues in the use of H_2O_2 and acetone and in the case of 3-carene actually improves selectivity (scheme 7).



Scheme 7. Comparison of batch (upper) and in flow (lower) oxidation of 3-carene.

6.2.5. Competition experiments

The zero order dependence of reaction rate on substrate concentration is advantageous in regard to obtaining higher yields for more recalcitrant substrates without sacrificing selectivity. This characteristic limits opportunities to use substrate variation (*e.g.*, LFER analysis) to elucidate the species formed upon reaction of the hydroperoxy species with the manganese catalyst, as the rate determining step lies before the reaction step involving the substrate. However, the relative reaction rates for pairs of substrates for that step can be explored through the use of competition experiments. However, it should not be overlooked that the oxidation of butanedione competes with the oxidation of substrates and ultimately limits the maximum conversion that can be achieved. Most substrates submitted to the reaction thus far, with the exception of maleate, react with the active form of the catalyst more readily than butanedione does and hence the conversion achieved by the time the reaction ceases gives insight into the relative reactivity of the substrates. In the case of styrene and diethyl maleate, as discussed above, styrene undergoes oxidation almost exclusively. Competition between the regioisomers of vic-diols was explored in the context of their selective oxidation to α-hydroxy ketones in chapter 4 where it was shown that selectivity can be achieved notwithstanding the zero order of reaction w.r.t. the substrate, and hence the catalyst is able to discriminate between different substrates. Competition experiments between 3-carene and styrene, also in different relative amounts, have been carried out in order to explore selectivity. Styrene is oxidized preferentially over 3-carene, indicating that the oxidation of the substrate is not diffusion controlled, and although the r.d.s. is the formation of the active form of the catalyst, there is still an activation barrier to overcome in subsequent steps.

6.3 Conclusions

In this chapter further insight into the phenomena that regulate the Mn/PCA system is obtained. The effect of butanedione, its competing oxidation to acetic acid which, itself, is the key to the onset of the reaction and whose addition is able to eliminate the lag phase, have been investigated. The apparent order of the reaction with respect to substrate is shown to be useful in achieving desired conversions even for those substrates that are not particularly reactive or even reluctant to undergo transformation, without sacrificing selectivity. The reasons for the reaction ceasing, under various conditions, after a particular time, were also elucidated, showing how oxidation of PCA is the main deactivation channel in the case of diethyl maleate, whereas oxidation of butanedione is limiting in the case of styrene.

Flow chemistry presents an answer to large scale reactions, especially when the use of acetone is essential for example for the further ring opening of the newly obtained epoxide to yield the corresponding diol, as described in chapters 3 and 4, where they were then submitted to C-C bond cleavage and diol oxidation, respectively.

6.4 Experimental

All reagents were of commercial grade and were used as received unless stated otherwise. Hydrogen peroxide was used as received (Acros Chemicals) as a 50 wt % solution in water; note that the grade of H_2O_2 employed can affect the outcome of the reaction, as some sources are stabilized using sequestrants. ^{1}HNMR (400.0 MHz) and ^{13}C NMR (100.59 MHz) spectra were recorded on a Varian Avance 400. Chemical shifts are relative to the following: ^{1}H NMR, $CDCl_3$ (7.26 ppm) and CD_3CN (1.94 ppm); ^{13}C NMR, $CDCl_3$ (77 ppm) and CD_3CN (118 ppm).

Caution! The drying or concentration of solutions that potentially contain H_2O_2 should be avoided. Prior to drying or concentrating, the presence of H_2O_2 should be tested for using peroxide test strips followed by neutralization on solid $NaHSO_3$ or another suitable reducing agent. When working with H_2O_2, suitable protective safeguards should be in place at all times due to the risk of explosion.

Caution! Butanedione has been linked with lung disease upon prolonged exposure to its vapors. It should be handled in a properly ventilated fume hood, and exposure to vapors should be avoided.

Typical Procedure for Catalytic Oxidations Described in Scheme 1. The substrate (1 mmol) was added to a solution containing $Mn(ClO_4)_2{\cdot}6H_2O$ and PCA in acetonitrile to give a final concentration of the substrate of 0.5 M. NaOAc (aqueous, 0.6 M) and butanedione (0.5 mmol) were added to give a final volume of 2 mL. The solution was stirred in an ice/water bath before addition of H_2O_2 (50 wt %). Conversion was verified by ^{1}H NMR by dilution of a part of the reaction mixture in CD_3CN. Product isolation involved addition of brine (10 mL) and extraction with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous), and filtered, and the dichloromethane was removed in vacuo. 1,2-Dichlorobenzene, which has a negligible effect on the reaction, was employed as internal standard for Raman and ^{1}H NMR spectroscopy. Reaction monitoring with Raman spectroscopy focused primarily on the intensity of the C=C and C=O stretching bands between 1550 and 1800 cm^{-1} (e.g., at 1650 cm^{-1} for cyclooctene and 1724 cm^{-1} for butanedione), between 600 and 900 cm^{-1} relating to the C=C and C=O bending modes (682 cm^{-1} for butanedione and 701 cm^{-1} for cyclooctene), and the O−O stretching mode of H_2O_2 at 870 cm^{-1}. UV/vis absorption spectra were recorded in 1 or 10 mm path length cuvettes on a AnalytikJena Specord 600 instrument. Raman spectra at 785 nm were recorded using a PerkinElmer Raman Station and at 532 nm using a custom-made Raman spectrometer; a 532 nm DPSS laser (25 mW, Cobolt Lasers) was fiber-coupled to a low-cost Raman probe (Inphotonics) and the collected scattering feed into a Shamrock163 spectrograph (500 nm blaze, 1200 l/mm grating, Andor Technology) and dispersed onto a Newton EMCCD (Andor Technology) operated in conventional CCD mode.

