Selective Oxidation of C16 Macrocyclic Diene to Epoxides and Ketones

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Abstract

(Z/E)-8-Cyclohexadecenone (trade name: Globanone®, 8-CHD), a macrocyclic musk used in the fine fragrance industry, is usually manufactured via the selective monoepoxidation of 1,9-(Z/E)-cyclohexadecadiene (CHDD) and subsequent rearrangement of the monoepoxide CHDO to the target ketone. During the former step, undesired diepoxides are formed as byproduct. Since the loss of starting material must be avoided due to its elevated production costs, the reaction must be stopped at a certain conversion, i.e. CHDO yield only reaches 20-25%.

In the present work, two approaches were followed to overcome the aforementioned problematic. Firstly, the epoxidation step was revised. The active catalyst responsible for this step is composed of a peroxotungstophosphate formed “in situ” and a quaternary ammonium salt used as phase-transfer catalyst. The screening of several parameters such as of the precursors of the peroxotungstophosphate, the anion of the quaternary ammonium salt and the structure of the ammonium cation led to different conversions of CHDD and a varied selectivity to CHDO.

Secondly, a one-step approach to synthesize the target product 8-CHD was also of interest. For this reason, the Pd^{II}-catalyzed Wacker-type oxidation was carried out under different conditions and using a number of palladium(II) complexes. The use of bis(β-diketonato)palladium(II) complexes as catalysts was of special interest because they showed the highest selectivity to 8-CHD. Nevertheless, the formation of additional oxygenated byproducts represents a serious problem and a big challenge for potential optimization of this approach.

Zusammenfassung

(Z/E)-8-Cyclohexadecenon (Handelsname: Globanone®, 8-CHD) ist ein makrozyklisches Keton, welches Anwendung in der Duftstoffindustrie findet. Es wird industriell durch die selektive Monoepoxidierung des makrozyklischen Diens 1,9-(Z/E)-Cyclohexadecadien (CHDD) mit anschließender Umlagerung des Monoepoxides CHDO zum Keton hergestellt. Während des ersten Reaktionsschritts wird mit zunehmendem Umsatz die Bildung des unerwünschten Diepoxids als Nebenprodukt beobachtet. Da es aufgrund der hohen Produktionskosten für CHDD wünschenswert ist, kein Material durch die Bildung unbrauchbaren Diepoxids zu verschwenden, wird die Reaktion zu einem Zeitpunkt gestoppt, an dem sich gerade noch kein Diepoxid gebildet hat. Unumgesetztes CHDD wird rezykliert. Das bedeutet, dass die technisch erreichte Ausbeute an CHDO bei ca. 20-25% liegt.

In meiner Dissertationarbeit wurden zwei mögliche Ansätze für die Verbesserung der Ausbeute an 8-CHD bzw. dessen Vorstufe CHDO erforscht. Zum einen wurde die Epoxidierung von 1,9-(Z/E)-Cyclohexadecadien untersucht. Der aktive, in situ hergestellte Katalysator für die Epoxidierung besteht aus einem Polyperoxowolframatophosphat und einem quartären Ammoniumsalz als Phasentransfer-Katalysator. Das Reaktionsscreening unter Variation verschiedener Komponenten der Aktivspezies, z.B. der Präkursoren des Polyperoxowolframats, des Anions des quartären Ammoniumsalzes und auch der Struktur des Ammonium-Kations, führte zu unterschiedlichen Umsätzen von CHDD und Selektivitäten in Bezug auf CHDO.

Des Weiteren war ein einstufiges Verfahren für die Synthese des Zielproduktes 8-CHD von Interesse. Aus diesem Grund wurde die Pd^{II}-katalysierte Wacker-analoge Oxidation von CHDD unter verschiedenen Bedingungen sowie mit unterschiedlichen Palladium(II)-Komplexen durchgeführt und untersucht. Die Nutzung von Bis(β-diketonato)palladium(II)-Komplexen führte mit der höchsten Selektivität zum erwünschten Produkt, dem 8-CHD. Die Bildung von oxygenierten Nebenprodukten war dabei von Nachteil und stellt für weitere Optimierungen eine große Herausforderung dar.

Declaration

I declare that the work presented in this thesis entitled “Selective Oxidation of C16 Macrocyclic Diene to Epoxides and Ketones” is original and carried out by myself to obtain the doctoral degree at the Leibniz Institute for Catalysis e. V., in Rostock, Germany, under the guidance of my supervisors PD Dr. habil. Andreas Martin (Head of Department of “Heterogeneous Catalytic Processes”) and Dr. Angela Köckritz (Group Leader “Liquid Phase Oxidations”). I further declare that this thesis has not been submitted, either wholly other in part, to any academic institution for the award of any other degree or qualification.

Diego A. Jaime Treviño

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Diego Jaime T.

List of abbreviations, acronyms and symbols

^{1}H	^{1}H NMR spectroscopy
^{31}P	^{31}P NMR spectroscopy
8-CHD	(E/Z)-8-cyclohexadecenone
acac	acetylacetonate
Aliquat 336	methyltrioctylammonium chloride
AMPA	aminomethylphosphonic acid
BHPA	bishydroxymethylphosphinic acid
BPhen	bathophenanthroline
$CDCl_3$	deuterated chloroform
CDT	(E, E, Z)-1,5,9-cyclododecatriene
CHDD	1,9-cyclohexadecadiene, isomeric mixture
CHDO	17-oxabicyclo[14.1.0]heptadec-8-en
CHDOO	1,2,9,10-diepoxycyclohexadecane
DFB	1,4-difluorobenzene (*p*-difluorobenzene)
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMPr	*N,N*-dimethylpropionamide
DPPA	diphenylphosphinic acid
ETM	electron-transfer mediator
FID	flame ionization detector
GBL	gamma-butyrolactone
GC	gas chromatography
GVL	gamma-valerolactone

H_2O_2	hydrogen peroxide
HMPA	hydroxymethylphosphonic acid
MS	mass spectrometry
MS-ESI	mass spectrometry-electrospray ionization
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
PA	phosphoric acid
$Pd(acac)_2$	palladium(II) acetylacetonate
$Pd(bmdm)_2$	butylmethoxydibenzoylmethanato palladium(II)
$Pd(dbm)_2$	dibenzoylmethanato palladium(II)
$Pd(hfacac)_2$	palladium(II) hexafluoroacetylacetonate
$Pd(OAc)_2$	palladium(II) acetate
$Pd(tfac)_2$	palladium(II) trifluoroacetylacetonate
$Pd(TMHD)_2$	palladium(II) 2,2,6,6-tetramethylheptanedionato
$PdCl_2$	palladium(II) chloride
Phen	1,10-phenanthroline
PhPA	phenylphosphonic acid
PTA	phosphotungstic acid
PTC	phase transfer catalyst
STD	internal standard (1,8-octanediol)
TBHP	*tert*-butyl hydroperoxide
THF	tetrahydrofuran

To the memory of my father

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1. Theoretical part

1.1. Fragrance industry and musks overview

The use of synthetic methods for the preparation of ingredients revolutionized the industry of fragrances since the end of the nineteenth century. In 2015, the total flavors and fragrances market was estimated at 22.3 billion EUR (24.7 billion US dollars) [1]; its production scale is close to that of the pharmacetical industry and product prices close to those of the bulk chemistry [2]. It trades in between 500 – 1,000 synthetic compounds, which can be categorized depending on their odor (see Figure 1). Especially interesting from a chemical point of view is the production of musk odorants, as it is based on identification of natural ingredients and its further synthetic preparation [3].

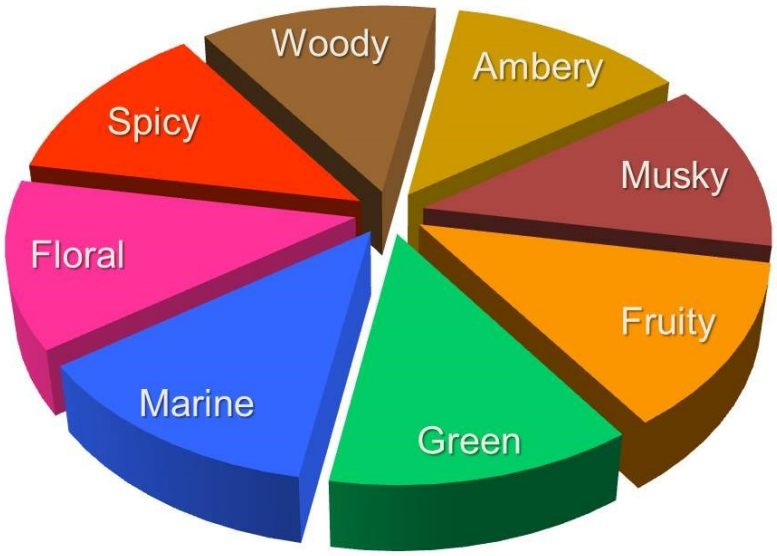


Figure 1. The olfactory spectrum [4]

Musk odorants have been used in the fragrance industry for more than 900 years, in part due to their abilities to improve the fixation of compounds and to round off fragrance compositions. Originally, macrocyclic musks were obtained from natural sources, *i.e.* extracted from animals, whose death was sometimes a must [5]. As a result, this practice was prohibited and the use of other types of organic compounds, *e.g.* nitromusks and polycyclic musks, with the same odor class was favored. In 1987 the total 7000 ton of musk compounds produced worldwide comprised 61% polycyclic musks, 35% nitro musks and 4% macrocyclic musks. [6].

However, it was discovered that nitro musks and polycyclic musks persist in the environment and are potentially dangerous for health; nowadays, products containing these types of musks are considered to be environmentally “unfriendly” in the European Union. Additionally, two of these synthetic musks were withdrawn from use by the industry due to their potential health concerns [7].

Macrocyclic musks have a better biodegradability in comparison to other musk families [8]. Even though their preparation and their use were avoided because of their usually expensive manufacture, advances in synthesis have reduced production costs and the popularity of macrocyclic musks has arisen among the fragrance industry. Just between 1999 and 2001, the presence of macrocyclic musks in commodities increased from 13.5% to 61% [9]. At the beginning of the twenty first century it was foreseen that in 2008, macrocyclic musks would represent around 65% of the global musk market [2]. Still chemistry must keep developing new technologies, which include the use of “greener” oxidants (e.g. hydrogen peroxide or molecular oxygen) and are capable of improving the effectiveness of the production processes, in order to decrease the manufacturing prices of interesting materials, which are currently too expensive to be commercialized.

There are already several cases which use catalysis to improve the effectiveness of a process, *e.g.* the “one-pot”-three (Ru-catalyzed)-step synthesis of (R)-(-)-Muscone [10], also obtained by the asymmetric hydrogenation of (Z/E)-3-methyl-2-cyclopentadecenone catalyzed by the complex Ru_2Cl_4(*p*-tolyl-BINAP)$_2NEt_3$ [11] and the industrial production of 15-pentadecanolide which includes a catalytic hydrogenation with Raney nickel [12]. These cases sustain the idea of applying such a convenient tool like catalysis for the further development and/or optimization of chemical reactions for obtaining compounds with use in the fragrance industry.

On the recent years, the number of publications and patents regarding the application of new technologies for the production of macrocyclic musks indicate the increasing interest of the industry on utilizing better and more environmentally friendly approaches. Catalysis represents an interesting approach to be investigated for the aforementioned purposes.

1.2. Catalysis

The concept of *catalysis* was first used by Jöns Jacob Berzelius in 1835, when he defined it as the ability of substances “to awaken affinities, which are asleep at a particular temperature, by their mere presence and not by their own affinity” [13]. Due to its high potential, catalysis has also been defined as “molecular marriage brokers and divorce

lawyers" [14]. In the recent years, the use of catalysts has become a useful tool for industrial and academic chemists interested in obtaining high-value chemicals. A catalyst is defined as a specie that, being added to a specific reaction, increases its rate by reducing the activation energy. It is also possible that the active species involved during the reaction differ from the ones added at the beginning of the reaction (i.e. as a precursor) [15].

Catalysis can be divided in two main areas. *Homogeneous catalysis* takes place when all of the reagents, including the catalyst, are soluble in each other, forming one single and liquid phase. On the other hand, liquids, gases or mixtures of liquids and gases can react in the presence of a solid catalyst, forming two or more phases. Due to this heterogeneity, this type of catalysis is called *heterogeneous catalysis* [16].

1.3. Catalysis in fine chemistry

There is neither a universal definition nor a classification for bulk, fine and specialty chemicals. Their classification (see Table 1) can —roughly— be related to the price of production and the amount that is manufactured per year, among other factors.

Because it provides improved production processes and helps to remove unwanted and eventually toxic by-products, catalysis is a helpful tool for the production of (bulk and fine) chemicals nowadays [17].

Table 1. Fine versus bulk chemicals [19]

	Fine Chemicals	Bulk Chemicals
Price	> 5$/kg	< 5$/kg
Volume	< 10 kt/year	> 10 kt/year
Product variety	high	low
Chemical complexity	high	low
Synthesis	multi stop	few steps
Catalysis	exception	often
Raw material and energy consumption	high	low
By-products	high	low
Toxic compounds	often (e.g. phosgene)	exception
Plants	often multi product/purpose plant, usually batch	Dedicated, often continuous
Investment	low ($) high ($/kg)	high ($) low ($/kg)
Labor	high	low
Market fluctuations	high	low

In the case of the fragrance and flavor industry, both heterogeneous and homogeneous catalysis have played an important role and their influence continues to grow with time. There are several contributions of catalysis to fine chemistry like the capacity of a metal to selectively activate a certain functionality, thus rendering a more efficient, selective and faster chemical reaction. A catalyst can also make possible certain transformations, which normally would be low-yielding or would not take place at all. There is also a “green” impact when using a catalyst, as the use of stoichiometric and hazardous reactants can be avoided [18].

1.4. Oxidation reactions

Historically, oxidation in organic chemistry refers to the elimination of hydrogen or the substitution of a hydrogen bonded to a carbon for a more electronegative atom (e.g. oxygen). The interaction between organic compounds and metal complexes is fundamental for metal-catalyzed oxidations to take place. Oxidation reactions are categorized in homolytic and heterolytic, depending on the intermediates formed during the reaction [15]:

- **Homolytic oxidations:** radicals are formed and used as oxidation species during the reaction. Such oxidations usually involve the use of transition metals like cobalt, manganese, iron or copper (either as soluble salts or as oxides) and the recycling of the metal species between several oxidation states by one electron change. Free radicals are formed as intermediates from the organic substrates.
- **Heterolytic oxidations:** either an active oxygen compound or a metal ion in a high valence state is needed for the oxidation of the substrate in a two-electron transfer reaction, thus preventing the formation of radicals. It is characterized by the metal complex acting as a Lewis acid or formally undergoing two-electron changes. Free radicals are not intermediates.

Catalysis plays a very important role for promoting oxidation processes of organic basic chemicals (e.g. olefins and alcohols) to more-valuable compounds. A great source of such compounds is petroleum, from which around 90% of organic chemicals are derived. Several petrochemical processes involve catalysis and the most important ones are catalytic oxidations [15]. In most cases, a terminal oxidant is needed in combination with a catalyst, which can be either present in the same phase as the reactants (i.e. liquid-phase oxidation catalyzed by a metal salt or complex dissolved in the reaction medium) or in an additional phase formed by the solid catalyst.

1.4.1. Oxidation agents and role of green oxidants in catalysis

The chemical products which are available in our days have a positive impact in our life. However, the high amounts of waste and undesired by-products obtained during the manufacture of these products have turned into a big issue that chemists have to overcome. An interesting approach in order to minimize the formation of hazardous materials is the substitution of antiquated stoichiometric oxidants for the so-called “green oxidants” such as H_2O_2 and O_2 (to a somewhat lesser extent also TBHP and N_2O) in combination with catalysts [20]. Such oxidants do not form waste products and therefore are classified as environmentally friendly. Considering the waste products formed during an oxidation reaction, molecular oxygen (O_2) would be the ideal terminal oxidant. It has the highest active content (100%) and forms no waste or only water as byproduct. However its diradical (triplet) nature compared to the closed shell nature (*i.e.* singlet) of most organic substrates makes its reaction forbidden and consequently quite slow.

Closed shell oxidants, which are able to transfer an oxygen atom to an organic substrate, can be used to overcome this issue (eq 1):

$$S + XO \rightarrow SO + X \quad (1)$$

In such a reaction an oxygen donor XO reacts with a given organic substrate S, transferring an oxygen atom. The desired oxidized product SO is obtained together with the reduced form of the oxidation agent X used [21]. H_2O_2 is an example of such oxidants whose only co-product is water.

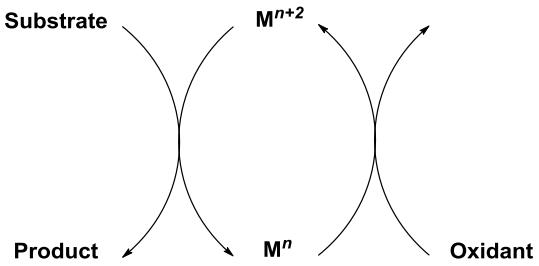


Figure 2. Oxidation with a substrate-selective redox catalyst [22]

The direct oxidation of organic substrates by either O_2 or H_2O_2 is however rare as the energy barriers for the electron transfer that takes place between the substrate and the oxidant during the reaction is usually high. For such purpose, transition metals are often used as substrate-selective catalyst (M^{n+2}/M^n) (see Figure 2). In a catalytic oxidation, the substrate is

oxidized to the target product. Subsequently, the reduced form of the catalyst is reoxidized by the stoichiometric oxidant [22].

There are two interesting types of reactions that use H_2O_2 as an oxidation agent. One of them is the decomposition of hydrogen peroxide to singlet oxygen ($^1O_2$), catalyzed by metal species such as W^{VI}, Mo^{VI} and La^{III} [23,24]. The second one is the epoxidation of alkenes using homogeneous and heterogeneous catalysts. Among the benefits regarding the use of H_2O_2 one can name (a) the high active oxygen content (47%, calculated from the O atom that can be delivered per molecule), which can be used to oxidize organic molecules, b) its availability (global production capacity in 2002 considering 100% H_2O_2 was estimated to be 2.8×10^6 t/a, excluding China) for an affordable price (<0.7 US dollar per kg) and in addition (c) it only generates water as a by-product [25]. For these reasons, the formation of epoxides via metal-catalyzed oxidations using hydrogen peroxide as terminal oxidant is one of the greenest and most elegant ways for the production of such compounds [26]. The direct epoxidation of propene with H_2O_2 is an interesting example of the usefulness of hydrogen peroxide. In 2008, Evonik started the titanium silicalite-1-catalyzed epoxidation of propene with a capacity of 100,000 ton per year. BASF and Dow started a plant based on similar technology for the same purpose and with a capacity 3 times higher a year later [27].

Among the drawbacks that could be named for H_2O_2 are its decomposition to molecular oxygen and the extra cautions that must be taken during its handling, storage and use as an oxidation agent (the high oxygen content (47 wt%) is not only available for partial oxidations but also for combustion reactions). In this sense, molecular oxygen would be a safer choice.

The use of molecular oxygen as terminal oxidant represents a great advantage for industrial processes and reactions carried out in a laboratory. “Chemical oxidase” reactions are of particular interest for the development of new aerobic oxidation methods [28,29]. In these processes molecular oxygen is used as a two-electron/proton acceptor and the oxygen atoms are afterwards released as water or hydrogen peroxide, hence no oxygen atom originated from molecular oxygen is transferred to the substrate during the reaction. An example of a “palladium oxidase” reaction is the Wacker oxidation, one of the first processes to use molecular oxygen as the terminal oxidant in the oxidation of ethylene to acetaldehyde.

1.5. Phase-transfer catalysis

Between 1960 and 1970 Makosza reported several reactions in biphasic mixtures and in the presence of triethylbenzylammonium chloride as catalyst [30-32] but it was in 1971 when the term “phase-transfer catalysis” was introduced by Charles Starks to explain that catalytic

amounts of a tetraalkylammonium or phosphonium salts (Q^+X^-) were needed for a reaction between two substances located in two immiscible phases to take place. He discovered that the transport into the organic phase of compounds such as inorganic anions, acids, H_2O_2 and ammonia was possible by the use of such salts and thus opened a new area in the field of catalysis [33] now known as phase-transfer catalysis. Nowadays several chemicals (> 6500) [34] are manufactured using this method, although it is mainly used for the production of fine chemicals. PTC is mostly suitable for reactions, where a substrate is found in an organic phase and one or more reactants in the aqueous phase.

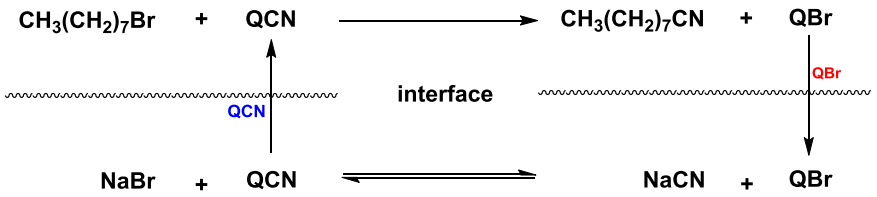


Figure 3. Catalytic displacement of cyanide on 1-bromooctane mediated by a PTC reported by Starks [33]

Arne Brändström stated that phase-transfer catalysis involves the transport of an anion into an organic layer by use of an “anion counter ion” or complexing agents and the reaction of the anion within the organic layer with the substrate. This transfer usually occurs rapidly in comparison to the rest of the reaction [35]. PTC has several special advantages over other procedures, *e.g.* [36]:

- Occurrence of reactions that normally would not take place in homogeneous media.
- Modification of selectivity and product ratio.
- Increase of yield through the suppression of side reactions.

