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Epoxidation of Terpenes with Molecular Catalysts in Homogeneous Phase

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A mes parents, mon frère, ma sœur et mes amis

*Toute action naturelle est engendrée par la nature,
de la plus courte façon que l'on puisse trouver.*

*Human subtlety... will never devise an invention more beautiful, more simple or more
direct than does nature, because in her inventions nothing is lacking,
and nothing is superfluous.*

Leonardo da Vinci

Die vorliegende Arbeit entstand in der Zeit von Oktober 2009 bis Oktober 2012 am
Anorganisch-chemischen Institute der Technischen Universität München

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Abbreviations

| | |
|---------------------------------|---|
| B-CDs | beta-Cyclodextrins |
| [BMIM]PF ₆ | 1-butyl-3-methylimidazolium hexafluorophosphate |
| CH ₂ Cl ₂ | Dichloromethane |
| CHCl ₃ | Chloroform |
| Cp | Cyclopentadienyl |
| Cp* | Pentamethylcyclopentadiene |
| DMSO | Dimethylsulfoxide |
| DPO | Dipentene dioxide |
| e.e. | Enantiomeric excess |
| equiv. | Equivalent |
| L | Limonene |
| LO | Limonene oxide |
| mCPBA | meta-Chloroperoxybenzoic acid |
| MCM 41-48 | Mobil Crystalline Material No. 41- No. 48 |
| MeOH | Methanol |
| MOF | Metal Organometallic framework |
| MTO | Methyltrioxorhenium |
| OPVP | Poly(vinylpyridine N-Oxide) |
| PSI | Polystyrenebound imidazole |
| PVP | Poly(vinylpyridine) |
| Tach | 1,3,5-Triaminocyclohexane |
| TBHP | tert-Butylhydroperoxide |

| | |
|-------------|------------------------|
| THF | Tetrahydrofuran |
| TOF | Turn over frequency |
| UHP | Urea Hydrogen Peroxide |
| USY-Zeolite | Ultrastable Y- Zeolite |

A.INTRODUCTION

I. Scope of the present work

Methyltrioxorhenium (MTO) and molybdenum (VII) based catalysts have been successfully applied in a broad range of oxidation reactions, and have proven to be especially active in the catalytic epoxidation of simple olefins.[1] This work deals with the epoxidation of more challenging alkenes: terpenes, employing these complexes as catalyst. The oxidation of terpenes leads to regio- or stereo-selectivity problems and to the formation of acid sensitive epoxides readily converted in diols. The introduction will focus on a presentation of the terpene family including the use of terpene oxides and an overview of the current literature in epoxidation catalysis using MTO and Molybdenum based complexes as catalysts.

II. Terpenes

1. Generalities

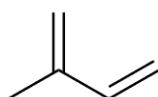
The term terpene used to refer to some hydrocarbons from turpentine, also called “resin of pine trees”. This term is now more generally employed for all natural compounds composed by isoprene units.[2]

Terpenes are either extracted or distilled from plants. These extracts, also known as ethereal or essential oils, are mostly employed in the perfume industry, to refine flavor and as aromas in the food industry. They are also important starting materials for the pharmaceutical industry.

In nature, plants produce either volatile terpenes to attract or repulse insects or animals, or heavy terpenes, which are toxic or possess a strong bitter-taste to protect them from predators. The terpenes consumed by insects are further

metabolized into pheromones to be used as communication means: to alarm or seduce their fellow creature.[2]

The terpenes are oligomeres composed by isoprene units as monomer (see scheme A.1).



Scheme A.1.

The terpenes are categorized depending on the number of isoprene units they contain (table II.1).

Table II.1. Classification of terpenes

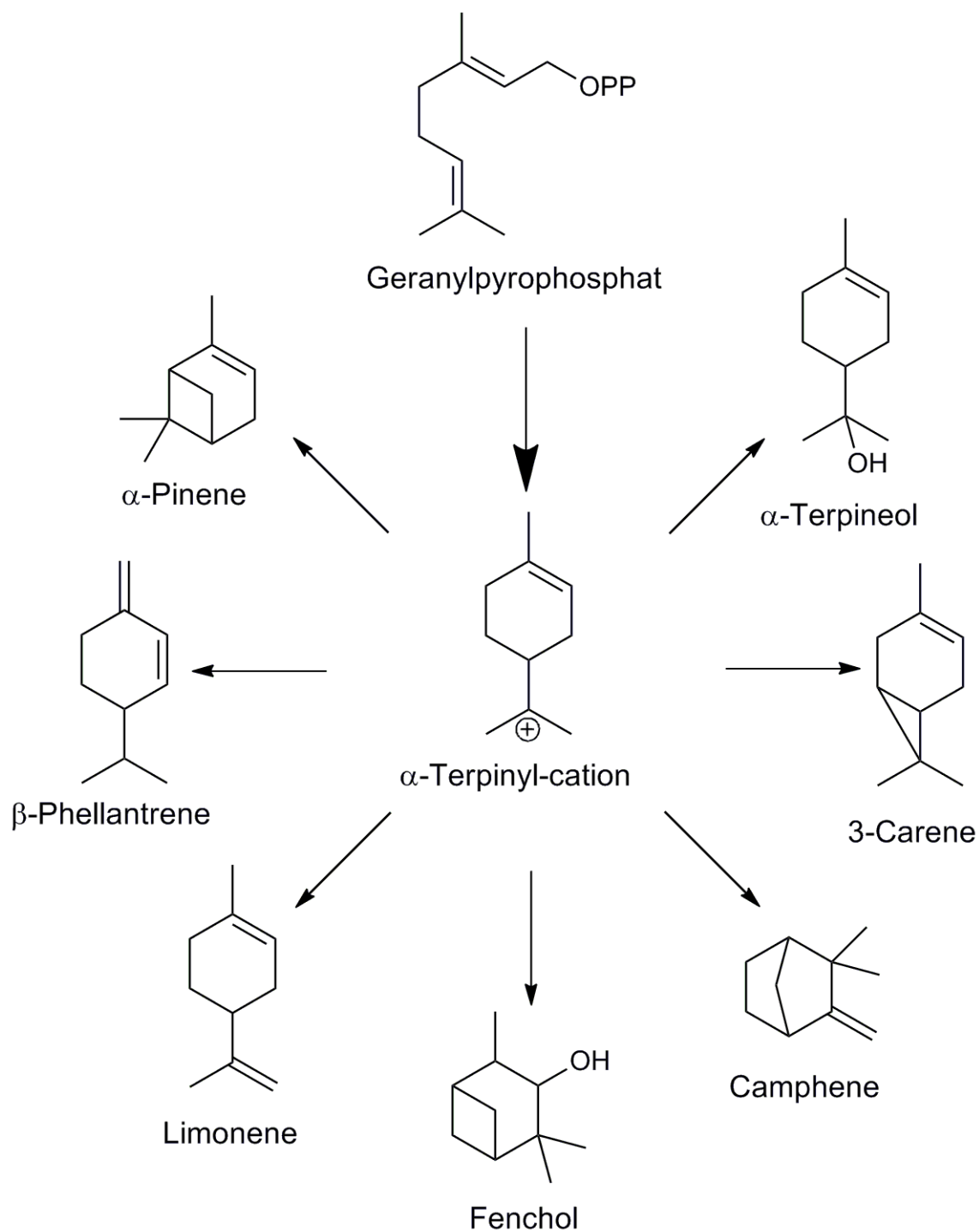
| Class name | Number of isoprene units | Number of carbons |
|----------------------|---------------------------------|--------------------------|
| Monoterpene | 2 | 10 |
| Sesquiterpene | 3 | 15 |
| Diterpene | 4 | 20 |
| Sesterpene | 5 | 25 |
| Triterpene | 6 | 30 |
| Tetraterpene | 8 | 40 |
| Polyterpene | > 8 | > 40 |

Each class of terpenes has particular properties: the lightest ones are highly volatile and find application as component of perfumes, the heaviest ones are found in polymers or plastics. Polyene is, for instance, a component of Latex.

2. Monoterpenes

Monoterpenes contain two isoprene units and thus 10 carbons. They are volatile molecules widely applied for their pleasant smell in perfume. Higher terpenes such as sesquiterpenes are employed as “basis” in perfume to stick volatile compounds and thus lengthen the perfume lifetime.

In nature, most of the monoterpenes are formed by rearrangement of the acyclic geranylpyrophosphate.^[3]



Scheme A.2. Biosynthesis of monoterpenes.[4]

Monoterpenes are divided in different categories depending on their structure: acyclic such as linalool or geraniol, monocyclic (limonene), bicyclic (α -pinene, camphene) or tricyclic (tricyclene).[5]

3. Epoxidation of terpenes

Oxygenated terpenes have many applications in synthetic chemistry and are used as raw materials in the synthesis of a range of important commercial products [6]. Optically pure epoxides and their corresponding 1,2-diols are important building blocks in asymmetric synthesis.[7]

Terpene oxides and their isomeric analogues are key starting materials for the synthesis of perfume and flavours.[8] Pinene oxide is, for instance, a starting material for the synthesis of the sandalwood fragrance.[9]

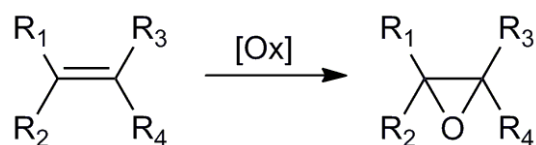
Oxygenated terpenes are also of high interest for the pharmaceutical industry. Camphene oxide is employed as precursor for the synthesis of spiro ring systems containing a benzopyran moiety connected with camphene derivatives.[10] This system is known for its pharmaceutical applications in anti-inflammatory and anti-allergic drugs.[11]

Terpenes oxide are also useful intermediates in polymer chemistry since 1,2-limonene oxide was applied as a bio-renewable monomer in the formation of biodegradable polymers via copolymerization with CO₂. [12]

III. Olefin epoxidation

1. Generalities

The epoxidation reaction is known since more than a century. It was first discovered by the Russian chemist N. Prileschajew in 1909 using peracids (RCO_3H) as oxidant.[13]



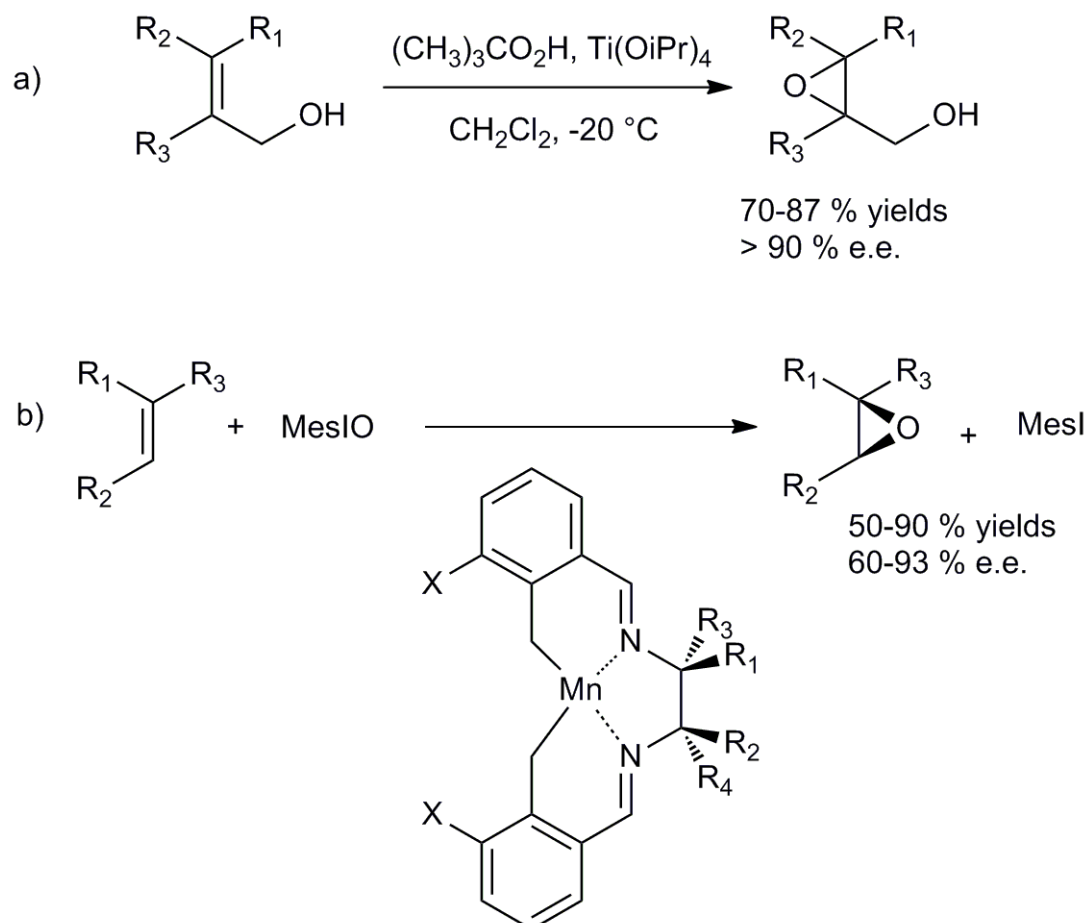
Scheme A.3. Epoxidation of olefin

The epoxidation of olefins is of high interest for many industrial applications. Epoxides are intermediates in the synthesis of numerous fine chemicals, such as perfumes or pharmaceutical compounds. They are also applied in the synthesis of various polymers such as polyglycols, polyamids or polyurethanes.[14] Epoxides are also employed as chiral precursors in the synthesis of chiral fine chemicals.

Nowadays, ethylene oxide and propylene oxide represent the major market for epoxide synthesis. Propylene oxide is produced in 8 million tons per years. For both epoxides heterogeneous catalysts are used in industrial processes for example $\text{Ag@Al}_2\text{O}_3$ with O_2 for ethylene oxide[15] and titania-doped-zeolite-type silicates (TS-1) developed by EniChem, Evonik, Dow and BASF.[16]

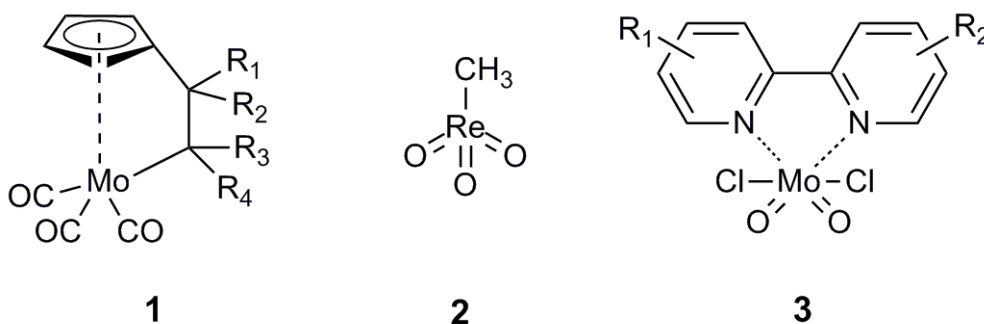
Most of the industrial processes employ heterogeneous catalysts. They are known to show higher recycling and separation properties than homogeneous ones. However, heterogeneous catalysts cannot induce enantioselectivity, whereas chiral molecular catalysts have this ability. Some well-known epoxidation catalysts are:

Sharpless' catalyst able to epoxidize allylic alcohol[17] and Jacobsen's catalyst (Mn(salen)).[18]



Scheme A.4. (a) Sharpless; (b) Jacobsen's asymmetric epoxidation.

Both catalysts owe their success to their ability to induce high enantiomeric excess (ee) in the epoxidation of olefins. However, the scope of Sharpless' catalyst is limited to allylic alcohol and Jacobsen's catalyst is too expensive for industrial processes.[19] Consequently, other molecular catalysts were investigated.



Scheme A.5. Catalysts employed in olefin epoxidation.

Among them, molybdenum based catalysts were extensively studied in the epoxidation of olefins. A Mo-based catalyst is already applied in the industrial production of propylene oxide and derivatives of this family of molecule can easily be prepared, allowing the synthesis of chiral and immobilized catalysts. These catalysts would have the advantage to be easily recycled and to induce high e.e. They will consequently be interesting alternative to the heterogeneous catalyst used up to date in industrial processes.[1b, 20] Methyltrioxorhenium also shows high activity in the epoxidation of olefins. However, all attempts to induce chirality to the complex failed up to now.[21]

2. Methyltrioxorhenium: An Overview

The first class of organorhenium (VII) compounds was described in the 1960-70s. Beattie et al. discovered MTO in 1979 by exposing $(\text{CH}_3)_4\text{ReO}$ to air for some weeks.[22] MTO was found to be the first air and water stable complex containing a Rhenium-carbon bond.[22]

The synthesis and catalytic applications of the organorhenium family were investigated by Herrmann et al. In 1984, they synthesized the first “sandwich” catalyst $(\eta^5\text{-C}_5\text{R}_5)\text{ReO}_3$. [23] However all their effort to find catalytic applications with this complex failed.[24]

The enthusiasm for catalytic applications of the organorhenium (VII) compounds began when Herrmann et al. discovered the first applicable synthesis of MTO in 1988.[25] Among all the applications of MTO, Herrmann et al. demonstrated the activity of MTO towards olefin epoxidation in 1991.[26] In this last paper, they also described a storage method of MTO by its polymerization into $[\text{CH}_3\text{ReO}_3]_\infty$.

2.1. Methyltrioxorhenium: Properties and Synthesis

2.1.1. Properties

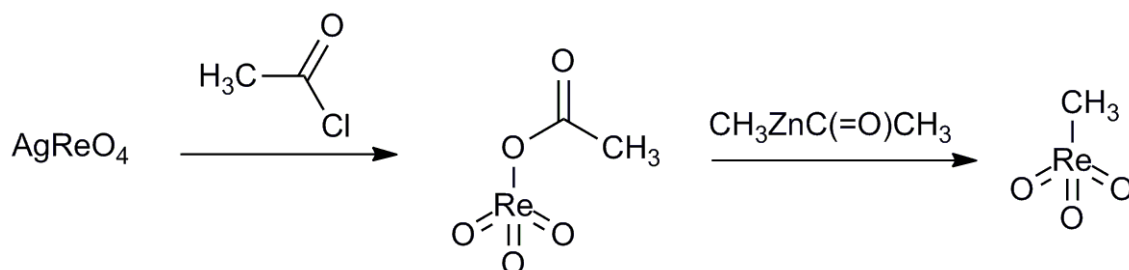
MTO is an unusually thermally stable compound decomposing above 300 °C.[27] It is highly volatile and soluble in all common solvents (from pentane to water). Its structure was determined by gas-phase electron diffraction and by a low temperature (5 K) neutron powder diffraction of CD_3ReO_3 . [28] The molecule is pseudotetrahedral with a short Re-C bond (206.3(2) pm). This value is between the typical Re-C single bond (215 pm) and Re-C double bond (195 pm) distances.[28a, 29] The ^1H NMR spectrum is solvent dependent due to the strong interactions between the solvent and the Lewis acidic metal center. These interactions are apparent both in the chemical shift variations in the ^1H NMR and ^{17}O resonances.[30]

MTO is photosensitive and splits into CH_3 and ReO_3 radicals by UV/vis irradiation.[31] It rapidly hydrolyzes in basic solutions to $[\text{ReO}_4]^-$ and CH_4 , [32] and in acidic solution, a highly interesting conducting material known as “poly-MTO” is formed.[33]

2.1.2. Synthesis

Methyltrioxorhenium was first discovered by “mistake” by Beattie et al. in 1979. Herrmann et al. found the first synthesis of MTO (see scheme A.6.).[34]

The main drawback of this method is the use of highly toxic organotin compounds in the reaction. In 2007, Herrmann et al. developed a new method employing Zn complexes allowing the formation of MTO without the use of the organotin.[37]



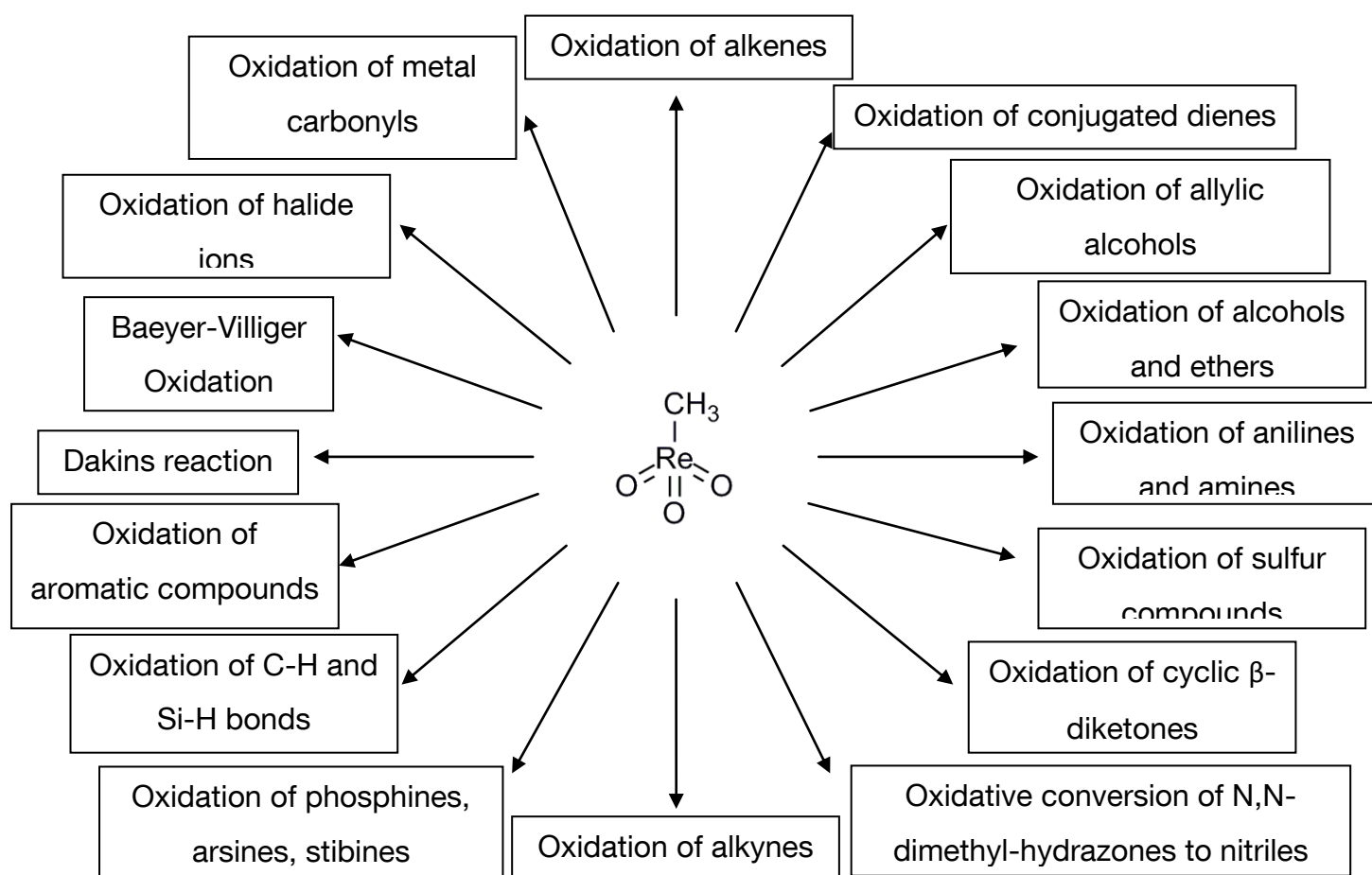
Scheme A.9. Formation of MTO employing organozinc compound.