6.5. References

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[5] C. M. Ho, W. Y. Yu, C. M. Che, *Angew. Chem. Int. Ed.*, **2004**, 43, 3303 –3307.

Summary

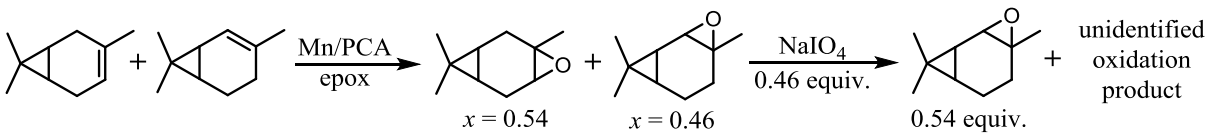
Oxidation chemistry is perhaps the most important to human history. The oxidizing nature of the atmosphere and of catabolic activity means that everything is exposed to oxidative degradation.

Oxidations represent a key transformation in organic chemistry, as it is often possible to obtain highly valuable products starting from cheap/abundant compounds, and in many cases even to control the stereochemistry of the product, making it a powerful tool for organic synthesis. The field of oxidation has been explored from the dawn of organic chemistry: a remarkable example, also reported in chapter two, is the use of ozonolysis for structure determination of compounds containing double bonds (an application supplanted by NMR and Mass spectrometry in routine analysis). Notably, this case also highlights a major drawback that has accompanied oxidation reactions in organic chemistry: where the applicability (scope) is wide, selectivity is often an issue. In particular, indeed, are efforts to stop a multistep oxidations at an intermediate step (oxidation of primary alcohols to corresponding aldehydes for example).

The attention that sustainable chemistry has drawn over recent years has generated a major interest towards those processes which use of atom-economic oxidants (O_2 or H_2O) and first row transition metals as catalysts. The impracticality of using molecular oxygen in many cases, despite its atom efficiency, and the ease of access to H_2O_2 (whose only byproduct is water), makes the latter oxidant a highly attractive alternative to common oxidants such as Oxone® and peracids. Notwithstanding its oxidation potential, hydrogen peroxide often needs to be activated, as it has been shown from transition metals. Though second and third row transition metals have already proven extremely useful in regard to yields and selectivity (Osmium, etc.), the drive for a sustainable chemistry directs the research towards first row transition metals for the previously mentioned reasons.

The Mn/PCA oxidation system, recently developed in our group, already showed remarkable flexibility, used in the epoxidation/*cis*-dihydroxylation of alkenes,[1] of secondary alcohols to ketones and alkanes to alcohols.[2]

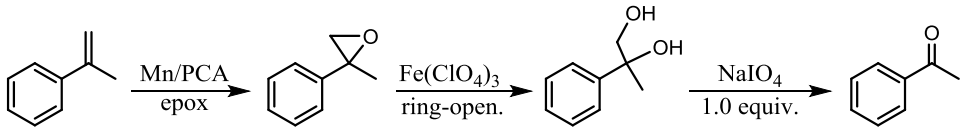
In chapter 2 an approach a practical problem is discussed, regarding the separation of the oxidation products of 2- and 3-carene, making use of the Mn based oxidation methods previously developed in our group and the tools used to tune them (including Raman spectroscopy, scheme 1).



Scheme 1. Selective oxidation of 2-carene oxide in presence of 3-carene oxide.