Reactions that involve the transfer of species from one phase to the other might have been performed even earlier. However, this tool is still used nowadays and remains to be the solution for a set of reactions.

1.5.1. Quaternary ammonium salts as PTCs

Of the many possible phase-transfer catalysts, quaternary ammonium salts are widely used. Some of the beneficial factors when using such salts include their reactivity, ability to induce selectivity, easy separation from the product, cost, low toxicity and availability [37].

However, a phase-transfer catalyst, which gives excellent yields for a specific reaction, can have low or no reactivity for similar reactions. Landini et al. intensively studied the effect of

anions as a function of the structure of catalyst in heterogeneous mixtures and concluded that the effectiveness of a phase-transfer catalyst strongly depends on its organophilicity (i.e. ability of extracting species from the aqueous to the organic phase) “with other structural factors being much less important” [38]. Another study carried out by Halpern et al. revealed a strong influence of the number of methyl groups and alkyl chains present in the ammonium salts for the alkylation of deoxybenzoin [39]:

Table 2. Dependence of conversion on the PTC structure [39]

Number of carbons	Cation formula	Chains[a]				Conversion[b] [%]
4	$(CH_3)_4N^+$	1	1	1	1	21
10	$(C_4H_9)N^+(C_2H_5)_3$	2	2	2	4	100
16	$(C_4H_9)_4N^+$	4	4	4	4	54
25	$CH_3N^+(C_8H_{17})_3$	1	8	8	8	67
72	$(C_{18}H_{37})_4N^+$	18	18	18	18	16

[a]Number of carbons on each alkyl chain bonded to the N atom of the quaternary salt, [b]after 30 minutes.

The cation of a quaternary ammonium salt basically consists of two parts, the hydrophilic “head” formed by the nitrogen atom and the hydrophobic “tails” consisting of the different alkyl chains bonded to it. Sirovski stated that small, highly hydrophilic cations are located mainly in the aqueous phase, whereas large cations are likely to be found in the organic phase [40].

Quaternary ammonium salts are usually inert under phase- transfer conditions and are applied as phase-transfer catalysts for several reasons:

- The length of the alkyl chains that surround the N atom of the ammonium salt can vary and influence the lipophilicity of the cation (see Figure 4). This has a direct influence in the reaction rate since a symmetrical quaternary ammonium salt with relative long alkyl chains can isolate the nitrogen cationic (hydrophilic) center.
- The bulkiness of the catalyst could also reduce the concentration of nitrogen atoms close to the interface. The exchange of alkyl chains for methyl groups can give the catalyst an unsymmetrical character.

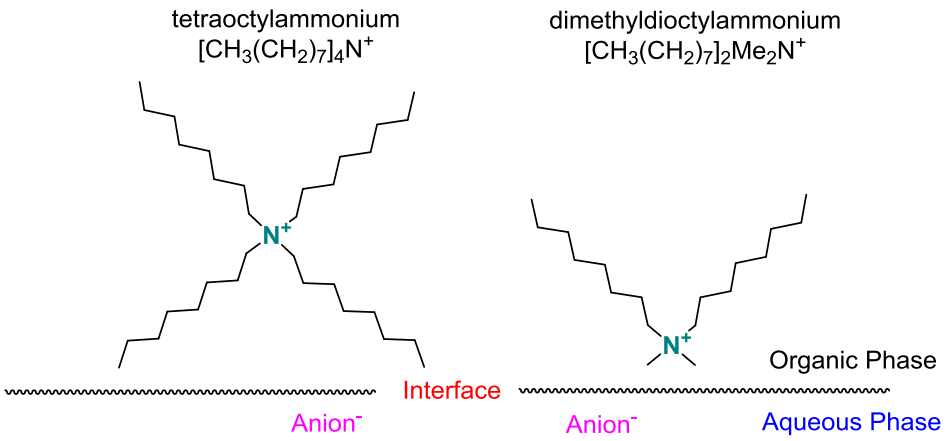


Figure 4. Effect of alkyl chains and methyl groups of an ammonium salt [41]

Each reaction under phase-transfer conditions has several factors (e.g. structure of the phase-transfer catalyst, anion of the phase-transfer catalyst) that must be individually studied in order to find the best catalytic system an optimal process.

1.5.2. Role of the anion of the quaternary ammonium salt

The exchange of the anion of a quaternary ammonium salt [Q^+X^-] present in an organic phase with the anion of a NaY aqueous solution has been studied repeatedly [42,43]. A study for a toluene/water heterogeneous solution was performed creating the following results [44] (from lipophilic to hydrophilic):

$$ClO_4^- > I^- > NO_3^- > C_6H_5CO_2^- > Br^- > Cl^- > HSO_4^- > HCO_3^- > CH_3CO_2^- > F^- > OH^-$$

The same order of lipophilicity is usually observed for tetraphenylphosphonium, arsonium and triphenylsulfonium cations in combination with the anions mentioned. An important aspect to consider is that anions of di- or tribasic acids are more difficult to extract than its related hydrogen monobasic anion when cations with short alkyl chains like tetrabutylammonium$^+$ are used. In this case, a hydrogen sulfate anion would be extracted easier than the sulfate anion.

This conclusion can be used when an ammonium salt must be chosen for a specific reaction. In this case, small- to medium-sized cations together with hydrogen sulfates would become quite useful for PTC.

1.5.3. Epoxidation of olefins under phase-transfer conditions

Epoxides are valuable intermediates for the manufacture of fine and bulk chemicals and the demand for such processes is high. Recently, the use of greener oxidants (*e.g.* H_2O_2 and TBHP) has increased, as the handling of organic peracids is more problematic and expensive. Direct epoxidation of alkenes by H_2O_2 was achieved in the past by means of catalysts based on Ti, Re, Mo and W [45-48].

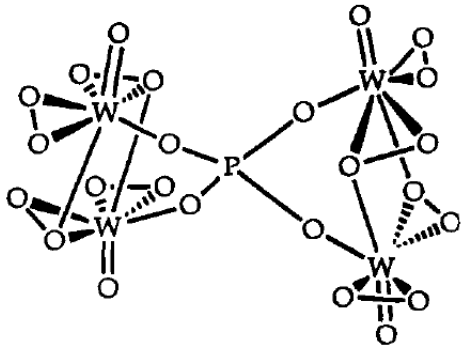


Figure 5. The $PO_4[W(O)(O_2)_2]^{3-}$ anion appears to be the active species in the epoxidation of olefins using $H_2O_2/WO_4^{2-}/PO_4^{3-}$ under phase-transfer conditions [49]

The epoxidation of olefins that use H_2O_2 as oxidation agent under phase-transfer conditions was developed by Venturello [50] (involving the usage of both phosphate and tungstate) and Ishii [51] (involving heteropolyacids). In the aqueous phase, the precursor (or precursors) reacts with H_2O_2 and forms the active specie (see Figure 5). The peroxotungstophosphate anion is transferred into the organic phase by a quaternary ammonium salt, where the organic substrate resides and the reaction takes place. After this, the reduced anion is again transferred into the aqueous phase, where it is once again activated by H_2O_2.

The formation of the active species responsible for the epoxidation was investigated by Aubry et al [49,52]. It is stated that either tungstic acid (H_2WO_4) with PA or tungstophosphoric acid ($H_3[PW_{12}O_{40}]$) together with H_2O_2 can be used to form the anion (Figure 5). The extraction of the anion from the aqueous into the organic phase using a PTC, in this case tetrabutylammonium chloride, was also successful. Duncan et al [53] carried out a series of interesting experiments to identify which species are required for olefin epoxidation. Following Ishii's process $H_3[PW_{12}O_{40}]$ was titrated with *n* equivalents of H_2O_2 and the formation of $PO_4[W(O)(O_2)_2]^{3-}$ was monitored using ^{31}P NMR. Solutions with a ratio of $[H_2O_2]/[H_3[PW_{12}O_{40}]]$ above 15 were needed for $PO_4[W(O)(O_2)_2]^{3-}$ to generate and no epoxide was produced until the concentration of the active species was appreciable.

The anion originally present in the phase-transfer catalyst has also an influence on the yield of the epoxides under phase-transfer conditions. Venturello's procedure [54] using a catalytic system composed by sodium tungstate together with phosphoric acid and Aliquat 336 was able to oxidize terminal and internal olefins. Noyori et al. [55] improved the yields in the epoxidation of terminal olefins by using a similar catalyst system formed by sodium tungstate, aminomethylphosphonic acid (AMPA) and methyltrioctylammonium hydrogensulfate (same cation as Aliquat 336) instead of Aliquat 336 as PTC. According to Noyori, the use of a PTC with hydrogensulfate instead of chloride as anion and the addition of AMPA is crucial for catalytic activity towards olefinic substrates. PhPA or even PA can be used for the reaction to take place. Using ^{31}P NMR spectroscopy, it was found that large amounts of the phosphonic acid are decomposed to PA under the reaction conditions, which means that the role of the acid is still unclear.

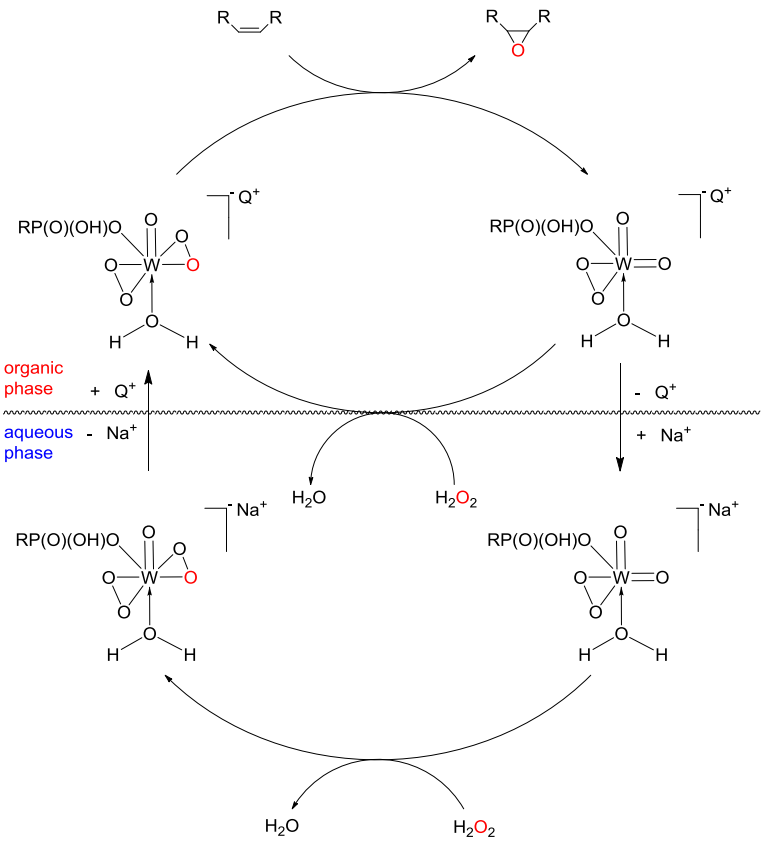


Figure 6. Catalytic cycle of epoxidation proposed by Noyori [55]

Although the aforementioned and similar systems have been used for the epoxidation of linear (terminal and internal) and model cyclic olefins like cyclopentene [56], cyclohexene and cyclododecene [57], few has been done for bigger unsaturated rings like CHDD. In a work reported by Lewandowski et al. [58], (*Z,E,E*)-1,5,9-cyclododecatriene (CDT) was oxidized under phase-transfer conditions using Ishii's method: Aliquat 336 as PTC and $H_3PW_{12}O_{40}$ to form the species responsible for the epoxidation. In this work, no solvent was needed to obtain the monoepoxide. The influence of different factors like stirring speed and molar ratio of the substrate and H_2O_2 were studied and the conditions were optimized for the formation of the monoepoxide. In all cases the target product was found and the selectivity to the monoepoxide started to decrease once the conversion of CDT increased. The consecutive epoxidation of CDT could not be circumvented, as the diepoxide 1,2,5,6-diepoxycyclododecene was mostly found as a by-product.

Since the basis of phase-transfer catalysis was set, and since the discovery of the Venturello and Ishii's catalysts, numerous similar systems have been developed for the epoxidation of olefins using H_2O_2 as oxidant. Still, the effort has been focused on the oxidation of model molecules and less has been done using bigger cyclic olefins with more than one unsaturation in their structure. Their selective oxidation to obtain the monoepoxide under phase-transfer conditions for the preparation of fine chemicals remains still a challenge.

1.6. Wacker oxidation

The Wacker oxidation is a well-established process, which converts α-olefins into the corresponding methyl ketones. Phillips discovered in the late 1800s an oxidation related to palladium and olefins [59]. However, it was in 1958 when Smidt and his co-workers truly developed the oxidation of ethylene on an industrial scale to obtain acetaldehyde using $PdCl_2$ and copper(II) chloride as the catalyst system and oxygen as the terminal oxidant for the reoxidation of the catalyst (see Figure 7). The Wacker process yielded a mixture of products containing acetaldehyde (approximately 95%) plus acetic acid (2%), carbon dioxide (1%) and chlorinated compounds (1%) [15].

The big discovery behind this reaction was the catalytic system, in which the reduced Pd^0 is reoxidized by Cu(II) and in turn Cu(I) is readily oxidized to Cu(II) by oxygen present in air [60].

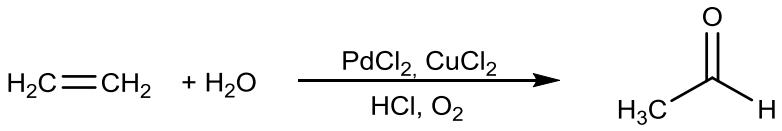


Figure 7. Wacker process developed by Smidt and co-workers [15]

Palladium belongs to the group of the so-called “noble metals” and has its outermost shell (4d) completely filled. It is not easily oxidized, being more stable as Pd^0 than as Pd^{2+} [61]. Therefore, its oxidation from Pd^0 to Pd^{II} is not easy and that it does take place in combination with copper (see Figure 8) seems to be an exception. Since the discovery of the Wacker process, palladium chemistry has progressed rather quickly and many reactions involving palladium compounds have been discovered. Being one of the first homogeneous catalytic systems to be industrially implemented, it encountered difficulties when it was tested for the oxidation of higher olefins.

For the Wacker oxidation to be used in the oxidation of longer terminal olefins, pure or mixed organic solvents can be used. In most cases, the formation of the methyl ketone instead of the aldehyde is favored.

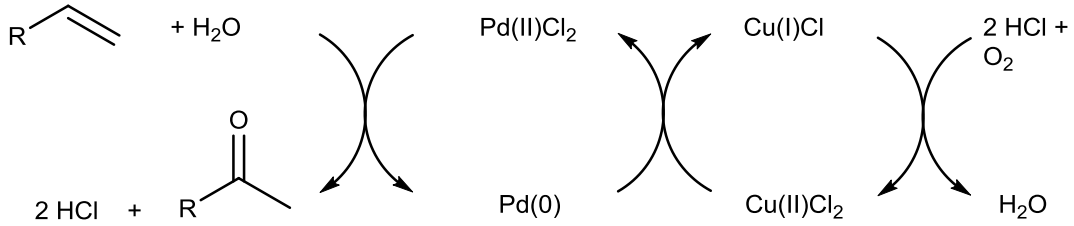


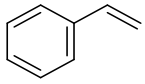
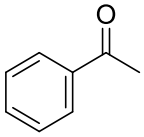
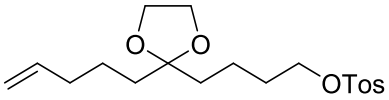
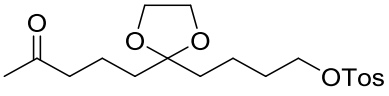
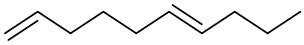
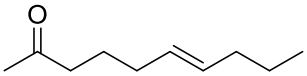
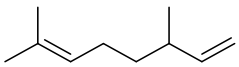
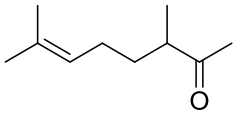
Figure 8. Catalytic cycle of a Wacker-type oxidation of olefins

Terminal olefins can also be seen as masked methyl ketones and can be really useful in organic synthesis. They are also stable under acidic and basic conditions and also inert to nucleophiles. The presence of functional groups (e.g. aldehyde, carboxylic acid, ester, alcohol, ether, acetal, chloride, bromide, sulfonyl, ester and sulfone) at suitable positions is, in principle, not an impediment for a terminal olefin to be oxidized via a Wacker oxidation when the conditions are mild. The reaction with functional groups such as acetal hydrolysis or oxidation of alcohols usually takes longer than the oxidation of the double bond [62].

Some examples, in which terminal olefins were oxidized under the Wacker oxidation conditions and with retention of the functional group, are shown on Table 3. Interesting is the case of 3,7-dimethylocta-1,6-diene **(7)**, which yielded only traces of the target ketone **(8)** [64].

The success of the Wacker process greatly increased the interest of chemists to study similar reactions involving the use of homogeneous catalysts. Nevertheless, internal olefins are roughly oxidized under such reaction conditions.

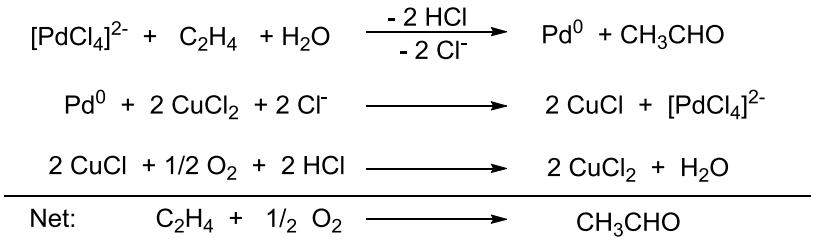
Table 3. Palladium-catalyzed selective oxidation of terminal olefins with functional groups to methyl ketones

Substrate	Product	Yield (%)	Ref.
 **1**	 **2**	63	[62]
 **3**	 **4**	70	[63]
 **5**	 **6**	78	[62]
 **7**	 **8**	traces*	[64]

* (-)-α-terpineol and a Pd π-allyl complex were formed in similar ratios

1.6.1. Mechanism of the Wacker process

Since its establishment, the mechanism concerning the Wacker process has been a matter of debate. The individual reactions of the Wacker process are shown in Scheme 1.



Scheme 1. Individual reactions of the Wacker process [65]

The majority of research on the Wacker mechanism has focused on identifying whether the reaction proceeds via a rate-limiting intramolecular *cis* attack (*syn*) of a Pd-bound olefin or via an equilibrium *trans* (*anti*) attack by H_2O, followed by rate-limiting chloride ion dissociation (see Figure 9). Bäckvall and co-workers stated that the nucleophilic attack occurs in an *anti* fashion followed by the rate-limiting chloride ion dissociation [66]. However, their kinetic analyses were done under high [Cl^-], which critics believe skewed the results [67]. Henry, considered an *anti* nucleophilic attack possible [68]. Nevertheless, he later supported a *syn* mechanistic pathway [69], in which the rate determining step is the intramolecular attack of OH^- to the double bond. Under the low [Cl^-] employed by Henry and co-workers, dissociation of two chloride ions is proposed, followed by binding of 1 equiv. of water and olefin, leading to an intramolecular *syn* attack. This assertion has been corroborated by Nelson and co-workers [70].

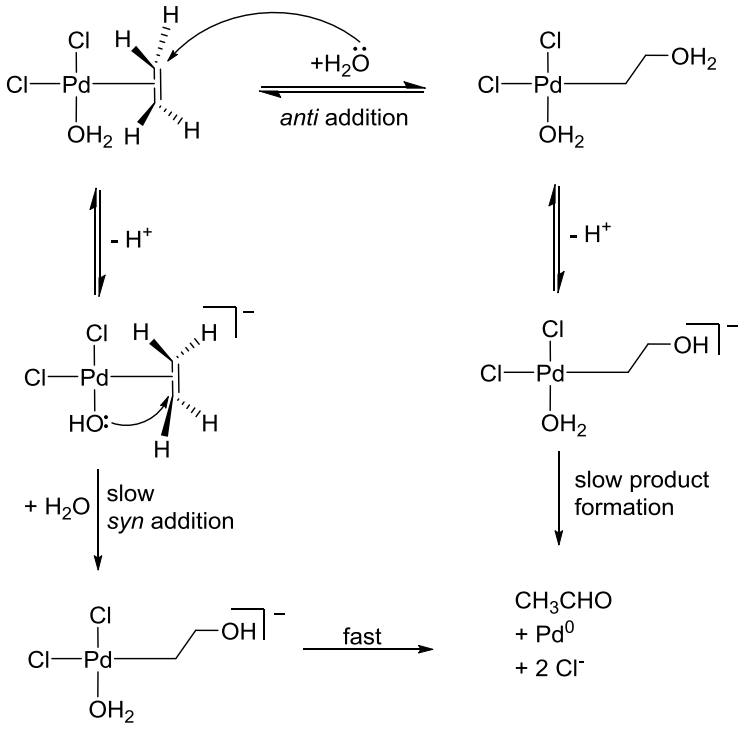


Figure 9. The two originally postulated reaction schemes for the Wacker ox. of ethylene [65]

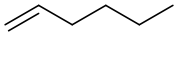
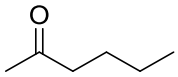
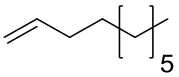
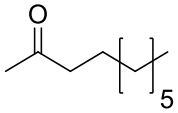
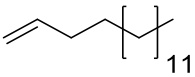
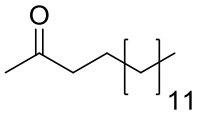
Unfortunately, an important factor omitted in these mechanistic studies is the role of Cu^{II}. Since the development of the Wacker process, it has been assumed that the main role of copper is to facilitate the reoxidation of Pd^0. However, this assumption has been put into question based on the isolation of Pd/Cu bimetallic species, which was found to be a competitive catalyst in the oxidation of 1-decene under aqueous aerobic conditions [71].