For industrial applications, the organozinc $\text{CH}_3\text{ZnC(=O)CH}_3$ can be replaced by the cheaper organozinc $\text{Zn[OC(=O)CH}_3\text{]}_2$. [38]

2.2. Catalytic application of Methyltrioxorhenium

2.2.1. Methyltrioxorhenium as homogeneous oxidation catalyst

Methyltrioxorhenium is a very versatile catalyst which has been employed in a wide range of catalytic oxidation reactions as depicted in scheme A.10.[1a, 39]

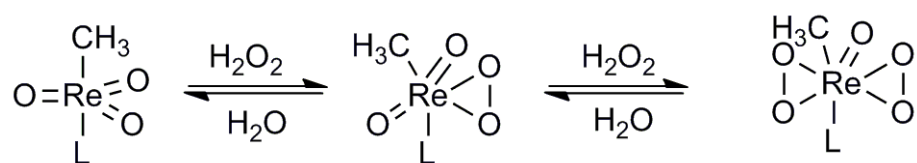


Scheme A.10. Oxidation process catalyzed by MTO[40]

Among all the applications of MTO, olefin epoxidation is the most widely studied reaction. One main advantage in employing MTO as epoxidation catalyst is the possible use of H_2O_2 as oxidant. It is an environmentally friendly oxidant since water is produced as only byproduct, as compared to other epoxidation oxidants which release alcohols or carboxylic acids. Moreover the concentration of MTO needed to undergo epoxidation of simple olefins is rather low (< 0.1 mol %). Some recent studies showed that MTO also presents high activities in ionic liquids.[41] Ionic liquids have two advantages: they are sustainable solvents and allow recycling of the catalyst, which present a high interest for industrial applications.[41-42]

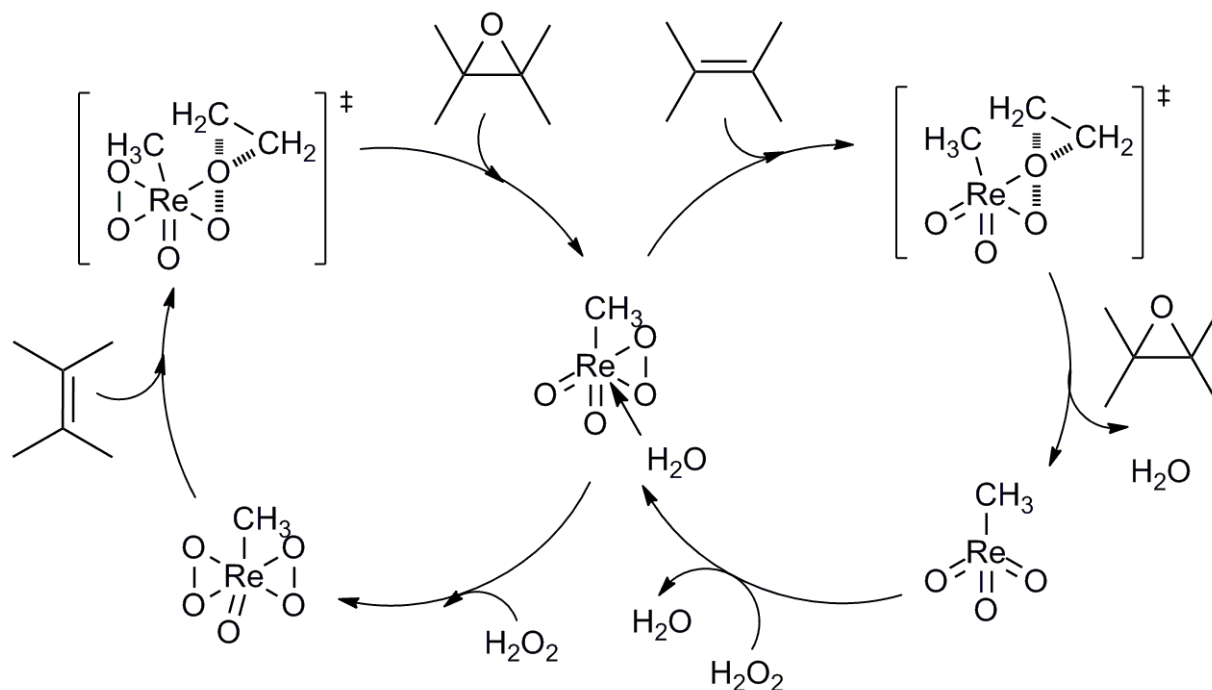
2.2.2. Mechanistic studies in the epoxidation reaction

The first mechanistic investigation performed on the epoxidation of olefin employing MTO as catalyst was done by Herrmann et al. They were able to isolate and characterize the active species of the reaction: the mono- and bis-peroxo species (Scheme A.11).[43]



Scheme A.11. Formation of the mono- and bis-peroxo species

The existence of these two species is not a surprise, as it is the prevalent mode of coordination between peroxide and many d^0 -metal centers such as Molybdenum and Tungsten.[44] From this starting point, the mechanism has been widely studied.[21a, 45] Owens et al showed that both the mono- and bis- peroxo species take part in the reaction.[39b] To obtain a better understanding of the mechanism, Espenson et al. explored different conditions leading to the decomposition of MTO.[46] The most acknowledge mechanism of the epoxidation of MTO is a bicyclic mechanism involving both the mono- and bis- peroxo complexes.[47]



Scheme A.12. Mechanism of the epoxidation of olefin catalyzed by MTO

However, a drawback in the use of MTO for the epoxidation of olefin was soon discovered: the acidity of the metal center induces the ring opening of acid sensitive epoxides. The use of non-aqueous oxidants such as UHP (urea hydrogen peroxide) and/or Lewis base adducts solve this issue.[1a, 39a]

2.2.3. N-Base adducts of Methyltrioxorhenium

Lewis base ligands were found to be effective adducts to decrease the acidity of the Re center and thus avoid the formation of diols.[34, 48] However, the use of these ligands induced a decrease in the activity of MTO compared to MTO alone.[49] Nevertheless, the addition of a large excess of ligand (L) allowed even higher activities than the use of MTO only.[50]

The activity of the catalytic species MTO/L depends on the choice of L. Mono or bidentate N-donor ligands did not affect the activity of the catalytic species.[51] The most commonly employed N-Donor Lewis base adducts with MTO are *tert*-butylpyridine, 4,4'-dimethyl-2,2'-bipyridine and pyrazole.[51]

2.2.4. MTO properties towards enantioselectivity

MTO is a non chiral catalyst, which means that it is impossible for it to induce chirality as such. One of the main challenges is to form a chiral MTO based complex because the product of pro-chiral starting material is essential in the industry.

For this purpose, chiral Lewis base adducts can be employed. However, the bond between MTO and the ligand is very labile, leading to the formation of racemic MTO-L species which proved to be unable to induce enantioselectivity.[21b, 52]

Another way to obtain chirality is to synthesize MTO derivatives by modifying the CH₃ group. This area has been intensively studied and these compounds revealed to be challenging to form. Moreover, most of the time, they showed low or no activity towards any oxidative reactions.[26]

2.2.5. Heterogenous derivatives of methyltrioxorhenium

In industry, heterogeneous catalysts are far more employed than homogeneous one. The difficulty to recycle and/or separate the homogeneous catalyst from the product is an important disadvantage for industrial use.

In the recent years, significant efforts have consequently been carried out to immobilize MTO and study its activity on various reactions. Niobium has been used to support MTO and has been applied in olefin epoxidation with H₂O₂ as oxidant. This system depicted even better activities than the homogeneous one.[53]

Zeolites have also been investigated: in general, the system Zeolite-Y/MTO showed higher chemoselectivity than the homogeneous system since no diol formation in olefin epoxidation and no siloxane formation were observed in the oxidation of silane.[54]

MTO was immobilized on various materials such as polymers[55] or mesoporous aluminium.[56] Another way to immobilize MTO is the use of UHP [47f, 57] or ionic liquid.[58] Both are able to trap MTO by dissolving or binding it. As they are both non soluble in most of the organic solvents, the catalyst can be recycle by simple extraction of the organic layer.

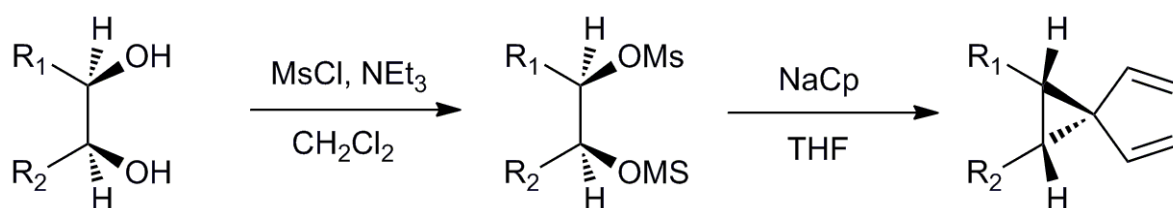
3. Molybdenum (VI) Catalysts

3.1. Molybdenum (VI) complexes: An overview

3.1.1. Properties and synthesis of CpMo(ansaalkylbridge) complexes

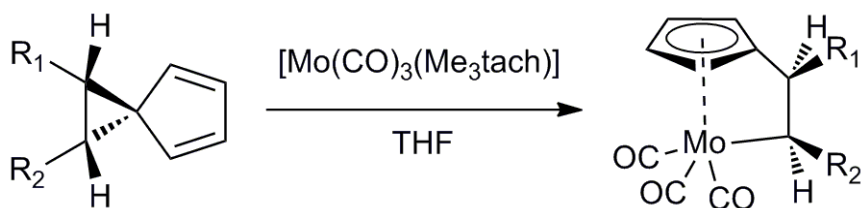
This class of transition metal ansa complexes bears at least one η^5 -coordinated cyclopentadienyl moiety ligated by an alkyl chain of at least two carbon atoms length. This alkyl chain is also η^1 -sigma-coordinated to the metal center.

The synthesis of this complex class was done in two steps. The first one is the synthesis of the spiro ligand containing the Cp and the alkyl bridge.



Scheme A.13. Synthesis of the spiro ligand

The second step is the formation of the definitive complex by adding the spiro ligand to a $[\text{Mo}(\text{CO})_3(\text{Me}_3\text{tach})]$ complex.



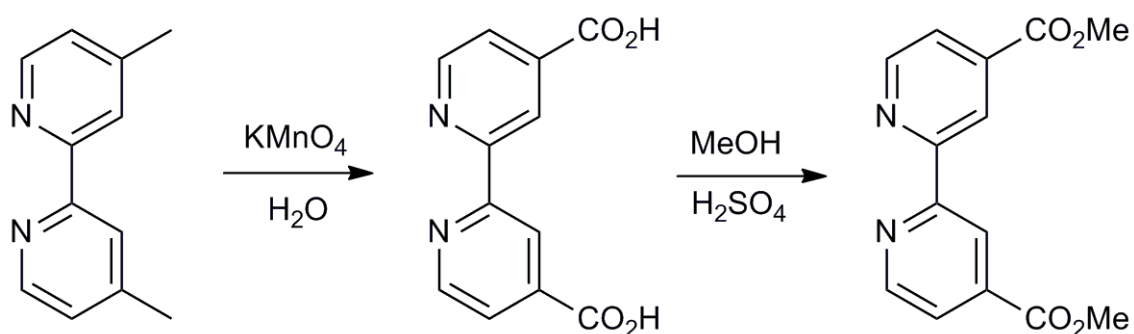
Scheme A.14. Synthesis of the Mo ansa complex

3.1.2. Properties and synthesis of $L_2Mo_2O_2Cl_2$ complexes

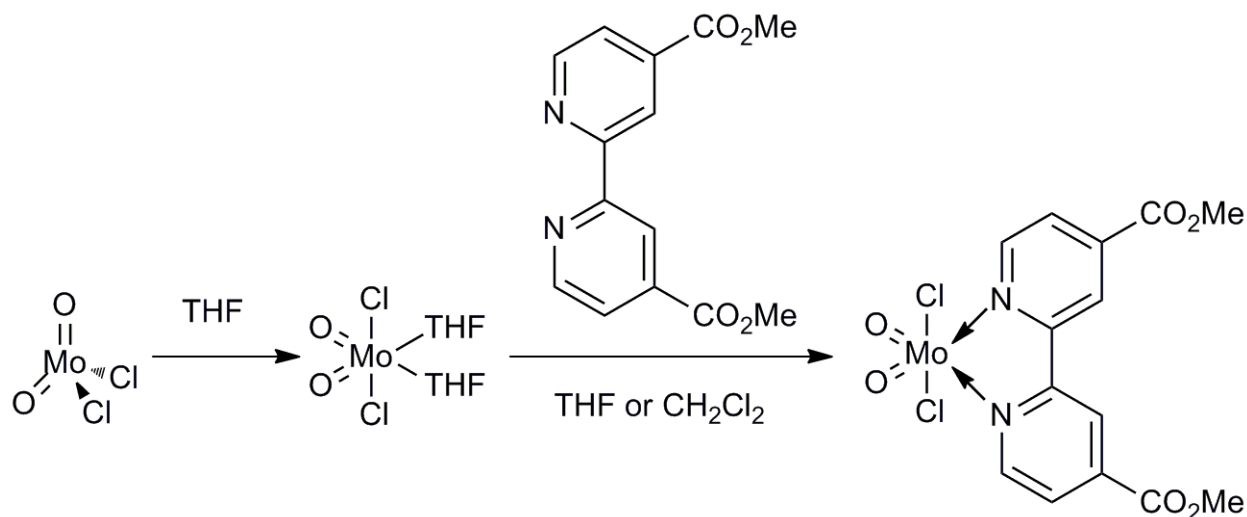
$[MoO_2X_2]$ are coordinatively unsaturated when $X = Cl, Br$ or Me and coordinate to labile solvent molecules when $X = THF, DMSO$ or THF .^[40] These complexes are highly air and moisture sensitive. The adduct formation of $[MoO_2X_2]$ with a strong basic donor ligand, such as 2,2'-bipyridine or derivatives, stabilizes the complex.^[59]

The first X-Ray crystal of a $[MoO_2X_2L_2]$ -type complex was reported in 1966.^[60] $[MoO_2X_2L_2]$ are monomeric complexes and possess a distorted octahedral geometry, with the oxido ligand *cis* to each other.^[61]

The synthesis of this class of complex also consists in two steps: the formation of the ligand and then its reaction with the metal center to obtain the catalyst.



Scheme A.15. Synthesis of the ligand.^[62]



Scheme A.16. Synthesis of the catalyst.[63]

3.2. Catalytic application of Mo (VI) based catalysts

3.2.1. Olefin epoxidation

CpMo(ansa bridge)(CO)₃- as well as MoO₂Cl₂(bipyridine)-based complexes have proven to be active in epoxidation of olefin.[1b, 59, 64] Numerous papers have been published showing the influence of the different ligands for both classes of complexes.

In the case of the Mo ansa bridge, a certain length of the ansa bridge (> 2 carbons in the bridge) is necessary to obtain a good complex stability and high activities towards epoxidation.[62, 64a, 65]

For MoO₂Cl₂(bipyridine) based complexes, the activities of the complex depends on the Lewis base, the redox stability of the ligands and the stability of the adduct complexes.[40, 51a, 66] The first bipyridine adduct, for instance, was insoluble in most of the organic solvents preventing its use in homogeneous catalysis.[67]

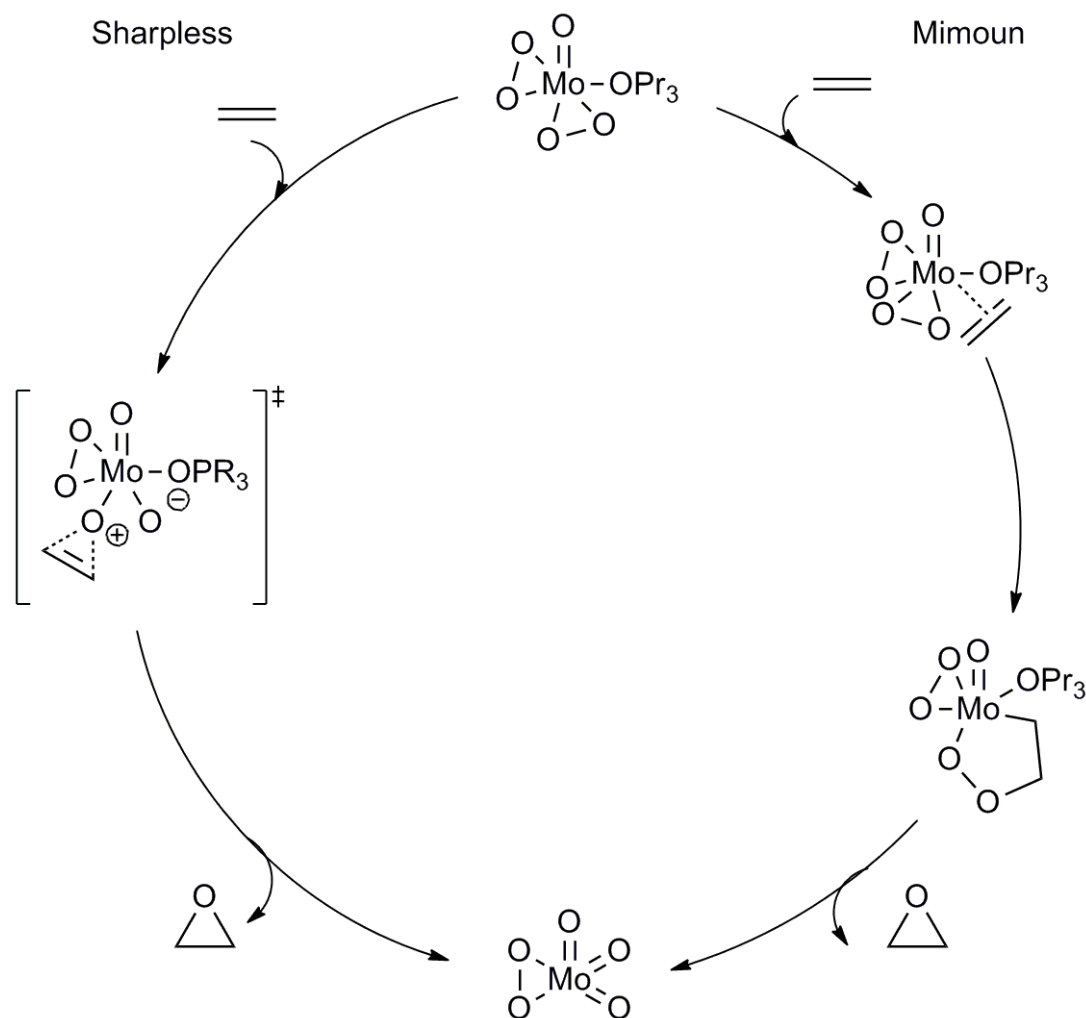
However, the use of substituted bipyridines enhanced the catalyst solubility in organic solvents.[68] The electronic and steric nature of the Lewis base influences

also the activity of the complex.[62, 65b, 69] 4,4'-bipyridine and its derivatives are particularly suitable adducts to $[\text{MoO}_2\text{Cl}_2]$ in the epoxidation of olefins.[1b]

The major drawback of $\text{MoO}_2\text{Cl}_2\text{L}_2$ based complexes is the adduct stability since bipyridine ligands dissociate in solution (more particularly in polar solvent such as THF or CH_3CN). The loss of the ligand decreases the catalyst activity and leads to the oxidation of the free bipyridine ligand.[40] The use of these complexes in homogeneous catalysis is thus disfavored.

3.2.2. Mechanistic study in the epoxidation reaction

The two fundamental mechanisms for the epoxidation of olefins employing Molybdenum diperoxo species were proposed in the 1970s by Mimoun et al. and Sharpless et al (Scheme A.17).[70]



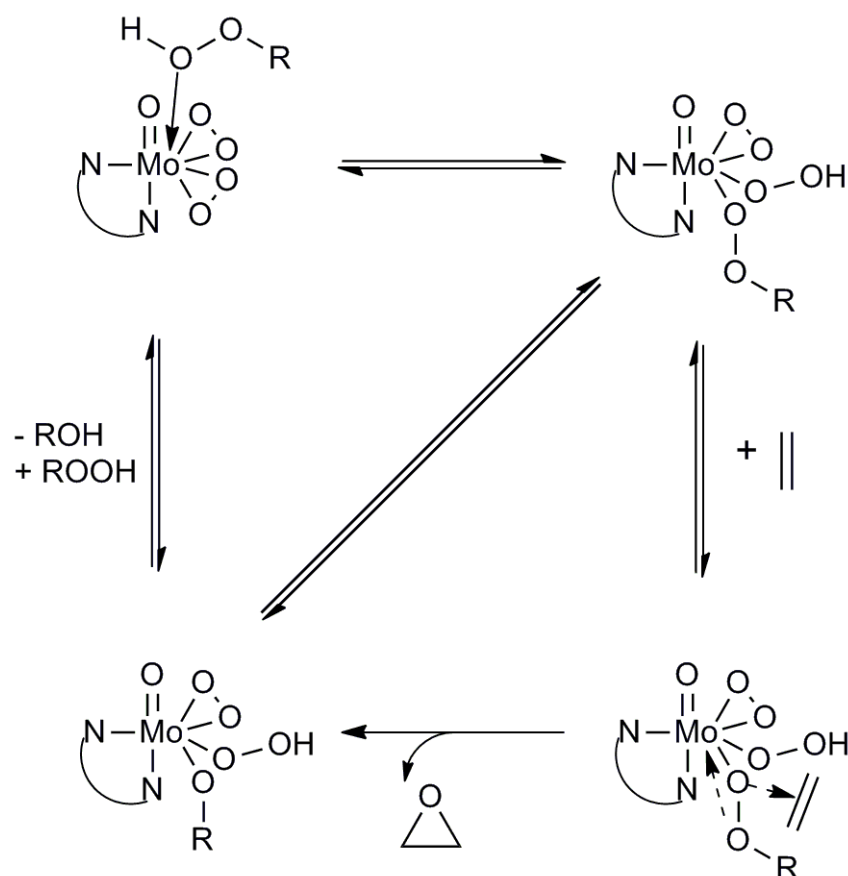
Scheme A.17. Mechanisms proposed by Mimoun et al. and Sharpless et al.

As depicted in Scheme A.17, Mimoun et al. proposed a coordination of the olefin to the metal center followed by the formation of a 5-membered ring intermediate. On the other hand, Sharpless et al. suggested a transition state where the olefin coordinates to one of the peroxo oxygen.

The clarification of the mechanism aroused much interest. Evidences were found against the formation of a 5-membered ring intermediate.[71] Moreover, the hypothesis of Sharpless et al. tends to be confirmed by the researches.[47b, 72]

However, up to this time point hydrogen peroxide was used in the calculation. As it is known that Molybdenum based complexes do not undergo epoxidation of olefins

in presence of H_2O_2 but with *tert*-butylhydroperoxide (TBHP), other studies on the mechanism employed TBHP, in particular, Thiel et al. (Scheme A.18).[66, 73]



Scheme A.18. Mechanism proposed by Thiel et al. in the epoxidation of olefins employing Mo based catalyst and TBHP as oxidant.[73b]

Further research on this area also supported this proposed mechanism.[20b, 69b, 74] In particular, Poli et al. presented a detailed computational study involving CpMoO_2X ($\text{X} = \text{Cl}$ or Me) complexes.[75]

3.2.3. Enantioselectivity properties of Mo (VI) based catalysts

Non chiral molybdenum (VI) based catalysts such as $\text{MoO}_2\text{X}_2\text{L}_2$ or $\text{CpMo}(\text{CO})_3\text{Me}$ showed high activities in the epoxidation of olefins. Moreover, active derivatives of these catalysts can easily be produced. These two properties led to the belief that their chiral derivatives could induce enantioselectivity.[20a, 52a]

Research focused initially on the synthesis of dioxomolybdenum bearing chiral Lewis base adducts as ligands, such as derivatives of pyridyl alcohols,[65a, 76] oxazolines and bis(oxazolines),[65a, 77] sugar derived Schiff bases,[78] tetradentate salen ligands [13,18][79], diazabutenes [19][80], oximes, *cis*-diols and 8-phenylthiomenthols.[65e] However, the enantiomeric excess obtained with these complexes was rather low (20 to 40 %). As for MTO, these results can be explained by the lability of the Mo-L bond.

Research on chiral derivatives of Mo (VI) based catalysts thus concentrated on the CpMo(CO)₃X family. The introduction of a chiral substituent to the Cp ring did not induce chirality because of the Cp ring rotation.[81]

Kühn et al. consequently stabilized the Cp ring by binding it to the metal center via an ansa bridge.[64b, 81] In this last case, two possibilities are available to synthesize chiral catalysts: adding a chiral substituent to the Cp ring or to the ansa bridge. The synthesis of such complexes as well as their influence on epoxidation is still ongoing in the group.

3.2.4. Heterogeneous derivatives of Molybdenum based catalysts

Homogeneous Molybdenum (VI) based catalysts show high activity and selectivity towards olefin epoxidation. Their immobilization thus arouses much interest since heterogeneous catalysts are essential in industrial processes.

Corma et al. obtained a catalyst for asymmetric epoxidation of allylic alcohols by “tethering” a chiral complex with bidentate O,O-ligands to the internal surface of a mesoporous USY-zeolite.[82] The catalytic activities of these heterogenized complexes were similar to the corresponding homogeneous ones. The epoxyalcohols were obtained in high yields and selectivities but moderate enantioselectivity. Moreover, no loss of activity was observed after several runs.[82]

Molybdenum (VI) dioxo complexes bearing hydrosalen derivatives as ligands were also grafted on ordered mesoporous silicas surfaces.[83] beta-Cyclodextrin (β -CDs) has been used to immobilize Mo (VI) based complexes and applied in olefin epoxidation. This system depicted high selectivity towards epoxide formation.[84]

Several groups have successfully heterogenized homogeneous Mo based catalysts on mesoporous silicas (MCM-41 and MCM-48) by various methodologies and found that the resulting heterogeneous materials are as active and stable as the homogeneous ones.[85]

Another way to immobilize molybdenum (VI) based catalysts is the use of ionic liquids. The complex binds in the ionic phase whereas the products and reactants stay in the organic layer, allowing the separation and the recycling of the catalyst.[86]

A promising way to immobilize molybdenum (VI) based complexes is the MOF structure. They were successfully applied for manganese [87] and vanadium [88] catalysts. Research is ongoing in the group to apply this structure to molybdenum complexes and test its activity towards olefin epoxidation.

IV. Objectives of this work

Terpenes such as α -pinene and limonene have been widely studied in the literature. However, the synthesis of their epoxides in high yield and selectivity is challenging. In particular, the formation of byproducts was reported for limonene and only low conversions were obtained for α -pinene. Camphene was far less studied probably due to the difficulties in the epoxidation of low substituted alkenes.

The terpenes such as α -pinene, limonene and camphene are highly sensitive to reaction media for the formation of their respective epoxides. Consequently, the effects of the catalyst, ligand and oxidant concentrations are tested in order to determine the optimal conditions for their epoxidation.