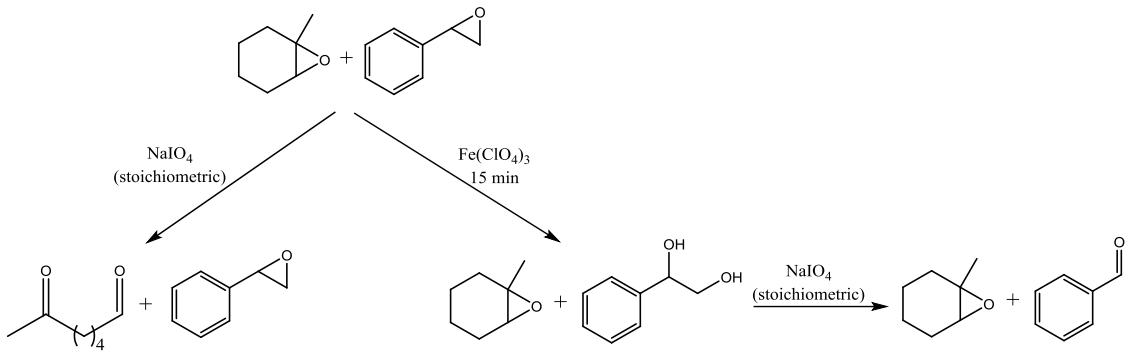
Even though the approach was not successful per se, as the product of oxidation that could be isolated was derived from the cheaper 3-carene (sometimes it is a matter of luck!), the search for selective oxidations stimulated ideas that were developed in subsequent chapters.

The idea developed in chapter 3 arose indeed from the attempt to perform a selective oxidation of 2-carene oxide with respect to its regioisomer 3-carene oxide. The former proved to be more reactive, and underwent full conversion in the presence of the latter when stoichiometric amounts of $NaIO_4$, which is the standard reagent for the cleavage of diols, were added. This selectivity is rationalized by considering several factors: as with 2-carene (in which the planar portion of the molecule is directly connected to the already strained cyclopropane structure), in its epoxide the two 3 membered rings, each of which are connected to the six membered ring, are only one carbon removed, making the structure susceptible to undergo ring opening to release ring strain. On the other hand, even if direct cleavage of epoxides with $NaIO_4$ was already reported by Binder et al.[3], it is clear that the reaction passes through a diol intermediate, thus explaining the selectivity towards 2-carene. The method was applied in chapter 3 to cyclic, linear and aromatic diols (scheme 2), with good yields and selectivities, using for the first oxidation step the same catalytic system already developed in our group, with minor adjustments regarding reaction conditions.



Scheme 2. 3-step one-pot catalytic oxidation of β–methyl styrene to acetophenone.

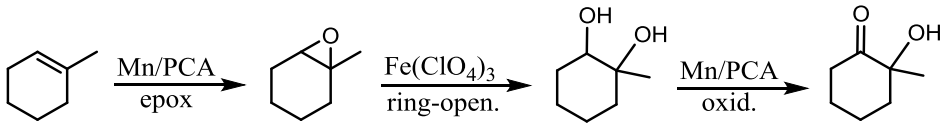
It thus represents an practical alternative to ozonolysis: not only does it yield the same product in cases where only one double bond is present, but it offers new selectivity, either through discrimination between distinct double bonds, or through epoxide and diols (easily accessible through Fe(III) perchlorate assisted *in situ* ring opening), or finally through different epoxides directly. The different timescale of the ring opening reactions shown by aromatic and aliphatic substrates could be extremely useful in a novel selective oxidation of epoxides or diols, starting from alkenes. As aromatic (benzylic) epoxides undergo Fe(III) perchlorate assisted *in situ* ring opening rapidly (usually 15 min) to yield the diol, whereas the aliphatic substrates usually take 3 to 4 h under the same conditions (2-carene oxide is an exception due to its high reactivity), it is reasonable to envisage a selective C-C bond cleavage of aromatic epoxides in the presence of aliphatic epoxides with a stoichiometric amount $NaIO_4$ (see scheme 3). On the other hand, aromatic (benzylic) epoxides are reluctant to undergo cleavage directly upon addition of $NaIO_4$, while this approach gives good conversion with aliphatic epoxides. It is thus possible to tune the selectivity in an simple and intuitive way.



Scheme 3. Tunable selective oxidation of aliphatic and aromatic epoxides.

Another important feature of this method, to be developed further, is the possibility of obtained *cis*-diols from electron poor alkenes: the C-C bond cleavage of these diols would therefore be performed readily in a two-step one pot reaction, in about 30 min, moreover opening new ways towards selective oxidation of multiple double bonds in the same molecule. This selectivity is remarkable as electron poor substrates hardly undergo such transformations.

Chapter 4 shows the broadening of the scope of application of the Mn/PCA system to the selective oxidation of diols to α-hydroxy ketones, which are powerful and useful synthons, though often neglected as they are difficult to synthesize. Starting from the alkene, it is possible to obtain acyloins, using essentially the same reaction conditions used for the oxidation of alkenes (scheme 4). Selectivity is the key in this case, as it is not facile to stop the reaction at the stage of monooxidation of the glycols; even with hydrobenzoin, yields were good, considering its tendency to undergo oxidation of both alcohols and therefore give a completely conjugated product.



Scheme 4. 3-step one-pot catalytic oxidation of methylcyclohexene to the corresponding α-hydroxy ketone.

The use of electron poor substrates would be convenient in this case also, as the readily obtained *cis*-diols would be oxidized with the essentially the same reaction conditions. An advantage in this case would be that of developing a one pot procedure for consecutive oxidation steps, in order to avoid work ups.