Therefore, the assumed active catalyst species in the mechanistic studies of Wacker oxidations using $PdCl_2$,$CuCl_2$ and DMF might be inaccurate.

1.6.2. Wacker-type oxidation of terminal and internal olefins

Since internal olefins are inert under normal Wacker conditions, isomerization of the terminal double bond can lead to a lower yield of the corresponding methyl ketone [72]:

Table 4. Oxidation of α-olefins under Wacker oxidation conditions [72]

Substrate	Catalyst and oxidant	Product	Yield (%)
 **9**	$PdCl_2/H_2O/CuCl_2/O_2$	 **10**	95
 **11**	$PdCl_2/H_2O/CuCl_2/O_2$	 **12**	92
 **13**	$PdCl_2/H_2O/CuCl_2/O_2$	 **14**	88

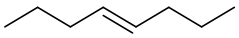
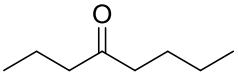
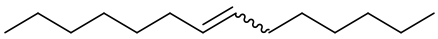
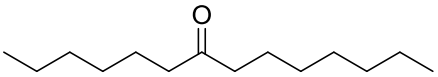
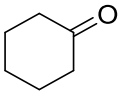
The Wacker oxidation system has been inevitably limited to the oxidation of terminal olefins [73]. This limitation arises because the oxidation of internal and cyclic olefins under the usual conditions is extremely slow and shows limited selectivity. The rate of the oxidation can also decrease due to steric hindrance. Even model molecules (e.g. cyclopentene, cyclohexene and cyclooctene) were hardly converted into the corresponding cyclic ketone. Therefore, the original Wacker reaction system has been modified. For example, palladium(II)sulfate and a heteropolyacid ($H_3PMo_6W_6O_{40}$) as reoxidant in aqueous DMF yielded 85% cyclohexanone [62].

A system composed of $Pd(OAc)_2$ and $Cu(OAc)_2$ was used for the Wacker-type oxidation of CDT, a scarce example for the application of a larger cyclic unsaturated compound. To overcome the difficulty of the low solubility of cyclic olefins in water, methanol was used as solvent. This resulted in a mixture of products consisting of ketones and ethers even at a relatively low conversion (33%). It was also found that, besides the oxidation, isomerization

of the double bond and coupling reactions of the cyclic triene compete in alcoholic solvents [74].

Kaneda and his collaborators discovered a copper-free oxidation system formed by $PdCl_2$ and DMA that catalyzes the Wacker-type oxidation of terminal and internal olefins into the corresponding ketones using O_2 as oxidant [75]. The use of DMA as solvent seems to play an important role in the stabilization of Pd^0 species during the catalytic cycle. Although DMF has been successfully used for the Wacker-type oxidation of higher α-olefins, it did not work for Kaneda's system. On the other hand NMP, a lactam, showed a somewhat lower activity. Some examples of internal olefins are shown in Table 5. The formation of the ketone in the presence of other functional groups (e.g. alcohol, nitrile and ether) was also possible under these conditions. It was demonstrated by using labeled water $H_2{}^{18}O$ that the oxygen atom incorporated into the product comes from water and not from molecular oxygen, just like with the traditional Wacker system. An oxygen pressure above 3 bar was necessary to prevent the precipitation of inactive palladium "black" [73].

Table 5. Wacker type oxidation of internal and cyclic olefins reported by Kaneda et al.[73]

Substrate	t (h)	X (%)	Product	Yield (%)
 **15**	10	91	 **16**	91
 **17**	20	81	 **18**	81
 **19**	10	85	 **20**	73

Although several internal olefins were converted into the corresponding ketone, different reaction conditions were needed for the reaction to take place. In the case of cyclohexene, a model molecule usually used for testing catalytic systems, 20 mol% of the catalyst was needed and allylic oxidation also took place, yielding a mixture of cyclohexanone and 2-cyclohexen-1-one with an 8.5:1.5 ratio, respectively.

This catalytic system has already been successfully applied for the oxidation of other internal olefins with other functionalities such as methyl esters in the oxidation of methyl oleate

(methyl-Z-9-octadecenoate). Full conversion was obtained with a $PdCl_2$ loading of 2.5mol% and an oxygen pressure of 10 bar at 70ºC after 24 hours. The reaction can also be performed using 50 bar synthetic air, which corresponds to a partial oxygen pressure of 10 bar [76].

Sheldon and coworkers discovered a catalytic system that allows the direct O_2-coupled Wacker-type oxidation of terminal olefins in water [77]. The strategy followed was to eliminate the need of high concentrations of Cu(II) and Cl^-, typically present under Wacker conditions [78-80], by using a bathophenanthroline (BPhen) disulfonate palladium(II) complex (see Figure 10). The incorporation of the sulfonate groups in the ligand is essential for the solubility of the catalyst in aqueous media [81]. The ligand is supposed to stabilize the reduced formed of palladium during the catalytic cycle and decrease the redox potential of Pd^{II}/Pd^0. The catalyst was prepared by stirring $Pd(OAc)_2$ in presence of the ligand (1 equiv.) in water. The oxidation was carried out in an autoclave pressurized with 30 bar air and heated to 100°C for 10 h. Although the complex shows complete selectivity for methyl ketones, the conversion decreases with higher olefins: $X_{1\text{-pentene}} = 50\% > X_{1\text{-hexene}} = 48\% > X_{1\text{-octene}} = 25\%$.

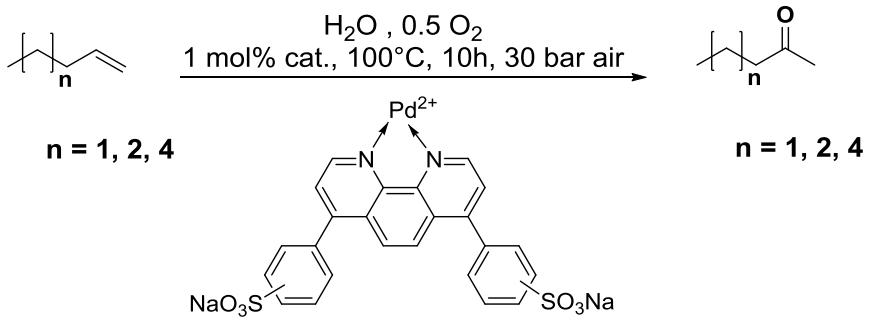


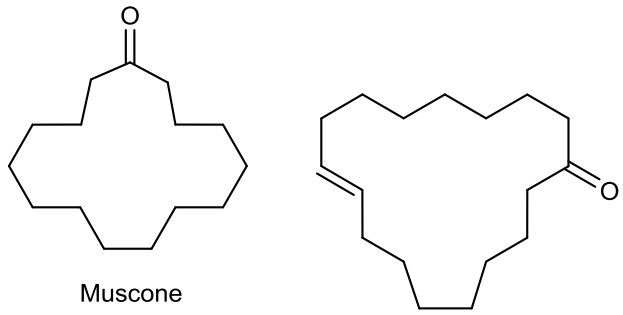
Figure 10. Direct O_2-coupled Wacker-type oxidation with a water-soluble ligand discovered by Sheldon and coworkers [82]

Such water-soluble complex and the palladium(II) complex of neocuproine have also been used for conversions of alcohols to ketones [83,84] in water.

1.7. Musk scents in the fragrance industry

Musk compounds are used in the fragrance industry because of their characteristic odor but also due to their ability to fix other more volatile compounds. One characteristic of these compounds is their high boiling point, which delays the evaporation of lower-boiling compounds when used in a perfume blend [85].

Originally, musk components were extracted from the anal glans of animals (*e.g.* muscone from the musk deer and civetone from the civet cat, see Figure 11) and from plant sources (*e.g.* trade names Exaltone®, Exaltolide® and Ambrettolide®). Today such methods are forbidden due to ethical and economic reasons and compounds with musk scent must be synthesized. Several musks "families" (see Figure 12), which are classified depending on their structure, have been developed by chemists. Nitromusks were discovered in 1888 by Baur during his work concerning the alkylation of trinitrotoluene (TNT). After this first discovery, he prepared analogue molecules with different odor which were used in the industry until the middle of the twentieth century. During this time, the structure of musks obtained from natural sources had not yet been elucidated.



Muscone

Civetone

Figure 11. Musk compounds extracted from animal sources

Because of their difficult preparation and phototoxicity [86,87], nitro musks slowly became obsolete and some of them have even been banned by the European Parlament [88]. Apart from nitro musks, polycyclic and macrocyclic musks were discovered and developed. Galaxolide and Tonalide are polycyclic musks, which have been widely used since their discovery. Among the advantages of polycyclic musks are their characteristic odor and relative cheap price (US$ 15-20/kg) However, studies have demonstrated their low biodegradability and tendency to accumulate in bio-organisms and in the environment [89,90], causing big concern.

These properties differ from the ones of the now widely utilized macrocyclic musks, which are found in natural sources and are readily biodegradable. Moreover, new synthetic methods have facilitated the preparation of macrocyclic compounds [85], although their high preparation cost represents a big drawback [91]. The odor of macrocyclic musks is determined by their functional groups (e.g. ketones, lactones and double bonds) and their structure. Correlations between structure and odor have been made and structural

differences such as the presence or absence of a double bond were found to play an important role in the odor's quality [92].

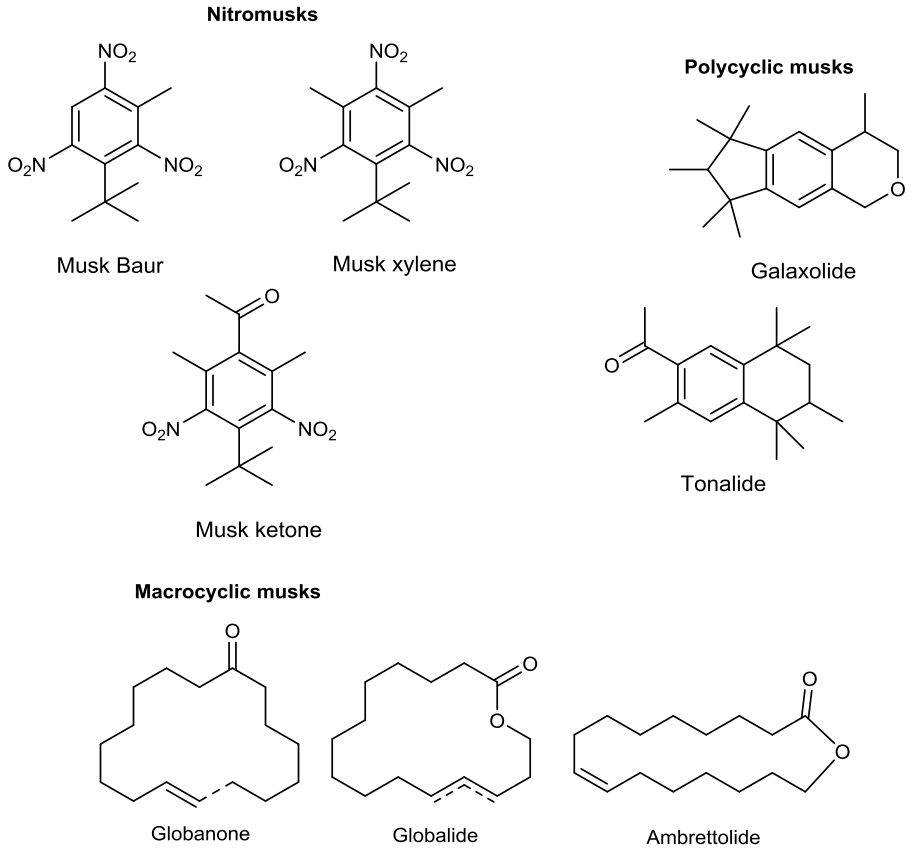
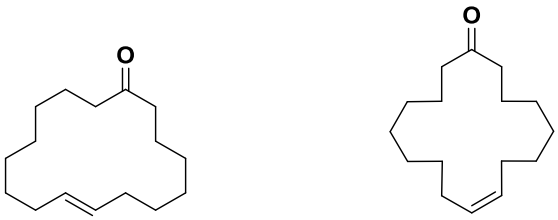


Figure 12. Types of musks used for the fragrance industry

In the future it is expected that affordable preparation processes plus their environmentally friendly properties will favor the exclusive use of macrocyclic musks in the industry [88].

1.8. Globanone® - (Z/E)-8-cyclohexadecenone

8-CHD (see Figure 13) is a member of the so-called macrocyclic musk family with the chemical formula $C_{16}H_{28}O$. It is a viscous, colorless to slightly yellow liquid with an elegant, fine, musk odor with a sweet-powdery nitro musk undertone and balsamic, tobacco shades [93]. Both the *cis*- and *trans* isomers of 8-CHD have been identified as minor constituents of the glandular secretions of the civet cat.



***E*-8-cyclohexadecenone** ***Z*-8-cyclohexadecenone**

Figure 13. isomers of 8-cyclohexadecenone. Its mixture is commercialized by Symrise under the name Globanone®

Its excellent stability and long-lasting properties make it suitable for a wide range of applications, especially for fine fragrances, personal care and for fabric care perfumes [93]. It can also be used to prepare (Z,E)-7-cyclohexadecen-1-one when reacted in the presence of a suitable catalyst (e.g. a Brønsted acid or a catalyst containing a metal from the VIII group). The mixture of both (E,Z)-7-cyclohexadecen-1-one and 8-CHD isomers is commercialized under the trade name Aurelione® by Symrise [94]. 8-CHD can also be used as substrate for the preparation of 7,9-cyclohexadecadien-1-one and similar derivatives (e.g. 8-cyclohexadecynone) with potential application in the fragrance industry [95].

In 1932, Leopold Ruzicka was the first to synthesize 8-CHD from the yttrium salt of 7-pentadecenedicarboxylic acid when he was investigating the properties of unsaturated 16- and 18-membered carbon rings [96,97]. Stoichiometric, highly toxic oxidants (e.g. sodium dichromate, chromic sulfate) have been also used in the past for the preparation of 8-CHD. Wideman reported the synthesis of 8-cyclohexadecen-1-one via monohydroboration of CHDD and subsequent oxidation using chromic sulfate [98]. Mookherjee et al. prepared 8-cyclohexadecen-1-one by monoepoxidation of CHDD using a peracid and subsequent rearrangement to the cyclic alcohol using $LiAlH_4$. The hydroxyl group was then further oxidized into ketone using the stoichiometric oxidant sodium dichromate $Na_2Cr_2O_7$ [99]. This method was also used by Warwel et al. to prepare 8-CHD. The novelty of this procedure was the preparation of CHDD via a metathesis catalyzed by a heterogeneous Re(VII) catalyst supported on alumina [100]. 8-CHD can also be manufactured through the selective monoepoxidation of CHDD [99] and subsequent rearrangement of the oxirane ring to the corresponding ketone. The starting material, CHDD, is prepared from two molecules of Z-cyclooctene by a metathesis reaction [93].

2. Objectives

The purpose of the present work was to study two different reaction pathways for the preparation of (Z/E)-8-cyclohexadecenone (trade name: Globanone®, 8-CHD) starting from the macrocyclic diene (Z/E)-1,9-cyclohexadecadiene. Of special interest were the use of suitable catalysts or catalytic systems and the application of the "so-called" green oxidants: hydrogen peroxide and/or molecular oxygen. For an easier explanation, a scheme of the two approaches followed in the present thesis is shown in Figure 14.

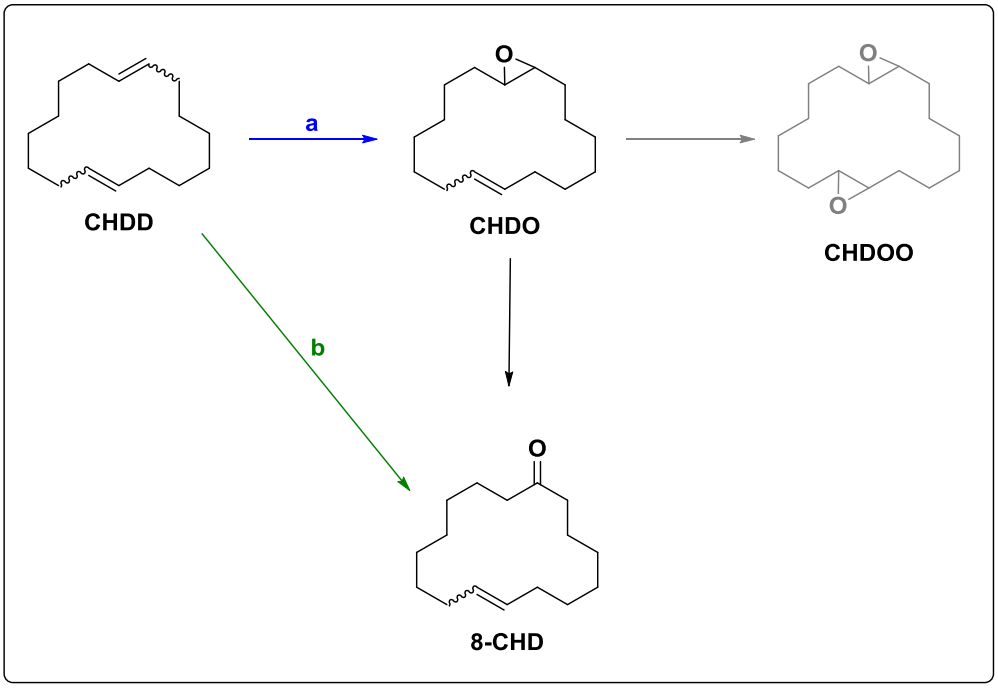


Figure 14. Approaches studied in the present work for the preparation of (Z/E)-8-cyclohexadecenone (8-CHD)

The first approach to be investigated was the selective monoepoxidation of CHDD (Figure 14, a). For this purpose a catalyst system combining a polyperoxotungstate and a quaternary ammonium salt as phase-transfer catalyst should be used. The peroxotungstophosphate was formed "*in situ*" by stirring together phosphoric acid and a tungsten^{VI} precursor, in this case sodium tungstate, in water. The addition of H_2O_2 enables the catalytic reaction to take place, as it acts as oxidant for the formation of the peroxotungstophosphate species. The use of a phase-transfer catalyst which transports the active catalytic species was also a necessity, as CHDD resides in an additional organic phase formed by the substrate itself and toluene. A major drawback of this process is the inevitable formation of the diepoxide as a result of the oxidation of the second double bond present in CHDO; this reaction is also catalyzed by the active peroxotungstophosphate species. In an attempt to maximize the yield of CHDO, the

catalyst system (both the peroxotungstophosphate and the phase-transfer catalyst) were modified; other suitable phosphorus-containing compounds replacing phosphoric acid (e.g. aminomethyl-, hydroxymethyl- and phenylphosphonic acid such as two different phosphinic acids) were used to prepare the peroxotungstophosphate. The screening of several anions and cations forming the phase-transfer catalyst was also done. Finally, the effect of these combinations on the selective monoepoxidation of CHDD using H_2O_2 as oxidant was evaluated. It is important to clarify that the rearrangement (or opening) of the oxirane ring of the monoepoxide into the desired ketone was not investigated in this thesis.

The second approach should check the possibility of a single-step reaction catalyzed by palladium(II) complexes (Figure 14, b). The Wacker oxidation is a well-established industrial process for manufacturing acetaldehyde from ethylene using $PdCl_2$-$CuCl_2$ as catalytic system and O_2 as final oxidant. However, when internal and cyclic olefins were treated under the same conditions, no formation of the corresponding ketone was observed. In the recent years, elegant strategies such as the use of ligands, additives and a number of different solvents have been used for obtaining similar results as in the Wacker process. The advantage of these new approaches is that, in most cases, the O_2-coupled reaction without the need of additional co-oxidants is possible. Although these strategies successfully oxidize internal linear olefins into the corresponding internal ketones, cyclic olefins still remain a difficult challenge. The target of this approach is to obtain as much of the 8-CHD as possible, avoiding the loss of CHDD to undesired by-products.

3. Experimental Part

3.1. Preparation of phase-transfer catalysts and $[(C_8H_{17})_3NCH_3)]_3[(PO_4(W(O)(O_2)_2)_4)]$

In this section, the methods followed for the preparation of three phase-transfer catalysts and the $[(C_8H_{17})_3NCH_3)]_3[(PO_4(W(O)(O_2)_2)_4)]$ complex is presented. These phase-transfer catalysts and the complex were used in the epoxidation of CHDD under phase-transfer conditions.

3.1.1. Anion exchange of methyltrioctadecylammonium bromide with sulfuric acid

Into a 250 mL three-necked round-bottom flask, 1.26 g (2 mmol) of methyltrioctadecylammonium bromide was weighted and dissolved in 50 mL of toluene. To this solution, 50 mL of a H_2SO_4 49wt% solution was added. The heterogeneous mixture obtained was vigorously stirred overnight at room temperature. On the next day, the stirring was stopped and the phases were separated. The aqueous phase was tested for residual halide with an $AgNO_3$ aqueous solution, prior acidification with HNO_3. Halide was still detected. Therefore, the organic phase was washed with deionized water again until no traces of acid were found and then a new charge of 50 mL of a H_2SO_4 49wt% solution was added. The heterogeneous mixture was vigorously stirred overnight at room temperature. On the next day, the phases were separated. The aqueous phase was once again tested with an $AgNO_3$ aqueous solution. This time, silver bromide did not precipitate. The organic phase was washed with deionized water until it was free of acid. Afterwards it was concentrated under reduced pressure to obtain a white powder. The compound obtained was denominated as **PTC-C**.