Moreover the influence of the different reactants is investigated: different Lewis base adducts such as *tert*-butylpyridine, pyrazole, 4,4'-dimethyl-2,2'-bipyridine or Schiff bases are applied as ligand. An aqueous (H_2O_2) and non-aqueous (UHP) hydrogen peroxide are used in the epoxidation reaction to determine the effect of water on the selectivity towards the epoxide formation. Moreover the influence of polar (THF, MeNO_2 or CH_2Cl_2) as well as non-polar solvents (toluene) is tested on the epoxidation of the different terpenes

B.RESULTS AND DISCUSSION

I. Epoxidation of α -pinene

1. Epoxidation of α -pinene catalyzed by methyltrioxorhenium (VII): Influence of Additives, Oxidants and Solvents

This Chapter originated from the following publication:

Typhène Michel, Daniel Betz, Mirza Cokoja, Volker Sieber, Fritz E. Kühn

J. Mol. Catal. A: Chem. **2011**, 340, 9-14

1.1. Abstract

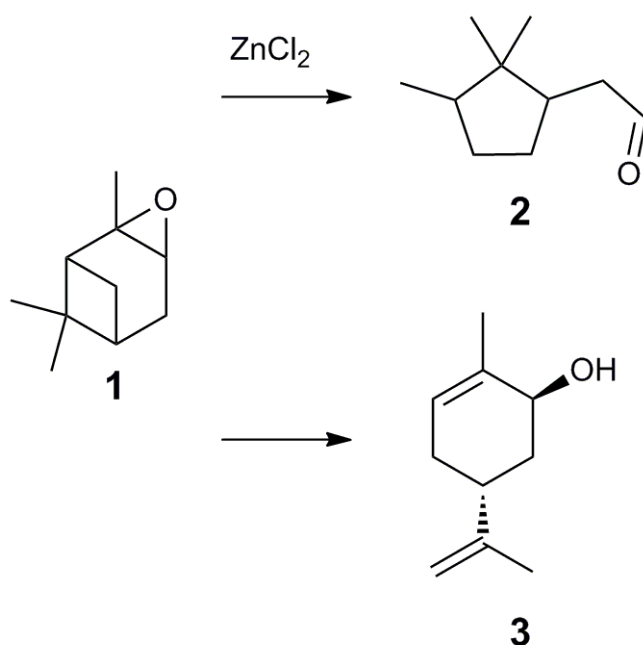
The epoxidation of α -pinene employing methyltrioxorhenium as catalyst is examined. The influence of mono- and bidentate Lewis basic additives (e.g. *tert*-butylpyridine, 4,4'-dimethyl-2,2'-bipyridine, and Schiffbases) is investigated. Additionally the impact of the oxidant (H_2O_2 in water or urea-hydrogen peroxide (UHP)) on the catalytic performance is studied. The effect of the solvent is also examined in order to determine the optimal conditions for the epoxidation of α -pinene. The best and straightforwardly applicable result is obtained when a ratio α -pinene: MTO: *tert*-butylpyridine: UHP of 200: 1: 40: 600 is applied at 0 °C in nitromethane. In this case, α -pinene oxide is formed with 95 % yield after 3 h with a turnover frequency (TOF) of 610 h^{-1} .

1.2. Introduction

α -Pinene is a monoterpene which is an important ingredient of some flavoring plants such as mint, lavender and ginger. It is extracted from turpentine oil (350,000 t/year), which is a product of the paper pulp industry.[9]

α -Pinene is particularly utilized as starting material in terpene chemistry to obtain flavors and fragrances. It is also an intermediary species in the synthesis of Taxol®, an anticancer drug.[89]

The epoxidized product of α -pinene, α -pinene oxide is used to synthesize campholeic aldehyde, an intermediate in the synthesis of the sandalwood fragrance.[9] α -Pinene oxide is additionally employed in the synthesis of trans-carveol, which is an important component for perfume bases and food flavor compositions (Scheme I.1).[90]



Scheme I.1. Reaction of α -pinene oxide to campholeic aldehyde and to trans-carveol.

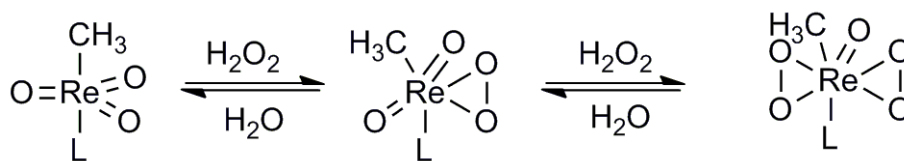
The epoxidation of α -pinene in homogeneous phase has been studied in some detail in the past. Among the homogeneous catalysts applied for this reaction, methyltrioxorhenium [1a, 20a, 52a] (MTO) is among the most widely used. However, in almost all cases the epoxidation suffers from either low conversion or low yield because of the formation of α -pinene diol as byproduct. Using the MTO-Lewis base adducts as catalysts does neither prevent diol formation nor does it improve the epoxide yields.[50e, 91] A change of the oxidant to urea hydrogen peroxide (UHP)

and addition of the base (+)-2-aminomethylpyrrolidine does not lead to a better selectivity according to the literature reports.[52b] The reported conversion is still very low (< 7 %), when MTO is anchored to polymers such as poly(vinylpyridine) (PVP) or poly(vinylpyridine N-oxide) (OPVP).[92] Although some reports claim that with MTO as catalyst, nearly quantitative yields of α -pinene oxide can be reached,[93] we were unable to reproduce these results. Accordingly, the need for a straightforward, unproblematic procedure towards α -pinene oxide still remains.

A wide range of other metals has been applied for the epoxidation of α -pinene. Molybdenum (VI) complexes have been studied for this reaction.[77a, 85b, 94] Co (III) supported material on hexagonal mesoporous silica (HMS) or Co supported by zeolite (NaCoY₉₃) was investigated.[95] The synthesis of α -pinene oxide was also carried out with [Cu(pyridine)₂Cl₂] and the [CrO₃(2,2'-bipyridine)] as catalysts.[96] Lipase activity towards epoxidation of α -pinene has been studied.[97] [Ru(salophen)Cl-PSI] (PSI = polystyrenebound imidazole) with NaIO₄ has also been employed for the formation of α -pinene oxide.[98] The epoxidation of α -pinene using (N,N-bis(salicylidene)ethylenediammine)Ti-salan complex is reported to lead to 85 % epoxide yield after 7 h reaction time.[99]

Based on these results, we set out to re-examine MTO as catalyst in the presence of Lewis basic additives, since such MTO based systems proved to be superior to other catalyst systems in many epoxidation reactions, provided optimal conditions were found.

Additionally, MTO requires H₂O₂ as oxidant (Scheme 1.2), which has the advantage of being environmentally benign and cheap in comparison to other conventional oxidants used in epoxidations, e.g. meta-chloroperoxybenzoic acid (mCPBA).



Scheme I.2. Reaction of a MTO-Lewis base complex with H₂O₂ forming amino- and bis(peroxo) complex, L = electron donor ligand.[41a, 50b-g]

Nevertheless, due to the high Lewis acidity of the Re (VII) center in presence of H₂O (the byproduct formed during the oxidation), ring opening of (sensitive) epoxides to diols occurs. It was shown that employing Lewis basic additives (Lewis base ligands) decreases the acidity of the rhenium center [1a] and allows the synthesis of sensitive epoxides.[50] Particularly the use of pyridine and some of its derivatives, as well as Schiff-base ligands leads in many cases to both good activity and high selectivity towards epoxidation of olefins.[51a, 59, 100]

In this work, we investigated the optimal and reproducible conditions for the epoxidation of α-pinene with MTO as catalyst. For this purpose, several mono- and bidentate base adducts were applied. Additionally, to eliminate potential problem sources, the effect of using different oxidants and reaction media, including ionic liquids, was examined.

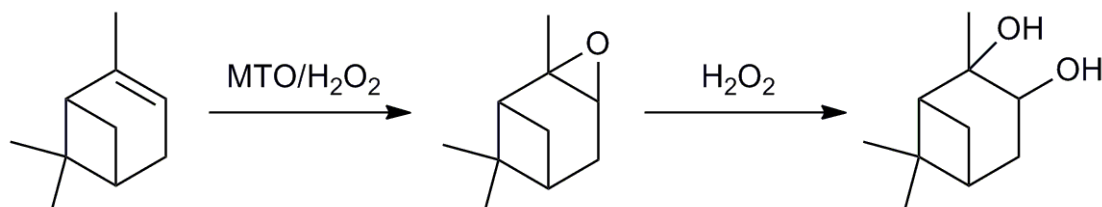
1.3. Results and discussion

1.3.1. Optimization of the conditions for the epoxidation of α-pinene

Lewis base concentration and temperature effects

In a previous work, optimal conditions for cyclooctene epoxidation with the system MTO/*tert*-butylpyridine/H₂O₂ were determined.[100a] The best result was obtained when a molar ratio cyclooctene: MTO: *tert*-butylpyridine: H₂O₂ of 100: 1: 5: 300 in CH₂Cl₂ at 25 °C was applied.

The same conditions were used for the epoxidation of α -pinene. However, the formation of α -pinene diol was observed. From this observation it was deduced that α -pinene oxide appears to be more acid sensitive than cyclooctene oxide, being easily transformed to α -pinene diol in the presence of MTO and water (Scheme I.3).



Scheme I.3. Reaction from α -pinene to α -pinene diol in presence of MTO/ H_2O_2 and water.

Accordingly, the Lewis acidity of the system has to be reduced by addition of an appropriate Lewis-base. Due to the beneficial effects of excess Lewis-base, originating from the weak Re–N interaction,[49a] an excess of *tert*-butylpyridine was applied. To strengthen the base effect the reaction temperature was kept low.

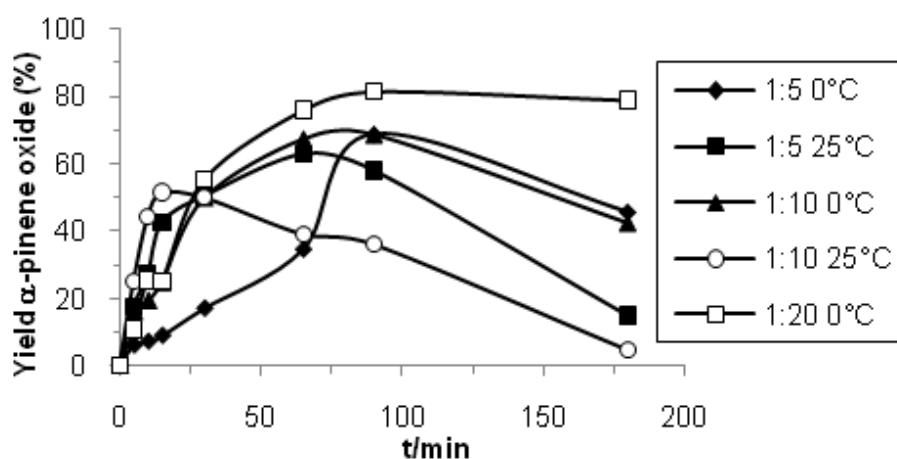


Figure I.1. Kinetics of the α -pinene epoxidation with different molar ratios of MTO: *tert*-butylpyridine at 0 °C and 25 °C, ratio α -pinene: MTO: H_2O_2 is 100: 1: 300 in CH_2Cl_2 .

All kinetic curves depicted in Figure I.1 show a feature which has not yet been described in detail in the previous reports on α -pinene epoxidation. The formation of

α -pinene oxide is fast at the beginning of the reaction but after some time, the product yield not only becomes stagnant but decreases, reflecting the somewhat slower reaction to the respective diol becoming dominant.

The formation of α -pinene diol is observed for all MTO: *tert*-butylpyridine ratios. However, a ratio of 1:20 at 0 °C leads to the highest yield of α -pinene oxide observed. Besides, the diol formation is less pronounced in comparison to the other cases. Thus, in the following reactions, the molar ratio between MTO and the ligands was kept at 1:20 and the reactions were performed at 0 °C.

Oxidant concentration effects

Another method to reduce the diol formation is to decrease the concentration of H_2O_2 in the reaction (see Figure I.2).

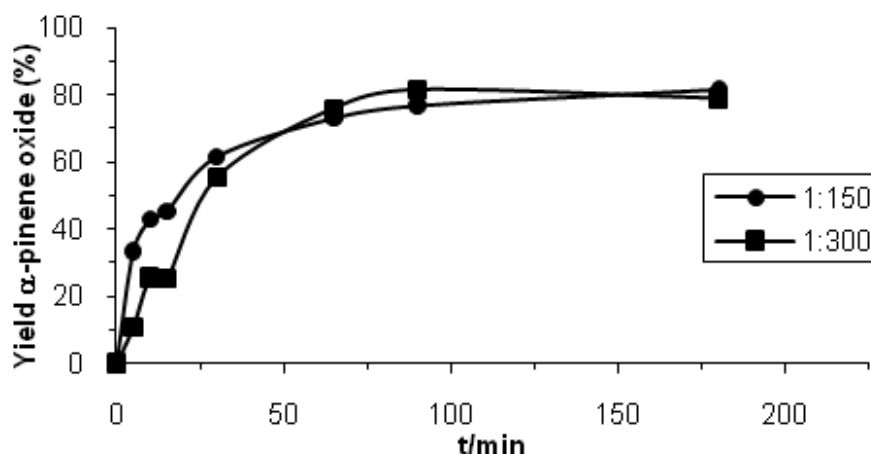


Figure I.2. Kinetics of the α -pinene epoxidation at 0 °C with a molar ratio of α -pinene: MTO: *tert*-butylpyridine 100: 1: 20 at different MTO: H_2O_2 ratios in CH_2Cl_2 .

In the case of a molar MTO: H_2O_2 ratio of 1: 300, the epoxide yield reaches a maximum (82 %) after 1.5 h (conversion α -pinene = 96 %) and then decreases, whereas in the case of a ratio of 1:150, the conversion is somewhat slower and reaches a maximum epoxide yield of 81 % after 3 h (conversion α -pinene = 84 %). Follow up diol formation is largely suppressed in the latter case. It is therefore more

economical to use the lower concentration of hydrogen peroxide for the epoxidation of α -pinene.

Catalyst concentration effects

The concentration of MTO was decreased to establish the minimum concentration of catalyst needed to perform this reaction without activity loss. The ratio α -pinene: *tert*-butylpyridine: H_2O_2 used was 10: 2: 15.

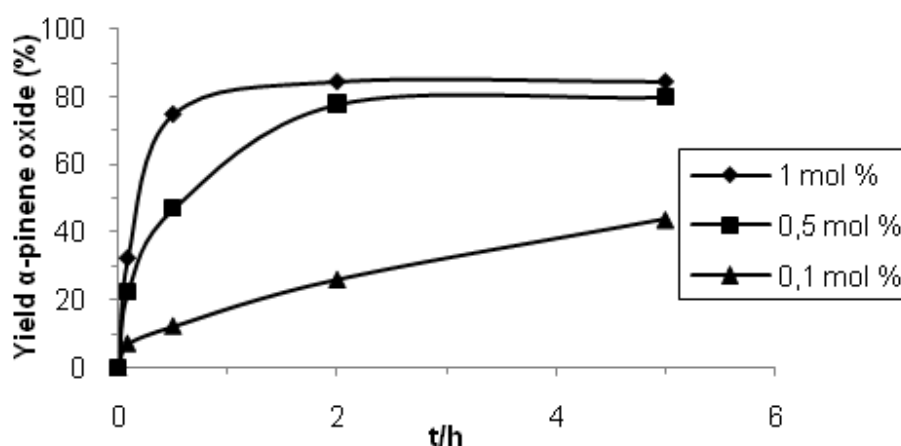


Figure I.3. Kinetics of the epoxidation of α -pinene with different MTO concentrations in CH_2Cl_2 .

Decreasing the concentration of MTO in the reaction from 1 mol % to 0.5 mol % leads to quite similar results (Figure I.3). The formation of α -pinene oxide is slightly higher after 2 h with 1 mol % (84 % yield) than with 0.5 mol % (77 % yield). Yet, the long-term activity (>1 d) of the catalyst is decreasing for concentrations below 1 mol %; the activity decreases more significantly when the concentration of MTO in the reaction is reduced to 0.1 mol %. To ensure both maximum yield and good activity the concentration of MTO was kept at a 1 mol % level for all following reactions.

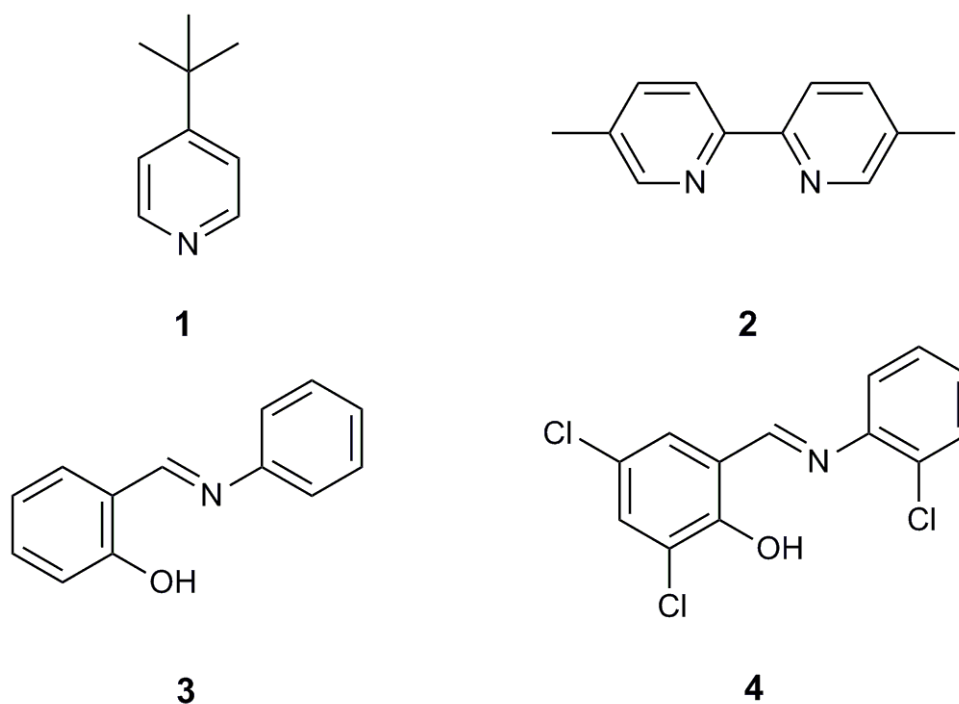
The poor activity at a catalyst concentration of 0.1 mol % may be due to several effects: first, MTO can decompose to methanol and perrhenate to a higher degree in

the presence of large excess of oxidant.[50c] Second, the Lewis base can also be oxidized in the presence of H₂O₂. [35, 37] Oxygen donor adducts of MTO, however, which are formed during this ligand oxidation process are less active than N-base adducts.[35, 37] Third, impurities of oxidant and solvent have a stronger impact on catalyst deactivation when very low catalyst amounts are applied. In practical applications, however, a rigorous cleaning of the ingredients of the reaction mixture might be counterproductive with respect to reaction efficiency and costs.

1.3.2. Ligand-, oxidant-, and solvent- influence on the epoxidation of α -pinene

Ligand effects

The influence of a bidentate ligand (4,4'-dimethyl-2,2'-bipyridine), two different Schiff-base ligands (2-[(E)-(phenylimino)methyl]phenol and 2,4-dichloro-6-[[2-chlorophenyl]imino]methyl] phenol) on the α -pinene oxide yield was examined (Scheme I.4).



Scheme I.4. Lewis base ligands used in this study: 4-*tert*-butylpyridine **1**, 4,4'-dimethyl-2,2'-bipyridine **2**, 2-[(*E*)-(phenylimino)methyl]phenol **3** and 2,4-dichloro-6-[[2-chlorophenyl]imino]methyl]phenol **4**.

The epoxidation of α -pinene was originally performed with a ratio substrate: MTO: ligand: H_2O_2 (100: 1: 20: 150) in CH_2Cl_2 at 0 °C. The results are summarized in Table I.1.

Table I.1 Comparison of the influence of ligands **1–4** on the epoxidation of α-pinene.

| Ligand | Yield α-pinene oxide (Time) | TOF (h ⁻¹) | Observation |
|----------|-----------------------------|------------------------|-------------------------------|
| 1 | 85 % (5 h) | 390 | Minor α-pinene diol formation |
| 2 | 81 % (5 h) | 200 | Minor α-pinene diol formation |
| 3 | 6 % (5 h) | 20 | α-pinene diol as main product |
| 4 | 11 % (5 h) | 20 | α-pinene diol as main product |

The activity of the catalytic system MTO: *tert*-butylpyridine **1**: H₂O₂ (TOF = 390 h⁻¹) is higher than the catalytic system MTO: 4,4'-dimethyl-2,2'-bipyridine **2**: H₂O₂ (TOF = 200 h⁻¹). Moreover, the formation of α-pinene diol is less pronounced when *tert*-butylpyridine **1** is employed as Lewis basic additive, compared to 4,4'-dimethyl-2,2'-bipyridine **2**. In contrast to pyridine-based Lewis bases, Schiff-base ligands **3** and **4** lead to a low selectivity in the formation of α-pinene oxide (Table I.1). In both examined cases, the main product is α-pinene diol. Consequently, *tert*-butylpyridine **1** appears to be the best of the examined ligands as additive for the epoxidation of α-pinene. It was thus used for the following experiments.

Oxidant effects

In all the previous experiments, α-pinene diol formation was observed. It was thus important to investigate other oxidants, which might prevent this unwanted follow-up reaction. Several reports describe the utilization of urea hydrogen peroxide (UHP)

as an alternative oxidant to aqueous H_2O_2 in metal complex catalyzed olefin epoxidation reactions when acid sensitive epoxides are formed.[47f, 101]

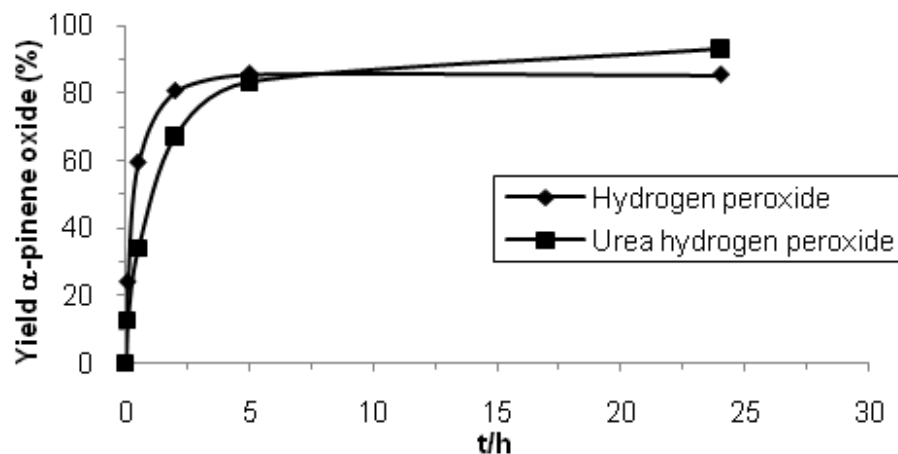


Figure I.4. Kinetics of the α -pinene epoxidation in CH_2Cl_2 at 0°C employing a ratio α -pinene: MTO: *tert*-butylpyridine: oxidant (100: 1: 20: 150) with different oxidants.

The catalytic reaction undertaken with the system MTO: UHP has approximately the same activity as the MTO: H_2O_2 system (see Figure I.4). However, the formation of α -pinene diol is only observed when H_2O_2 is used. UHP as oxidant does not lead to byproduct formation. However, the use of UHP can be problematic due to its solubility: it is barely soluble in most common organic solvents. Therefore, the real concentration of UHP in solution is hardly predictable, and the reaction cannot be described as really homogeneous. Based on these considerations, both UHP and H_2O_2 have certain advantages as oxidants for the epoxidation of α -pinene and will be used in the following experiments.

Solvent effects

Nitromethane, the ionic liquid ($[\text{BMIM}]\text{PF}_6$), chloroform and tetrahydrofuran were selected as solvents. Sharpless et al. demonstrated that the use of nitromethane and dichloromethane as solvent leads to similar efficiency in the epoxidation of cyclohexene.[50a] Previous work [41-42, 86, 102] on epoxidation reactions in ionic

liquids shows in many cases a yield improvement compared to organic solvents.[41b]

Table I.2 Comparison of the influence of H₂O₂ and UHP in different solvents.^a

| Entry | Solvent | Yield % (TOF) | |
|-------|---------------------------------|-------------------------------|----------|
| | | H ₂ O ₂ | UHP |
| 1 | CH ₂ Cl ₂ | 85 (400) | 93 (150) |
| 2 | MeNO ₂ | 51 (330) | 63 (290) |
| 3 | CHCl ₃ | 87 (100) | 83 (100) |
| 4 | THF | 47 (17°) | 29 (120) |

a. Reaction condition: ratio α -pinene: MTO: *tert*-butylpyridine: oxidant (100: 1: 20: 150) after 24 h reaction time.

The epoxidation of α -pinene is favored when dichloromethane is used as solvent at 0 °C. The use of other solvents such as nitromethane, chloroform or THF leads to lower formation of α -pinene oxide. However, the turnover frequencies measured for dichloromethane and nitromethane are close (see Table I.2).

In the case of the ionic liquid [BMIM]PF₆, the measurements proved to be problematic due to a significant amount of solid residue. Nevertheless, α -pinene diol appears to be the main product formed according to GC analysis. In the following experiments, dichloromethane and nitromethane were further used as solvent.