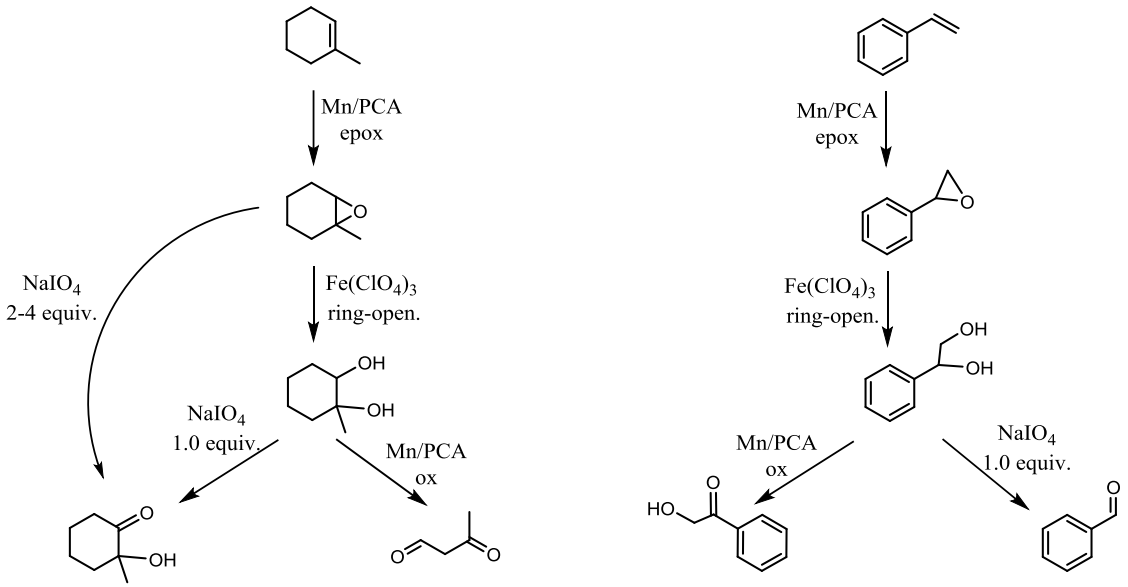
Chapter 5 demonstrates the application of the system to the epoxidation of EPDM polymers. We previously encountered problems in the oxidation of highly apolar compounds (1-octene and 1,2-octandiol), ascribed to the low solubility of the starting materials, whose full conversion was easily achieved by decreasing their concentration. The use of highly apolar solvents were not considered primarily out of concern for phase separation. However the challenge presented by such an apolar substrate class as EPDM polymers, forced efforts towards this direction. Though some degree of polarity is needed

in order to dissolve $Mn(ClO_4)_2$ and PCA, the system is surprisingly flexible such that even a mixture of cyclohexanone/cyclohexane is suitable to achieve conversion of the alkene bonds in the polymers (we had already anticipated that polymers containing less substituted double bonds to be less are even unreactive, by analogy with low molecular weight alkenes). Overall, it can be concluded that it is sufficient for a solvent, or even a mixture of solvents, to maintain a homogeneous system in order to ensure activity and conversion.

This project has therefore greatly broadened the scope of the system, which was this far untested on highly apolar substrates and in highly apolar media.

Chapter 6, which is in part published in a broader study by our group,[4] explores several mechanistic aspects of the Mn/PCA system: (apparent) order of reaction and reaction rate are explored with Raman spectroscopy, especially making use of competition reactions. Though light was shed on some critical aspects such as relative reaction rates and reasons that the conversion stops suddenly, it is clear that this is only still the beginning of our efforts to understand the system.

The aim of my work was that to explore the possibilities given by the Mn/PCA system in the oxidation of alkenes; while it was apparent from the beginning that the catalytic system was versatile/flexible, many opportunities emerged during the course of the PhD and many others possibilities are clearly feasible. As already mentioned in the discussion of chapters 3 and 4, is it possible to convert alkenes to epoxides, diols, α-hydroxy ketones, formal C=C double bond cleavage etc. (scheme 5). The real advantage of the method lies in the fact that it is essentially "off the shelf", as it does not require ligand synthesis nor the use of expensive components. Notably, not only the same catalytic system and therefore almost identical reaction conditions are used but, given its high activity and fast reactions, it is even possible to use the same stock solutions to perform several oxidation steps.



Scheme 5. Opportunities offered by the flexibility of the multi-step one-pot oxidation system for various classes of substrate.

Furthermore, this approach opens new routes towards selective oxidations in compounds bearing two or more distinct double bonds, as it is in possible to oxidize each of them selectively at different stages, and often in one pot reactions.