Elemental analysis: $C_{55}H_{115}NO_4S$ (886.59): theoretical: C 74.51%, H 13.07%, N 1.58%,S 3.62%; found C 74.66%, H 13.42%, N 1.95%, S 3.43%

3.1.2. Anion exchange of dimethyldioctadecylammonium bromide with sulfuric acid

The same procedure as the one described in section 4.1.1 was followed. The following starting materials were used: 1.74 g (2 mmol) of dimethyldioctadecylammonium bromide, 50 mL of toluene and 50 mL of a H_2SO_4 49wt% solution (twice). The compound obtained was denominated as **PTC-D**.

Elemental analysis: $C_{38}H_{81}NO_4S$ (648.13): theoretical: C 70.42%, H 12.60%, N 2.16%,S 4.95%; found C 74.46%, H 13.07%, N 2.21%, S 4.09%

3.1.3. Anion exchange of tetraoctadecylammonium bromide with sulfuric acid

The same procedure as the one described in section 4.1.1 was followed. The following starting materials were used: 2.22 g (2 mmol) of tetraoctadecylammonium bromide, 50 mL of toluene and 50 mL of a H_2SO_4 49wt% solution (twice). The compound obtained was denominated as **PTC-E**.

Elemental analysis: $C_{72}H_{149}NO_4S$ (1125.05): theoretical: C 76.87%, H 13.35%, N 1.25%,S 2.85%; found C 76.80%, H 13.62, N 1.27%, S 3.25%

3.1.4. Preparation of $(C_8H_{17})_3NCH_3)_3(PO_4(W(O)(O_2)_2)_4)$ complex

The preparation of the peroxo complex, first reported by Venturello, is based on the method described in the literature [101]:

2.5 g of tungstic acid (10 mmol) was treated with 4 mL of hydrogen peroxide 50wt% (70 mmol), heated to 60°C and stirred until a colorless solution was obtained. The solution was then filtered and a PA solution (ca. 2.5 mmol) was added. The solution was stirred for 30 min and diluted to 30 mL with deionized water. To the obtained solution, 2.10 g of methyltrioctylammonium chloride (ca. 5 mmol) in toluene (40 mL) was added dropwise with vigorously stirring for 10 minutes. The solution was stirred for another 10 minutes before the two phases were separated. The aqueous phase was discarded and the isolated organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. A slightly yellow syrup-like product was obtained.

Elemental analysis: $C_{75}H_{162}N_3PW_4O_{24}$ (2256.7): theoretical: C 39.91%, H 7.24%, N 1.86%, W 32.6%, P 1.37% found C 39.97%, H 7.21%, N 1.73%, P 1.25%, W 34.76%

3.2. Epoxidation under phase-transfer conditions

3.2.1. Epoxidation of CHDD under phase-transfer conditions using different phase-transfer catalysts and phosphoric acid

Into a three-necked 50 mL round-bottom flask, 0.165 g of Na_2WO_4 (or the corresponding amount of Na_2MoO_4) (0.50 mmol), phosphoric acid (0.50 mmol) and the corresponding PTC (0.50 mmol) was weighted. 5.51 g of CHDD (25 mmol), water (5.00 g) and toluene (20.00 g) was then added. Two phases were then formed, an organic phase consisting of toluene and

the substrate and an aqueous phase with the precursors of the catalyst. The mixture was then stirred at 800 rpm and heated up to the reaction temperature (T=60°C). When the temperature was reached, the first charge of H_2O_2 50wt% (0.47 g, 6.75 mmol, 0.25 mol equiv.) was added and the reaction time started. After 60 minutes, the second charge of H_2O_2 was added (0.47 g, 6.75 mmol, 0.25 mol equiv.). For sampling, the stirring was stopped until the two phases were separated. The organic phase was sampled every 20 minutes during the first 120 minutes. A final sample was taken after 180 minutes. The reaction was followed using GC/MS for qualitative purposes and GC-FID using the internal standard technique for quantification of the formed products. The amounts of PTC and phosphoric (or phosphonic or phosphinic) acid used for the epoxidation of CHDD with H_2O_2 under phase-transfer conditions is presented in Table 6.

Table 6. Amount of starting material used in the epoxidation reaction of CHDD

PTC	**PA**	**PhPA**	**AMPA**	**HMPA**	**DPPA**	**BHPA**
A	**0.049 g**	**0.079 g**	**0.055 g**	**0.056 g**	-	-
	0.202 g	*0.202 g*	*0.202 g*	*0.202 g*	-	-
B	**0.049 g**	**0.079 g**	**0.055 g**	**0.056 g**	**0.109 g**	**0.063 g**
	0.232 g	*0.232 g*	*0.232 g*	*0.232 g*	*0.232 g*	*0.232 g*
C	**0.049 g**	**0.079 g**	**0.055 g**	**0.056 g**	-	-
	0.443 g	*0.443 g*	*0.443 g*	*0.443 g*	-	-
D	**0.049 g**	-	-	-	-	-
	0.324 g	-	-	-	-	-
E	**0.049 g**	-	-	-	-	-
	0.562 g	-	-	-	-	-
F	**0.049 g**	-	-	-	-	-
	0.170 g	-	-	-	-	-
G	**0.049 g**	-	-	-	-	-
	0.228 g	-	-	-	-	-

The amount of acid added is shown in **bold**. The amount of PTC added is shown in *italics*

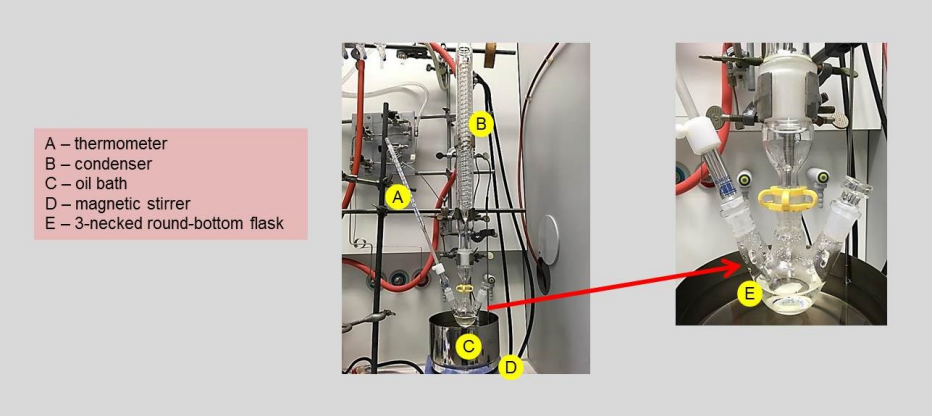


Figure 15. Setup used for the epoxidation of CHDD under phase-transfer conditions

3.2.2. Epoxidation of CHDD under phase-transfer conditions using different phase-transfer catalysts and phosphonic or phosphinic acids

The same procedure as the one described in section 4.2.1 was followed. The following starting materials were used: 0.165 g of Na_2WO_4 (0.50 mmol), the corresponding phosphonic or phosphinic acid (0.50 mmol), the corresponding phase transfer catalyst (0.50 mmol), 5.51 g of CHDD (25 mmol), water (5.00 g), toluene (20.00 g) and H_2O_2 50wt% (0.94 g, 13.5 mmol, 0.50 mol equiv. in two equal portions).

3.2.3. Epoxidation of CHDD under phase-transfer conditions with $[(C_8H_{17})_3NCH_3)]_3[(PO_4(W(O)(O_2)_2)_4)]$

Into a three-necked 25 mL round-bottom flask, 0.56 g of the peroxo complex $(C_8H_{17})_3NCH_3)_3(PO_4(W(O)(O_2)_2)_4)$ (0.25 mmol), was weighted. 2.75 g of CHDD (2.5 mmol), water (2.50 g) and toluene (10.00 g) were then added. Two phases were then formed, an organic phase consisting of toluene and the substrate and an aqueous phase. The mixture was then stirred at 800 rpm and heated up to the reaction temperature (T=60°C). When the temperature was reached, the first charge of hydrogen peroxide 50wt% (0.24 g, 3.37 mmol, 0.25 mol equiv.) was added and the reaction time started. After 60 minutes, the second charge of hydrogen peroxide was added (0.24 g, 3.37 mmol, 0.25 mol equiv.). For sampling, the stirring was stopped until the two phases were separated. The organic phase was sampled every 20 minutes during the first 120 minutes. A final sample was taken after 180 minutes. The reaction was followed using GC/MS for qualitative purposes and GC-FID using the internal standard technique for quantification of the formed products.

3.3. Preparation of palladium(II) complexes

In this section, the preparation of several palladium(II) complexes is described. The method followed for the preparation of the β-diketonate complexes is based on the procedure reported in the literature for similar compounds [102] [103] [104]. If such complexes possess an unsymmetrical ligand, they can exist as *cis* or *trans* isomers (Figure 16). The Pd^{II} complexes were characterized by elemental analysis (C, H, N, F and Pd) and NMR (^1H and ^{13}C) spectroscopy (see Appendix section).

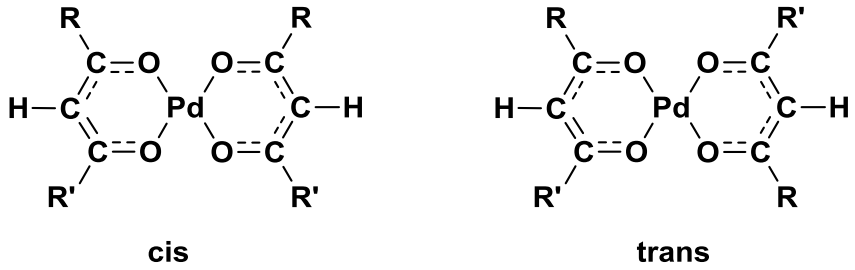


Figure 16. General structure of bis(β-diketonato)palladium(II) complexes

The $Pd(OAc)_2$ and $PdCl_2$ complexes of bathophenanthroline were prepared whereas the complexes of 1,10-phenanthroline were commercially available. These heterocyclic organic ligands act as chelating agents, whose N atoms can bind to palladium and form a complex.

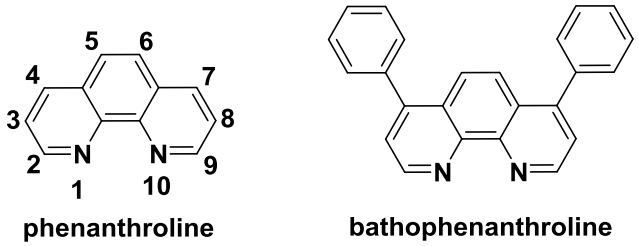


Figure 17. N-heterocyclic ligands used for the formation of Pd(II) complexes

3.3.1. Preparation of bis(β-diketonato)palladium(II) complexes

A general procedure was followed for the preparation of six bis(β-diketonato)palladium(II) complexes (see Table 7).

A filtered solution of 0.147 g of sodium tetrachloropalladate(II) (0.50 mmol) in 10 mL methanol was added to a solution containing 2 equivalents of the corresponding β-diketone (see Table 8) in 10 mL of methanol and stirred for 10 minutes. Additionally, 0.20 g of sodium methylate in 5 mL methanol was added and the obtained mixture was stirred for 2 hours at room temperature. The collected precipitate was filtered off, intensively washed with methanol and dried under reduced pressure. The filtered solution was allowed to stand overnight at room temperature to precipitate another crop of the product. The analytical data of the bis(β-diketonato)palladium(II) complexes are summarized in Table 7:

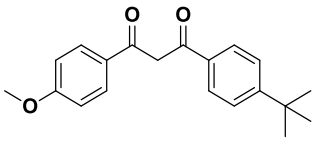
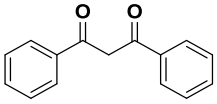
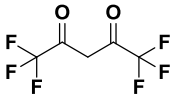
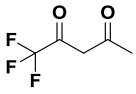
Table 7. Analytical data of the bis(β-diketonato)palladium(II) complexes

Pd(II) complex	R	R'	% Found				% Calculated			
			C	H	Pd	F	C	H	Pd	F
A[a]	methyl	methyl	40.66	4.53	32.04		39.43	4.63	34.93	-
B[a]	tert-butyl	tert-butyl	56.33	8.13	19.56	-	55.87	8.10	22.50	-
C	methoxy phenyl	*tert*-butylphenyl	66.70	5.89	12.94	-	66.25	5.84	14.67	-
D	phenyl	phenyl	65.07	4.10	17.14	-	65.17	4.01	19.25	-
E[a]	CF_3	CF_3	22.32	0.32	18.34	38.86	23.07	0.39	20.44	43.80
F	methyl	CF_3	29.11	1.76	25.87	27.1	29.11	1.95	25.79	27.63

[a] purchased and used without further purification. For R and R' see Figure 16

The β-diketones used for the preparation of the complexes are shown in Table 8:

Table 8. β-diketone used for the preparation of the bis(β-diketonato)palladium(II) complexes

β-diketone	Structure	Used for palladium complex
1-(4-methoxyphenyl)-3-(4-tert-butylphenyl)-1,3-propanedione		**C**
1,3-diphenyl-1,3-propanedione		**D**
1,1,1,5,5,5-hexafluoro-2,4-pentanedione		**E**
1,1,1-trifluoro-2,4-pentanedione		**F**

3.3.2. Preparation of (di)amine bidentate palladium(II) complexes

(1,10-Phenanthroline)Pd(II) chloride and acetate complexes could be purchased and used without further purification. A general procedure for the preparation of $Pd(OAc)_2$ and $PdCl_2$ complexes of BPhen is presented herein:

A filtered solution of $Pd(OAc)_2$ (or $PdCl_2$) (0.50 mmol) in 10 mL of methanol was added to a solution containing 1.3 equivalents of bathophenanthroline in 15 mL of methanol. The solution was vigorously stirred and a precipitate appeared almost immediately. The solution was allowed to stir for 2 hours at room temperature. The precipitate was filtered off and intensively washed with methanol. Finally, the collected solid was dried under reduced pressure. The analytical data of both 1,10-phenanthroline and BPhen palladium(II) complexes are summarized in Table 9.

Table 9. Analytical data of the 1,10-phenanthroline-like complexes prepared "ex situ"

Pd(II) salt	Ligand	% Found					% Calculated				
		C	H	N	Cl	Pd	C	H	N	Cl	Pd
$PdCl_2$	BPhen	56.86	3.29	5.69	13.54	18.77	56.55	3.16	5.50	13.91	20.88
$Pd(OAc)_2$	BPhen	57.98	3.01	5.54	-	18.70	60.39	3.98	5.03	-	19.11
$PdCl_2$[a]	Phen	40.94	2.22	7.73	21.54	25.66	40.31	2.26	7.84	19.83	29.77
$Pd(OAc)_2$[a]	Phen	48.71	3.24	6.95	-	22.87	47.48	3.49	6.92	-	26.29

[a] purchased and used without further purification

3.4. Wacker-type oxidation of linear and cyclic olefins

3.4.1. Wacker-type oxidation of α-olefins

The Wacker-type oxidation of α-olefins was carried out in a 300 mL stainless-steel Parr autoclave equipped with a pressure sensor, a thermocouple, a Teflon-coated magnetic stir bar and a carrousel-type inset with seven slots. The gas pressure concentration in the autoclave was measured using the pressure sensor together with a PC using the SpecView software provided by Parr Instrument Company. The temperature was measured by setting the thermocouple inside of a glass reactor filled with the solvent used for the reaction. To heat the autoclave to the target temperature, a heating sleeve from the company Keller Ihne&Tesch and a temperature controller from the company Heju Juchheim Solingen were used. The construction of the set-up used for these experiments is shown in Figure 18.

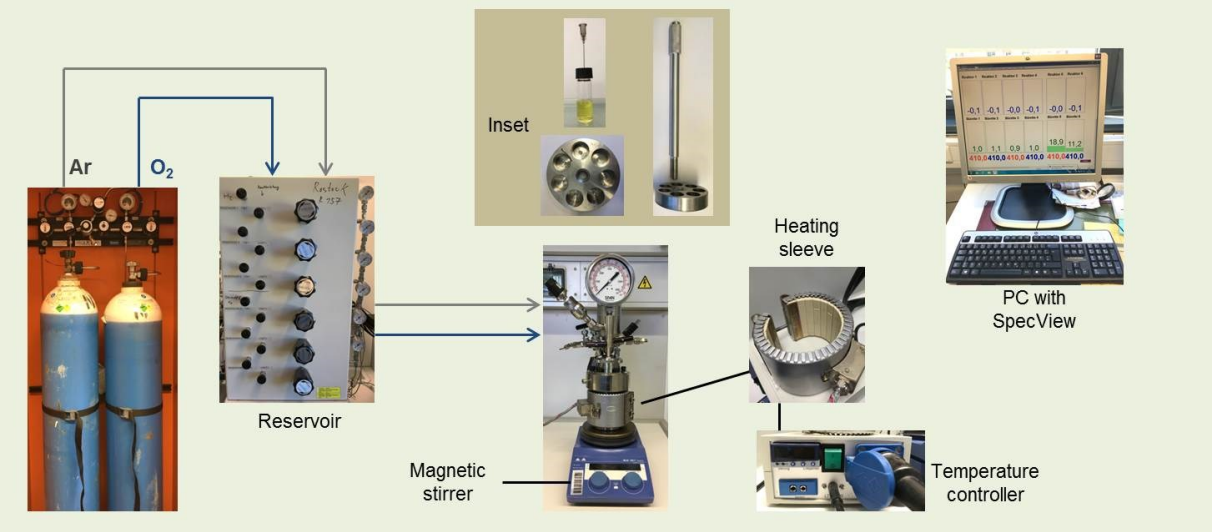


Figure 18. Scheme of the set-up used for the Wacker-type oxidation of α-olefins

The test of higher α-olefins included 1-octene, 1-nonene, 1-decene, 1-undecene, 1-dodecene and 1-hexadecene. These linear alkenes (see Figure 19) possess a chemical formula C_xH_{2x}.

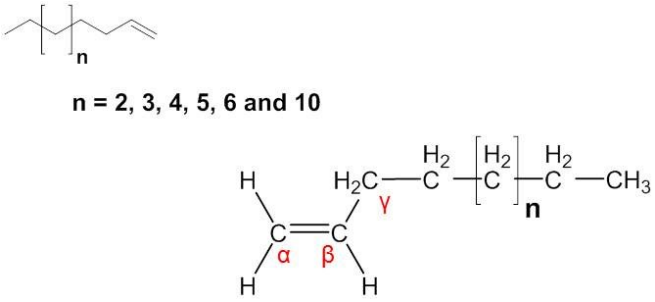


Figure 19. Structure of an α-olefin and olefins tested as substrates

The procedure followed for the screening tests of the palladium(II) complexes mentioned above and the α-olefins is described below:

In a typical experiment, 0.55 mmol of the corresponding α-olefin and 0.001 g of $PdCl_2$ (0.005mmol, 1 mol%) were added to a solution formed by 2.5 mL of DMA and 0.2 mL of deionized H_2O. The inset was put inside the autoclave, and afterwards it was tightly sealed. The autoclave was purged 3 times with 5 bar of Ar and subsequently 3 times with 5 bar of O_2. After the pretreatment, the autoclave was pressurized to 3 bar of O_2, and then the mixture was vigorously stirred and heated up to 80°C. The reaction time started when the target temperature was reached. After a reaction time of 2.5 h, the reactor was cooled to room temperature, and then the O_2 pressure was carefully released to the atmospheric

pressure. GC analysis of the mixture obtained after the reaction indicated the corresponding methyl ketone as the sole product. The product was then transferred to a separatory funnel and extracted using a 1:1 diethyl ether/water mixture (2 x 30 mL). Subsequently, the organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and finally concentrated under reduced pressure. The quantification of the resultant product was carried out by means of ^{1}H and ^{13}C NMR using 1,4-difluorobenzene DFB as standard.

3.4.2. Wacker-type oxidation of *cis*-5-decene and *trans*-5-decene

The Wacker-type oxidation of internal olefins was carried out using the setup shown in Figure 18. The reaction conditions used for the oxidation of terminal, internal and cyclic olefins are shown in Table 10.

Table 10. Reaction conditions for the Wacker-type oxidation of α-, internal- and cyclic olefins

Olefin type	Pd(II) catalyst	t [h]	T [°C]
α-olefin	1 mol%	2.5	80
internal olefins	1 mol%	2.5	80
	5 mol%	20	80
cyclic olefins	5 mol%	20	80
	20 mol%	20	80

The procedure followed for the oxidation of the *cis*- and *trans*- isomers of 5-decene and the work-up is already described in section 3.4.1. The starting materials used were: 0.55 mmol of the corresponding isomer (*cis* or *trans*) of 5-decene, $PdCl_2$ (1-5mol%), 2.5 mL of DMA and 0.2 mL of deionized H_2O. The quantification of the resultant product was carried out by means of ^{1}H and ^{13}C NMR using DFB as standard.

3.4.3. Wacker-type oxidation of (Z/E)-cyclohexadecene

(Z/E)-Cyclohexadecene was used as substrate to evaluate the behavior of the palladium(II) chloride-DMA system with a macrocyclic olefin with only one insaturation. The substrate was prepared at the production facilities of Symrise in Holzminden, Germany. CHDD was partially hydrogenated in a 5 L autoclave using a palladium catalyst 5 wt% supported on Al_2O_3. GC analysis of the mixture obtained after the reaction indicated both cyclohexadecene and cyclohexadecane were present in the product mixture. The crude product mixture was distilled and 8 fractions were obtained. A fraction constituted of 45.6% of (Z/E)-

cyclohexadecene and 53.1% of cyclohexadecane (GC areas) was used as the substrate for the Wacker-type oxidation of (Z/E)-cyclohexadecene. This mixture was a solid at room temperature.