The conditions of α -pinene epoxidation were optimized for H₂O₂ as oxidant. So far, the best efficiency is obtained with either H₂O₂ or UHP as oxidant with a ratio of α -pinene: MTO: *tert*-butylpyridine: oxidant of 100: 1: 20: 150. This condition leads to the formation of α -pinene oxide in 85 % yield after 5 h. Further experiments were

done to determine the optimal conditions of the epoxidation of α -pinene employing UHP as oxidant. For this purpose, the concentration of UHP was increased and the concentration of MTO was decreased.

Table I.3 Optimization of α -pinene epoxidation employing UHP as oxidant.

| Solvent | Ratio α -pinene: MTO: <i>tert</i> -butylpyridine: UHP ^a Yield % (TOF h ⁻¹) | | | |
|-------------------------------------|--|--------------|--------------|--------------|
| | 100:1:20:150 | 200:1:40:300 | 100:1:20:300 | 200:1:40:600 |
| CH₂Cl₂ | 83 (150) | 80 (450) | 93 (200) | 83 (210) |
| MeNO₂ | 65 (290) | 84 (420) | 96 (270) | 100 (610) |

a. Samples taken after 5 h.

As depicted in Table I.3, increasing the concentration of UHP from 150 equiv. to 300 equiv. leads to higher formation of α -pinene oxide. Moreover, the formation of α -pinene diol is not observed in all these experiments. Decreasing the concentration of catalyst in the reaction leads to similar efficiency in nitromethane.

From this set of experiments, the optimal condition for the epoxidation of α -pinene was found to be a ratio α -pinene: MTO: *tert*-butylpyridine: UHP of 100: 0.5: 20: 300 in nitromethane at 0 °C. Formation of α -pinene oxide occurs with 95 % yield after 3 h and quantitative yield after 5 h with a TOF of 610 h⁻¹.

1.4. Experimental

1.4.1. Starting materials

Hydrogen peroxide was used 35 % in water (Aldrich). (1R)-(+)- α -pinene was purchased from Aldrich. Urea Hydrogen Peroxide (UHP) contained 35 wt. % H₂O₂ (Acros organics). Methyltrioxorhenium and the ionic liquid 1-butyl-3-

methylimidazolium hexafluorophosphate [BMIM]PF₆ were synthesized according to literature procedures.[37, 103]

1.4.2. Gas chromatography

Gas chromatography was performed using a DB23 column (30 m, 0.25 mm, 0.25 μm film thickness). The isothermal temperature profile is: 60 °C for the first 2 min, followed by a 10 °C/min temperature gradient to 105 °C for 10 min, then by 4 °C/min to 155 °C and finally 20 °C/min to 260 °C. The injector temperature was 320 °C. Chromatography grade helium was used as the carrier gas.

1.4.3. Epoxidation of α-pinene in different solvents

Method A

MTO was dissolved in the solvent and the solution brought to the appropriate reaction temperature. The ligand, the two standards (mesitylene: 100 μL, ethylbenzene: 100 μL), and the oxidant (H₂O₂ 35 % or UHP) were added to the solution. α-Pinene was then added to the reaction. The different catalyst:ligand:oxidant ratios are given in Table I.4.

Samples were taken after 5min, 10 min, 15 min, 30 min, 60 min, 90 min, 3 h, 5 h and 24 h. For each sample, 200 μL of the reaction mixture was taken and mixed with a catalytic amount of MnO₂ to decompose excess H₂O₂. The mixture was then filtered through MgSO₄ in order to remove H₂O. CH₂Cl₂ (1.8 mL) was then added and the solution was analyzed by GC or stored in the freezer for several hours.

In this method, the samples are not stable; consequently, it is important to measure them directly in GC or to store them in the freezer. It is not possible to do several reactions in the same time. Consequently, a new method was found to stabilize the GC samples and allowed measurement over night.

Method B

MTO was dissolved in the solvent and the solution brought to the appropriate reaction temperature. The ligand, the two standards (mesitylene: 250 μ L, ethylbenzene: 250 μ L), and the oxidant (H_2O_2 35% or UHP) were added to the solution. α -Pinene was then added to the reaction.

The different catalyst: ligand: oxidant ratios are given in Table I.5. Samples were taken after 5 min, 30 min, 2 h, 5 h and 24 h. For each sample, 1.5 mL of the reaction mixture was taken and mixed with a catalytic amount of MnO_2 to decompose excess H_2O_2 . The mixture was then filtered and extracted 4 times with 1.5 mL of water to remove MTO. The organic layer was then dried over MgSO_4 and filtered. 0.18 mL (for H_2O_2) or 0.2 mL (for UHP) was taken from this solution and diluted with 1.3 mL of CH_2Cl_2 . The solution was then analyzed by GC.

Table I.4 Summary of the different ratios employed in the epoxidation of α -pinene

| Entry | α -Pinene ratio | MTO ratio (mmol) | <i>tert</i> -butylpyridine ratio | H_2O_2 ratio | CH_2Cl_2 (mL) |
|-------|------------------------|------------------|----------------------------------|------------------------------|-------------------------------|
| 1 | 100 | 1 (0.048) | 5 | 300 | 2.3 |
| 2 | 100 | 1 (0.048) | 10 | 300 | 2.3 |
| 3 | 100 | 1 (0.048) | 20 | 300 | 2.3 |
| 4 | 100 | 1 (0.048) | 20 | 150 | 1.2 |

Table I.5 Summary of the different ratios employed in the epoxidation of α-pinene.

| Entry | α-Pinene ratio | MTO ratio (mmol) | Ligand ^a ratio | H ₂ O ₂ ratio | Solvent ^b (mL) |
|-------|----------------|------------------|---------------------------|-------------------------------------|---------------------------|
| 1 | 100 | 1 (0.12) | 20 | 150 | 7.6 |
| 2 | 100 | 0.5 (0.06) | 10 | 150 | 7.6 |
| 3 | 100 | 0.1 (0.012) | 2 | 150 | 7.6 |
| 4 | 100 | 1 (0.06) | 20 | 150 | 7.8 |

| Entry | α-Pinene ratio | MTO ratio (mmol) | Ligand ^a ratio | UHP ratio | Solvent ^b (mL) |
|-------|----------------|------------------|---------------------------|-----------|---------------------------|
| 5 | 100 | 1 (0.12) | 20 | 150 | 8.4 |
| 6 | 100 | 0.5 (0.06) | 20 | 150 | 8.4 |
| 7 | 100 | 1 (0.12) | 20 | 300 | 8.4 |
| 8 | 100 | 0.5 (0.06) | 20 | 300 | 8.4 |

a. *tert*-butylpyridine, 4,4'-dimethyl-2,2'-bipyridine or two Schiff-bases.

b. CH₂Cl₂, MeNO₂, CHCl₃ or THF.

1.4.4. Epoxidation of α-pinene in ionic liquid

MTO (0.024 mmol) and *tert*-butylpyridine (5 equiv.) were dissolved in 1-butyl-3-methylimidazoliumhexafluorophosphate ([BMIM]PF₆) (0.2 mL). In a separate flask, mesitylene (100 μL), ethylbenzene (100 μL) and α-pinene (100 equiv.) were mixed together and a blank sample was taken from this solution. UHP or aqueous H₂O₂ (300 equiv.) was then added to the ionic liquid followed by the solution of α-pinene.

The sampling time is the same as for conventional solvents. At defined times, 41 μL of the organic phase was poured in a vial containing MnO_2 in order to destroy excess oxidant, dried over MgSO_4 and filtered. 2 mL of CH_2Cl_2 were then added and the sample was analyzed by GC.

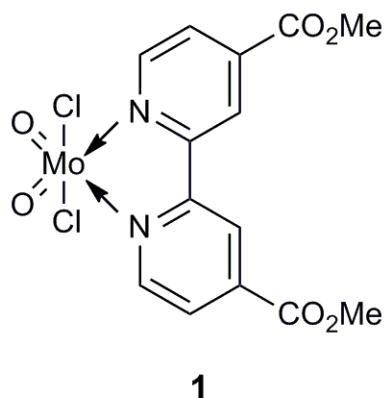
1.5. Conclusion

A MTO based catalytic system was examined and optimized for practically applicable laboratory scale epoxidation of α -pinene. The major challenge of this reaction is the usually unwanted formation of diol that had not been sufficiently addressed in previous reports.

Whereas the addition of ligands such as Schiff-bases or bipyridines does not suppress the formation of α -pinene diol, in the presence of *tert*-butylpyridine the formed α -pinene oxide does not further react to the diol. However, the epoxidation of α -pinene can be achieved with either H_2O_2 or UHP as oxidant. The condition leading to the best result employed MTO as catalyst, *tert*-butylpyridine as ligand and UHP as oxidant. It leads to the formation of α -pinene oxide in high yield (95 % after 3 h) and to an acceptable TOF of 610 h^{-1} . No formation of α -pinene diol is observed in this case. This result is straightforwardly obtained when applying a α -pinene: MTO: *tert*-butylpyridine: UHP ratio of 200: 1: 40: 600 in MeNO_2 at $0 \text{ }^\circ\text{C}$.

2. Epoxidation of α -pinene employing Mo (VI) based catalysts

2.1. α -Pinene epoxidation employing **1** as catalyst



Scheme I.5.

The epoxidation of α -pinene employing **1** as catalyst was tested with a molar ratio cyclooctene: Mo based complex: TBHP of 100: 1: 300 in CHCl₃ at 55 °C.

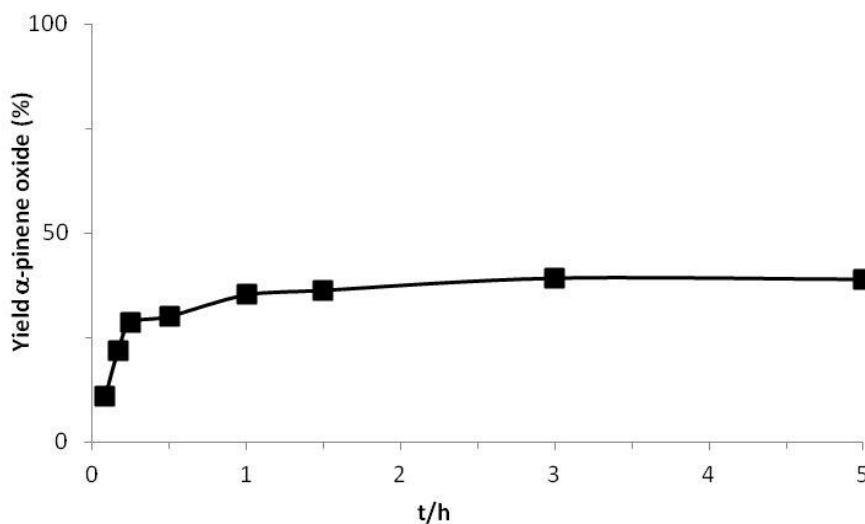


Figure I.5. Kinetics of the epoxidation of α -pinene employing **1** as catalyst

α -Pinene oxide is obtained in 32 % yield after 1 h with a conversion of α -pinene of 69 % and the formation of numerous byproducts is observed. Longer reaction time

do not improve the epoxide yield. The conditions of the reaction were consequently investigated in order to reduce the formation of byproducts and thus improve the selectivity towards α -pinene oxide formation.

2.1.1. Effect of the oxidant concentration

The oxidant concentration is an important parameter of the reaction to control the activity of the catalytic system. Various molar ratio of α -pinene: **1**: TBHP (100: 1: X) were applied.

Table I.6. Effect of the oxidant concentration on the epoxidation of α -pinene employing **1** as catalyst after 1 h.

| Molar ratio | 1:150 | 1:300 | 1:600 | 1:750 |
|----------------------------------|-------|-------|-------|-------|
| Yield α -pinene oxide (%) | 25 | 32 | 44 | 38 |
| Conversion (%) | 51 | 69 | 73 | 75 |
| Selectivity (%) | 49 | 47 | 60 | 50 |

The poor selectivity observed is explained by the formation of numerous byproducts. The oxidant concentration leading to the highest yield is MTO: TBHP 1: 600 (Table I.6). At this ratio, the selectivity also reaches a maximum. A higher concentration of oxidant enhances the activity of the catalytic system but leads to the formation of more byproducts. On the contrary, lower oxidant concentrations (1: 300 and 1: 150) imply slow formation of both the epoxide and byproducts. The **1**: H₂O₂ ratio of 1: 600 leads to the highest yield and selectivity within a reasonable reaction time and is thus applied for the testing of the catalyst concentration.

2.1.2. Influence of the catalyst concentration

The concentration of **1** was decreased to establish the minimal concentration of catalyst needed to perform this reaction without loss of activity using a ratio α -pinene: TBHP of 1: 600.

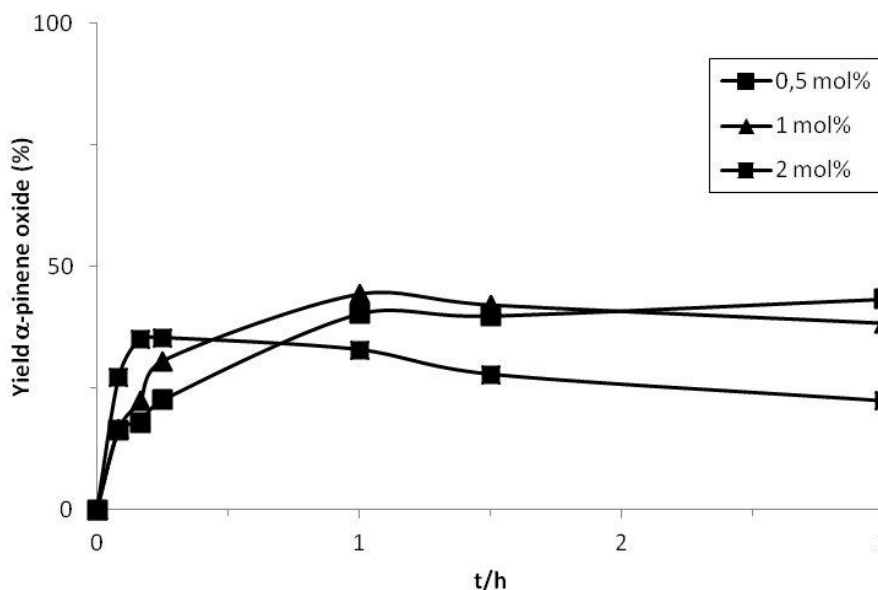


Figure I.6. Effect of the catalyst concentration on the yield of α -pinene oxide employing **1** as catalyst.

The activity of the system is similar with concentration of catalyst of 0.5 mol % and 1 mol %. At higher concentration, most likely not all catalyst molecules are involved in the reaction process. Additionally, a catalyst concentration of 2 mol % leads to fast byproducts formation since the catalyst molecule not involved in olefin epoxidation may instead promote further oxidations. The highest yield of α -pinene oxide of 43 % is reached with 0.5 mol % catalyst after 3 h.

2.1.3. Influence of Ionic liquid at room temperature

The use of ionic liquid ([BMIM]NTf₂) in the epoxidation of α -pinene does not improve the activity of the catalytic complex, since the conversion of α -pinene reaches around 65 % after 24 h. It does not favor either the epoxide formation and is not

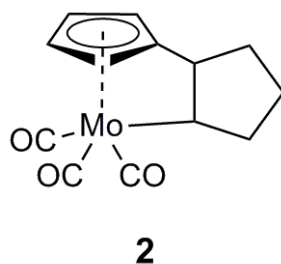
selective towards particular byproducts. Ionic liquids were consequently not further investigated in the epoxidation of α -pinene.

2.1.4. Reactivity of α -pinene in presence of **1** and TBHP

The formation of numerous byproducts raises the questions: does α -pinene oxide further react to form the observed byproducts or are these byproducts other oxidation products from α -pinene?

α -Pinene oxide was thus placed under the conditions of the epoxidation reaction. A molar ratio α -pinene: **1**: TBHP of 100: 1: 300 is applied. The conversion of α -pinene oxide already reaches 25 % after 5 minutes and around 43 % after 4 h 30. This result shows the readily conversion of α -pinene oxide to byproducts under the reaction conditions. It can thus explain the low yields obtained for α -pinene oxide (< 50 %).

2.2. Comparison between different catalysts



Scheme I.6.

In the epoxidation of olefins, the nature of the catalyst plays a crucial role. MTO, **1** and **2** are some of the most often used catalysts in olefin epoxidation. In this study, the influence of these three complexes was studied on the epoxidation of α -pinene.

A comparison is done with the optimal condition found for each complex (MTO, **1** and **2**), since the molybdenum complexes are almost inactive under the MTO

condition and MTO will decompose under the conditions for molybdenum based catalysts.

Molar ratio:

α -pinene: **MTO**: *tert*-butylpyridine: H_2O_2 of 100: 0.5: 10: 150 in $MeNO_2$ at 0 °C.

α -pinene: **1**: TBHP of 100: 0.5: 600 at 55 °C in $CHCl_3$.

α -pinene: **2**: TBHP of 100: 1: 300 at 55 °C in $CHCl_3$.

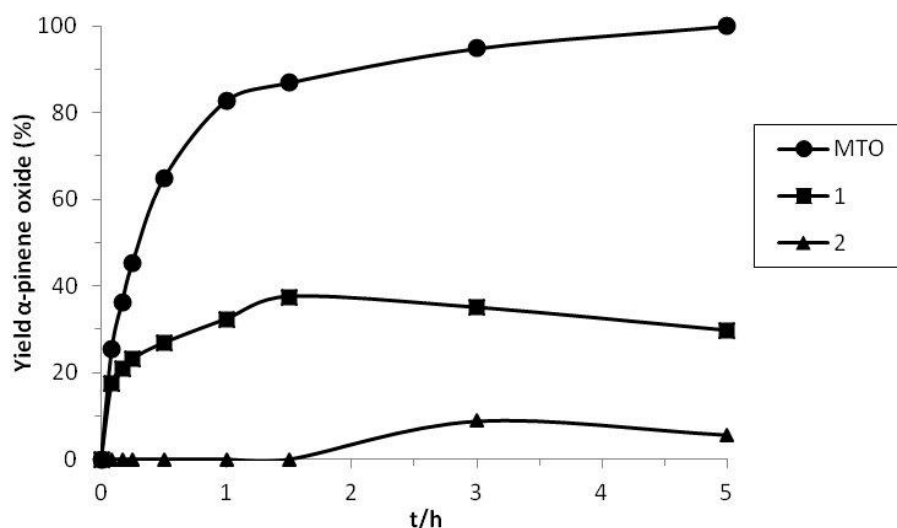


Figure I.7. Kinetics of the epoxidation of α -pinene employing the best conditions of different catalysts

As depicted in figure I.7, MTO displays the higher activity and selectivity towards the epoxidation of α -pinene. The complex **1** shows an enhanced selectivity towards the formation of the epoxide compared to **2**. This can be explained by the Lewis base adduct presents in the complex **1** which decreases the acidity of the metal acid center. However, the system is promoting the further oxidation of α -pinene oxide to byproducts leading to lower yields and selectivities than MTO. **2** is not selective to the formation of α -pinene oxide. It can be due to the Lewis acidity of the Molybdenum center which is not hampered by the ligands. MTO is thus the best of

the three tested catalysts for the epoxidation of α -pinene. It allows its formation in 96 % yield after 3 h and quantitative yield after 5 h.

II. Epoxidation of limonene

1. Selective epoxidation of (+)-Limonene employing Methyltrioxorhenium as catalyst

This Chapter originated from the following publication:

Typhène Michel, Mirza Cokoja, Volker Sieber, Fritz E. Kühn

J. Mol. Catal. A: Chem. **2012**, 358, 159-165

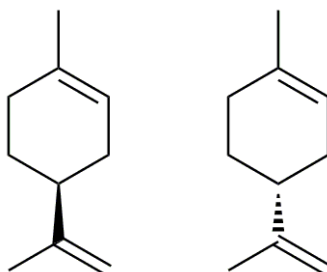
1.1. Abstract

This report presents a study of the epoxidation of limonene employing methyltrioxorhenium (MTO) as catalyst. The influence of base ligands, namely *tert*-butylpyridine, 4,4'-dimethyl-2,2'-bipyridine and pyrazole on the catalytic activity was investigated. The choice of the oxidant (H_2O_2 in water or H_2O_2 stabilized by urea) was also examined. The effect of the solvent has been studied in order to determine optimal conditions for the epoxidation of (+)-limonene. The best result was obtained when a molar ratio (+)-limonene: MTO: H_2O_2 : *tert*-butylpyridine of 100: 0.5: 10: 150 was used at 25 °C in dichloromethane. 1,2-limonene oxide was formed with 77 % yield and 96 % selectivity after 1 h with a TOF of ca. 900 h^{-1} .

1.2. Introduction

Monocyclic monoterpene hydrocarbons occur in many essential oils and their byproducts. Limonene is one of the most common monoterpenes and a widely used feedstock (30,000 tons per year).[9] For example, limonene can be found in cosmetics, as fragrance in perfume and as a flavoring to mask the bitter taste of alkaloids. It is used as a precursor of carvone in chemical synthesis and applied as solvent in cleaning products. It exists in two optically active forms: D-limonene,

possessing a strong orange smell is the main component of citrus oil, and L-limonene, which is found in pinewood and has a piney, turpentine-like odor.[104] Racemic limonene is known as dipentene.



Scheme II.1. Structures of (S)-(-) and (R)-(+)-limonene.

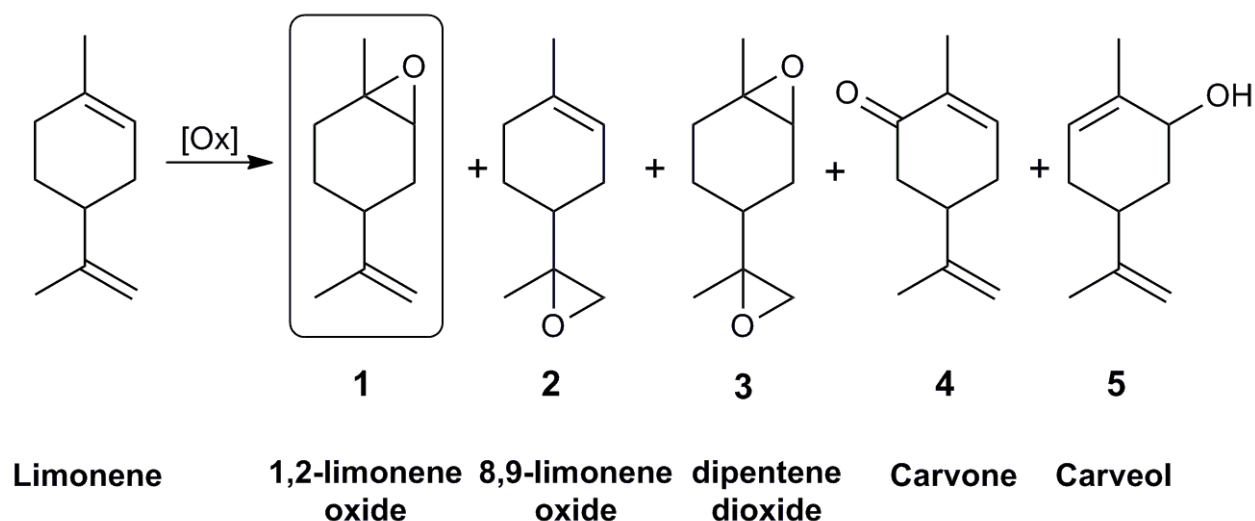
Terpene oxides such as 1,2-limonene oxide have many applications in synthetic chemistry. They are, in fact, the most important members of the terpene family for the perfume industry and are widely used as raw materials in the manufacture of a range of important commercial products.[6]

Optically pure epoxides, such as 1,2-limonene oxide and their corresponding 1,2-diols are important building blocks in asymmetric synthesis. They are more particularly used as chiral precursors.[7] 1,2-limonene oxide has also been used as a bio-renewable monomer in the formation of biodegradable polymers via copolymerization with CO₂. [12]

Epoxidation reactions have been extensively studied in the past. The organic peroxyacids, such as m-chloroperbenzoic acid are still the most widely used epoxidation agents, employing the stoichiometric peracid route. However, they are economically and environmentally undesirable as they produce waste, containing their corresponding acids, and are not selective in the formation of epoxides and their cleaved products, especially in the preparation of acid-sensitive epoxides.[105]

According to literature reports on limonene epoxidation employing homogeneous catalysts, the formation of 1,2-limonene oxide (**1**) is challenging, since it competes with the formation of byproducts, for example 8,9-limonene oxide (**2**) and 1,2-8,9-

limonene dioxide (**3**, also named dipentene dioxide). Moreover, other byproducts such as carvone (**4**) and carveol (**5**) are also observed depending on the catalyst used. This problem is different from difficulties encountered during the epoxidation of α -pinene. In the latter case, the major issue was to decrease the acidity of the rhenium center in order to avoid ring opening of the epoxide.[106]



Scheme II.2. Possible products of the oxidation of limonene.