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[1] J. Dong, P. Saisaha, T. G. Meinds, P. L. Alsters, E. G. Ijpeij, R. P. van Summeren, B. Mao, M. Fañ anas-Mastral, J. W. de Boer, R. Hage, B. L. Feringa,W. R. Browne, *ACS Catal.* **2012**, 2, 1087−1096.
[2] J. Dong, D. Unjaroen, F. Mecozzi, E. C. Harvey, P. Saisaha, D.Pijper, J. W. de Boer, P. Alsters, B. L. Feringa, W. R. Browne, *ChemSusChem* **2013**, *6*, 1774-1778.
[3] C. M. Binder, D. D. Dixon, E. Almaraz, M. A. Tius, B. Singaramb, *Tetrahedron Lett*. **2008**, *49*, 2764–2767.
[4] P. Saisaha, J. Dong, T. G. Meinds, J. W. de Boer, R. Hage, F. Mecozzi, J. B. Kasper, W. R. Browne, *ACS Catal*. **2016**, *6*, 3486–3495.

Samenvatting

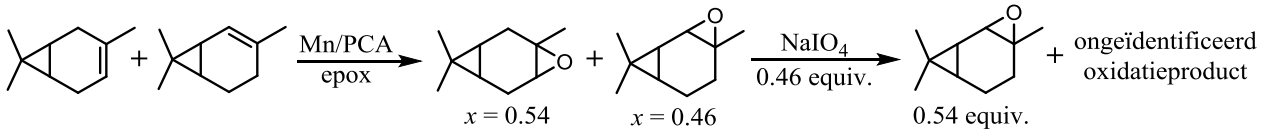
Over oxidatiechemie is wellicht het meest bekend in de loop van de geschiedenis van de mens. Aangezien oxidanten ruim aanwezig zijn in de atmosfeer is vrijwel alles onderhevig aan oxidatieve degradatie.

Oxidaties vertegenwoordigen een belangrijke transformatie in de organische chemie omdat ze vaak de mogelijkheid bieden om hoogwaardige producten van goedkope/ruim beschikbare startmaterialen te produceren, veelvuldig met behoud van de stereochemie van het product, wat het een zeer waardevol middel maakt voor organische synthese. Het veld van oxidatie is sinds mensenheugenis bestudeerd: een opmerkelijk voorbeeld (zie hoofdstuk twee), is hoe ozonolyse werd gebruikt voor structuurbepaling van materialen die dubbele bindingen bevatten (dit werd toegepast toen NMR en massaspectrometrie nog niet tot de mogelijkheden behoorden voor routine analyse). Noemenswaardig is dat dit voorbeeld ook het grote nadeel dat gepaard gaat met oxidatiereacties in de organische chemie illustreert: terwijl de toepassingen vrij breed zijn is de selectiviteit vaak een probleem. Enkele van deze problemen omvatten ook situaties waarbij het gewenste resultaat een intermediaire stap is in een oxidatieproces (bijvoorbeeld oxidatie van primaire alcoholen naar aldehydes).

Desalniettemin, de aandacht die milieuvriendelijke chemie heeft opgeëist in de afgelopen jaren heeft grote interesse opgeleverd voor processen die economische reagentia prefereren (zoals O_2 of H_2O) gepaard met overgangsmetalen van de eerste rij als katalysatoren. Het onpraktisch gebruik van moleculair zuurstof, ook al zou het extreem efficiënt zijn, en de gemakkelijke toegang tot H_2O_2 (welk bijproduct water is), maakt het laatstgenoemde een extra aantrekkelijk alternatief voor de gebruikelijke oxidanten zoals Oxone® en perzuren. Ondanks zijn oxidatiepotentiaal behoeft waterstofperoxide veelal geactiveerd te worden, zoals veelal gedemonstreerd met overgangsmetalen. Hoewel overgangsmetalen uit de tweede en derde rij zich uitstekend lenen voor hoge opbrengsten en selectiviteit (osmium, etc.) drijft de noodzaak voor milieuvriendelijke chemie het onderzoek richting overgangsmetalen van de eerste rij vanwege de eerdergenoemde redenen.

Het Mn/PCA oxidatiesysteem, onlangs ontwikkeld in onze groep, toonde al opmerkelijke flexibiliteit zoals het gebruik in de epoxidatie/*cis*-dihydroxylatie van alkenen,[1] van secundaire alcoholen naar ketonen en alkanen naar alcoholen.[2]

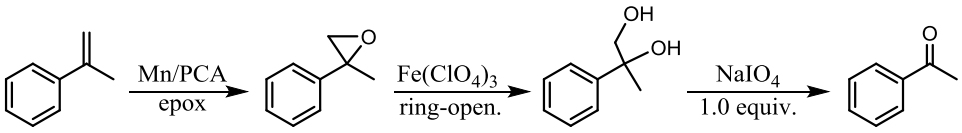
In hoofdstuk 2 hebben we aangetoond hoe een praktisch probleem te benaderen, zoals de scheiding van de oxidatieproducten van 2- en 3-careen, gebruik makende van de op mangaan gebaseerde oxidatiemethoden die eerder in onze groep ontwikkeld waren en middelen om deze aan te scherpen naar onze behoeftes (door middel van bijvoorbeeld Raman spectroscopy, zie Schema 1).