The procedure followed for the oxidation of (Z/E)-cyclohexadecene and the work-up is already described in section 3.4.1. The starting materials used were: 0.55 mmol of (Z/E)-cyclohexadecene, 0.005 g of $PdCl_2$ (0.027 mol), 2.5 mL of DMA and 0.2 mL of deionized H_2O. The quantification of the resultant product was carried out by means of ^{1}H and ^{13}C NMR using DFB as standard.

3.4.4. Wacker-type oxidation of CHDD

The Wacker-type oxidation of CHDD was studied under several conditions and parameters (e.g. catalyst together with cooxidants, solvents, solvents mixtures and palladium(II) precursors). The reaction was carried out using the setup shown in Figure 18. A brief description of the procedures followed for these tests is shown below:

3.4.4.1. Wacker-type oxidation of CHDD in different solvent mixtures

The solubility of the substrate is believed to have an influence in the Wacker-type oxidation of olefins. However most higher olefins show poor solubility in polar solvents such as water, methanol, ethanol or DMF [62]. In order to have a homogeneous reaction mixture, several tests have been carried out in a set of solvent mixtures that are able to dissolve both CHDD and water in one phase. For this reason, some of these solvents (see Figure 20) were tested for the Wacker-type oxidation of CHDD.

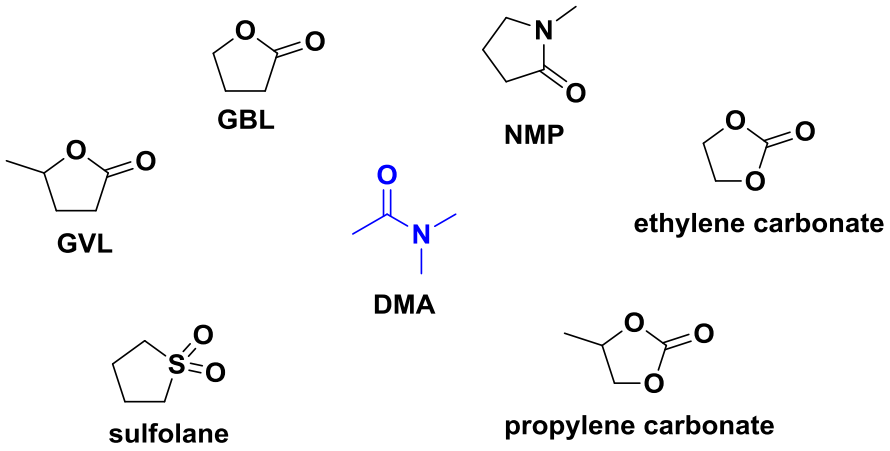


Figure 20. Solvents mixed with DMA and tested for the Wacker-type oxidation of CHDD

In a typical experiment, 0.55 mmol of CHDD (0.120 g) and 0.0012 g of $Pd(OAc)_2$ (0.005 mmol, 1 mol% of Pd^{II}) was added to a solution formed of 1 mL of DMA, 1 mL of the corresponding co-solvent and 0.2 mL of deionized H_2O. The inset was put inside the autoclave, and afterwards it was tightly sealed. The autoclave was purged 3 times with 5 bar of Ar and subsequently 3 times with 5 bar of O_2. After the pretreatment, the autoclave was pressurized to 3 bar of O_2, and then the mixture was vigorously stirred and heated up to 80°C. The reaction time started when the target temperature was reached. After 2 h, the reactor was cooled to room temperature, and then the O_2 pressure was carefully released to the atmospheric pressure. The reaction mixture was transferred to a volumetric flask and filled up with THF to a total volume of 5 mL. GC-MS analysis was done for qualitative purposes. GC-FID was used for quantification using 1,8-octanediol as internal standard.

3.4.4.2. Wacker-type oxidation of CHDD with bis(β-diketonato)palladium(II) complexes

A number of commercially available and self-prepared bis(β-diketonato)palladium(II) complexes (see Table 7) in different concentrations were tested as catalysts for the Wacker-type oxidation of CHDD.

Into a 4 mL glass reactor, 0.55 mmol of CHDD (0.120 g) and the corresponding amount of the bis(β-diketonato)palladium(II) complex (0.01 – 20 mol% Pd^{II}) was added to a solution formed of 2.5 mL of DMA and 0.2 mL of deionized H_2O. The inset was put inside the autoclave, and afterwards it was tightly sealed. The autoclave was purged 3 times with 5 bar of Ar and subsequently 3 times with 5 bar of O_2. After the pretreatment, the autoclave was pressurized to 3 bar of O_2, and then the mixture was vigorously stirred and heated up to 90°C. The reaction time started when the target temperature was reached. After the reaction (15 h), the reactor was cooled down to room temperature, and then the O_2 pressure was carefully released to the atmospheric pressure. The reaction mixture was transferred to a volumetric flask and filled up with THF to a total volume of 5 mL. GC-MS analysis was done for qualitative purposes. GC-FID was used for quantification using 1,8-octanediol as internal standard.

3.4.4.3. Wacker-type oxidation of CHDD with $Pd(acac)_2$ in different solvents

The Wacker-type oxidation of CHDD with $Pd(acac)_2$ was carried out in different solvents containing an amide functional group (e.g. DMF, DMA, DMPr, NMP).

In a 4 mL glass reactor 0.55 mmol of CHDD (0.120 g) and 0.0050 g of $Pd(acac)_2$ (0.016 mmol, 3 mol% Pd^{II}) were added to a solution formed by 2.5 mL of the corresponding solvent and 0.2 mL of deionized H_2O. The inset was put inside the autoclave, and afterwards it was tightly sealed. The autoclave was purged 3 times with 5 bar of Ar and subsequently 3 times with 5 bar of O_2. After the pretreatment, the autoclave was pressurized to 3 bar of O_2, and then the mixture was vigorously stirred and heated up to 90°C. The reaction time started when the target temperature was reached. After the reaction (5 - 15 h), the reactor was cooled to room temperature, and then the O_2 pressure was carefully released to the atmospheric pressure. The reaction mixture was transferred to a volumetric flask and filled up with THF to a total volume of 5 mL. GC-MS analysis was done for qualitative purposes. GC-FID was used for quantification using 1,8-octanediol as internal standard.

3.4.4.4. Wacker-type oxidation of CHDD with (di)amine bidentate palladium complexes

A number of commercially available and self-prepared palladium(II) complexes containing a (1,10-phenanthroline)-based ligand (see Table 9) were tested as catalysts for the Wacker-type oxidation of CHDD.

The procedure followed for the oxidation reaction is the same described in section 3.4.4.2.

3.5. Wacker-type oxidation of CHDD with $Pd(acac)_2$ using isotopically labeled water $H_2{}^{18}O$ as reactant

The preparations of the experiments with isotopically labeled water $H_2{}^{18}O$ were carried out inside a glovebox under inert argon atmosphere. The experiment was carried out using a 300 mL-Parr stainless-steel autoclave (see Figure 18). Prior to the preparations in the glovebox, DMA and CHDD were dried using molecular sieves 3Å (0.3 nm, Merck, previously activated: at 250°C for 20 h). Inside the glovebox, 0.55 mmol of CHDD (0.120 g) and 0.055 mmol of $Pd(acac)_2$ (0.0168 g, 10 mol% of Pd^{II}) were added to a mixture of 2.5 mL of DMA and 0.20 mL of $H_2{}^{18}O$ (97% O-18 enriched water, CAMPRO SCIENTIFIC) in a 4 mL glass reactor. Using a carousel-type inset, 5 of these reactors were put inside the autoclave. The autoclave was tightly sealed and taken out of the glovebox. The autoclave was purged 3 times with 5 bar of Ar and subsequently 3 times with 5 bar of O_2. After the pretreatment, the autoclave was pressurized to 3 bar of O_2, and then the mixture was vigorously stirred and heated up to 90°C. The reaction time started once the target temperature was reached. After the reaction (15 h) the reactor was cooled down to room temperature, and then the O_2 pressure was carefully released to the atmospheric pressure. The reaction mixture was transferred to a

volumetric flask and filled up with THF to a total volume of 5 mL. 0.90 mL of this solution were transferred to a 2 mL volumetric flask and further diluted with THF. GC-MS analysis was used for qualitative purposes.

A sample of this solution was also analyzed using LC/MS-ESI (see section 3.7.1.4)

3.6. Wacker-type oxidation of CHDD with $Pd(acac)_2$ using isotopically labeled molecular oxygen $^{18}O_2$

The preparations of the experiment with isotopically labeled molecular oxygen $^{18}O_2$ took place inside a glovebox under an inert argon atmosphere. The experiment was carried out using a 100 mL-Parr stainless-steel autoclave with a special inset for fitting the 4 mL glass reactor. Inside the glovebox, 0.55 mmol of CHDD (0.120 g) and 0.055 mmol of $Pd(acac)_2$ (0.0168 g, 10 mol% of Pd^{II}) were added to a mixture of 2.5 mL of DMA and 0.20 mL of H_2O in a 4 mL glass reactor. The autoclave was tightly sealed and taken out of the glovebox. Since the pressure inside the oxygen gas cylinder (2.5 bar, 0.4 L) was lower than the pressure needed for the experiment, the autoclave was pressurized with the help of a syringe gas pump (ISCO SYRINGE PUMP 100DX, 0.1 L). To minimize the presence of $^{16}O_2$, the pump was purged 5 times with 20 bar Ar. The labeled oxygen was compressed several times and pumped into the autoclave to obtain a final pressure ($p_{^{18}O_2}$) of 6.5 bar. The autoclave was then vigorously stirred and heated up to 90°C (± 5°C) using an oil bath for 16.5 h. A scheme of the setup used is shown in Figure 21. The reaction mixture was transferred to a volumetric flask and filled up with THF to a total volume of 5 mL. 0.90 mL of this solution were transferred to a 2 mL volumetric flask and further diluted with THF. GC-MS analysis was used for qualitative purposes. A sample of this solution was also analyzed using LC/MS-ESI (see section 3.7.1.4)

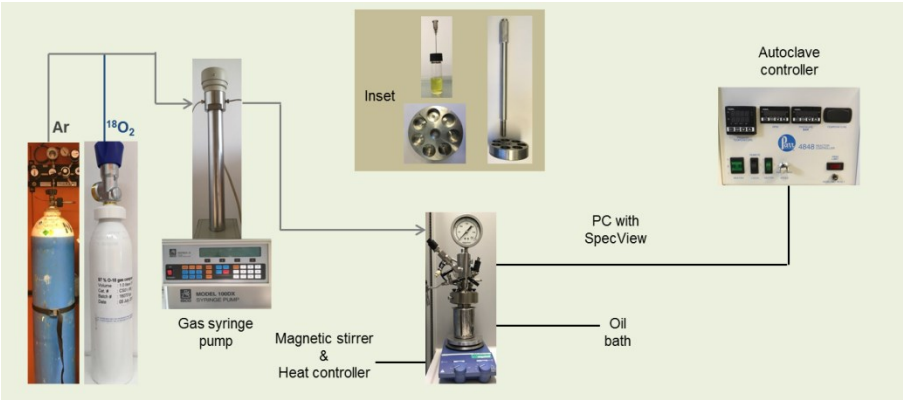


Figure 21. Scheme of the setup used for the Wacker-type oxidation of CHDD with labelled $^{18}O_2$

3.7. Analytical methods

3.7.1. Identification of reactants and products

3.7.1.1. NMR spectroscopy

The ^{1}H and ^{13}C NMR measurements were performed using an AV 300 Bruker spectrometer (proton resonance frequency 300 MHz). Bruker TopSpin 3.2 was the software used for the interpretation of the spectra.

The quantitative determination of the concentration of substrate and products of the Wacker-type oxidation of α-olefins was carried out using ^{1}H NMR spectroscopy. For this purpose, the addition of DFB as internal standard was needed. $CDCl_3$ was used as solvent for the samples and also as a signal reference.

In a typical procedure for the preparation of a sample, a known amount of the isolated product mixture was weighed, transferred to an NMR tube and diluted in $CDCl_3$ in the presence of a known amount of DFB. The integral of the shift corresponding to DFB in the NMR spectrum was calibrated to 4 (corresponding to the four protons present in DFB, see Figure 22). After the calibration of the internal standard, the signal corresponding to the protons used for the quantification were also integrated (see Figure 23).

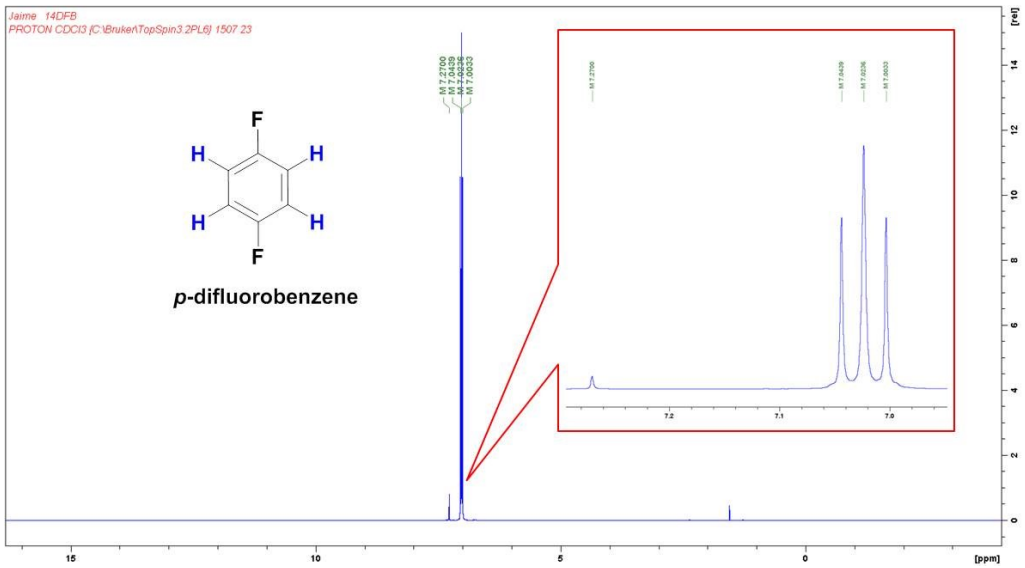


Figure 22. ^{1}H NMR spectrum of 1,4-difluorobenzene, which was used as internal standard for quantification purposes

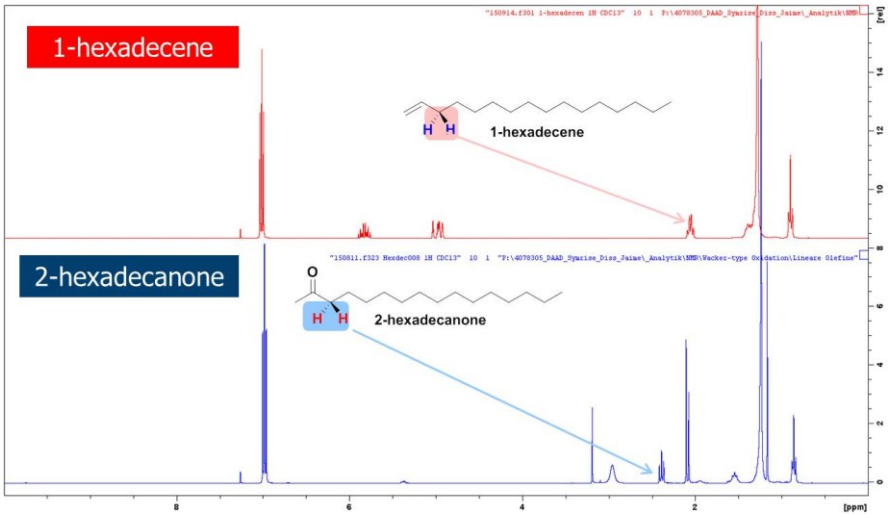


Figure 23. ^{1}H NMR spectrum of 1-hexadecene and its product after Wacker-oxidation

The area of the signal of the analyte used for the quantification was related to the area of the signal corresponding to DFB and used for the quantification of the target product. The moles of the target product were calculated using equation 2

$$n_{PROD} = \frac{n_{DFB} \cdot Integral_{PROD}}{H^{+}_{PROD}} \quad [mmol] \qquad (2)$$

The yield ***Y*** relates the concentration of a specific product to the concentration of the substrate charged at the beginning of the reaction. In the present work, the yield is given as the percentage of the relation between the moles of a specific product n_B found after the reaction and the moles of substrate n_A charged at the beginning of the reaction t_0. It was calculated using equation 3:

$$Y_B = \frac{n_B}{n_A} \cdot 100 \qquad (3)$$

3.7.1.2. ICP

ICP-OES is a commonly used technique for the quantification of an element in a sample. It is a type of Atomic Emision Spectroscopy, where the valence electrons of an element are excited and transferred to a higher energy level using inductively coupled plasma up to 8000-10000 Kelvin.

The excited electrons emit a radiation when they drop back to the ground state. Suited detectors optically measure the emitted characteristic electromagnetic radiation and

intensities. The intensity of the emission is used to evaluate the concentration of a specific element present in the sample.

For the determination of the elemental composition by means of ICP-OES technique, a Varian 715-ES ICP-Emission-Spectrometer was used. Approximately 20 mg of the sample was mixed with 8 mL of aqua regia and 2 mL of hydrofluoric acid. The digestion was performed in a microwave.assisted sample preparation system “MULTIWAVE” from Anton Paar/Perkin-Elmer at approximately 200ºC and 65 bar. The digested solution was filled up to 100 mL and analyzed. The data analysis was performed with a Varian 715-ES software “ICP Expert”.

3.7.1.3. Elemental analysis

The elemental composition of carbon, hydrogen, nitrogen and sulfur was quantified using the combustion analysis method.

The combustion analysis method was carried out for the quantitative determination of carbon (C), hydrogen (H), nitrogen (N) and sulfur (S) using a microanalysator (TruSpec Micro CHNS, Leco). Approximately 10 mg of the sample were catalytically combusted in oxygen and helium as carrier gas. An IR detector was used for the quantification of C, H and S. Nitrogen was quantified with a thermal conductivity detector.

The quantification of chloride (Cl^-) and bromide (Br^-) was performed with a potentiometric titrator (TitraLab TIM 870, Radiometer Analytical SAS. ± 2000 mV, resolution: 0.1 mV. Electrode: Kombielektrode MC6091Ag). An ion selective electrode ISE25F and a reference electrode REF 201 were used for the quantification of fluoride (F^-).

Atomic absorption spectroscopy was used for the quantitative determination of palladium. The spectra were recorded using an absorption and emission spectrometer (AAnalyst 300, Perkin Elmer) equipped with a deuterium and a hollow-cathode lamp and a flame atomizer for air-acetylene (temperature 2150-2400 °C) and for N_2O-acetylene (temperature 2650-2800 °C).

3.7.1.4. MS-ESI spectrometry

The MS-ESI measurements were carried out for two reasons: to calculate the molar mass of the obtained products and to evaluate the experiments done using labeled oxidants (water $H_2{}^{18}O$ and molecular oxygen ($^{18}O_2$)).

For the preparation of the samples, the mixture obtained after reaction was transferred to a 5 mL-volumetric flask and filled up with THF. From this solution, a 0.90 mL sample was taken and transferred to a 2 mL-volumetric flask and filled up with THF. A sample of this solution was analyzed using an Agilent Technologies 6210 TOF LC/MS. A mixture formed composed of methanol (90%) and H_2O + 0.1% formic acid (10%) was used as eluent for the analysis.

3.7.1.5. Gas chromatography (GC-FID and GC/MS) for qualitative determination and quantification of reaction mixtures

Figure 24. Gas chromatogram equipped with FID and MS detectors used in this thesis

The qualitative analysis and quantification of substrate and products were carried out using a gas chromatograph with an FID detector coupled to a mass spectrometer (GC/MS).

1,8-Octanediol was used as internal standard. Tetrahydrofuran was used as solvent to prepare the internal standard solution and to dilute the reaction mixtures. The samples were measured using a SHIMADZU GC/MS QP 2010S, equipped with a HP5-MS (5%-phenyl)-methylpolysiloxane capillary column (30 m x 0.25 mm x 0.25 µm). The analyzed samples were quantified using a calibration curve and the internal standard method.

For this purpose, stock solutions with known amounts of CHDD and the corresponding target product (CHDO or 8-CHD) were prepared. Aliquots of different volumes were taken from the stock solutions and diluted in THF with a constant amount of the internal standard stock solution. A summary of the concentrations of each solution used for the calibration of the GC are shown in Table 11 and Table 12.

Table 11. Internal standard calibration data for the epoxidation of CHDD

Analyte	Concentration [mmol/L]					
1,8-octanediol	11.6	11.6	11.6	11.6	11.6	11.6
CHDD	2.4	3.4	4.2	5.0	6.6	8.2
CHDO	0.6	0.8	1.2	1.6	2.0	2.6

Table 12. Internal standard calibration data for the Wacker-type oxidation of CHDD

Analyte	Concentration [mmol/L]						
1,8-octanediol	11.4	11.4	11.4	11.4	11.4	11.4	11.4
CHDD	1.8	2.6	3.6	4.4	6.0	7.4	9.0
8-CHD	1.0	3.0	2.0	5.0	7.8	9.8	-

3.7.2. Characterization of palladium(II) complexes

3.7.2.1. NMR spectroscopy

To prepare the sample, ca. 30 mg of the corresponding palladium(II) complex was weighed and transferred to an NMR tube and diluted in ca 0.5 mL of $CDCl_3$. The shift generated by $CDCl_3$ (δ (^1H) = 7.27 ppm) was used as reference for the identification of the signals for the chemical shift produced by the analytes.