The epoxidation of limonene with Al_2O_3 as catalyst leads to rather low conversion (max. 70 % after 4 h) and the formation of both monoepoxides and diepoxide.[107] The selectivity towards 1,2-limonene oxide is in the best case around 90 %. Cobalt base complexes, employed in the oxidation of limonene, lead to low conversion (40 %) and the formation of carvone and carveol as main products.[108] Dimethyldioxirane allows the formation of 1,2-limonene oxide with 94 % selectivity.[109] However, the conversion remains rather low (71 %). Iron-based catalysts employed in the epoxidation of limonene yield a mixture of carvone, carveol and 1,2-limonene oxide.[110]

Jacobsen's catalyst allows high conversions of limonene (up to 100 %) with a very good selectivity (90 %) towards dipentene dioxide.[111] However, employing N-methylimidazole as additive leads to a decrease in conversion (70 %) associated with enhanced selectivity towards 1,2-limonene oxide (74 %).[112] Begué et al. used

Mn(OAc)₃·2H₂O as catalyst with O₂/pivalaldehyde as oxidant in perfluoro-2-butyltetrahydrofuran, with 1,2-limonene oxide formed in 96 % yield after 1 h.[113]

Employing Mo based catalysts in limonene epoxidation leads, in general, to either low conversions or low selectivities towards 1,2-limonene oxide. A microwave-assisted study of the epoxidation of limonene employing [CpMo(CO)₃CH₃] as catalyst reports the formation of 1,2-limonene oxide with 93 % selectivity at 80 % conversion.[114]

The best results reported to date are, however, heterogeneously catalyzed processes. For instance, polyoxometalate catalysts lead to the formation of 1,2-limonene oxide with 98 % selectivity at 99 % conversion after 30 min at room temperature.[91] As seen in the previously published results of the epoxidation of limonene, the main challenge remains to favor the formation of 1,2-limonene oxide in high selectivity.

Methyltrioxorhenium (MTO) is well established as a very efficient catalyst for olefin epoxidation reactions.[39c, 93, 115] Some studies described the reactivity of MTO towards the epoxidation of limonene to 1,2-limonene oxide.[116] The best results known up to date were reported by Rudler et al., reaching a conversion of limonene of 98 % and a 1,2-limonene oxide selectivity of 86 % after 2 h at 4 °C.[50e] However, despite all efforts we were unable to reproduce these results (See Experimental Section, 1.4.3). Under the same conditions, we observed several other byproducts besides DPO, and the yield of the main product decreased constantly with the reaction time.

Thus, we set out to reinvestigate the optimal conditions for an efficient and selective epoxidation of limonene to 1,2-limonene oxide employing MTO as catalyst. Hydrogen peroxide was chosen as oxidant because of its environmental and economic advantages.[6b] Its only drawback, the ring opening of sensitive epoxides at the Lewis acidic Re center, can be overcome by the use of nitrogen containing

Lewis bases such as pyridine and derivatives, suppressing the formation of diols by reducing the Lewis acidic properties of MTO.[117]

In the present work, the optimal conditions for the regioselective epoxidation of (+)-limonene to 1,2-limonene oxide employing MTO as catalyst were investigated. For this purpose, several mono- and bidentate base adducts have been added to MTO. Additionally, the effect of using different oxidants and different reaction media was examined in order to study the optimal reaction conditions for the synthesis of 1,2-limonene oxide in high selectivity. Under the conditions examined, only dipentene dioxide was detected as byproduct. Another part of the work is dedicated to the study of the conditions favoring the formation of dipentene dioxide. It is of interest to investigate formation conditions of the byproduct in order to optimize the reaction conditions in a way to produce only one single product or one product in very large excess.

1.3. Results and discussion

1.3.1. Background

The epoxidation of olefins employing MTO as catalyst has been extensively studied.[51, 100e, f, 118] The influence of different ligands, oxidants and solvents on the activity of MTO was reported in detail for a variety of substrates.[47f, 100a, 101]

The most commonly applied oxidant for the epoxidation of olefins utilizing MTO as catalyst is aqueous hydrogen peroxide. It is an efficient oxidant, cheap and environmentally friendly since the only byproduct formed is water. However, the MTO/H₂O₂ system can lead to the formation of diols by ring opening of the epoxide at the Re center, due to its strong Lewis-acidic character.[1a]

This is particularly the case for acid-sensitive epoxides. It was shown that the ring opening can be prevented when the Lewis acidity of Re(VII) is reduced by coordination of σ -donor ligands to Re, which are typically aromatic N-bases, such

as for example pyridine derivatives.[28,29,37] The Lewis base adducts of MTO inducing the best activity in olefin epoxidation are pyridine based such as *tert*-butylpyridine or 4,4'-dimethyl-2,2'-bipyridine.[50a, b, 100a] Pyrazole was also described as an efficient Lewis base additive.[50c, d] To avoid water as solvent, anhydrous hydrogen peroxide adducts, e.g. UHP (urea hydrogen peroxide) can be applied.[47f, 101] The solvents are also known to have an influence on the activity of the catalytically active complexes. The most efficient solvents in the epoxidation of olefin employing MTO as catalyst are non or weakly coordinating solvents such as CH₂Cl₂ and CHCl₃ not competing with Lewis-base and substrate for coordination sites.[51b, 119] The preliminary study on the epoxidation of limonene described in this paper was thus undertaken with these reactants.

1.3.2. Epoxidation of (+)-limonene: formation of 1,2-limonene oxide

a. Oxidation of (+)-limonene, determination of the byproducts

The formation of 1,2-limonene oxide (LO) and byproducts is investigated. For this purpose, the molar ratio (+)-limonene: MTO: *tert*-butylpyridine: H₂O₂ of 100: 1: 20: 300 is applied in CH₂Cl₂ at 25 °C.

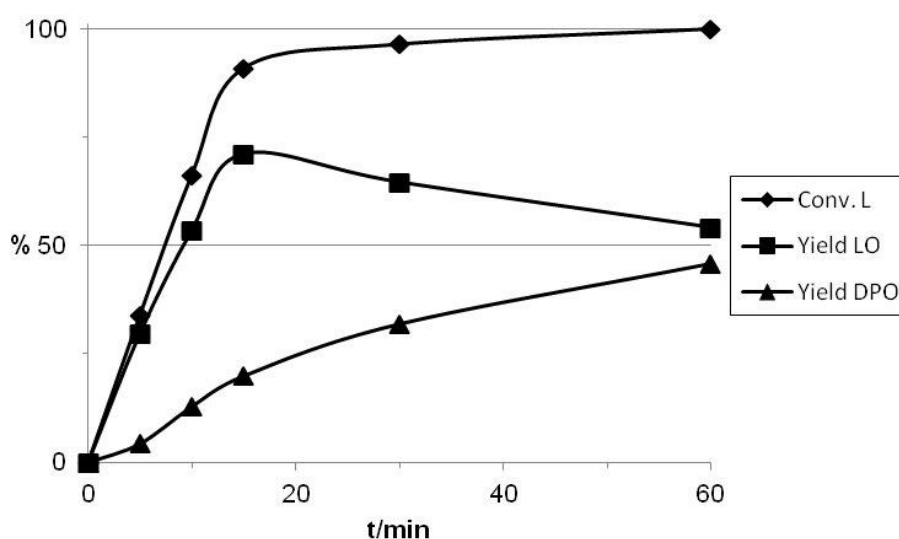


Figure II.1. Kinetics of the oxidation of (+)-limonene.

As depicted in Figure II.1, under the applied conditions the formation of 1,2-limonene oxide (LO) is fast at the beginning of the reaction. The yield of 1,2-limonene oxide reaches a maximum after 15 min and then decreases. The byproduct observed during the epoxidation of (+)-limonene (L) employing MTO as catalyst is dipentene dioxide (DPO). Other byproducts, e.g. 8,9-epoxide or (+)-limonene diol, were not observed.

b. Optimization of the reaction conditions

The synthesis of 1,2-limonene oxide is optimized employing MTO as catalyst, *tert*-butylpyridine as Lewis base adduct and aqueous hydrogen peroxide as oxidant in CH_2Cl_2 . The influence of the concentration of each reactant is investigated as well as the effect of temperature.

Temperature influence

Applying a molar ratio (+)-limonene: MTO: *tert*-butylpyridine: H_2O_2 of 100: 1: 20: 300 in CH_2Cl_2 leads to slower oxidation of (+)-limonene at 0 °C than at 25 °C (see Figure II.2). The temperature was decreased in an attempt to avoid the formation of the diepoxide.

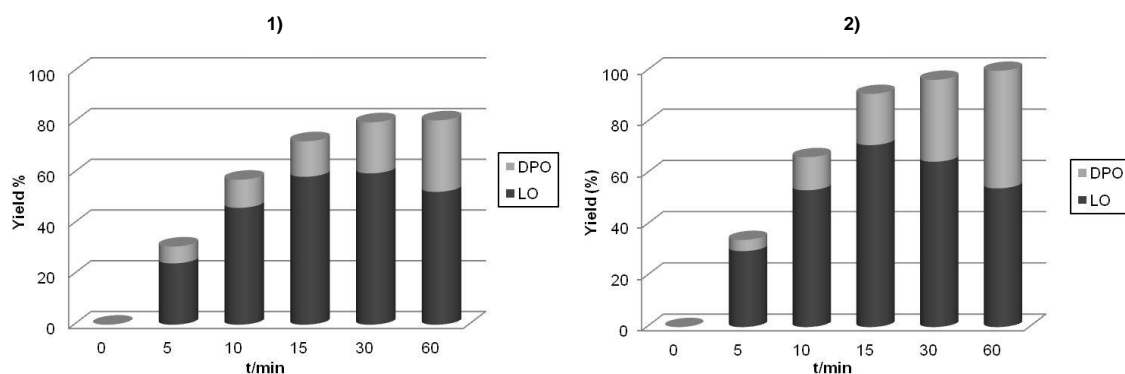


Figure II.2. Kinetics of the epoxidation of limonene at 1) 0 °C and 2) 25 °C. (Yields are determined by GC analysis)

From the structure of (+)-limonene, it is possible to deduce that the oxidation of the (1-2) double bond is easier than the (8-9) double bond. Moreover, the activity of the catalytic complex decreases with lower temperature.

This property could have led to the only formation of 1,2-limonene oxide avoiding the epoxidation of the second double bond, which cannot be easily oxidized at low temperature. However, as depicted in Figure II.2-1, the selectivity towards 1,2-limonene oxide is not improved at lower temperature. At the highest yield of 1,2-limonene oxide under both conditions (30 min for $T = 0\text{ °C}$ and 15 min for $T = 25\text{ °C}$), the selectivity towards LO is higher at 25 °C ($S = 77\%$ for 25 °C and $S = 60\%$ for 0 °C). This temperature is therefore applied in all following experiments.

Influence of the oxidant concentration

Again, a molar ratio (+)-limonene: MTO: *tert*-butylpyridine: H_2O_2 of 100: 1: 20: X is applied in CH_2Cl_2 at 25 °C.

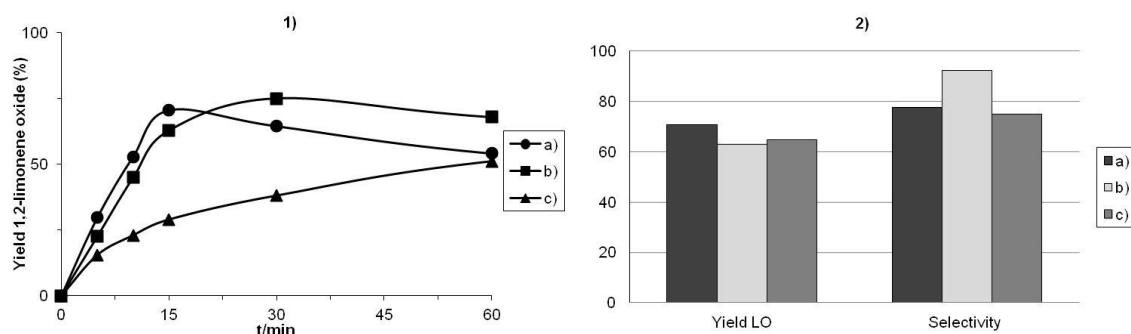


Figure II.3. Influence of the oxidant concentration on the 1) yield; 2) highest selectivity of (+)-1,2-limonene oxide at yield_{optimal}. Molar ratio MTO: H₂O₂ a) 1:300 / t_{opt} = 15 min; b) 1:150 / t_{opt} = 15 min; c) 1:100 / t_{opt} = 2 h.

The kinetics of the epoxidation of limonene depicted in Figure II.3-1 show how important it is to stop the reaction after a certain time to obtain the best ratio of yield vs. selectivity towards 1,2-limonene oxide. In the case of the molar ratio MTO: oxidant 1: 150, the selectivity towards 1,2-limonene oxide is optimal (100 %) after 10 min, however, the yield is low (45 %). If the reaction is stopped after 30 min, some good yields of 1,2-limonene oxide can be reached (75 %), however the selectivity is already beyond its optimum (77 %). Stopping at the time with the best selectivity/yield ratio is therefore a prerequisite.

In this example, the optimal time is 15 minutes with 63 % yield and 92 % selectivity towards 1,2-limonene oxide. The optimal time for the molar ratio MTO: H₂O₂ 1: 300 and 1: 100 are respectively 15 min and 2 h. The yield and selectivity showed in Figure II.3-2 are taken for each condition at this optimal time.

The oxidant concentration leading to the highest yield is MTO: H₂O₂ 1: 150 (Figure II.3-1). The selectivity reaches also a maximum when a ratio MTO: H₂O₂ of 1: 150 is used (Figure II.3-2). A higher concentration of oxidant enhances the activity of the catalytic system. As shown in Figure II.3-1, the formation of 1,2-limonene oxide is faster during the first 15 min. In the case of a 1: 300 ratio, however, after 15 min, the yield of 1,2-limonene oxide already decreases due to byproduct formation. In the case of a 1: 100 ratio, the formation of LO and DPO are both slow.

Consequently, the MTO: H₂O₂ ratio of 1:150 leads to the highest yield and selectivity within a reasonable time reaction and is thus applied for the following experiments.

Influence of the ligand concentration

It is known that the activity of the catalytic system increases, within certain border lines, with the quantity of the Lewis base adduct.[50a, 100a] The ligand is useful to prevent the formation of byproducts forming due to the Lewis acidity of the rhenium center.[117]

The influence of ligand concentration on the regioselectivity of the formation of 1,2-limonene oxide is therefore important to be determined. For this purpose, a molar ratio (+)-limonene: MTO: *tert*-butylpyridine: H₂O₂ of 100: 1: X: 150 was applied in CH₂Cl₂ at 25 °C.

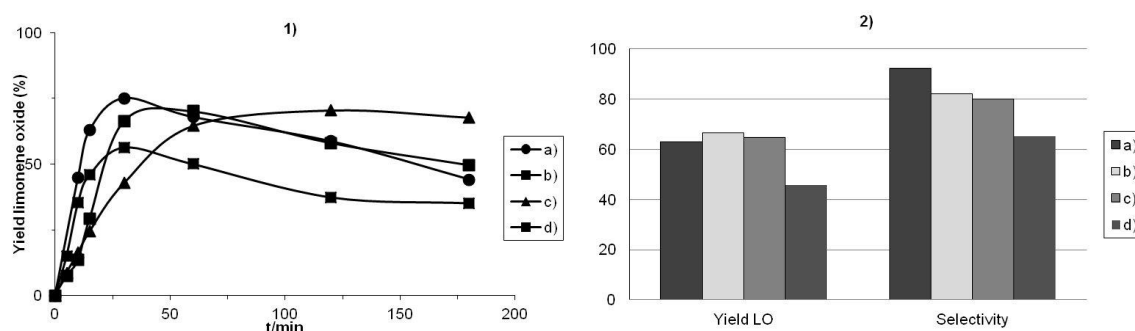


Figure II.4. Influence of the ligand concentration on the 1) yield; 2) highest selectivity of 1,2-limonene oxide at $yield_{optimal}$. Molar ratio MTO: *tert*-butylpyridine: a) 1:20 / $t_{opt} = 15$ min; b) 1:10 / $t_{opt} = 30$ min; c) 1:5 / $t_{opt} = 1$ h; d) 1:0 / $t_{opt} = 15$ min.

The activity of the catalytic system increases when the concentration of the Lewis base increases from 1:5 to 1:20.[50c] However, the activity of the examined catalytic system is better when no Lewis base adduct is added than for MTO: ligand ratios of 1: 5 and 1: 10.

The MTO/H₂O₂ in some cases oxidizes the N-base ligand to N-oxide. This reaction, however, is usually slower than the olefin epoxidation.[50c, 100b] The complex formed by the N-oxide ligand with MTO is also catalytically less active than the N-base MTO adduct. It is therefore important to use a significant excess of the Lewis base adduct.

As depicted in Figure II.4, the highest yield and selectivity towards 1,2-limonene oxide are reached when a molar ratio MTO: *tert*-butylpyridine of 1: 20 is applied. When no N-base adduct is added to the reaction, besides dipentene dioxide several other byproducts could be observed. It can reasonably be assumed that the byproducts are 8,9-limonene oxide and the corresponding diols to the found epoxides. The latter observation shows that employing the N-base adduct prevents the formation of other byproducts.

A MTO: *tert*-butylpyridine ratio of 1: 20 leads also to a fast formation of dipentene dioxide since the yield of 1,2-limonene oxide begins to decrease early (30 min). As a consequence, a high concentration of Lewis base adduct favors the formation of 1,2-limonene oxide. The optimal 1,2-limonene oxide yield was obtained after 15 min with a yield of 63 % and a selectivity of 92 %. Finally, the concentration of *tert*-butylpyridine was increased to a MTO: *tert*-butylpyridine ratio of 1: 40. Yield and selectivity towards 1,2-limonene oxide, however, decrease at this latter ratio. Consequently, the ratio MTO: *tert*-butylpyridine of 1: 20 appears to lead to the formation of 1,2-limonene oxide with the highest yield and selectivity.

Influence of the catalyst concentration

A molar (+)-limonene: MTO: *tert*-butylpyridine: H₂O₂ ratio of 100: X: 20: 150 is applied in dichloromethane at 25 °C.

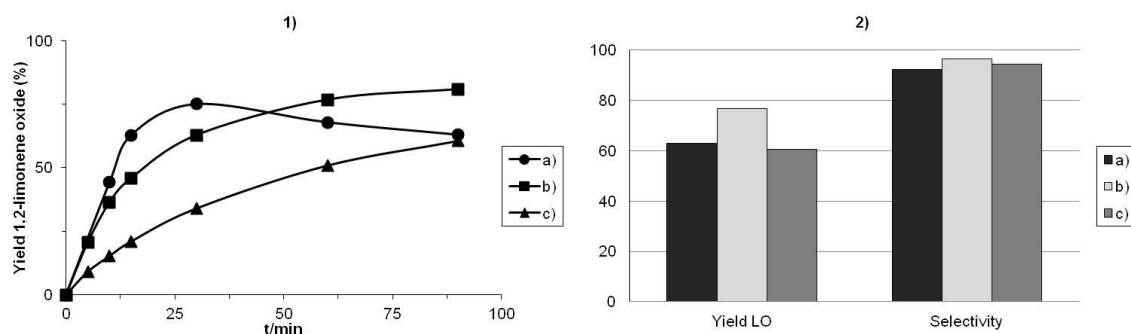


Figure II.5. Influence of the catalyst concentration on the 1) yield; 2) highest selectivity of 1,2-limonene oxide at yield_{optimal}. a) 1 mol % MTO / t_{opt} = 15 min; b) 0.5 mol % MTO / t_{opt} = 1 h; c) 0.1 mol % MTO / t_{opt} = 1 h 30.

The activity of the system appears to be best at the lowest applied concentration of 0.1 mol % catalyst. At higher concentration most likely not all catalyst molecules are involved in the reaction. Additionally, a catalyst concentration of 1 mol % leads to fast byproduct formation since the catalyst molecule not involved in olefin epoxidation may instead promote its transfer to diepoxide. An optimal selectivity and yield (96 and 76 %) is reached with 0.5 mol % catalyst after 1 h.

c. Ligand-, oxidant- and solvent effects on the epoxidation of (+)-limonene

Influence of the oxidant H₂O₂ vs UHP

A molar (+)-limonene: MTO: *tert*-butylpyridine: oxidant ratio of 100: 0.5: 10: 150 is applied in dichloromethane at 25 °C.

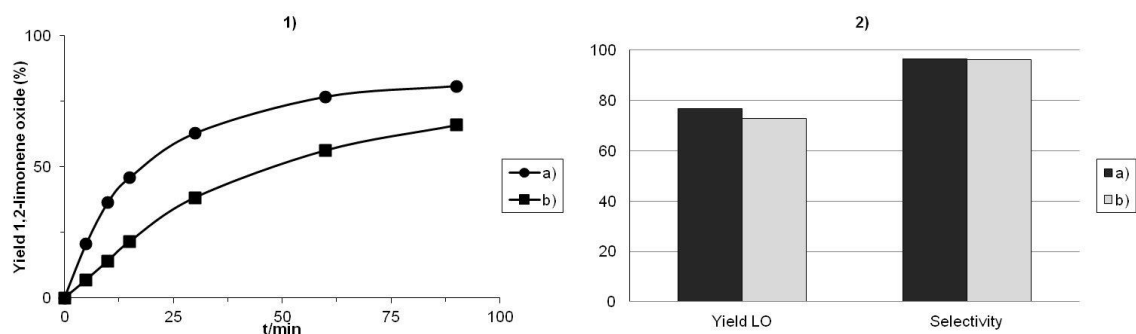


Figure II.6. Effect of the different oxidants on the 1) yield; 2) highest selectivity of 1,2-limonene oxide at yield_{optimal}. a) Hydrogen peroxide / t_{opt} = 1 h; b) UHP / t_{opt} = 2 h.

Figure II.6 shows a feature which is quite different compared to the epoxidation of α -pinene.[117] As for α -pinene, employing MTO: UHP as catalytic system does not decrease the velocity of the epoxidation compared to the catalytic system MTO: H₂O₂ but increases the selectivity towards the desired epoxide.

In case of (+)-limonene epoxidation, the catalytic system MTO: UHP is less efficient than MTO: H₂O₂ (Figure II.6-1). This decrease in catalytic activity can be explained by the fact that UHP is not soluble in most organic solvents. The access of the oxidant and the formation of the catalytic species are consequently slower. The selectivity towards 1,2-limonene oxide formation is not enhanced when UHP is used as oxidant (Figure II.6-2). The highest yield (77 %) and selectivity (96 %) are observed when aqueous hydrogen peroxide is used as oxidant.

Ligand influence

tert-butylpyridine, 4,4'-dimethyl-2,2'-bipyridine and pyrazole are applied as ligands. A molar ratio (+)-limonene: MTO: ligand: H₂O₂ of 100: 0.5: 10: 150 is applied in dichloromethane at 25 °C.

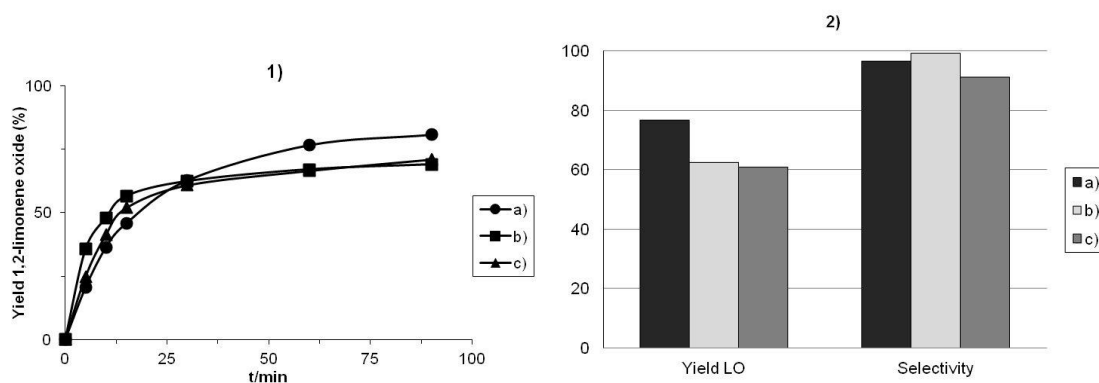


Figure II.7. Effect of the different Lewis bases on 1) yield; 2) highest selectivity of 1,2-limonene oxide at $\text{yield}_{\text{optimal}}$. a) *tert*-butylpyridine / $t_{\text{opt}} = 1$ h; b) pyrazole / $t_{\text{opt}} = 30$ min; c) 4,4'-dimethyl-2,2'-bipyridine / $t_{\text{opt}} = 30$ min.

It is known that N-base adduct such as *tert*-butylpyridine and 4,4'-dimethyl-2,2'-bipyridine can be oxidized to the corresponding N-oxide by the MTO/H₂O₂ system.[50c, 100b] Pyrazole was found to be a good alternative to the pyridine-based ligand since it is not easily oxidized by MTO/H₂O₂ and its MTO adducts shows good reactivity towards epoxidation activity.[50d]

As seen in Figure II.7-1, both 4,4'-dimethyl-2,2'-bipyridine and pyrazole lead to a somewhat higher rate of 1,2-limonene oxide formation than *tert*-butylpyridine. However, as depicted in Figure II.7-2, the use of *tert*-butylpyridine as N-base adduct leads to the best selectivity towards 1,2-limonene oxide and allows the highest product yield. Hence, in the following, *tert*-butylpyridine was used as additive.

Solvent influence

In the epoxidation of olefins, the solvent plays a crucial role. In this study, the influence of CH₂Cl₂, CHCl₃, THF and MeNO₂, which are often used in olefin epoxidation, was studied. Additionally, the alcohol *n*-butanol is also used to study the influence of a one-phase system, which could be of practical interest as well. For

this purpose, the molar ratio (+)-limonene: MTO: *tert*-butylpyridine: H₂O₂ of 100: 0.5: 10: 150 is applied in different solvents at 25 °C.