Schema 1. Selectieve oxidatie van 2-careenoxide in aanwezigheid van 3-careenoxide.

Ondanks dat de aanpak niet persé succesvol was, aangezien het oxidatieproduct dat geïsoleerd kon worden gerelateerd was aan het goedkopere 3-careen, heeft de zoektocht naar selectieve oxidaties ons naar interessante ideeën geleid die steeds meer vorm kregen zoals beschreven in de volgende hoofdstukken.

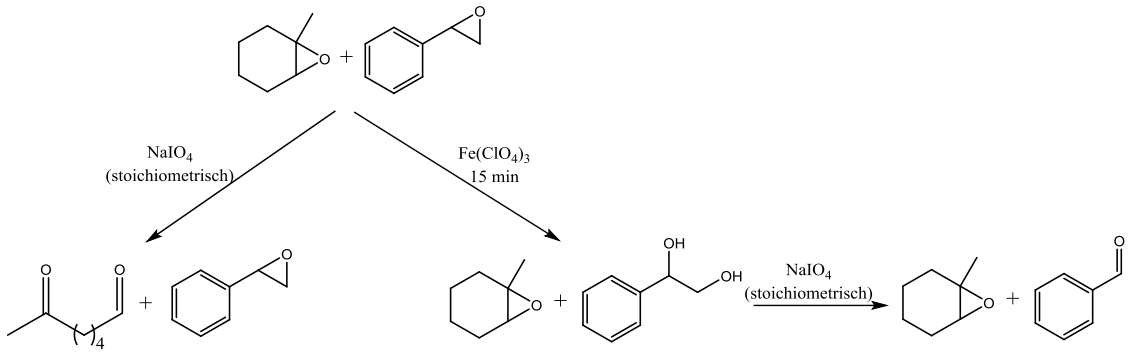
Het idee achter hoofdstuk 3 ontstond bij een poging om selectieve oxidatie van 2- of 3-careenoxide te bewerkstelligen. Het eerstgenoemde bleek een hogere reactiviteit te hebben, en onderging daarbij volledige conversie in aanwezigheid van 3-careenoxide en een stoichiometrische hoeveelheid $NaIO_4$, het standaardreagens voor de afsplitsing van diolen. Deze selectiviteit is te verklaren door verscheidene factoren in acht te nemen: gelijkend op wat gebeurt bij 2-careen (waarin het vlakke gedeelte van het molecuul direct verbonden is met de al gestreste cyclopropaanstructuur) zijn in het epoxide beide 3-voudige ringen, elk verbonden met de 6-ring, slechts 1 binding verwijderd van elkaar, wat de structuur gemakkelijk in staat stelt om ringopening te ondergaan ten gevolge van het reduceren van de stress in het systeem. Aan de andere kant, zelfs terwijl directe splitsing van epoxiden met $NaIO_4$ al gevonden is door Binder et al.[3], is het vrij duidelijk hoe de reactie via een diol intermediair verloopt, wat de selectiviteit richting 2-careen verklaard. De methode is later aangepast voor cyclische, lineaire en aromatische diolen (zie schema 2) met erg goede opbrengsten en selectviteiten, gebruik makend van hetzelfde katalytische systeem in de eerste oxidatiestap, en met slechts kleine aanpassingen van de reactieomstandigheden.



Schema 2. 3-Staps 1-pot katalytische oxidatie van β–methyl styreen naar acetophenon.

Op deze manier biedt deze reactie een gemakkelijkere en meer toegankelijke manier om ozonolyse af te dwingen: niet alleen wordt een en hetzelfde product gevonden in gevallen waar alleen een dubbele bindingen aanwezig is, maar ook bezit het een nieuwe eigenschap in selectiviteit, ofwel door verschil in positie van de dubbele bindingen, of van epoxides en diolen (gemakkelijk toegankelijk door ijzer(III) perchloraat geassisteerde *in situ* ringopening), of uiteindelijk direct door verschillende epoxiden. De verschillende tijdschaal van de ringopening zoals gevonden bij aromatische en alifatische substraten zou extreem bruikbaar kunnen zijn in een nieuwe selectieve oxidatie van epoxiden of diolen, uitgaande van alkenen. Omdat aromatische epoxiden vrij snel (gewoonlijk binnen 15 minuten) *in situ* ringopening ondergaan geassisteerd door Fe(III) perchloraat om het