3.7.3. Interpretation of Analysis

3.7.3.1. Calculation of concentrations using a calibration curve

The area of the peaks corresponding to each analyte (e.g. A_{CHDD}, A_{STD}) obtained as a response from the calibration curve was correlated to their known number of moles (e.g. n_{CHDD}, n_{STD}) and plotted on a graph. An example of such a plot is shown on Figure 25.

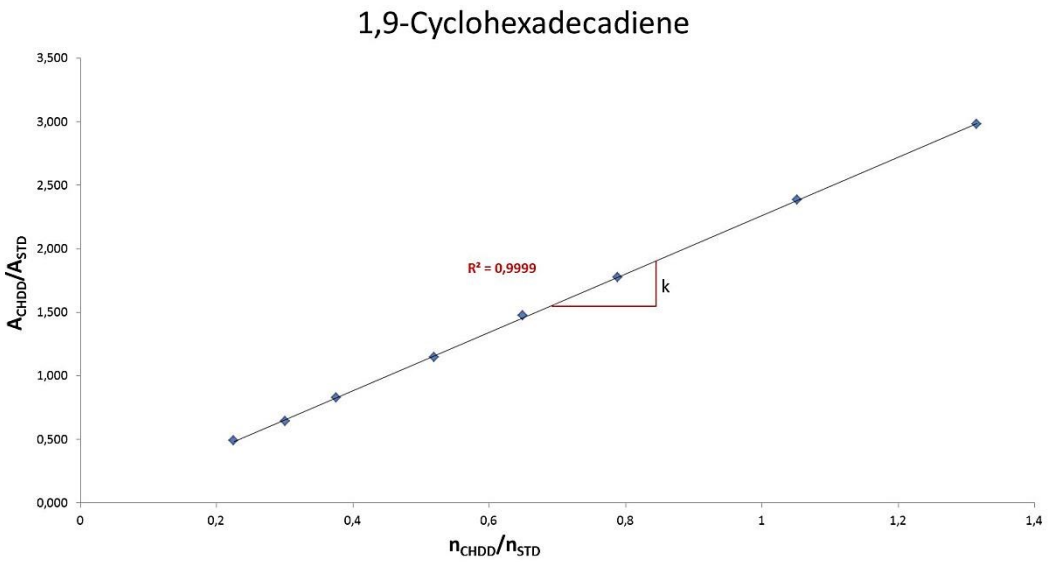


Figure 25. Plot of CHDD calibration curve for the Wacker-type oxidation of CHDD.

The slope of the regression line is also the factor ***k*** of the calibration of the GC-FID. The concentration of substrate and target products can be determined by means of equation 4:

$$n_A = \frac{Area_A}{Area_{STD}} \cdot \frac{n_{STD}}{k} \quad [mmol] \tag{4}$$

3.7.3.2. Determination of conversion, yield, selectivity and recovery rate

The determination of conversion, yield, selectivity and recovery rate was executed based on GC-FID analyses carried out after each reaction.

The conversion ***X***, which in this work is given as the percentage of the difference between the moles of substrate n_{A,t_0} charged at the beginning of the reaction t_0 minus the amount of moles of substrate $n_{A,t}$ found after the reaction time *t* divided by the moles of substrate n_{A,t_0} charged at the beginning of the reaction, was calculated using equation 5:

$$X_A = \frac{\Delta n_A}{n_{A,t_0}} = \frac{n_{A,t_0} - n_{A,t}}{n_{A,t_0}} \cdot 100 \tag{5}$$

The selectivity ***S*** embodies the concentration of a specific product among the total amount of products formed after a reaction. In the present work, the selectivity is given as the percentage % of the relation between the moles of the product divided by molar amount of substrate converted during the reaction. It was calculated by the quotient of Y/X using equation 6.

$$S_B = \frac{n_B}{n_{A,t_0} - n_{A,t}} \cdot 100 \quad (6)$$

The recovery rate RR was determined after each reaction to validate the analytic method used for the quantification of substrate and products. The recovery rate relates the summation of moles of the substrates n_{SUBS} and products n_{PROD} (i.e. sum of target and byproducts) obtained after the reaction to the number of moles n_{SUBS,t_0} charged at the beginning of the reaction. The recovery rate was calculated using equation 7.

$$RR = \frac{\sum n_{SUBS} + n_{PROD}}{n_{SUBS,t_0}} \cdot 100 \quad (7)$$

4. Results and Discussion

4.1. Epoxidation of CHDD under phase-transfer conditions

4.1.1. Screening of metals (molybdenum vs tungsten)

Early transition metals with high oxidation states (e.g. W^{6+} [51,54], Mo^{6+} [105], V^{5+} [106], Ti^{4+} [107,108], Ag [109]) and precious metals like Au [110] have been used as heterogeneous or homogeneous catalysts for the oxidation of lower and higher olefins to obtain the corresponding epoxides using organic peroxides as oxidants. Of special interest for the present work was to investigate processes with potential use in the industry, in which the yield of monoepoxide CHDO should be maximized. The so-called polyperoxocomplex of general formula $[PO_4[M_XO(O_2)_2]_4]^{3-}$ (M = W(VI), Mo(VI), *X*= 1) was chosen as catalyst for the selective monoepoxidation of CHDD. There are two synthetic pathways to obtain such complexes (see Figure 26): a) by decomposing phosphotungstic acid (PTA, $H_3[PW_{12}O_{40}]\cdot xH_2O$) or phosphomolybdic acid ($H_3[PMo_{12}O_{40}]\cdot xH_2O$) with an excess of H_2O_2 or b) by preparing the peroxo species using tungstic or molybdic acid or its salts (*e.g.* Na_2WO_4, K_2WO_4) and phosphoric acid as precursor with an excess of H_2O_2.

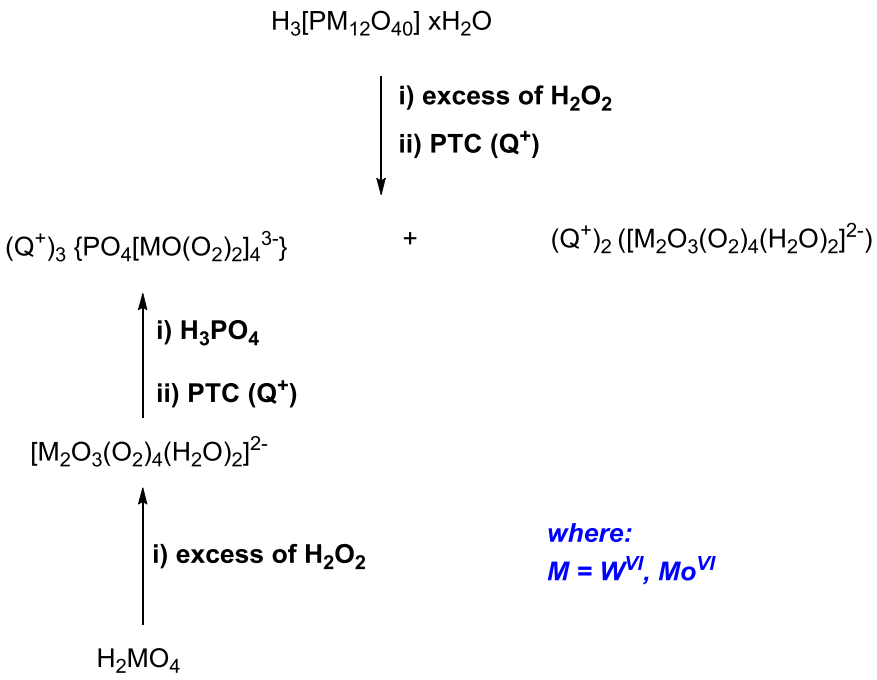


Figure 26. Synthesis of anionic peroxocomplexes. Edited from [49]

Prior to the test of the involved components (e.g. PTC and phosphorus source) for the selective epoxidation of CHDD, some preliminary tests were carried out to determine which

polyperoxocomplex has the highest catalytic activity in the epoxidation of CHDD under phase-transfer conditions (see Figure 27):

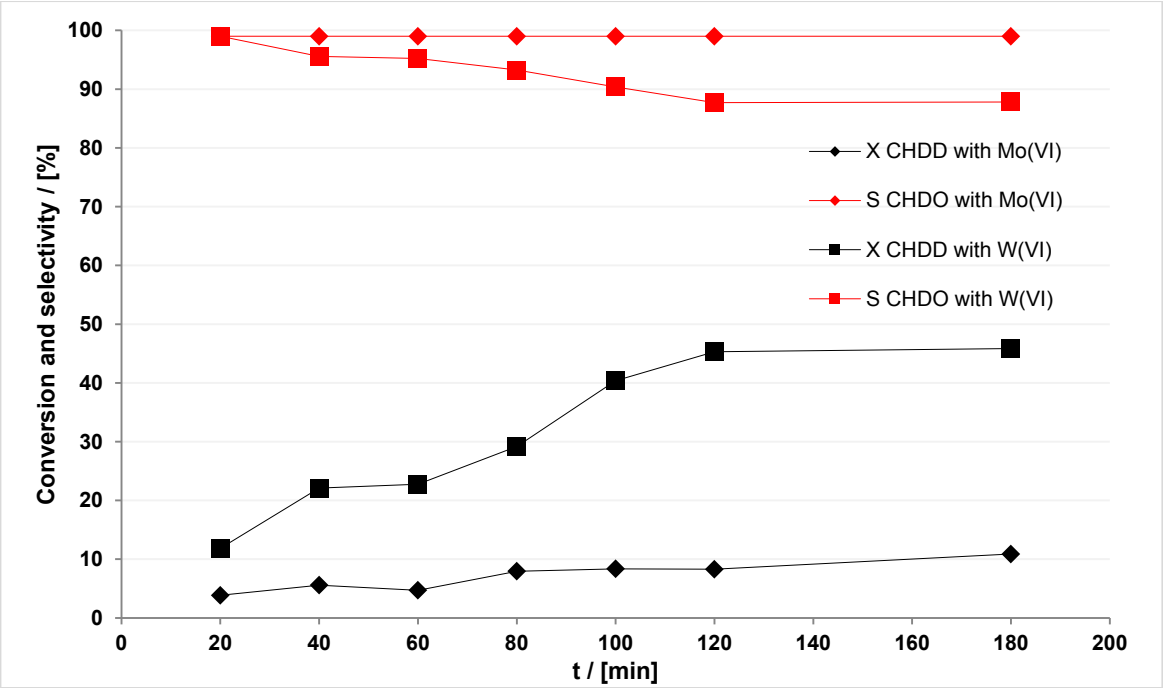


Figure 27. Comparison of the selective epoxidation of CHDD under phase-transfer conditions using (a) Na_2MoO_4 or (b) Na_2WO_4 as precursors of the polyperoxo complex. Reaction conditions: 0.5 mmol of Na_2WO_4 or Na_2MoO_4, 0.5 mmol PTC B, 0.5 mmol HMPA, two identical portions (0.25 eq.) of H_2O_2 were added after 0 and 60 min (0.5 eq. in total), t = 3 h, T = 60°C, U = 800 rpm.

The sodium salts of Na_2MoO_4 and Na_2WO_4 were used as precursors and mixed together with HMPA in a biphasic solution of toluene and water (4:1 in weight) to form the corresponding polyperoxo complex. Methyltrioctylammonium hydrogensulfate was used as the phase-transfer catalyst for the reaction. Two identical portions of H_2O_2 were added at the beginning and after 60 minutes of reaction time (2x 3.2 mmol of H_2O_2 50 wt.% aqueous solution). To minimize the influence of the stirring speed in the conversion of CHDD, the same stirring speed (800 rpm) was used for both experiments.

The reaction was monitored for 3 hours with both catalytic systems under identical reaction conditions to study the activity of each polyperoxo complex (see Figure 27). Surprisingly, under identical reaction conditions, the conversion of CHDD when using the tungsten-based polyperoxo complex as catalyst was considerably higher than the conversion when using the molybdenum-based complex. The difference in the activity of the complexes also increased during the reaction time. After 20 min of reaction time, the conversion of CHDD with the W^{VI} complex was 3.1 times higher than with the Mo^{VI} complex. After 60 min and 120 min this

difference increased to 4.8 times and 5.5 times, respectively. One explanation for this behavior could be the induction time needed for the formation of the polyperoxo complexes (tungsten and molybdenum) at the reaction temperature (T = 60°C). The W-based complex seems to be particularly active for the epoxidation of CHDD. After 40 and 60 min of reaction time, the conversion of CHDD was 22.1% and 22.7%, respectively. This means that the first charge of the oxidant H_2O_2 (0.25 equiv.) was completely consumed after only 40 min. After 120 and 180 min, the conversion of CHDD was 45.3% and 45.8%, respectively, which means that the oxidant was already consumed after 2 h of reaction time. The difference in the time needed for the total consumption of the two charges of oxidant can be explained by considering the formation of CHDO. At the beginning of the reaction, CHDD is the only molecule, which can be potentially oxidized by H_2O_2. For this reason, the total amount of the oxidant is consumed after only 40 min. When the second charge of oxidant is added after 60 min, the concentration of CHDO in the reaction mixture is higher and the total conversion of the added oxidant takes longer. The theoretical conversion of CHDD of 50% is not achieved because part of the oxidant is consumed in the consecutive epoxidation of CHDO for the formation of CHDOO (see Figure 28)

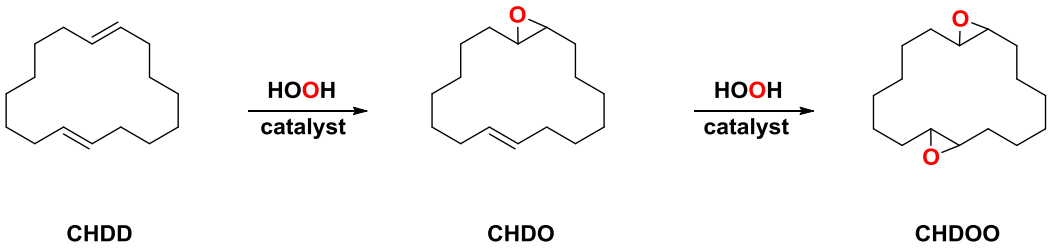


Figure 28. Epoxidation of CHDD and consecutive epoxidation of CHDO

Regarding the selectivity of the complexes towards CHDO, a notorious difference was also found. After 20 min, the selectivity of both complexes towards CHDO was above 99%. This is an interesting result, considering that the conversion of CHDD when using the W-based complex is higher. The selectivity of the W-based complex decreased during the reaction as the conversion of CHDD augmented. In the case of the Mo-based complex, the selectivity remained constant (>99%) after 180 min. This behavior was expected since the conversion of CHDD after this time was only 10.9%. The results obtained after these experiments showed that the W-based polyperoxo complex has a higher activity than the Mo-based one in the epoxidation of CHDD under phase-transfer conditions.

$$W^{VI} > Mo^{VI}$$

Based on these results and on the intrinsic poor activity of tungsten-based epoxidation systems for the decomposition of H_2O_2 [111], it was proceeded to investigate the influence of several phosphorus precursors (*e.g.* phosphoric, phosphonic and phosphinic acids) for the *in-situ* preparation of the active W-based polyperoxocomplex in combination with quaternary ammonium salts with different structures as PTCs for the selective monoepoxidation of CHDD.

4.1.2. Study of influences of the precursors of the catalysts system in the selective epoxidation of CHDD

Na_2WO_4 was chosen as the precursor for the *in situ* preparation of the W-based polyperoxocomplex. The influence of several phosphorus sources *e.g.* PA, PhPA, AMPA, HMPA, DPPA and BHPA (see Figure 29) in the preparation of the complex was evaluated. The influence of the structure of the PTC's cation was also studied. Among the differences studied were: a) the number of methyl groups present directly bonded to the N atom of the cation, b) the length of the alkyl chains bonded to the cation and c) the anion of the PTC. For an easier explanation, specific codes were given to each PTC (see Table 13) and the acids used (see Figure 29).

The results obtained from these studies are presented in the following sections.

Table 13. Tetraalkylammonium salts used as PTCs in the study

Code	PTC	Cation formula	Anion	Chains*			
				1	2	3	4
A	Aliquat 336 (methyltrioctylammonium chloride)	$(C_8H_{17})_3N^+CH_3$	Cl^-	8	8	8	1
B	methyltrioctylammonium hydrogensulfate	$(C_8H_{17})_3N^+CH_3$	HSO_4^-	8	8	8	1
C	methyltrioctadecylammonium hydrogensulfate	$(C_{18}H_{37})_3N^+CH_3$	HSO_4^-	18	18	18	1
D	dimethyldioctadecylammonium hydrogensulfate	$(C_{18}H_{37})_2N^+(CH_3)_2$	HSO_4^-	18	18	1	1
E	tetraoctadecylammonium hydrogensulfate	$(C_{18}H_{37})_4N^+$	HSO_4^-	18	18	18	18
F	tetrabutylammonium hydrogensulfate	$(C_4H_9)_4N^+$	HSO_4^-	4	4	4	4
G	hexadecyltrimethylammonium-p-toluenesulfonate	$(C_{16}H_{33})N^+(CH_3)_3$	$C_7H_7SO_3^-$	16	1	1	1

* Number of carbons present in the alkyl chain bonded to the N atom of the PTC.

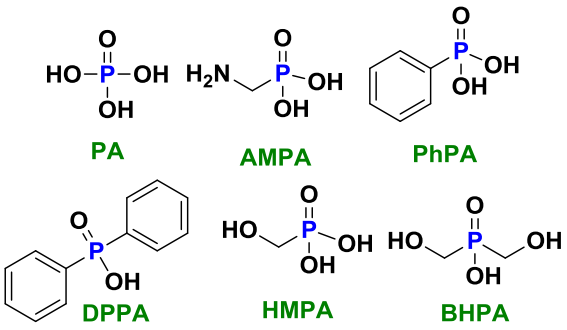


Figure 29. Phosphoric acid and phosphonic and phosphinic acids used for the monoepoxidation of CHDD

4.1.2.1. Comparison of phosphorus sources using methyltrioctylammonium chloride as PTC

The W-based polyperoxo complex formed *in situ* by mixing sodium tungstate and several phosphorus sources in the presence of H_2O_2 was tested as a catalyst in the monoepoxidation of CHDD. The polyperoxo complex was used in combination with PTC-A to form the catalytic system. The effectiveness of quaternary ammonium chloride salts as PTC has been extensively studied [112]. The results obtained from these reactions are shown in Figure 30.

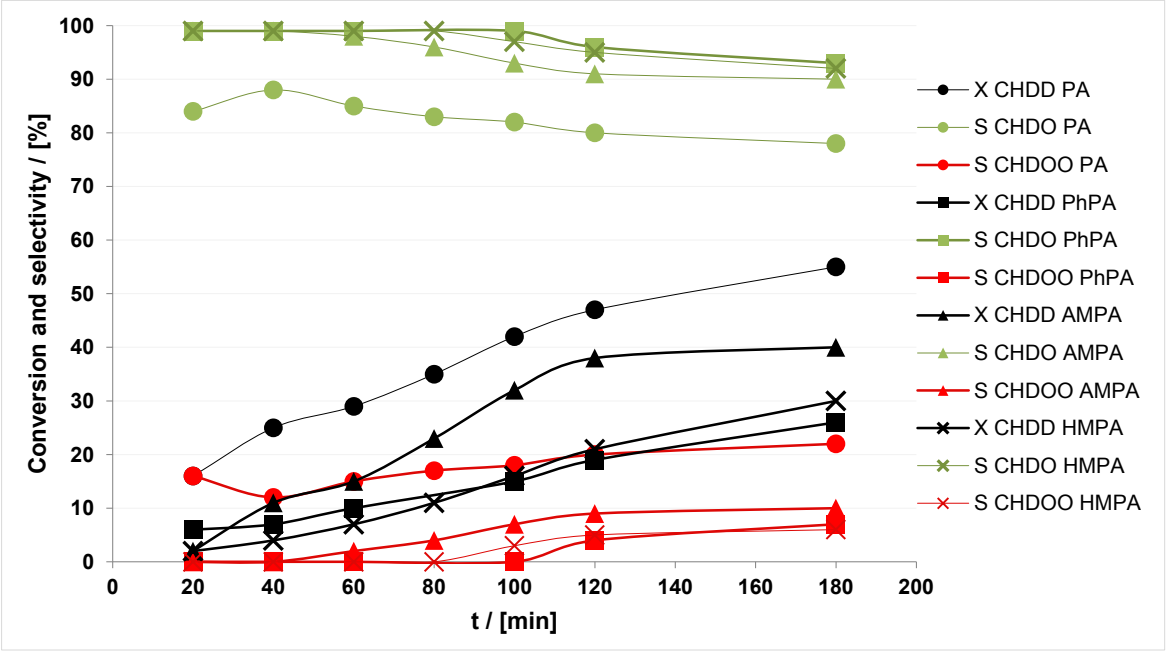


Figure 30. Selective monoepoxidation of CHDD using sodium tungstate and different phosphoric (or phosphonic acids) as precursors for the formation of the polyperoxocomplex. Aliquat 336 was used as PTC for these reactions. Reaction conditions: 0.5 mmol of Na_2WO_4, 0.5 mmol PTC-A, 0.5 mmol of phosphoric (or phosphonic) acid(s), two identical portions (0.25 eq.) of H_2O_2 were added after 0 and 60 min (0.5 eq. in total), t = 3 h, T =60 °C, U = 800 rpm.