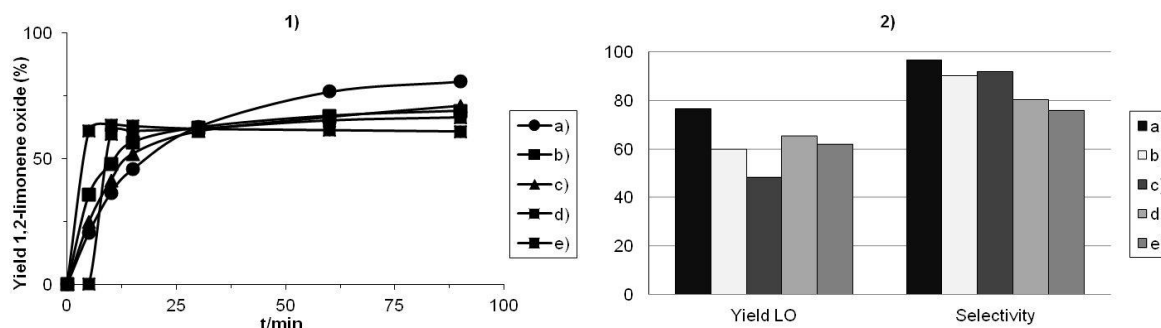


Figure II.8. Effect of the different solvents on the a) yield; b) highest selectivity of 1,2-limonene oxide at yield_{optimal}. a) CH₂Cl₂ / t_{opt} = 1 h; b) CHCl₃ / t_{opt} = 1 h; c) THF / t_{opt} = 4 h; d) nBuOH / t_{opt} = 30 min; e) MeNO₂ / t_{opt} = 30 min.

In n-butanol as well as in nitromethane, the formation of 1,2-limonene oxide is fast (5 min) but the yield does not increase significantly any more (Figure II.8-1). Selectivity towards 1,2-limonene oxide is ca. 60 % for both solvents, however, due to byproduct formation the conditions are not very promising, An explanation for the fast activity decrease when n-butanol is used is the presence of a one-phase system. As mentioned before, the system MTO/H₂O₂ catalyzes the transformation of *tert*-butylpyridine to *tert*-butylpyridine-N-oxide.

In a two phase system, the N-oxide adduct dissolves in the water phase, avoiding the formation of less active MTO/N-oxide base adduct. In the case of a one-phase system, a MTO/N-oxide base adduct is formed leading to an activity decrease (See Figure II.8-1). CH₂Cl₂ is the solvent allowing the highest activity of the catalytic system followed by CHCl₃ and THF (Figure 8-1). As depicted in Figure II.8-2, the latter order is maintained for the selectivity towards the 1,2-limonene oxide.

1.3.3. Epoxidation of (+)-limonene: formation of 1,2-8,9-limonene dioxide (DPO)

Parallel to the experiments on 1,2-limonene oxide formation, some experiences are executed to synthesize the byproduct dipentene dioxide in high yield and selectivity. Despite the main goal of this work being to synthesize the mono-epoxide in high selectivity, it is of interest to investigate the conditions which can lead to the formation of the byproduct dipentene dioxide in high yields and selectivity.

A systematic study of the formation of dipentene dioxide during the investigation of 1,2-limonene oxide synthesis shows that a highly active catalytic system favors the byproduct formation. Therefore, high concentrations of Lewis base adduct and oxidant should allow high yield formation of dipentene oxide. Dichloromethane was applied with a catalyst concentration of 1 mol %. In the following experiments, the effect of the concentration of either *tert*-butylpyridine or aqueous hydrogen peroxide on the oxidation of (+)-limonene was studied.

Table II.1. Influence of Lewis base adduct concentration towards the formation of dipentene dioxide.

| Conditions: molar ratio | | | | Yield _{max} DPO | Time (h) |
|-------------------------|-----|----------------------------|-------------------------------|-----------------------------|----------|
| (+)-limonene | MTO | <i>tert</i> -butylpyridine | H ₂ O ₂ | | |
| 100 | 1 | 20 | 600 | 55 % | 24 |
| 100 | 1 | 40 | 600 | 70 % | 24 |
| 100 | 1 | 60 | 600 | 83 % | 24 |

Table II.2. Influence of oxidant concentration towards the formation of dipentene dioxide.

| Conditions: molar ratio | | | | Yield _{max} DPO | Time (h) |
|-------------------------|-----|----------------------------|-------------------------------|-----------------------------|----------|
| (+)-limonene | MTO | <i>tert</i> -butylpyridine | H ₂ O ₂ | | |
| 100 | 1 | 40 | 300 | 90 % | 24 |
| 100 | 1 | 40 | 600 | 70 % | 24 |

As depicted in Table II.1, the formation of dipentene oxide is favored when the concentration of Lewis base adduct increases from a MTO: Ligand ratio 1: 20 to 1: 60. As seen in the previous paragraph, the yield of dipentene dioxide increases with the oxidant concentration between the molar ratio 1: 100 and 1: 300. However, this relation does not apply when the oxidant concentration is too high (Table II.2). The formation of dipentene oxide competes with other byproducts when the molar ratio MTO: H₂O₂ of 1: 600 is applied leading to lower dipentene oxide yields.

The conditions leading to the formation of dipentene dioxide in highest yield and selectivity are found applying a molar ratio (+)-limonene: MTO: *tert*-butylpyridine: H₂O₂ of 100: 1: 40: 300 in dichloromethane at 25 °C.

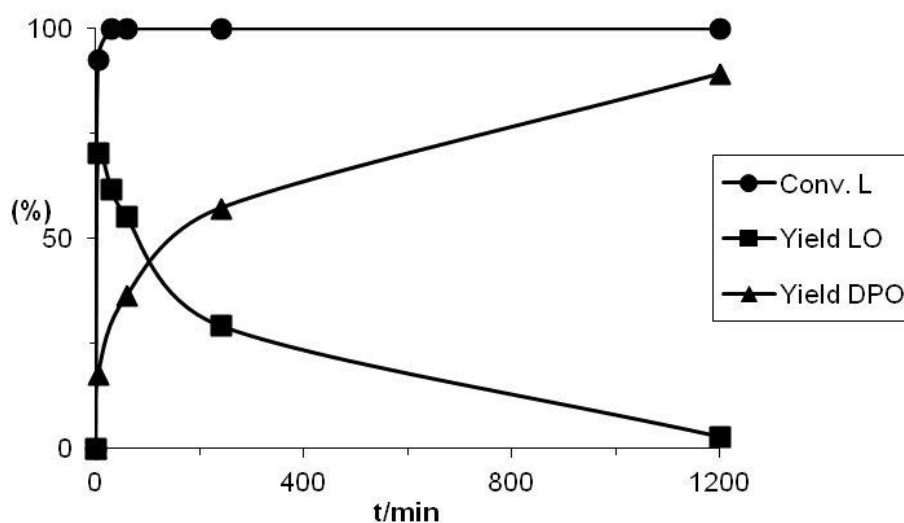


Figure II.9. Kinetics of the oxidation of (+)-limonene to dipentene dioxide.

As depicted in Figure II.9, the formation of 1,2-limonene oxide is very fast at the beginning. The yield of 1,2-limonene oxide reaches a maximum after only 5 min and then decreases significantly during the first 3 h of the reaction. After 24 h 1,2-limonene oxide is nearly entirely converted. Dipentene dioxide is obtained in 90 % yield and 90 % selectivity after 24 h. 2 % of the impurities is 1,2-limonene oxide, the other 8 % could not be unambiguously determined. However, it can reasonably be assumed that the byproducts are again 8,9-limonene oxide and the corresponding diols of the found epoxides.

1.4. Experimental

1.4.1. Starting materials

All commercial products were of the highest grade available and were used as such. A 35 % solution of H_2O_2 in water (Aldrich) was used for the catalytic test reactions. (+)-limonene was obtained from Aldrich. UHP contains 35 wt. % H_2O_2 (Acros Organics). Methyltrioxorhenium was synthesized according to the literature.[120]

1.4.2. Gas chromatography

Gas chromatography was performed using a DB23 column (30 m, 0.25 mm, 0.25 μ m film thickness). The isothermal temperature profile is 60 °C for the first 2 min, followed by a 10 °C/min temperature gradient to 105 °C for 10 min, then 4 °C/min to 140 °C and finally 10 °C/min to 260 °C. The injector temperature was 320 °C. Chromatography grade helium was used as carrier gas.

1.4.3. Literature conditions [50e]

Limonene (6 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 4 °C. MTO (1 mol % / olefin) and then 150 equiv. H_2O_2 (10 % in water) were added to the solution. The reaction was stirred for 2 h, quenched with MnO_2 and analyzed by GC. Result: Conversion limonene = 99 %; Yield 1,2-limonene oxide = 47 %; Yield dipentene dioxide = 23 %. Moreover, other byproducts (29 %), among them 8,9-limonene oxide and the corresponding diols of the found epoxides, were observed in the GC spectrum which explain the low 1,2-limonene oxide yield obtained compared to the conversion of limonene.

1.4.4. Epoxidation of (+)-limonene in different solvents

MTO was dissolved in the solvent and the solution was let at 25 °C or cooled at 0 °C. The ligand, the 2 standards (mesitylene: 0.5 mL, naphthalene (solution 2 g in 10 mL CH_2Cl_2): 0.5 mL), and the oxidant (H_2O_2 35 % or UHP) were added to the solution. (+)-limonene was then added to the reaction. Samples were taken after 5 min, 10 min, 15 min, 30 min, 60 min, 90 min, 3 h, 5 h and 24 h. For each sample, 1 mL of the reaction mixture was taken and neutralized by MnO_2 . The mixture was dried over MgSO_4 . 200 μ L from the dry solution was taken, 0.5 mL of a solution of 1 mL of methyl-naphthalene in 50 mL isopropanol and 0.8 mL of isopropanol were mixed in a vial and analyzed by GC.

Table II.3. Summary of the different molar ratio employed in the epoxidation of (+)-limonene ^a *tert*-butylpyridine, 4,4'-dimethyl-2,2'-dipyridine, pyrazole ^b H₂O₂, UHP ^c CH₂Cl₂, MeNO₂, CHCl₃, nBuOH or THF.

| Reaction condition: molar ratio | | | | | |
|---------------------------------|--------------|-----|----------------------------|-------------------------------|--------------------------------------|
| T (°C) | (+)-limonene | MTO | <i>tert</i> -butylpyridine | H ₂ O ₂ | CH ₂ Cl ₂ [mL] |
| 25 & 0 | 100 | 1 | 20 | 300 | 6.4 |
| 25 | 100 | 1 | 20 | 150 | 7.1 |
| 25 | 100 | 1 | 20 | 100 | 7.3 |
| 25 | 100 | 1 | 10 | 150 | 7.2 |
| 25 | 100 | 1 | 5 | 150 | 7.2 |
| 25 | 100 | 1 | 0 | 150 | 7.3 |
| 25 | 100 | 0.1 | 2 | 150 | 7.3 |
| 25 | 100 | 1 | 40 | 300 | 6.3 |
| 25 | 100 | 1 | 60 | 300 | 6.1 |
| 25 | 100 | 1 | 20 | 600 | 4.9 |
| 25 | 100 | 1 | 40 | 600 | 4.8 |
| 25 | 100 | 1 | 60 | 600 | 4.6 |

(+)-Limonene epoxidation

| T (°C) | (+)-limonene | MTO | Ligand ^a | Oxidant ^b | Solvent ^c [mL] |
|--------|--------------|-----|---------------------|----------------------|------------------------------|
| 25 | 100 | 0.5 | 10 | 150 | 7.2 |

1 equiv. MTO correspond to 0.06 mmol; 0.5 equiv. MTO correspond to 0.03 mmol; 0.1 equiv MTO correspond to 0.006 mmol

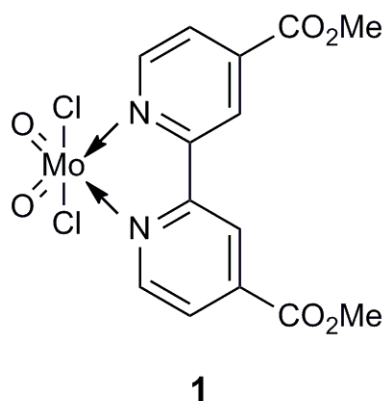
1.5. Conclusion

Optimal conditions for the epoxidation of (+)-limonene employing MTO as catalyst were established. To reach optimal 1,2-limonene oxide formation (high activity, selectivity and yield) MTO has to be applied in not too high concentrations to avoid secondary reactions of 1,2-limonene oxide (most prominent is diepoxide formation). When the Lewis base ligand/MTO ratio is too high or too low, byproduct formation also begins to dominate. With low Lewis base concentrations epoxide ring opening reactions are favored due to the Lewis acidity of the system. *tert*-Butylpyridine turned out to be optimal amongst the examined Lewis bases, it applied together with H₂O₂ as oxidant in a two phase system with dichloromethane as organic phase at room temperature (25 °C). Under these conditions, the highest selectivity towards 1,2-limonene oxide is obtained with a ratio of (+)-limonene: MTO: *tert*-butylpyridine: H₂O₂ of 100: 0.5: 10: 150. Under these conditions 1,2-limonene oxide is formed in 77 % yield with 96 % selectivity after 1 h.

For dipentene dioxide formation, the optimal condition is reached with a catalyst concentration of 1 mol % with enhanced ligand and oxidant concentration. The highest yield and selectivity are obtained with a (+)-limonene: MTO: *tert*-butylpyridine: H₂O₂ ratio of 100: 1: 40: 300 at 25 °C. Dipentene dioxide is formed under these conditions in 90 % yield and selectivity after 24 h.

2. Epoxidation of limonene employing Mo (VI) based complexes

The epoxidation of limonene is investigated employing **1** as catalyst. The concentration of the different reactants is varied in order to determine the optimal condition for this reaction.



Scheme II.3.

2.1. Epoxidation of (+)-limonene employing MoO₂Cl₂L₂ based catalyst

2.1.1. Influence of the oxidant concentration

The oxidant concentration is an important parameter of the reaction to control the activity of the catalytic system. Various molar ratios of α -pinene: 1: TBHP (100: 1: X) were applied.

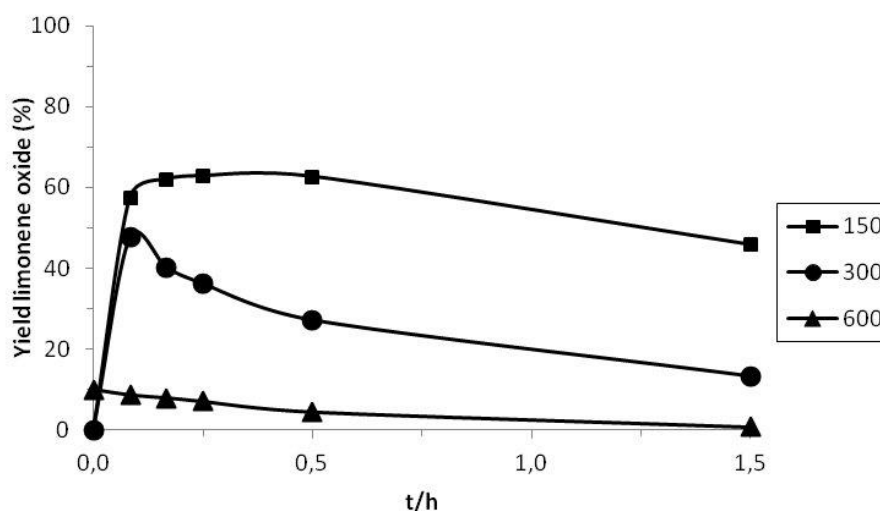


Figure II.10. Kinetics of the epoxidation limonene employing **1** as catalyst at different oxidant concentration

The molar ratio 1: TBHP of 1: 150 leads to the highest yield of limonene (63 % yield at 93 % conversion after 30 min). The byproduct formation is also lower than for 1: 300 as seen in figure II.10 since in the latter case, the epoxide yield reaches a maximum (47 %) after 5 min (conversion limonene = 77 %) and then decreases.

The selectivity of the catalytic system towards the epoxide formation is decreased by the presence of high excess of oxidant. Increasing further the concentration of oxidant to 1: 600 implies lower selectivity of the catalytic complex for the formation of the epoxide since the byproducts formation is favored. Consequently, the MTO: H₂O₂ ratio of 1: 150 leads to the highest yield and selectivity and is applied for the following experiments.

2.1.2. Influence of the catalyst concentration

Another way to affect the rate of the reaction and its selectivity towards the epoxide is to vary the concentration of the catalyst. A molar ratio (+)-limonene: **1**: TBHP of 100: X: 300 is applied in chloroform at 55 °C.

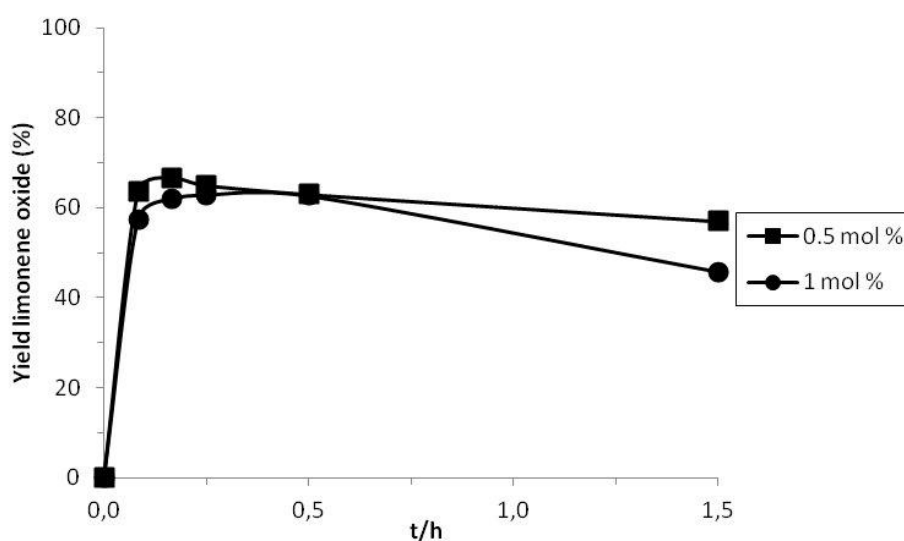
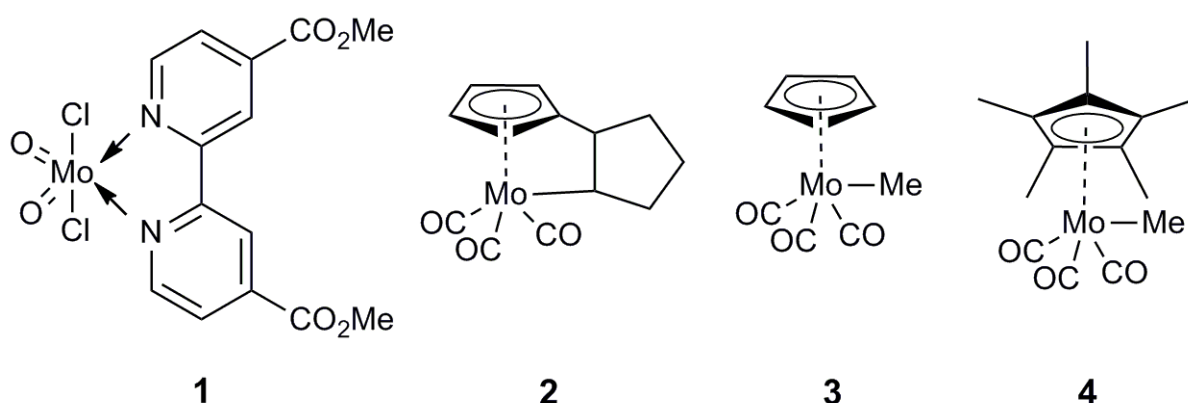


Figure II.11. Kinetics of the epoxidation of limonene: influence of the catalyst concentration

As depicted in figure II.11, similar results are obtained with the concentrations of MTO 1 mol % and 0.5 mol %. At higher concentration most likely not all catalyst molecules are involved in the reaction. Additionally, a catalyst concentration of 1 mol % leads to faster byproduct formation since the catalyst molecule not involved in olefin epoxidation may instead promote its conversion to byproducts. An optimal selectivity and yield (70 % and 66 %) are reached with 0.5 mol % catalyst after 10 min.

2.2. Influence of different catalysts



Scheme II.4. Complexes applied in the epoxidation of (+)-limonene

The influence of different Mo (VI) based catalysts on the epoxidation of limonene was investigated employing the molar ratio of limonene: catalyst: TBHP of 100: 1: 300 at 55 °C in CHCl_3 .

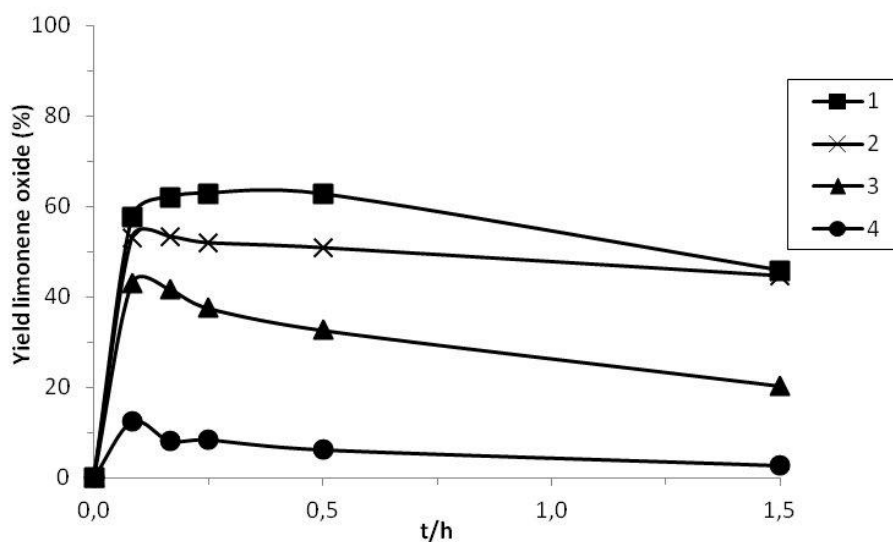


Figure II.12. Kinetics of the epoxidation of limonene: influence of different catalysts.

As depicted in figure II.12., the highest yield and selectivity are reached with catalyst 1. This higher selectivity towards the formation of the desired epoxide could be

explained by the presence of the Lewis base adduct which decreases the acidity of the metal center.

All the CpMo(CO)₃ based complexes have the same behavior: the desired epoxide is formed in high rate during the 5 first minutes of the reaction followed by the formation of byproducts. In this class of molecule, the Molybdenum containing an ansa bridge (**2**) shows, higher activity than the two complexes with a methyl group bond to the metal (**3** and **4**). It is also observed that (**4**), containing Cp*, shows the lowest activity towards limonene epoxidation.

Complex **1** is thus the optimal catalyst of the Molybdenum based catalyst studied in the epoxidation of limonene. As for α -pinene, however, MTO is still the best catalyst tested in the epoxidation of limonene with 97 % yield after 3 h at room temperature.

III. Catalytic epoxidation of camphene using methyltrioxorhenium (VII) as catalyst

This Chapter originated from the following publication:

Typhène Michel, Mirza Cokoja, Fritz E. Kühn, *J. Mol. Catal. A: Chem*, **2012**, submitted

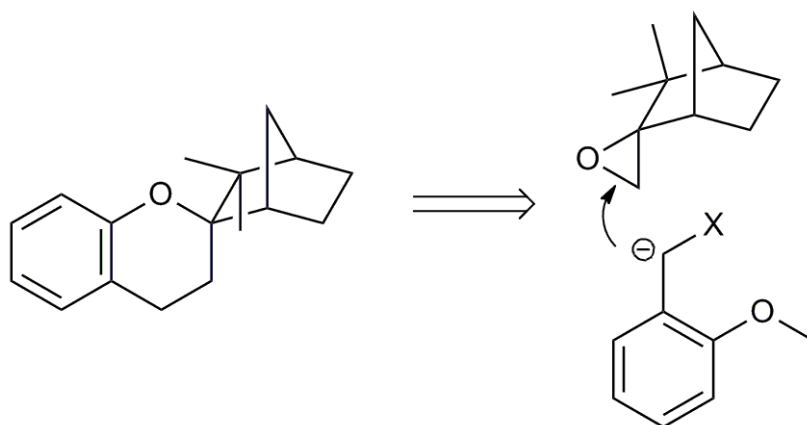
1. Abstract

This work presents the epoxidation of camphene employing methyltrioxorhenium(VII) (MTO) as catalyst. The effect of different factors on the formation of camphene oxide with respect to high yield and selectivity was investigated. First, the ratio camphene:MTO:pyrazole:H₂O₂ was studied in dichloromethane as solvent in order to determine the optimal condition. Moreover, the influence of the Lewis base adduct (*tert*-butylpyridine, 4,4'-dimethyl-2,2'-bipyridine, imidazole or pyrazole) was investigated. The effect of an aqueous oxidant, namely H₂O₂ and a solid oxidant, namely urea hydrogen peroxide (UHP) was also examined. Finally solvent was varied from dichloromethane to chloroform, toluene and nitromethane. Based on the results the optimal conditions for the epoxidation of camphene using MTO as catalyst were determined. The molar ratio camphene:MTO:pyrazole:H₂O₂ of 100:0.5:10:110 in dichloromethane at room temperature leads after 3 h to 97 % yield and 98 % selectivity towards camphene oxide at 99 % conversion.