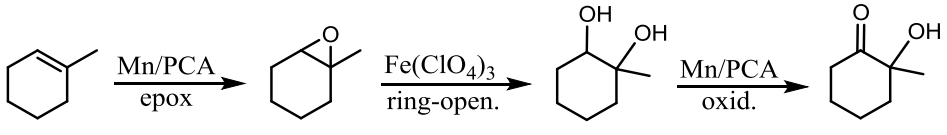
diol te vormen, terwijl alifatische substraten ongeveer 3 tot 4 uur nodig hebben onder dezelfde condities,[1] is het aannemelijk om een selectieve C=C bond splitsing van aromatische epoxides in aanwezigheid van alifatische epoxides met een stoichiometrische hoeveelheid van $NaIO_4$ (zie schema 3) te voorzien. Aan de andere kant, aromatische epoxiden zijn in staat om splitsing direct bij toevoeging van $NaIO_4$ te ondergaan, terwijl deze methode prima lijkt te werken voor alifatische epoxiden. Op deze manier zou het mogelijk zijn om de selectiviteit aan te passen op een eenvoudige en intuïtieve wijze.



Schema 3. Aanpasbare selectieve oxdaties van alifatische en aromatische epoxides.

Nog een belangrijke eigenschap van deze methode, die verder ontwikeld dient te worden, is de mogelijkheid om *cis*-diolen uit electrondeficiënte alkenen te vormen: de splitsing van de C=C binding in deze diolen zou daardoor gemakkelijk uitgevoerd kunnen worden in een twee-staps een-pot reactie in ongeveer 30 minuten, daarbij een weg biedend naar nieuwe manieren voor selectieve oxidatie van meervoudige bindingen in hetzelfde molecuul. Dit is opmerkelijk aangezien electrondeficiënte substraten zich moeilijk voor dit soort reacties lenen.

Hoofdstuk 4 toont het verbreden van de toepassingen van het Mn/PCA system naar selectieve oxidaties van diolen naar α-hydroxyketonen, welke zeer bruikbaar zijn in de synthese, maar vaak niet werden gebruikt vanwege de synthetisch moeilijke toegankelijkheid. Zo ook in dit geval, uitgaande van het alkeen, is het mogelijk om acyloïnen te verkrijgen, gebruik makend van praktisch dezelfde reactiecondities als voor de oxidatie van alkenen (zie schema 4). Selectiviteit is het sleutelwoord in dit geval, aangezien het niet makkelijk is om de reactie bij mono-oxidatie van de glycolen stop te zetten; zelfs met hydrobenzoïne was de opbrengst zeer goed, in acht nemend dat er een neiging is om beide C-OH's te oxideren naar het volledig geconjugeerde product.



Schema 4. 3-Staps 1-pot katalytische oxidatie van methylcyclohexeen naar het α-hydroxy keton.

[1] 2-careenoxide is een uitzondering vanwege zijn hoge selectiviteit.

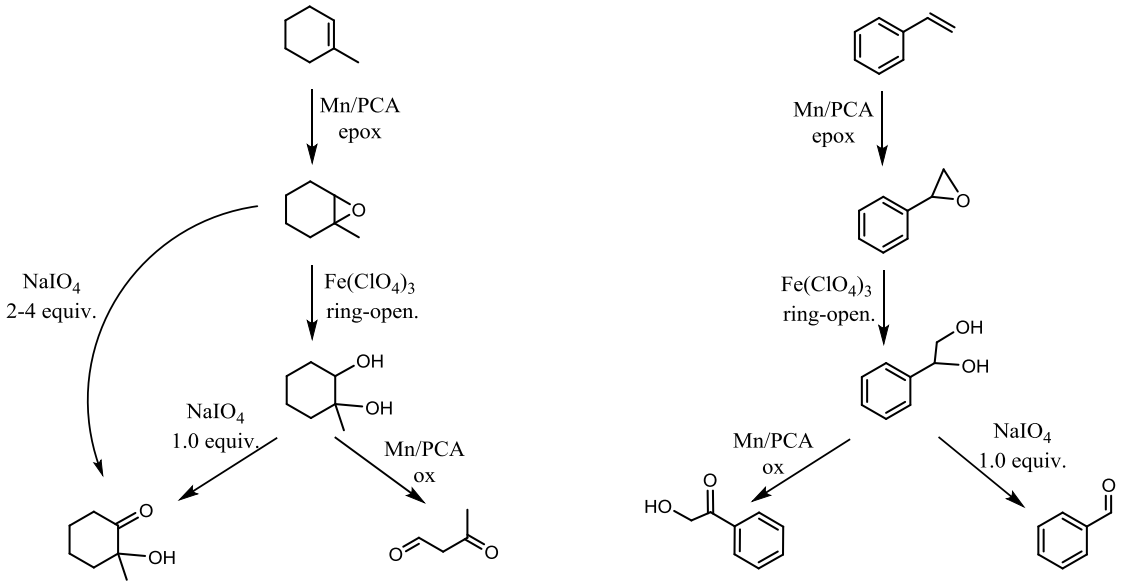
Het gebruik van electrondeficiënte substraten zou erg handig zijn in dit geval, aangezien de gemakkelijk te verkrijgen *cis*-diolen zouden worden geoxideerd onder praktisch dezelfde reactieomstandigheden. Een groot voordeel in dit geval zou de ontwikkeling van een 1-pots procedure voor opvolgende oxidatiestappen zijn, om zo intermediaire zuiveringen te vermijden.