From the results obtained, it can be concluded that PA together with sodium tungstate in presence of H_2O_2 and PTC-A formed the catalytic system with the highest activity. However, the selectivity of this complex towards the monoepoxide was rather low (S_{CHDO} < 90%) during the first 2 h of the reaction and the lowest (S_{CHDO} < 78%) of all the catalytic systems after 3 h. In the case of AMPA, the activity was somewhat lower, particularly at the beginning of the reaction. Still the activity increased during the reaction time and a conversion of 38% was achieved after 2 h. The conversion slightly increased to 40% after 3 h. The selectivity towards CHDO slowly decreased during the reaction. This was most certainly due to an increase in the concentration of monoepoxide as the reaction took place. Yet the selectivity after 3 h was 90%. On the other hand, HMPA also showed a similar behavior to the one shown by AMPA but this behavior did not change during the reaction time. After 60 min the conversion of CHDD was only 7%. Nevertheless the activity of the catalyst increased and the conversion of CHDD was 21% after 120 min and 30% after 180 min. This means that in the second hour of reaction, the amount of CHDD converted increased two times. Concerning the selectivity of monoepoxide, it remained relatively high during the whole reaction time (92% after 3 h). This was most probably because of the low amount of monoepoxide formed during the reaction. PhPA showed a higher activity than HMPA during the first hour of reaction, this trend changed after 100 min. After 3 h, 26% of CHDD was converted with 93% selectivity. The amount of CHDD converted after 180 min depended on the phosphorus source used and followed the next order:

PA > AMPA > HMPA > PhPA

4.1.2.2. Comparison of phosphorus sources using methyltrioctylammonium hydrogensulfate as PTC

In this series of experiments, phosphoric acidand several phosphonic and phosphinic acids were used as phosphorus precursors together with sodium tungstate to form the polyperoxocomplex. PTC-B was used phase-transfer catalyst to form the catalytic system. The results obtained from these reactions are shown in Figure 31.

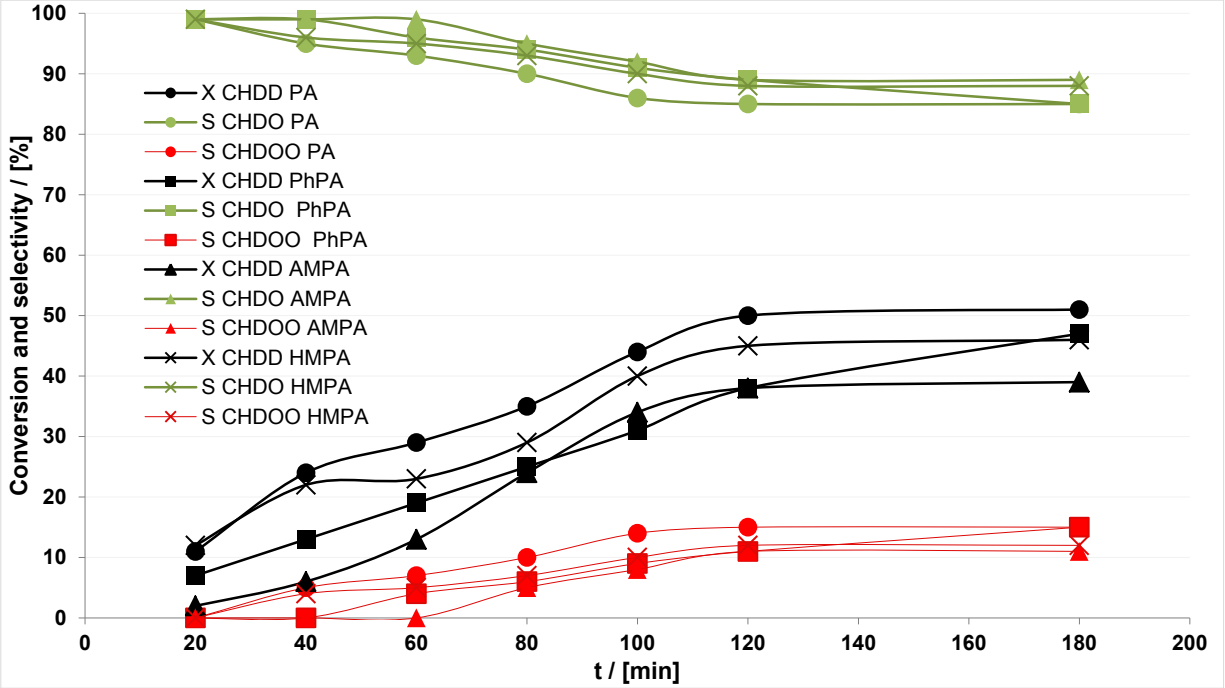


Figure 31. Selective monoepoxidation of CHDD using sodium tungstate and different phosphoric (or phosphonic) acid(s) as precursors for the formation of the polyperoxo complex. Methyltrioctylammonium hydrogensulfate was used as PTC for these reactions. Reaction conditions: 0.5 mmol of Na_2WO_4, 0.5 mmol PTC A, 0.5 mmol of phosphoric (or phosphonic) acid(s), two identical portions (0.25 eq.) of H_2O_2 were added after 0 and 60 min (0.5 eq. in total), t = 3 h, T = 60 °C, U = 800 rpm.

From these set of results it can be concluded that replacement of hydrogensulfate for chloride as the anion of the PTC has an influence in the reaction rate of most catalyst systems. As in the case of PTC-A, the system formed by sodium tungstate, PTC-B and PA showed the highest activity, achieving a conversion of 29% after 1 h and complete conversion (50%) after only 2 h. Yet again, selectivity of 85% towards CHDO after 2 h was also the lowest when this system was used. Surprisingly, the next system with the highest activity was when HMPA was used as the phosphorus source. Apparently, the presence of the hydrogensulfate anion enhances the activity of this catalyst system. The conversion of CHDD with HMPA was 45% after 2 h with a CHDO selectivity of 88% and the latter did not change in the last hour of the reaction time. By changing the anion of the PTC, the final conversion of CHDD with HMPA increased from 30% to 45%. Similarly, the activity of the PhPA catalyst system was improved and a conversion of 46% was achieved after 3 h of reaction time. However, the selectivity of CHDO with this catalyst system was 85%. During the first 2 hours of reaction, the conversion of CHDD with PhPA was lower than with HMPA. This might be due to a longer induction time for the formation of the active species. The conversion of CHDD (39%) and selectivity of 89% towards CHDO after 3 h with AMPA and

PTC-B presented basically no change and a very similar behavior throughout the reaction time compared to PTC-A. The amount of CHDD converted after 180 min depended on the phosphorus source used and followed the next order:

PA > HMPA > PhPA > AMPA

This result is contradictory to the one reported in the literature [113], in which the catalyst system formed by sodium tungstate, PTC-B and AMPA gave better results than PA and PhPA in the epoxidation of cis-cyclooctene with the same catalyst system. According to Noyori et al., a large amount of HMPA (around 60%) is decomposed to PA during the epoxidation but it still is more effective than PA. For this reason, the decomposition of AMPA, HMPA and PhPA to PA during the epoxidation of CHDD was followed using ^{31}P NMR spectroscopy (see Figure 32).

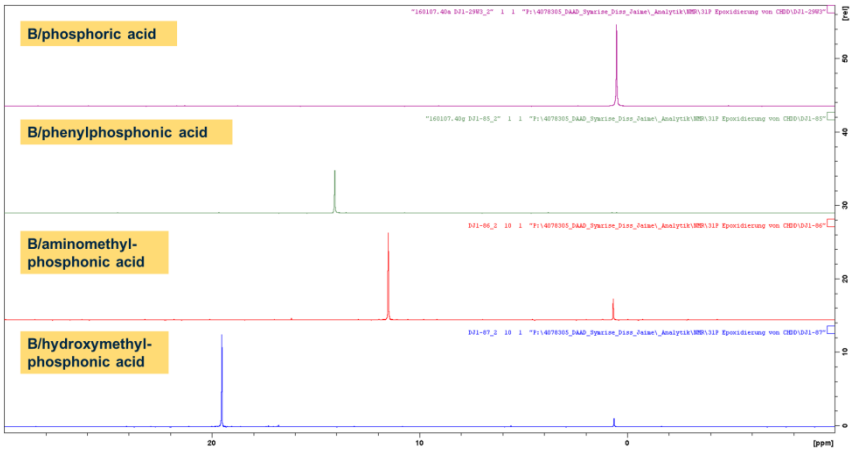


Figure 32. ^{31}P NMR spectra of the aqueous phase using PTC B and different phosphorus-containing acids after 180 min of reaction time

The chemical shift corresponding to phosphoric acid in ^{31}P NMR spectra was found in small amounts in the aqueous phase of the reaction mixtures when AMPA and HMPA were used. This would support the idea that these phosphonic acids first decompose to phosphoric acid and then form the active species responsible for the epoxidation of CHDD. However, this signal was not found when the experiment with PhPA was sampled.

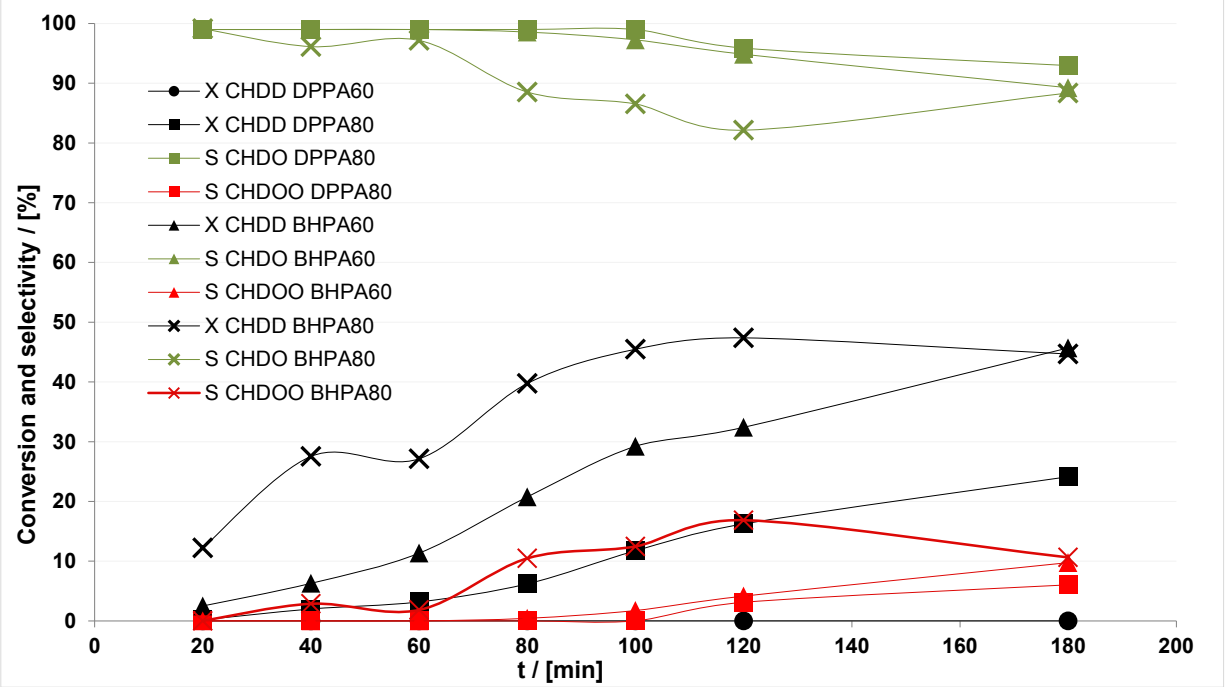


Figure 33. Selective monoepoxidation of CHDD using sodium tungstate and different phosphinic acids as precursors for the formation of the polyperoxo complex. Methyltrioctylammonium hydrogensulfate was used as PTC for these reactions. Reaction conditions: 0.5 mmol of Na_2WO_4, 0.5 mmol PTC A, 0.5 mmol of phosphonc acid, two identical portions (0.25 eq.) of H_2O_2 were added after 0 and 60 min (0.5 eq. in total), t = 3 h, T = 60 - 80 °C, U = 800 rpm

DPPA and BHPA were also tested for the monoepoxidation of CHDD under phase-transfer conditions. The usage of phosphinic acids showed a lower activity compared to PA and phosphonic acids. For this reason, the results obtained were analyzed separately and are shown in Figure 33. A test using DPPA run at 60°C resulted in extremely low conversion of CHDD and only traces of CHDO after 180 min. The catalyst system showed activity when the reaction temperature was increased to 80°C. However, the conversion of CHDD only reached 3.1% after the first 60 min of reaction time. The conversion increased to 16.2% after 120 min. This means that during the second hour of reaction, the conversion of CHDD was almost 4.3 times higher than during the first hour. The reason might be an induction time needed for the active species to form, probably caused by time for hydrolysis of phosphinic acids. After 3 h, the conversion of CHDD was only 24.1% with 93% selectivity for CHDO. Among all the phosphorus sources, DPPA showed the worst catalytic activity in the monoepoxidation of CHDD. Surprisingly, when using another phosphinic acid like BHPA, the results obtained were considerably better. Considering the extremely low activity of DPPA at 60°C, the first reaction conducted with BHPA was also done at 80°C. Already after 40 min the first charge of oxidant was consumed and 27% of CHDD was converted with 96% selectivity for CHDO. The conversion increased to 47% after 120 min but the selectivity of

CHDO dropped considerably to 82%. The result obtained after 180 min is clearly a GC error and was not considered for the discussion. Based on the unexpected conversion achieved with BHPA, another test at 60°C was done. As expected, the activity of the BHPA catalyst system decreased and after 60 min of reaction only 11.3% of CHDD were converted with full selectivity towards CHDO. After 180 min, the conversion of CHDD was 45.7 with 89.2% selectivity. The catalyst system with BHPA is clearly better than DPPA among the phosphinic acids tested. Additionally, complete conversion of H_2O_2 was achieved already after 100 min at 80°C. Nevertheless, a slightly higher selectivity at the same conversion can be achieved by running the reaction at 60°C instead of 80°C. The activity of the catalyst system in relation to the phosphinic acids tested at 60°C and 80°C was:

BHPA80 > BHPA60 > DPPA80 >> DPPA60

By comparing PhPA and DPPA when the same PTC was used, interesting conclusions can be drawn. The presence of a second phenyl group directly bonded to the P central atom, like the in case of DPPA, is enough to hinder any catalytic activity at 60°C in the conversion of CHDD. When the reaction was carried out at 80°C, the conversion of CHDD was 3% after 60 min, approximately 6 times less than the conversion achieved with PhPA at 60°C, which was 19%. During the second hour of reaction time, the activity of the DPPA catalyst system increased and 16% of CHDD were converted after 120 min, only 2.4 times lower than the conversion achieved with PhPA at 60°C, which was 38%. During the last 60 min, a final CHDD conversion of 24% was achieved with DPPA. In a similar way, the presence of a second hydroxymethyl group bonded to the P central atom seemed to slow down the reaction´s rate at 60°C. The conversion of CHDD after 60 min was only 11.3% with BHPA. However, the conversion reached 45.7% after 180 min, which was the same conversion obtained with HMPA at 60°C after 180 min. When the reaction using BHPA was carried out at 80°C, the reaction rate was basically the same as the one with HMPA at 60°C.

4.1.2.3. Comparison of phosphorus sources using methyltrioctadecylammonium hydrogensulfate as PTC

In this series of experiments, PA and several phosphonic acids were used as phosphorus precursors together with sodium tungstate to form the polyperoxocomplex. PTC C was used as phase-transfer catalyst to form the catalytic system. The results obtained from these reactions are shown in Figure 34

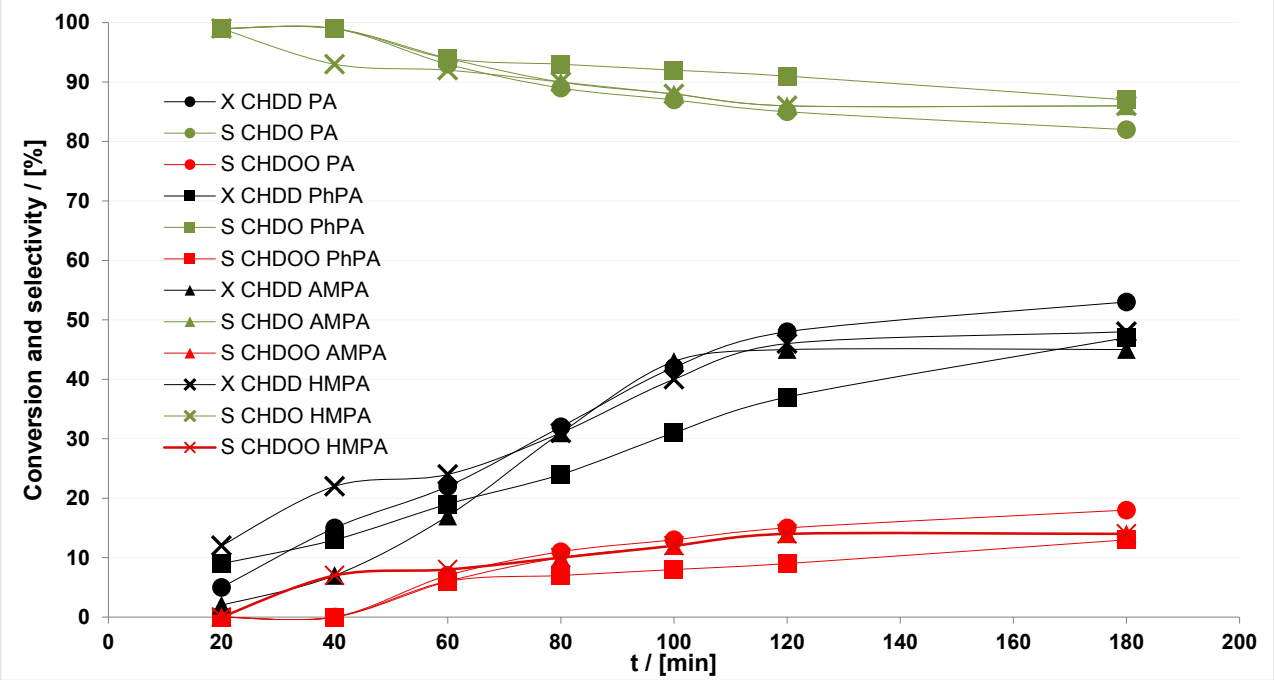


Figure 34. Selective monoepoxidation of CHDD using sodium tungstate and different phosphoric (or phosphonic) acid(s) as precursors for the formation of the polyperoxocomplex. Methyltrioctadecylammonium hydrogensulfate was used as PTC for these reactions. Reaction conditions: 0.5 mmol of Na_2WO_4, 0.5 mmol PTC A, 0.5 mmol of phosphoric (or phosphonic) acid(s), two identical portions (0.25 eq.) of H_2O_2 were added after 0 and 60 min (0.5 eq. in total), t = 3 h, T = 60°C, U = 800 rpm

An effect can be noticed when the PTC used has a longer alkyl chain in comparison to PTC-A and B. During the first 60 min of reaction, HMPA showed the highest catalytic activity and reached 24% conversion of CHDD. However, this high reaction rate also means a CHDO selectivity of 92%. The conversion of CHDD with PhPA was the second highest after 20 min. Nevertheless the reaction rate dropped and became slower with time. After 60 min, 19% of CHDD were converted with 93% selectivity of CHDO. Surprisingly, the catalyst system with PA had a slower start compared to HMPA and PhPA when PTC-C was used. This phase-transfer catalyst was the first to show a different trend during the early stage of the reaction. A possible explanation would be a synergistic effect between the structure of the polyperoxocomplex and the longer length of the alkyl chain bonded to the N atom in the PTC. Still, the conversion of CHDD after 60 min was 22% with 93% selectivity of CHDO. The slowest catalyst system after 60 min of reaction was the one with AMPA. During the 40 min of reaction the conversion of CHDD took place somewhat slow and afterwards it became faster. It might be possible that with AMPA it took longer for the active species to form. The conversion of CHDD with AMPA was 17% with a CHDO selectivity of 94%. Although the conversion of CHDD was sacrificed, AMPA showed the highest selectivity of CHDO after 1 h of reaction. The catalytic activity shown by HMPA, AMPA and PA was very similar during the

second hour of reaction. These three catalysts systems basically achieved the theoretical complete conversion in regard to the amount of oxidant added. With HMPA, the conversion of CHDD was 46% with 86% selectivity to CHDO. With PA 48% of CHDD were converted with a CHDO selectivity of 85%. During the second hour of reaction time, the catalyst system formed with PA showed again the highest activity, like when PTC-A and B were used. With AMPA, a conversion of 45% was achieved with a selectivity of 85.5%. In the case of PhPA, the reaction rate seemed to slow down and the conversion of CHDD was only 37%, the lowest one among these catalyst systems after 120 min of reaction time.

After 180 min, the CHDD conversion with PhPA was 47% with a CHDO selectivity of 87%. Even though it took longer for this catalyst system to achieve the same conversion previously achieved by the other systems, the selectivity of CHDO was slightly higher. The amount of CHDD converted after 180 min depended on the phosphorus precursor used and followed the next order:

PA > AMPA > HMPA > PhPA

A comparison between the results obtained when PTC-B and C were used can also be done. The most evident difference was noticed when PA was used. When the length of the alkyl chain was increased from C_8 to C_{18}, a slower reaction rate during the first 60 min of reaction could be noticed. This caused a drop in the conversion, which was 0.25 times lower when using PTC C. Still, the reaction rate increased during the remaining reaction time and similar conversions were achieved with both catalyst systems. The CHDO selectivity was somewhat lower when PTC-C was used. This was most probably caused by the slightly higher conversion of CHDD with PTC-C.