2. Introduction

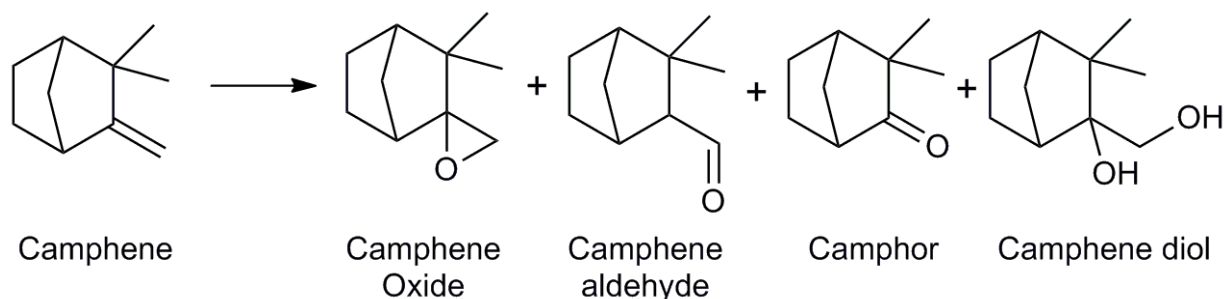
Terpenes, which are found in woods and other plants, are considered as being promising renewable carbon resources like other biomass products, such as starch, cellulose and lignin.[121]

Besides having the potential to be of general use as carbon feedstock, terpenes are mostly being used as precursors for fine chemicals, e.g. in pharmaceuticals, food additives or for the flavor and fragrance industry.[122] Camphene, for example, is a natural monoterpene, which is found in fossilized amber and living conifers,[123] and is known for its bacteriostatic and fungicidal properties.[124] Camphene oxide is of interest as precursor for the synthesis of spiro ring systems containing a benzopyran moiety connected with camphene derivatives (Scheme III.1).[10]



Scheme III.1. Retro-synthesis of a spiro ring system containing a benzopyran moiety joined to a terpene-derived ring from camphene oxide.

This system is found in various natural products and known for its pharmaceutical applications, such as anti-inflammatory and anti-allergic component.[11] The epoxidation of camphene has already been studied with different metal-based complexes. The main challenge is the selectivity towards the formation of the epoxide (Scheme III.2).



Scheme III.2. Products of camphene oxidation.

Molybdenum-based complexes lead to poor conversion of camphene and poor selectivity towards camphene oxide. The use of a $[\text{MoO}_2]$ moiety bearing a chiral tetradentate oxaline ligand leads to yield lower than 3 % of camphene oxide at 6 % conversion. $[(n\text{Bu}_3\text{Sn})_2\text{MoO}_4]$ forms camphene oxide with 70 % selectivity at 20 % conversion after 10 h.[77a, 105b] The epoxidation of camphene employing beta zeolite also induces low conversion (ca. 30 % after 3 h).[125] The use of Palladium complexes results in low conversion with high selectivity towards the desired epoxides (32 % conversion and 90 % selectivity after 12 h) or in good conversion accompanied by a mixture of byproducts (86 % conversion, 69 % yield of camphene diol, 31 % yield of camphene aldehyde and 2 % yield of camphene oxide).[126] Saalfrank et al. employed synthetic metalloporphyrin analogues $[\text{FeL}_3]$ associated with molecular oxygen for the epoxidation of camphene.[127] Camphene oxide is formed in 87 % yield after 4 h in presence of O_2 at room temperature. However, an aldehyde (isobutylaldehyde) is also needed under these conditions as an electron source to perform the reaction.

Manganese complexes also show good activity and selectivity towards the epoxidation of camphene. Tangestaninejad and Mirkhani used Mn(III)-porphyrin complexes as catalysts, which were immobilized on polystyrene for the epoxidation of camphene, using sodium periodate as oxidant.[128] The conversion of camphene was reported to be 84 % conversion and 100 % product selectivity after 3 h. Bahramian et al. reported a camphene conversion of 97 % and 100 % product selectivity towards camphene oxide employing a $(\text{Salen})\text{Mn}(\text{OAc})$ catalyst, which is

so far the highest reported yield.[129] Yet, the very expensive oxidant NaIO_4 was applied.

MTO was also investigated as catalyst by Adam et al., camphene oxide was obtained in a yield of 95 % at a conversion of 92 % after 30 h at 20 °C, employing a ratio of camphene:MTO:UHP of 100:1:100 in CDCl_3 . When aqueous H_2O_2 (85 % in water) was used instead of UHP, camphene aldehyde was formed in 95 % yield at a rather low conversion of 27 % after 3 h in CDCl_3 at 20 °C with a molar ratio of camphene:MTO: H_2O_2 of 100:1:100.[47f] The activity of MTO was increased by adding the zeolite NaY in CDCl_3 with H_2O_2 (85 % in water) as oxidant, the conversion increased to 89 % with a selectivity towards the epoxide of 95 % after 10 h. The residual 5 % were found to be camphene diol.[54]

From the literature, MTO shows an interesting activity towards the epoxidation of camphene, yet exhibiting some room for improvement in terms of the reaction rate and the selectivity towards epoxide formation. Moreover, the oxidant, hydrogen peroxide, is cheaper and environmentally friendlier (water is formed as byproduct) than almost all other oxidants used in the literature (*vide supra*), including UHP, which is poorly soluble in nearly all conventional solvents. Hence, in this work, the influence of different reaction parameters (catalyst concentration, solvent, Lewis base, temperature) on the conversion of camphene and the selectivity of camphene oxide formation catalyzed by MTO/aq. H_2O_2 is presented.

3. Experimental Section

3.1. Starting materials

For the epoxidation reactions, aqueous hydrogen peroxide (35 wt.% solution in water) and camphene were purchased from Aldrich. Urea hydrogen peroxide (UHP) contained 35 wt. % H_2O_2 (Acros Organics). MTO was generously donated by Clariant AG. 1-Methylnaphtalene and ethylbenzene were purchased, respectively,

from Merck and Fluka,. Camphene oxide was synthesized as described in the literature,[130] the purification is, however, described in this paper (*vide infra*).

3.2. Gas chromatography

Gas chromatography was performed using a DB23 column (30 m, 0.25mm, 0.25 μ m film thickness). The temperature profile was: 100 °C as initial temperature, followed by a 5 °C/min temperature gradient to 180 °C, kept for 1 min and finally a gradient of 20 °C/min to 240 °C, which was kept for 10 min. The injector temperature was 320 °C. Chromatography grade helium was used as the carrier gas.

3.3. Synthesis of camphene oxide for GC calibration via the peracid route [130]

Camphene (10 g, 73 mmol) was dissolved in 60 mL CH_2Cl_2 and treated with $\text{CH}_3\text{CO}_3\text{H}$ (10 mL) at 25 °C. The mixture was diluted with 60 mL CH_2Cl_2 , then Na_2CO_3 (11.3 mg, 107 mmol) was added. The reaction was stirred at room temperature (r.t.) during 4 h. The reaction mixture was treated with a saturated solution of Na_2CO_3 , washed with water until neutral pH, and dried over MgSO_4 .

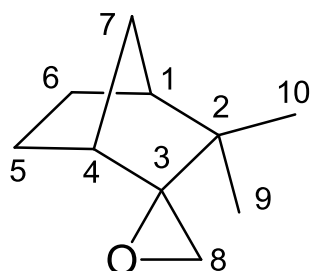
In order to separate camphene oxide from unreacted starting material and byproducts (camphor and camphene aldehyde), column chromatography was performed using neutral and basic alumina, as well as silica gel. However, only using neutral alumina, camphene oxide could be extracted, whereas in the case of basic alumina and silica gel, camphene oxide could either not be separated, or it reacted in the column to camphor and camphene aldehyde.

The quality of the neutral alumina has an effect on the purification of camphene oxide. Neutral alumina from Applichem reacts directly with camphene oxide to form the camphene aldehyde whereas the Merck sample provides pure camphene oxide. Most presumably, the different content of water in Al_2O_3 is the reason for this

finding. It is known that the more water is present in the Al_2O_3 the less this product is active. It is possible to obtain pure camphene oxide at any time when Al_2O_3 neutral is mixed with water and dried before being used. The quantity of water still present in low amounts is enough to deactivate Al_2O_3 and it is consequently possible to use it to purify camphene oxide without any loss.

The camphene oxides were consequently separated from unreacted compound by column chromatography on deactivated neutral Al_2O_3 with hexane as eluant. Camphene oxide was obtained in 44 % yield.

^1H NMR δ (ppm): 0.79 (s, 3H, C^9H); 0.89 (s, 3H, C^{10}H); 1.12 (m, 2H, C^7H), 1.25 (m, 2H, C^5H); 1.36 (m, 2H, C^6H); 1.84 (m, 1H, C^1H); 1.95 (s, 1H, C^4H); 2.67 (d, 1H, C^8H); 2.75 (d, 1H, C^8H). ^{13}C NMR δ (ppm): 21.08 (q); 23.23 (t); 24.10 (t); 27.42 (q); 35.01 (t); 37.32 (s); 43.65 (d); 48.81 (d); 51.51 (t); 71.32 (s). Retention time in GC: 11.8 min.



3.4. Epoxidation of camphene

MTO was dissolved in the solvent and the solution was heated to the appropriate reaction temperature (0 or 25 °C; see Table III.1). Ligand and oxidant (H_2O_2 35 % or UHP) were added to the solution. Camphene was then added to the reaction. The different (catalyst: ligand: oxidant) ratios are given in Table III.1. Samples were taken after 5 min, 30 min, 60 min, 90 min, 3 h, 5 h and 24 h. The reaction conditions used in this paper are described in Table III.1.

Camphene epoxidation

Table III.1. Reaction conditions (molar ratio) used in the epoxidation of camphene:

| Temperature (°C) | Camphene | MTO | pyrazole | H ₂ O ₂ | CH ₂ Cl ₂ (mL) |
|------------------|----------|-------------|---------------------|-------------------------------|--------------------------------------|
| 25 | 100 | 1 (12 mmol) | 20 | 110 | 18.7 |
| 0 | 100 | 1 | 20 | 110 | 18.7 |
| 25 | 100 | 0.5 | 10 | 110 | 18.7 |
| 25 | 100 | 0.1 | 2 | 110 | 18.7 |
| 25 | 100 | 0.5 | 5 | 110 | 18.7 |
| 25 | 100 | 0.5 | 2.5 | 110 | 18.7 |
| 25 | 100 | 0.5 | 0 | 110 | 18.7 |
| 25 | 100 | 0.5 | 10 | 200 | 17.6 |
| 25 | 100 | 0.5 | 10 | 300 | 16.5 |
| | Camphene | MTO | Ligand ^a | Oxidant _b | Solvent ^c |
| 25 | 100 | 0.5 | 10 | 110 | 18.7 |

^a *tert*-butylpyridine, pyrazole, 4,4-dimethyl-2,2'-bipyridine or imidazole.

^b aq. H₂O₂ or UHP.

^c CH₂Cl₂, CHCl₃, THF, MeNO₂ or toluene.

3.5. Sample preparation for the catalytic measurements

The conversion and product yield were determined by gas chromatography. For this, the oxidant has to be destroyed, otherwise the reaction continues in the GC sample damaging the column and resulting in inaccurate results.

Noteworthy, it was found that MnO_2 , which is usually used to destroy H_2O_2 , leads to further reactions of camphene oxide to camphor and camphene aldehyde. From this observation, it is clear that employing MnO_2 to stop the epoxidation reaction is not an appropriate method. Other ways to destroy H_2O_2 were consequently investigated. The use of Iron(III)sulfate or FeCl_3 was investigated for their reactivity towards H_2O_2 . Both of them are able to destroy H_2O_2 but the reaction is so exothermic that they also react with camphene oxide.

Metal powders are also known to react with H_2O_2 to H_2O . Zn, Fe and Ni powder were tested. All these powders have the advantage not to react too violently with H_2O_2 . However, these powders have low reactivity and thus only the Zn powder was found to be able to destroy all H_2O_2 present in the sample without affecting any of the compounds, which are also present in the sample.

The use of Zn powder on the real conditions of the epoxidation of camphene was examined with the reactants camphene, MTO, pyrazole, ethylbenzene and methylnaphthalene in CH_2Cl_2 . However, the color of the sample was changing when mixing the sample with Zn. It was thought that it may be possible that one or both of the internal standards react with Zn powder. The same mixture was tested again without internal standards. The color change when the sample was mixed with Zn is now as expected (from yellow to colorless due to the destruction of the active catalyst). Consequently, the standards were added in the volumetric flask and were not applied as internal standards before anymore. The epoxidation of camphene under the condition camphene: MTO: pyrazole: CH_2Cl_2 of 100:1:20:110 was performed several times. The conversion and yield are reproducible.

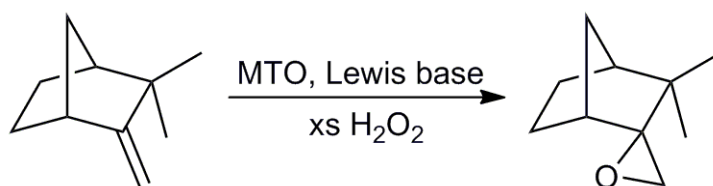
The reaction kinetic of the catalytic reactions, carried out as described in Section 2.4, was investigated by gas chromatography. For this, samples from the reaction were treated with Zn powder and allowed to stand for 30 min. The samples were then filtered, washed with 3 x 2 mL water and dried over MgSO₄. A known volume of this purified sample (see Table III.2) was put in a 5 mL volumetric flask. 1.5 mL of this last solution was put in a GC vial and measured.

Table III.2. Sample volume.

| Sample volume (μL) | Ratio MTO: H ₂ O ₂ |
|--------------------|--|
| 150 | 1: 300 |
| 160 | 1: 200 |
| 170 | 1: 110 |
| 200 | UHP |

4. Results and discussion

The reaction of camphene to camphene oxide catalyzed by MTO was carried out according to Scheme III.3. In order to study the kinetics of the reaction, samples were taken in equivalent time intervals to determine the conversion and product yield by gas chromatography.



Scheme III.3. Catalytic epoxidation of camphene oxide with MTO

The epoxidation of camphene shows the same behavior as the epoxidation of limonene employing MTO as catalyst. It is known that limonene oxide reacts further to dipentene dioxide in presence of the catalytic system MTO/H₂O₂. The optimal time to stop the reaction is, thus, of importance to obtain the highest yield and selectivity towards limonene oxide.[131] In the case of camphene epoxidation, camphene oxide reacts further to camphor and camphene aldehyde in the presence of the catalytic system MTO/H₂O₂. The optimal time to stop the reaction needs also to be determined in order to obtain high yield and selectivity towards camphene oxide.

4.1. Influence of different Lewis bases, oxidants and solvents

4.1.1. Influence of different Lewis base adducts

The choice of the ligating Lewis base is known to be of significant importance for the epoxidation of olefins. Their role is to avoid the formation of byproduct, but it has also been proven that some Lewis base adducts can additionally improve the catalytic activity of the MTO/H₂O₂ system.[1a, 47f, 50a, 100a, 101] It was thus decided to investigate the influence of a pyridine derivative: tert-butylpyridine, a bidentate ligand such as 4,4'-dimethyl-2,2'-bipyridine, imidazole and pyrazole, four widely applied Lewis base ligands. The molar ratio camphene:MTO:Ligand:H₂O₂ of 100:0.5:10:110 was applied in all cases in dichloromethane at 25 °C.

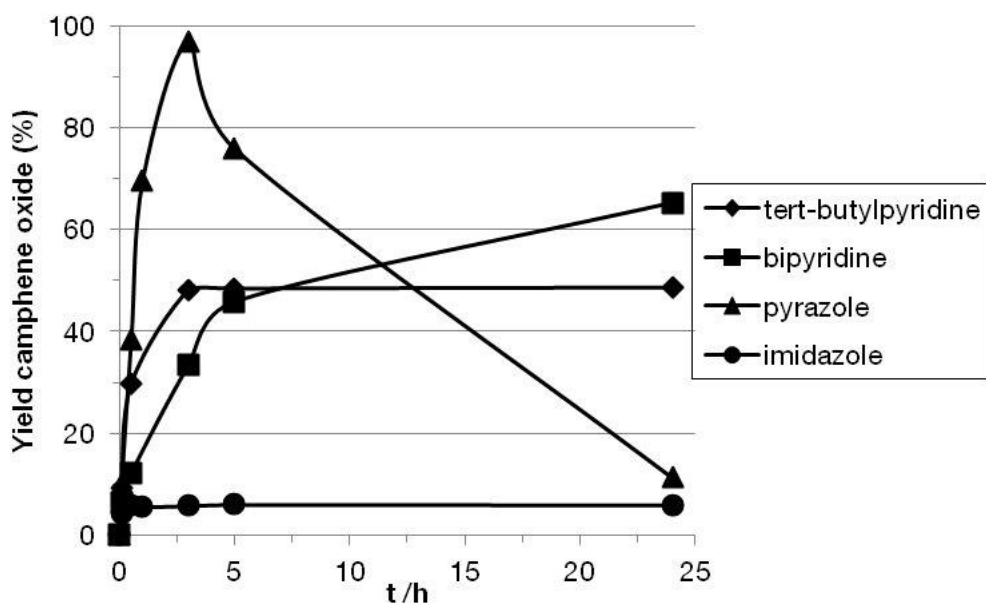


Figure III.1. Kinetics of the epoxidation of camphene: influence of the ligand choice.

Table III.3. Turnover frequency, selectivity and conversion measured by GC: influence of ligand choice.^a

| t = 3 h | Tert-butylpyridine | Bipyridine | Pyrazole | Imidazole |
|-----------------------------|--------------------|------------|------------|-----------|
| TOF (h⁻¹) | 290 | 200 | 360 | 130 |
| Selectivity (%) | 86 | 80 | 98 | 100 |
| Conversion (%) | 56 | 42 | 99 | 5.4 |

^a Molar ratio camphene:MTO:Ligand:H₂O₂ 100:0.5:10:110.

As shown in Figure III.1, the highest yield is obtained when pyrazole is used as ligand. The activity of the catalytic species is also the highest when pyrazole is applied as ligand. Moreover, as seen in Table III.3, the selectivity towards the formation of camphene oxide is high (98 % after 3 h) when pyrazole is used as ligand. As depicted in table III.3, the activity of the catalytic species is lower when

other Lewis base adduct than pyrazole, namely tert-butylpyridine, 4,4'-dimethyl-2,2'-bipyridine or imidazole, are used.

The improvement in the rate of formation of camphene oxide can be explained by the use of pyrazole as ligand since it was not investigated so far in the epoxidation of camphene, but is known in the literature to lead – for some alkenes – to higher yield and selectivity than the pyridine based ligand systems.[50d] Some further experiment has been done on ligand concentrations to test the activity of pyrazole towards the other Lewis Base adducts.

Table III.4. Turnover frequency, selectivity and conversion measured by GC: influence of ligand choice. ^a

| Conversion at t = 3 h | Tert-butylpyridine | Bipyridine | Pyrazole |
|--------------------------|--------------------|------------|----------|
| X = 20 | 49,3 | 25,9 | 100 |
| X = 10 | 49 | 40,5 | 100 |
| X = 5 | 42,7 | 25,7 | 98 |

^a Molar ratio camphene:MTO:Ligand:H₂O₂ 100:1:X:110

As depicted in Table III.4, the activity of the catalytic species is increased by the use of pyrazole as Lewis base adduct. The conversion of camphene does not goes up to 50 % at 3 h when tert-butylpyridine or 4,4'-dimethyl-2,2'-bipyridine are used as Lewis base adduct, whereas it goes up to 100 % with pyrazole. Pyrazole is the best Lewis base ligand among those under examination in this work for catalytic camphene oxidation and was applied in all further experiments accordingly.

4.1.2. Influence of different oxidants: H₂O₂ vs. UHP

It is also possible to avoid the formation of byproducts by decreasing the presence of large amounts of water in the reaction medium. For this purpose, urea hydrogen peroxide (UHP) can be used instead of hydrogen peroxide.

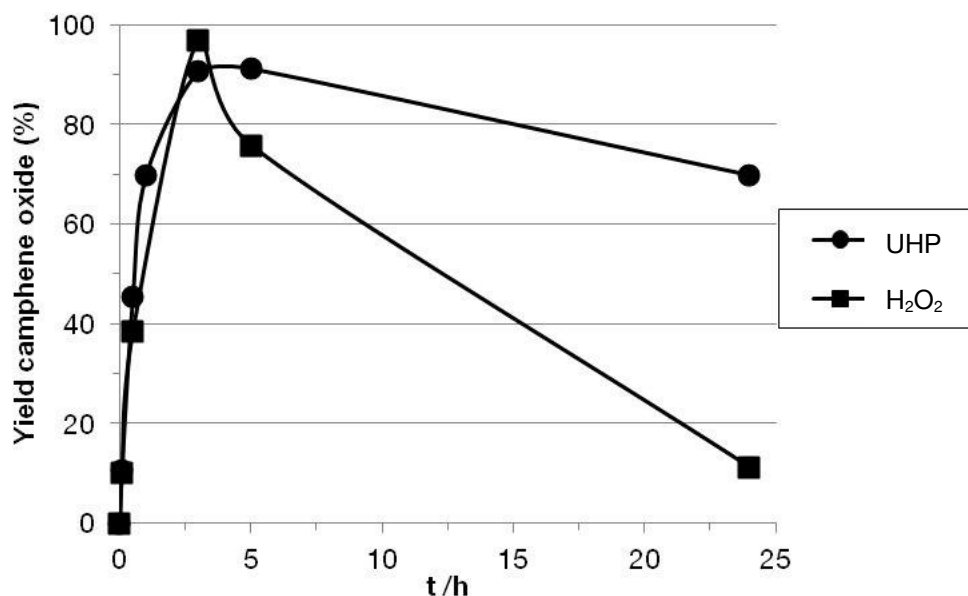


Figure III.2. Kinetics of the epoxidation of camphene: influence of the oxidant choice.

Table III.5. Turnover frequency, selectivity and conversion measured by GC: H₂O₂ vs. UHP.^a

| t = 3 h | H ₂ O ₂ | UHP |
|------------------------|-------------------------------|-----|
| TOF (h ⁻¹) | 360 | 300 |
| Selectivity (%) | 98 | 92 |
| Conversion (%) | 99 | 98 |

^a Molar ratio camphene:MTO:pyrazole:oxidant 100:0.5:10:110

As depicted in Figure III.2, the formation of camphene oxide does not seem to be greatly affected by exchanging H_2O_2 by a “non aqueous form of H_2O_2 ”. However, it appears that the yield decreases more slowly when UHP is used instead of H_2O_2 . From table III.5, the TOF and thus the activity of the catalytic species as well as the selectivity towards camphene oxide are higher when aqueous H_2O_2 is used as oxidant than with applying UHP. Even if aqueous H_2O_2 seems to be the best choice, UHP was tested as well in the following experiments.

4.1.3. Optimization of the conditions for UHP application

As UHP seems to be an appropriate oxidant for the epoxidation of camphene, its concentration influence was investigated. The molar ratio of camphene:MTO:pyrazole:UHP of 100:0.5:10:X (X = 110; 200 or 300) was applied in dichloromethane at 25 °C.

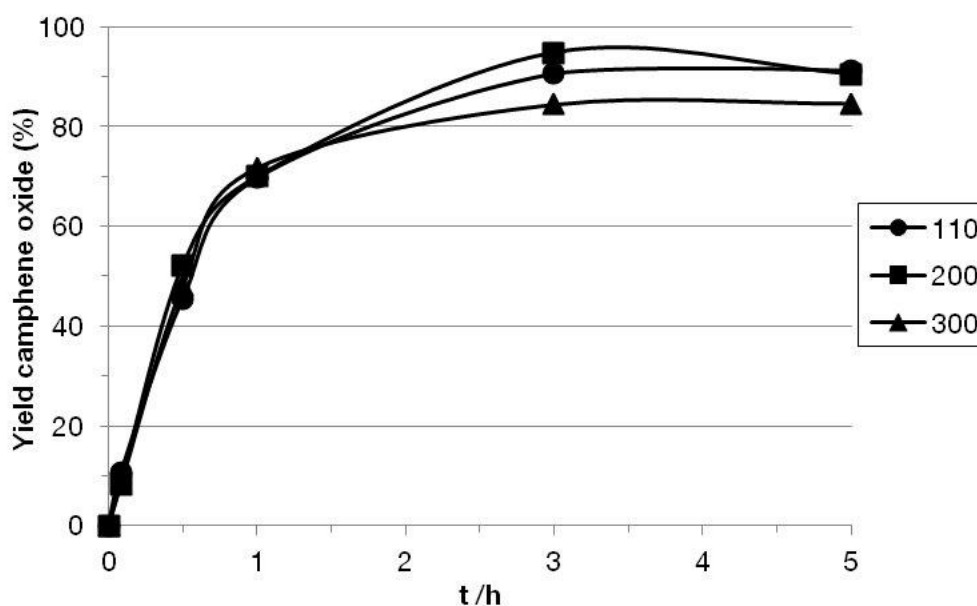


Figure III.3. Kinetics of the epoxidation of camphene: influence of the UHP concentration.