Hoofdstuk 5 laat de toepassing van het systeem voor de epoxidatie van EPDM polymeren zien. Voorheen zijn wij problemen tegengekomen in de oxidatie van sterk apolaire moleculen (1-octaan en 1,2-octaandiol), vanwege voornamelijk de lage oplosbaarheid van de startmaterialen, waarvoor volledige oxidatie kon worden bereikt door verlaging van concentratie. Op dit punt hadden we niet het gebruik van hoog apolaire oplosmiddelen in beschouwing genomen, tot de vraag ernaar opkwam bij hoog-apolaire substraten (zoals EPDM polymeren). Hoewel enige polariteit is vereist om $Mn(ClO_4)_2$ en PCA op te lossen, is ons systeem zodanig flexibel dat zelfs een mix van cyclohexanon/cyclohexaan voldoende was om omzetting naar het gewenste polymeer te bewerkstelligen (voor de polymeren met minder gesubstitueerde dubbele bindingen werd al verwacht dat zij minder of niet reactief zouden zijn, zoals bij laag-molecule-gewicht alkenen). Kort gezegd is een oplosmiddel, of een mix van oplosmiddelen, in staat het systeem homogeen genoeg te houden om activiteit en omzetting te bewerkstelligen.

Dit project heeft om die reden het aantal toepassingen flink vermeerderd, omdat het systeem tot dusver nog niet getest was op sterk apolaire moleculen en in sterk apolaire media.

Het zesde project, wat deels is gepubliceerd binnen een breder onderzoek in de groep,[4] verkent enkele mechanistische inzichten van het Mn/PCA systeem in een bredere context: de (schijnbare) reactieorde en –snelheid zijn verkend met Raman spectroscopie, daarbij vooral gebruik makend van competitieve reacties. Hoewel er antwoorden waren gevonden op vraagstukken over enkele belangrijke aspecten zoals relatieve reactiesnelheden en redenen voor de reactie om te stoppen, is er nog steeds veel ruimte voor verder onderzoek.

Het doel van mijn werk was om de mogelijkheden die het Mn/PCA systeem bieden in de oxidatie van alkenen te verkennen; hoewel het vanaf het begin duidelijk was dat we een vrij flexibel katalytisch systeem in handen hadden, waren we verrast om te ontdekken dat het daarnaast nog steeds zo veel nieuwe mogelijkheden te bieden had. Zoals eerder genoemd, in hoofdstuk 3 en 4, is het goed mogelijk om van alkenen naar epoxiden, diolen, en α-hydroxy ketonen te gaan, en splitsing van de C=C dubbele binding te induceren (zie schema 5). Het grote voordeel aan deze methode is dat geen dure startmaterialen of lange synthetische routes zijn vereist. Noemenswaardig is dat niet alleen hetzelfde katalytische systeem en daarom vrijwel identieke reactiecondities worden gebruikt, maar, gezien de hoge efficiëntie en snelheid van reacties, het ook de mogelijkheid biedt om dezelfde standaard oplossingen voor verscheidene oxidatiestappen te gebruiken.



Schema 5. Verscheidene mogelijkheden die de flexibiliteit van onze multi-stap een-pot oxidatiesysteem biedt voor verschillende klassen van substraten.

Daarnaast opent deze aanpak de weg naar nieuwe selectieve oxidaties voor gevallen waarin twee of meerdere dubbele bindingen die aanwezig zijn in hetzelfde molecuul, in verschillende stadia te oxideren, veelal gebruik makend van slechts een 1-pots reactie.

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[1] J. Dong, P. Saisaha, T. G. Meinds, P. L. Alsters, E. G. Ijpeij, R. P. van Summeren, B. Mao, M. Fañanas-Mastral, J. W. de Boer, R. Hage, B. L. Feringa,W. R. Browne, *ACS Catal.*, **2012**, 2, 1087−1096.

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[3] C. M. Binder, D. D. Dixon, E. Almaraz, M. A. Tius, B. Singaramb, *Tetrahedron Lett.*, **2008**, 49, 17, 2764–2767.

[4] P. Saisaha, J. Dong, T. G. Meinds, J. W. de Boer, R. Hage, F. Mecozzi, J. B. Kasper, W. R. Browne, *ACS Catal.*, **2016**, 6, 3486–3495.

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To all my friends and family, and above all my parents for the unending support and love you have given me.

Thanks everybody/Grazie a tutti.

"Ma guardate l'idrogeno tacere nel mare

guardate l'ossigeno al suo fianco dormire:

soltanto una legge che io riesco a capire

ha potuto sposarli senza farli scoppiare."

Un Chimico

Fabrizio De Andrè