Table III.6. Turnover frequency and selectivity measured by GC: applying UHP. ^a

| t = 3 h | 110 | 200 | 300 |
|-----------------------------|------------|------------|------------|
| TOF (h⁻¹) | 300 | 250 | 270 |
| Selectivity (%) | 92 | 98 | 86 |
| Conversion (%) | 98 | 97 | 97 |

^a Molar ratio camphene:MTO:pyrazole:UHP 100:0.5:10:X

Different concentrations of UHP lead to comparable activities and high selectivities (see Figure III.3 and Table III.6). UHP is a solid, badly soluble in almost all organic solvents. It is thus possible that oxidant present in the organic layer is almost the same with the different concentrations of UHP applied. Consequently, the ratio MTO:UHP of 1:110 was used in the following experiments for both oxidants.

4.1.4. Influence of different solvents

The influence of more or less protic solvents was also investigated for the epoxidation of camphene. CH₂Cl₂, MeNO₂, CHCl₃, THF and toluene were tested for both H₂O₂ and UHP as oxidant. The molar ratio applied was camphene:MTO:pyrazole:oxidant of 100:0.5:10:110.

Table III.7. Results of the epoxidation of camphene employing different solvents. Comparison between H₂O₂ and UHP.^a

| | aq. H ₂ O ₂ | | | UHP | | |
|-------------------------------------|-----------------------------------|----------------------|---------------------------|----------------|----------------------|---------------------------|
| | Yield (3 h) | Selectivity (3 h) | TOF (h ⁻¹) | Yield (3 h) | Selectivity (3 h) | TOF (h ⁻¹) |
| CH₂Cl₂ | 97 % | 98 % | 360 | 91 % | 93 % | 300 |
| CHCl₃ | 87 % | 89 % | 410 | 87 % | 92 % | 170 |
| MeNO₂ | / | / | / | 73 % | 86 % | 170 |
| Toluene | 57 % | 99 % | 110 | 67 % | 62 % | 90 |

^a Molar ratio camphene:MTO:pyrazole:oxidant 100:0.5:10:110

As depicted in table III.7, in the case of aqueous H₂O₂, dichloromethane leads to higher yields of camphene oxide than in the other solvents used in this study. The selectivity obtained in CH₂Cl₂ is also high. MeNO₂ was also investigated; however, as water is more soluble in this solvent than in CH₂Cl₂, CHCl₃ or toluene, H₂O₂ could not be totally destroyed by Zn powder even after 24 h. Consequently, the samples could not be measured by GC. Toluene leads to the best selectivity towards camphene oxide, however the reaction is very slow since the highest yield of 69 % is obtained only after 5 h. The use of CHCl₃ as solvent leads to high activity of the catalytic system, however, more byproducts are observed by using this solvent, which can explain the lower yield and selectivity obtained in this solvent compared to dichloromethane.

In the case of UHP, as for H₂O₂, CH₂Cl₂ is the solvent leading to the highest yield of camphene oxide (see table III.7). The other solvents, CHCl₃, MeNO₂ and toluene

were also tested for the epoxidation of camphene. However, they lead to lower activities of the catalytic system. Moreover, the selectivity towards the formation of camphene oxide decreases also compared to CH_2Cl_2 .

In summary, for both H_2O_2 and UHP, CH_2Cl_2 is the best of the solvents under examination. The activity of the catalytic system is slightly higher when aqueous H_2O_2 is used as oxidant instead of UHP. The solvents leading to better solubility of H_2O_2 such as MeNO_2 or THF could not be fully investigated because the Zn powder used to destroy the oxidant was not active enough to destroy all H_2O_2 present in the organic phase.

4.2. Optimization of the epoxidation of camphene

The best reactants for the epoxidation of camphene employing MTO as catalyst were determined by the above described experiments: Pyrazole as Lewis base adduct, aqueous H_2O_2 as oxidant and CH_2Cl_2 as solvent. The concentration of each reactant is now varied to determine the optimal reaction condition for the epoxidation of camphene.

4.2.1. Temperature influence

The epoxidation of camphene was investigated employing a molar ratio of camphene:MTO:pyrazole: H_2O_2 of 100:1:20:110 in dichloromethane. The influence of the temperature on the epoxidation of camphene was studied by decreasing it from 25 °C to 0 °C. The ratio mentioned was consequently applied at 0 °C and 25 °C.

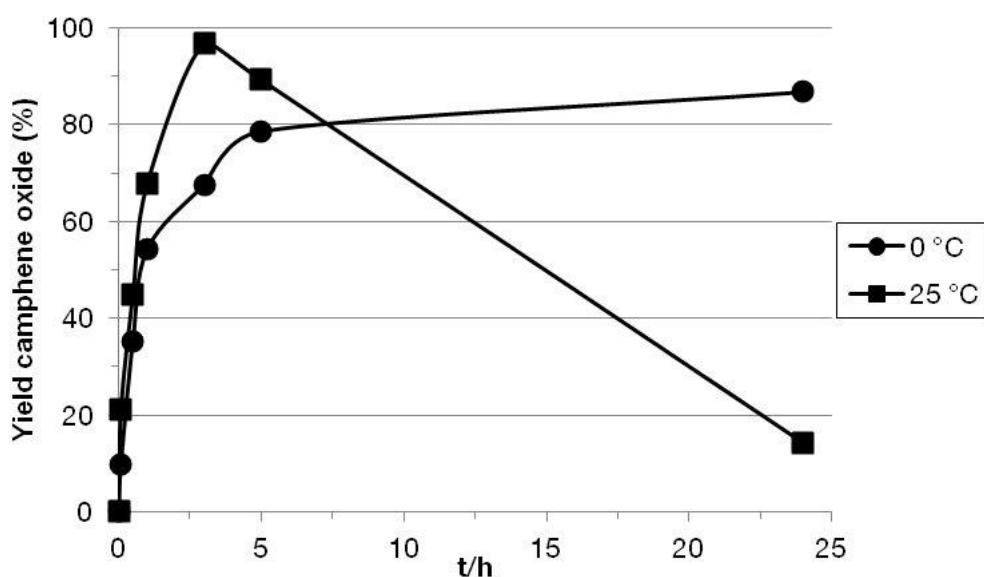


Figure III.4. Kinetics of the epoxidation of camphene at 0 °C and 25 °C.

Table III.8. Turnover frequency, selectivity and conversion measured by GC at 0 °C and 25 °C.^a

| t = 3 h | 0 °C | 25 °C |
|-----------------------------|------|------------|
| TOF (h⁻¹) | 170 | 340 |
| Selectivity (%) | 76 | 97 |
| Conversion (%) | 89 | 100 |

^a Molar ratio camphene:MTO:pyrazole:H₂O₂ 100:1:20:110

As depicted in Table III.8, the catalytic activity is – as to be expected - higher at 25 °C than at 0 °C with TOFs of 360 h⁻¹ and 170 h⁻¹, respectively. Moreover, the highest selectivity is reached at room temperature with still 97 % selectivity towards camphene oxide after 3 h against 76 % at 0 °C. As seen in Figure III.4, the highest yield is also achieved at room temperature.

However and as for limonene epoxidation, the time to stop the reaction is crucial. After 3 h, the high activity of the catalytic system leads to the formation of byproduct that explains the decrease of camphene oxide yield.

The reaction will consequently be kept at 25 °C for the following reactions.

4.2.2. Oxidant concentration

The optimal concentration of oxidant is of importance, since high excess of oxidant can lead to a situation favoring the formation of byproducts. On the other hand, a poor concentration of oxidant may result in poor activity of the catalyst system and consequently poor yield of the desired product. For this purpose, different amounts of H₂O₂ in dichloromethane at 25 °C were examined. The molar ratios of camphene: MTO: pyrazole: H₂O₂ of 100:1:10:X (with X = 110; 200 and 300) were applied.

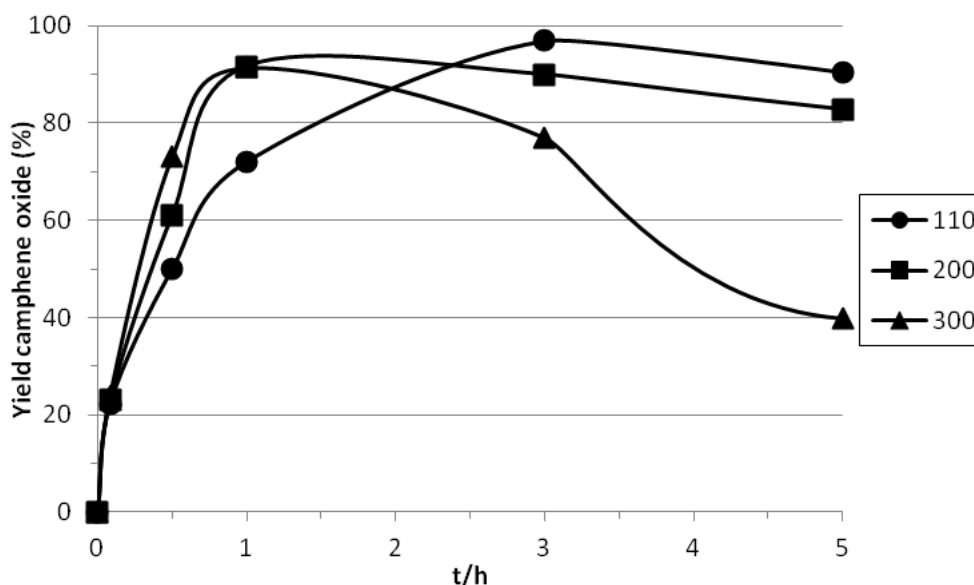


Figure III.5. Kinetics of the epoxidation of camphene: influence of the oxidant concentration.

Table III.9. Turnover frequency, selectivity and conversion measured by GC at different oxidant concentration. ^a

| t = 3 h | 110 | 200 | 300 |
|-----------------------------|------------|------------|------------|
| TOF (h⁻¹) | 380 | 390 | 410 |
| Selectivity (%) | 97 | 90 | 78 |
| Conversion (%) | 100 | 100 | 100 |

^a Molar ratio camphene:MTO:pyrazole:H₂O₂ 100:1:10:X

As depicted in Table III.9, higher concentrations of oxidant lead to higher catalytic activity of the catalytic specie. However, the selectivity towards camphene oxide decreases with the oxidant concentration. The highest yield of camphene oxide is obtained with the ratio 1:110 as well as the highest selectivity (see Figure III.5 and Table III.9).

The optimal concentration of H₂O₂ is thus applied in the molar ratio of camphene:MTO:pyrazole:H₂O₂ of 100:1:10:110 in CH₂Cl₂ at 25 °C. Camphene oxide was formed in 97 % yield at 100 % conversion after 3 h. This molar ratio is then added for the following experiments.

4.2.3. Catalyst concentration

The efficiency of the catalyst in the epoxidation of camphene is also an important aspect, which requires to be investigated. For this purpose, the concentration of the catalyst was decreased from 1 mol % to 0.5 mol % and 0.1 mol %.

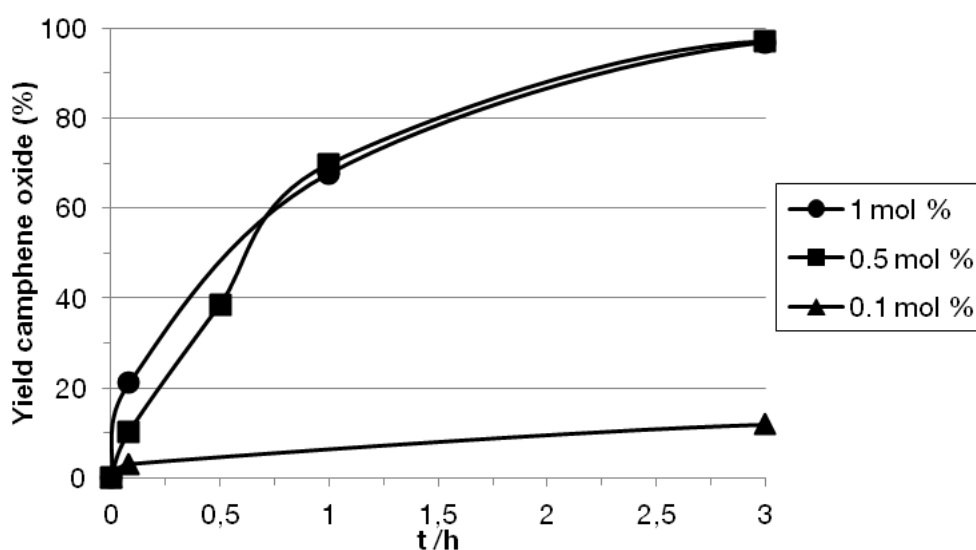


Figure III.6. Kinetics of the epoxidation of camphene: influence of the catalyst concentration.

Table III.10. Turnover frequency, selectivity and conversion measured by GC at different catalyst concentration. ^a

| t = 3 h | 1 mol % | 0.5 mol % | 0.1 mol % |
|-----------------------------|---------|-----------|-----------|
| TOF (h⁻¹) | 380 | 360 | 220 |
| Selectivity (%) | 97 | 98 | 100 |
| Conversion (%) | 100 | 99 | 12 |

^a Molar ratio camphene:MTO:pyrazole:H₂O₂ 100:X:20X:110

The molar ratios of camphene:MTO:pyrazole:H₂O₂ of 100:1:20:110; 100:0.5:10:110 and 100:0.1:2:110 were applied in dichloromethane at 25 °C. From Figure III.6 and Table III.10, it is visible that decreasing the catalyst concentration from 1 mol % to 0.5 mol % does not have a significant effect on the activity of the catalytic system or the selectivity. This means that a considerable amount of catalyst is not used when a concentration of 1 mol % is applied. However, decreasing the concentration of

MTO to 0.1 mol % leads to a considerable loss of activity as seen in Figure III.6. The concentration 0.5 mol % was consequently used for all further experiments.

4.2.4. Ligand concentration

The use of Lewis base adducts in the epoxidation of acid sensitive olefins was already described extensively in the literature.[117] The complex formed between active catalyst species and the ligand allows higher activity,[1a, 47f, 50a, 100a, 101] and decreases the formation of byproducts.[117] It is thus important to determine the optimal ligand concentration, which allows highest activity of the active species and highest selectivity towards camphene oxide. For this purpose, different molar ratios of camphene:MTO:pyrazole:H₂O₂ were applied: 100:0.5:10:110; 100:0.5:5:110; 100:0.5:2.5:110 and 100:0.5:0:110 (i. e. no Lewis base ligand). The reaction was done in dichloromethane at 25 °C in all cases.

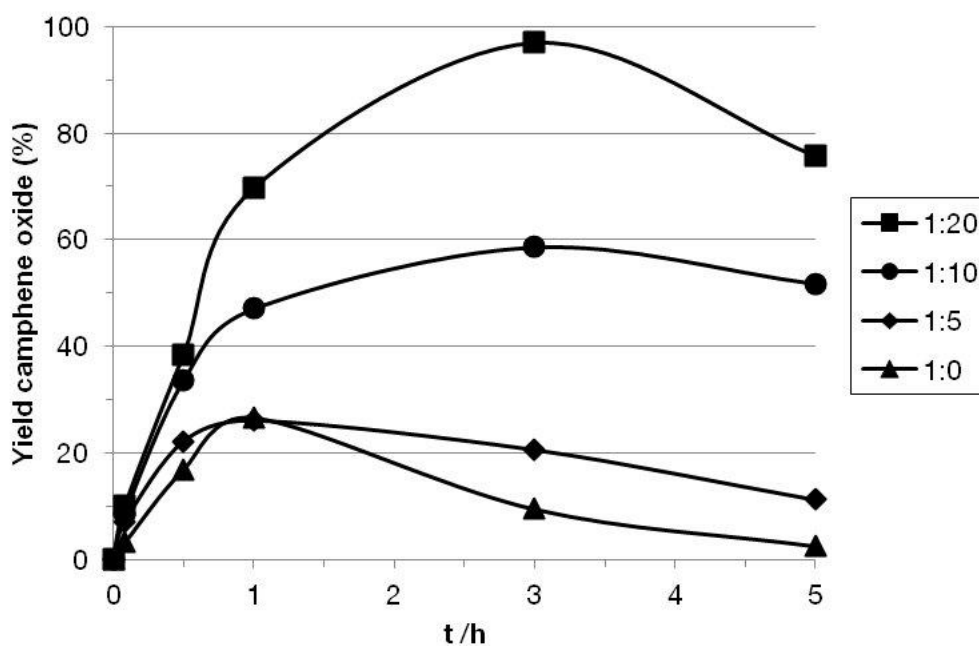


Figure III.7. Kinetics of the epoxidation of camphene: influence of the ligand concentration.

Table III.11. Turnover frequency, selectivity and conversion measured by GC at different ligand concentration. ^a

| t = 3 h | X = 10 | X = 5 | X = 2.5 | X = 0 |
|-----------------------------|---------------|--------------|----------------|--------------|
| TOF (h⁻¹) | 360 | 310 | 200 | 70 |
| Selectivity (%) | 98 | 78 | 72 | 14 |
| Conversion (%) | 99 | 75 | 29 | 67 |

^a Molar ratio camphene:MTO:pyrazole:H₂O₂ 100:0.5:X:110

As depicted in Figure III.7, the activity decreases with the concentration of the Lewis base applied. The molar ratio MTO:ligand leading to the highest activity and selectivity toward the formation of camphene oxide is 1:20 (see table III.11).

5. Conclusion

The epoxidation of camphene employing MTO as catalyst (precursor) was investigated. The optimal condition for the epoxidation of the desired epoxide in high yield and selectivity has been determined by varying several parameters.

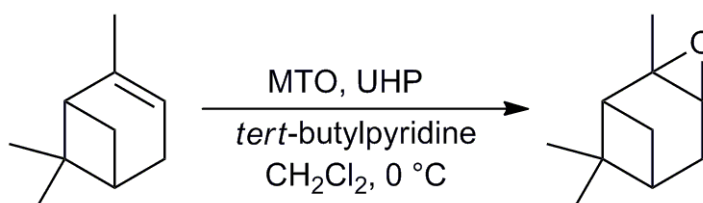
The choice of different reactants was investigated. Tert-butylpyridine, 4,4'-dimethyl-2,2'-bipyridine or pyrazole were tested as Lewis base adduct. The effect of an aqueous or a non aqueous hydrogen peroxide oxidant was also determined on the epoxidation of camphene. Dichloromethane, chloroform and toluene were tested as solvent. From all these experiences, the best reactants for the selective epoxidation of camphene to camphene oxide in high yield are pyrazole as Lewis base adduct, aqueous hydrogen peroxide as oxidant and dichloromethane as solvent.

The concentration of each reactant (ligand and oxidant) is also crucial to avoid the formation of byproducts such as camphene aldehyde or camphor. In order to find the optimal condition, the concentration of each reactant was varied. The highest yield and selectivity of camphene oxide is obtained when the molar ratio camphene:MTO:pyrazole:H₂O₂ of 100:0.5:10:110 is applied at room temperature in dichloromethane. Camphene oxide is formed in 97 % yield and 98 % selectivity after 3 h. This result is by far the best obtained up to date in the epoxidation of camphene employing MTO as catalyst. Adam et al. obtained 89 % conversion and 95 % selectivity towards camphene oxide after 10 h.[47f] They used MTO/NaY, H₂O₂ in CDCl₃.

C. SUMMARY

A MTO based catalytic system was examined and optimized for the epoxidation of α -pinene, limonene and camphene. The major challenge of the epoxidation of terpenes is the formation of byproducts. The moiety of the reaction is thus crucial for the synthesis of the desired epoxide. Several parameters, such as reactant concentration and nature, were varied in order to determine the optimal conditions for the epoxidation of those terpenes.

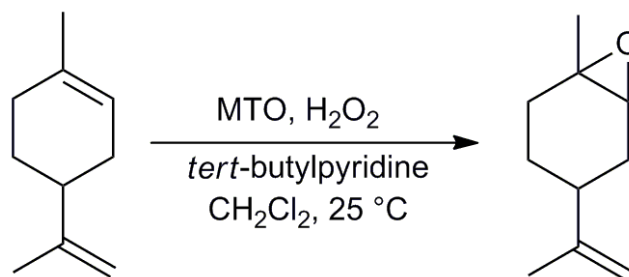
The main issue in the epoxidation of α -pinene is the readily conversion of α -pinene oxide to α -pinene diol in acidic conditions and in presence of water.



Scheme C.1. α -Pinene epoxidation

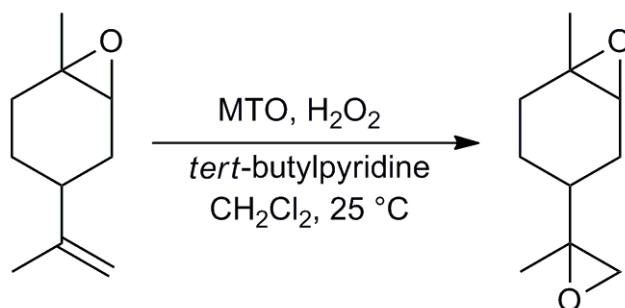
One way to suppress byproduct formation is to decrease the acidity of the metal center by the addition of a Lewis base adduct. The use of Schiff-bases or bipyridines does not suppress the formation of α -pinene diol. On the contrary, in presence of *tert*-butylpyridine, the epoxidation of α -pinene is selective to the epoxide. Another way to suppress diol formation is to employ a non aqueous oxidant. A slight improvement in the selectivity towards α -pinene oxide was thus observed by using UHP instead of aqueous H₂O₂. The conditions leading to the best results employed MTO as catalyst, *tert*-butylpyridine as ligand and UHP as oxidant in a molar ratio α -pinene: MTO: *tert*-butylpyridine: UHP of 200: 1: 40: 600 in MeNO₂ at 0 °C. It leads to the selective formation of α -pinene oxide in high yield (95 % after 3 h) and to a TOF of 610 h⁻¹.

To reach optimal 1,2-limonene oxide formation (high activity, selectivity and yield) MTO has to be applied in low concentrations to avoid secondary reactions of 1,2-limonene oxide (most prominent is the formation of diepoxide).



Scheme C.2. Limonene epoxidation

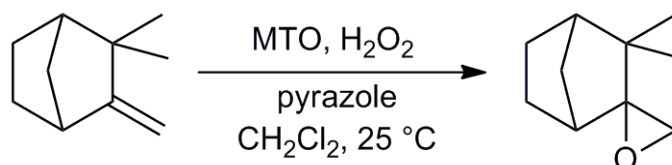
When the Lewis base ligand/MTO ratio is not optimal, the formation of byproducts dominates. With low Lewis base concentrations epoxide, ring opening reactions are favored due to the Lewis acidity of the system. *tert*-Butylpyridine turned out to be optimal amongst the examined Lewis bases. It is applied at room temperature (25 °C) together with H₂O₂ as oxidant in a two phases system with dichloromethane as organic phase. Under these conditions, the highest selectivity towards 1,2-limonene oxide is obtained with a ratio of (+)-limonene: MTO: *tert*-butylpyridine: H₂O₂ of 100: 0.5: 10: 150. 1,2-Limonene oxide forms in 77 % yield with 96 % selectivity after 1 h. The optimal condition for the formation of the main byproduct (dipentene dioxide) is reached with a catalyst concentration of 1 mol % with enhanced ligand and oxidant concentrations.



Scheme C.3. Dipentene oxide formation

The highest yield and selectivity are obtained with a (+)-limonene: MTO: *tert*-butylpyridine: H₂O₂ ratio of 100: 1: 40: 300 at 25 °C. Dipentene dioxide is formed under these conditions in 90 % yield and selectivity after 24 h.

The highest yield and selectivity of camphene oxide is obtained when the molar ratio camphene: MTO: pyrazole: H₂O₂ of 100: 0.5: 10: 110 is applied at room temperature in dichloromethane.



Scheme C.4. Camphene epoxidation

Camphene oxide forms in 97 % yield and 98 % selectivity after 3 h. This result is by far the best obtained up to date in the epoxidation of camphene employing MTO as catalyst. Adam et al. obtained 89 % conversion and 95 % selectivity towards camphene oxide after 10 h using the system MTO/NaY, H₂O₂ in CDCl₃.^[23] Our result can be explained by the use of pyrazole as ligand. The other well-known and often used Lewis bases such as *tert*-butylpyridine or 4,4'-dimethyl-2,2'-bipyridine lead to similar activities of the catalytic system as described in the literature.^[47f] Pyrazole was not investigated so far in the epoxidation of camphene, but is known in the literature to lead – for some alkenes – to higher yields and selectivities than the pyridine based ligand systems.^[50d]

Mo (VI) based catalysts were also tested on the epoxidation of α -pinene and limonene. The influence of the concentration of TBHP and the catalyst were investigated as well as the effect of different solvents. However, the further oxidation of the desired epoxide in presence of the catalytic system Mo/TBHP was always observed, leading to poor epoxide yield (< 50 %) and numerous byproducts formation.

One of the most important challenges for the epoxidation of olefins is to induce chirality. It was first thought to find optimal conditions with the “standard” Mo (VI) based catalysts for the formation of the desired epoxides and then synthesize derivatives of these catalysts by introducing chiral ligands. However, as

Mo based catalysts show poor selectivity towards epoxide formation, another way to induce enantioselectivity in the epoxidation of terpenes is to synthesize chiral MTO derivatives. As described in the literature, derivatives of MTO are either unstable and thus decomposed under oxidative conditions or too stable to be active in olefin epoxidation. Further researches on this area are undertaken by two Ph-D students in the group.

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Catalytic Epoxidation Of Limonene Employing Methyltrioxorhenium As Catalyst

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