4.1.2.4. Comparison of different PTC and phosphoric acid

In this series of experiments, several quaternary ammonium salts with structural differences (i.e. number of methyl groups bonded to the N atom of the cation of the PTC, length of the alkyl chain (or chains) present in the ammonium cation and type of anion of the PTC). Since PA showed the highest catalytic activity after 180 min and the fastest reaction rate among the phosphorus sources tested, it was selected for these series of experiments. The structures of the PTCs investigated, both the cation and anion, are shown in Figure 35.

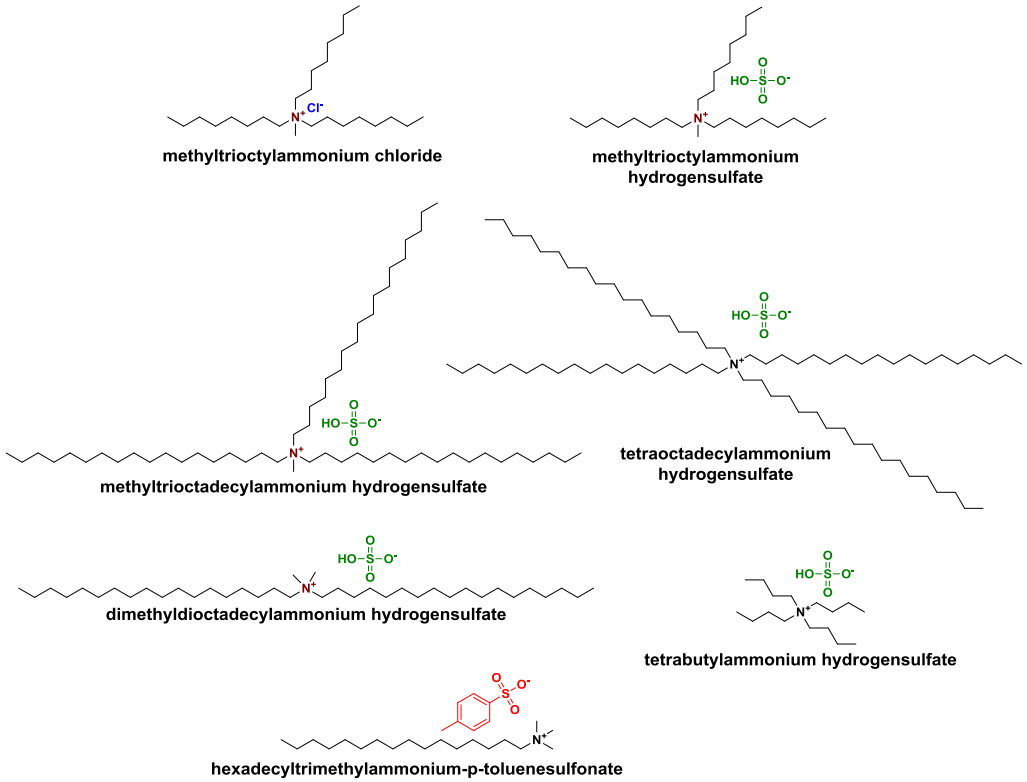


Figure 35. Structures of the different PTCs tested for the epoxidation of CHDD

Even though phase-transfer catalysis was developed to enable the transfer of hydrophilic anions into an organic medium [114], it was of special interest to investigate the influence of the PTC structure for the extraction of the polyperoxo species into the organic phase. An important parameter to consider is that the anion originally present in the PTC (e.g. chloride or hydrogensulfate) might have a higher extraction constant than the anion of H_2O_2 or the activated polyperoxotungstatophosphate. Regarding the problematic of extracting anions into an organic phase, Dehmlow et al have also stated that the extraction of oxidizing anions from an aqueous phase into a nonpolar medium can be relatively easy [115,116]. Concerning the two ions that conform the PTC (both cation and anion); it is known that both affect its lipophilicity i.e. its ability to extract the desired ion from the aqueous into the organic phase. Based on this, there must be an effect on the transfer of the polyperoxo specie from the aqueous into the organic phase. Based on these ideas, a set of PTCs with different structures was tested for the monoepoxidation of CHDD (see Figure 36).

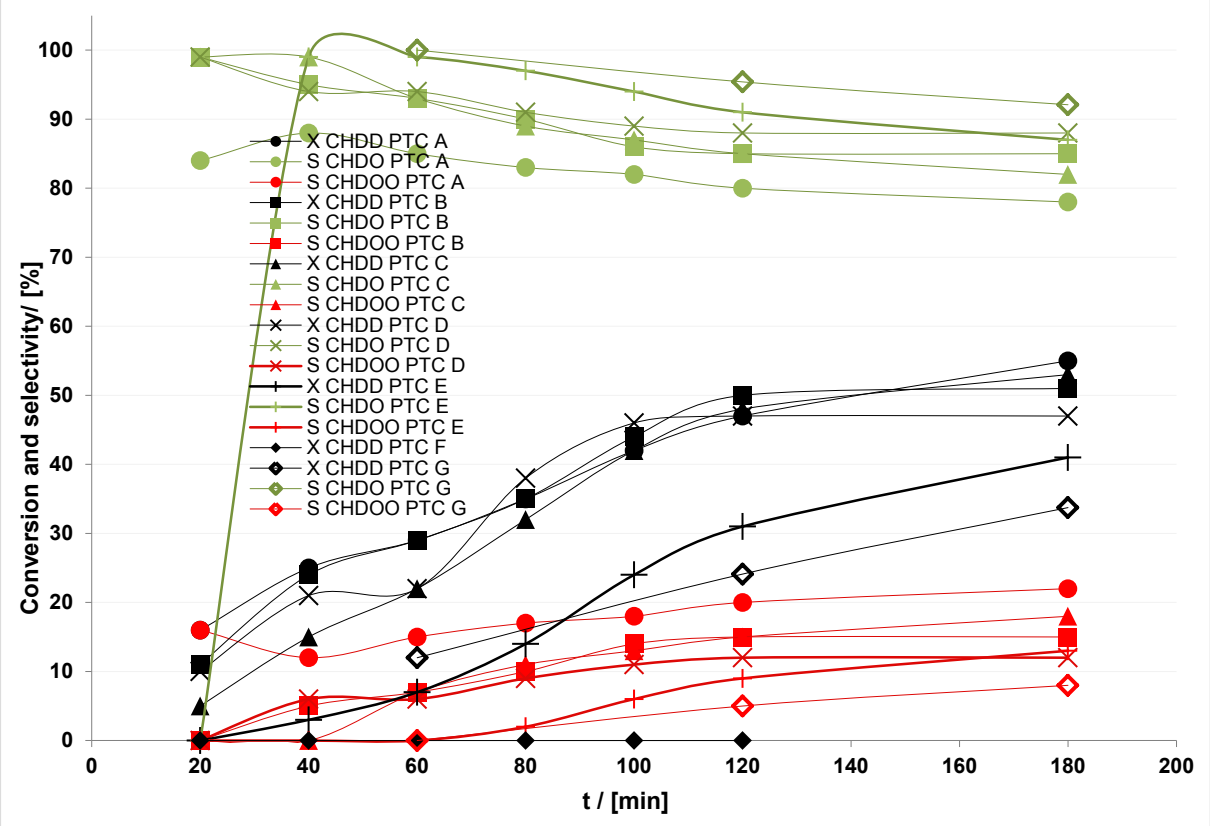


Figure 36. Selective monoepoxidation of CHDD using sodium tungstate and phosphoric acid as precursors for the formation of the polyperoxocomplex. Several quaternary ammonium salts were used as PTC for these reactions. Reaction conditions: 0.5 mmol of Na_2WO_4, 0.5 mmol PTC, 0.5 mmol phosphoric acid, two identical portions (0.25 eq.) of H_2O_2 were added after 0 and 60 min (0.5 eq. in total), t = 3 h, T = 60 °C, U = 800 rpm

The catalytic activity shown by the PTCs was diverse and a dependence on the structure of the cation could be noticed. However, the catalytic activity was very similar when the only difference was the anion (either Cl^- or HSO_4^-), as in the case of PTC-A and B. After 60 min, the conversion of CHDD with both PTCs was 29%. Still, a remarkable difference was seen in the CHDO selectivity of these systems, which was 85% for PTC-A and 93% for PTC-B. Since the cationic part of the quaternary ammonium salt is exactly the same, this difference in the selectivity was most probably related to the interactions of each anion with hydrogen peroxide and the effect related to its extraction from the aqueous phase into the organic phase. After 120 min of reaction time the conversion with PTC B was 50%, slightly higher than with PTC-A (47%). The CHDO selectivity with PTC B was 85% and 80% for PTC-A. Again, the presence of the hydrogensulfate anion in the reaction mixture influenced the selectivity towards CHDO. After 180 min, the conversion of CHDD using PTC-B did not increase and thus the selectivity of CHDO remained the same. In the case of PTC-A, the conversion of CHDD increased to 55% and the selectivity, as expected, decreased to 78%. It

can be concluded from these results, that the anion of the PTC indeed has an influencing role in the epoxidation reaction of CHDD. Both the conversion of CHDD and selectivity towards CHDO were different during and at the end of the reaction. Although a higher conversion of CHDD was achieved with PTC-A, the selectivity towards CHDO was also than with PTC-B. Since PTC-B showed both a higher selectivity towards CHDO and relatively high conversion of CHDD, a PTC with a longer cationic radius (i.e. longer alkyl chains) like PTC-C was additionally tested. To avoid extra effects caused by the structure of the cation, the presence of a methyl group directly bonded to the N atom was kept constant. A difference in the conversion of CHDD was noticed, especially during the first 60 min of reaction. With PTC-B a CHDD conversion of 29% was reached with selectivity towards CHDO of 93%. This difference is most probably due to the amount of N^+-containing cations present in the interface and responsible for accomplishing the extraction of the active species from the aqueous into the organic phase (see Figure 37). However, the activity of the catalyst system formed with PTC-C increased and the conversion of CHDD was 48% with selectivity towards CHDO of 85% after 120 min. The conversion of CHDD with PTC-B was 50%, still slightly better than PTC-C. After 180 min, the conversion of CHDD and selectivity towards CHDO did not change with PTC-B. In the case of PTC-C, the conversion of CHDD kept increasing and reached 53%. Nevertheless, the selectivity dropped down to 82%. The cationic radius also has an influence in the epoxidation of CHDD, especially during the beginning of the reaction, in which the PTC with a smaller cationic radius had a higher activity. After 3 hours, although the selectivity towards CHDO was insufficient, the conversion with PTC-C was the highest.

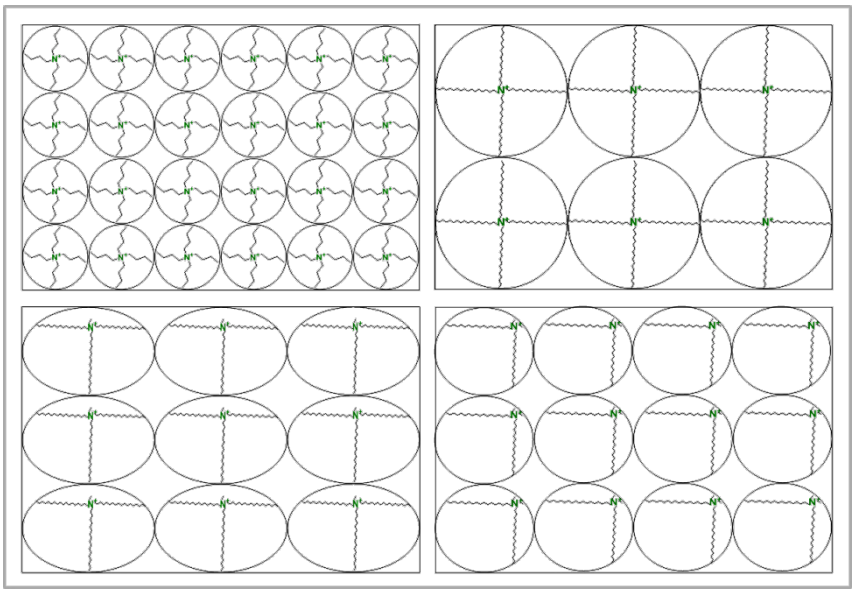


Figure 37. Effect of bulkiness of a PTC at phase interface

To evaluate the steric effect of methyl groups and long alkyl chains in the cation of the PTC (alkyl chains:methyl groups ratio), the catalytic activity in the monoepoxidation of CHDD with a PTC with one methyl group (PTC-C) was compared with the catalytic activity of a PTC with two methyl groups (PTC-D) and a PTC without methyl groups (PTC-E). Phase-transfer catalysts with alkyl chains of such length have already been successfully used for the epoxidation of cyclic olefins and other functional groups [117,118].

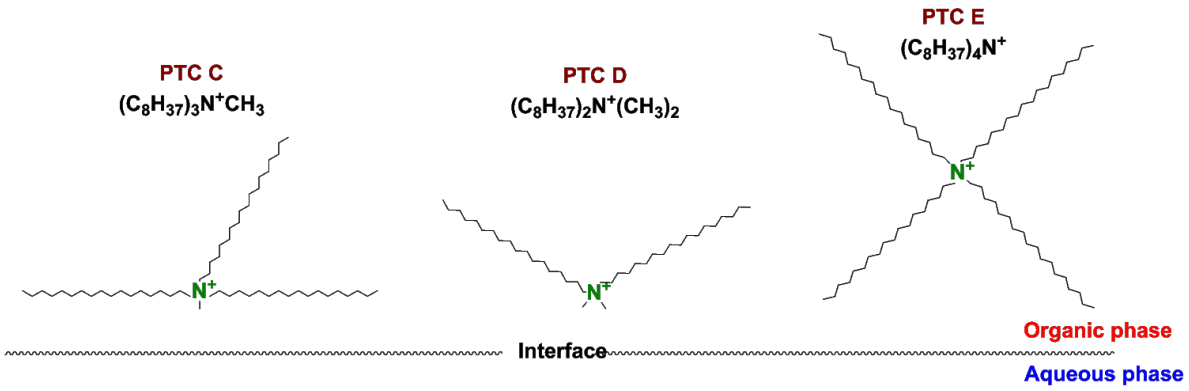


Figure 38. Different arrangement of quaternary ammonium cations at the phases interface

To eliminate additional factors related to the structure of the cation that could potentially influence the extraction of the polyperoxotungstate species during the reaction, the PTCs used in these experiments contained only linear chains formed by 18 carbons (*octadecyl*, $C_{18}H_{37}$). Interestingly a difference in the catalytic activity within these three catalysts was only noticeable when no methyl group was present in the cation of the quaternary ammonium salt. After 60 min, 22% of CHDD was converted with PTC-C and D, whereas only 7% of CHDD were converted with PTC-E. Apparently, the presence of a second methyl group bonded to the N atom of the ammonium salt has no big influence in the extraction of the active species from the aqueous into the organic phase. The selectivity of CHDO, 93% for PTC-C and 94% for D, was also very similar. Due to the low amount of CHDD converted, an expected complete selectivity of CHDO was achieved with PTC-E after 60 min. After 120 min, the catalytic activities shown by PTC-C and D were again similar. The conversion of CHDD with PTC-C was 48% while with PTC-D 47% of CHDD were converted. With both PTCs, a selectivity of 85% towards CHDO was achieved. In the case of PTC-E, the conversion was 31% with a selectivity of CHDO of 91%. This means that during the second hour of reaction, the amount of CHDD converted was almost 3 times higher than after the first hour.

During the last hour of reaction, the conversion and selectivity using PTC-D remained the same while the conversion using PTC-C increased to 53% with a selectivity of CHDO of

82%. The conversion of CHDD with PTC-E reached 47%. This is a surprisingly high conversion, considering the rather slow conversion presented at the beginning of the reaction with PTC-E. The selectivity of CHDO with PTC-E was 87%. The results obtained with these PTCs confirm influence on the monoepoxidation of CHDD. The conversion of CHDD with PTC-C and D was approximately 3 times higher than with PTC-E. Although it might look like this difference disappeard after 180 min of reaction time, it is important to notice that after 120 min, the theoretical complete conversion of CHDD had been already achieved with PTC-C and D. This should not mislead to the idea that the ability to extract the actives species from the aqueous into the organic phase with PTC-D increases with time. Nevertheless, it is an interesting result because of the low hydrophilicity of such a quaternary ammonium salt due to its long alkyl chains and the lack of a methyl group in the cation part of the PTC. Due to the activity shown by the catalyst system with PTC-E, a PTC with shorter alkyl chains in its cation (PTC-F) was also investigated. The butyl chains present in the ammonium salt are 4.5 times shorter than the ones present in PTC-E. Unexpectedly no reaction took place when PTC-F was used. There might be several explanations for this. The fact that the alkyl chains of PTC-E are fairly longer might be the key for this behavior. It is expected that the lipophilicity of the PTC increases with the length of the alkyl chains. If this assumption is true, then it would be more difficult for a more lipophilic catalyst such as PTC-E to extract the active species from the aqueous phase into the organic phase for the epoxidation to take place. Nevertheless, it might also be possible that, because of their length, these chains are not as strained as the butyl chains and thus they can move more “freely”. This would make it possible for the cation of the PTC to reach the interface and carry out the extraction process of the species between the two phases. An extra experiment using a tetraalkyl ammonium salt with alkyl chains, which have a length between C_4 and C_{18} might corroborate this hypothesis.

The effect of the cation’s structure of a PTC in a biphasic epoxidation reaction using the same polyperoxo complex and H_2O_2 as oxidant had already been discussed; it was concluded that epoxidation, which takes place in the organic phase, is the rate-determining step [119]. Those PTCs possessing longer alkyl chains are more lipophilic, *i.e.* have a higher concentration in the organic phase, and thus can better extract the polyperoxotungstatophosphate species into the organic phase. This theory would explain why the highest CHDD conversions were obtained using PTCs A, B, C and D. Using unsymmetrical quaternary cations is also relevant, as the steric hindrance caused by symmetrical cations might be higher when the catalyst tries to reach the double bond of CHDD. This would also explain why the highest CHDD conversions were achieved with the

unsymmetrical PTCs A, B and C. There might also be an effect caused by the length of the alkyl chains. This can be appreciated when comparing PTC-B and C during the first 60 min of the reaction, in which the CHDD conversion was higher when using PTC-B; however, this effect seems to disappear as the conversion with PTC-C was higher than with PTC-B at the end of the reaction.

Finally, the effect caused by the anion of the PTC can be investigated by comparing PTC-A and B, which possess the same cation. The advantages of using PTC-B over chloride-containing PTC-A for the epoxidation of terminal olefins has been reported by Noyori and coworkers [120]; these include a higher catalytic activity and selectivity towards the epoxide. The absence of Cl^- also is highlighted. Surprisingly, in the case of CHDD there seems to be no influence on the conversion achieved by the catalyst formed with both PTCs. The conversion of CHDD with PTC-A was higher than with PTC-B during most of the reaction time and at the end of the reaction. On the other hand, the selectivity towards CHDO was clearly higher with PTC-B during the reaction; after 180 min, the selectivity towards CHDO with PTC-B was 85%, whereas with PTC-A it was only 78%.

4.1.3. Epoxidation using $[(C_8H_{17})_3NCH_3)]_3[(PO_4(W(O)(O_2)_2)_4)]$ complex "ex-situ"

The $[(C_8H_{17})_3NCH_3]_3[PO_4[W(O)(O_2)_2]_4]$ complex, first reported by Venturello and coworkers, can be isolated and used for the epoxidation of olefins [101]. Besides being a good stoichiometric oxidant, it can also act as a catalyst in the presence of H_2O_2. The goal was to test its activity in the epoxidation of CHDD and verify if the selectivity of CHDO could be improved by preparing the catalyst *ex situ* (see Table 14).

Table 14. Epoxidation of CHDD using Venturello's $[(C_8H_{17})_3NCH_3)]_3[(PO_4(W(O)(O_2)_2)_4)]$ complex

t [min]	X_{CHDD} [%]	S_{CHDO} [%]	S_{CHDOO} [%]
20	29	96	3
60	32	91	5
80	53	70	12
180	53	74	11

Reaction conditions: 0.25 mmol of Venturello catalyst, two identical portions (0.25 eq) of H_2O_2 were added after 0 and 60 min (0.5 eq. in total), t = 3 h, T = 60°C, U = 800 rpm

To enable a comparison with the catalyst prepared *in situ* (see Figure 30), the same amount of catalyst was added. Surprisingly, the catalyst prepared *ex situ* was extremely active. CHDD underwent 29% conversion to give CHDO in 96% selectivity after only 20 min.

Apparently, most of the H_2O_2 was consumed during this time because the increase in the conversion of CHDD was minimal before the second charge of oxidant was added. After 60 min, the second portion of H_2O_2 was added. The conversion of CHDD increased to 53% with 70% selectivity towards CHDO after 80 min. The reaction was stopped after 180 min with no further increase in the conversion of CHDD.

Clearly, the reactivity of the Venturello catalyst was higher when it was prepared *ex situ*. The selectivity towards CHDO obtained during the first 60 min of reaction by the ex situ catalyst resulted promising. However, after 180 min both the conversion of CHDD and the selectivity towards CHDO was slightly lower than that of the catalyst prepared *in situ*. Thus, although the reactivity of the catalysts was higher when it was prepared *ex situ*, there was no improvement in relation to the results obtained when the catalyst was prepared *in situ*.

4.1.4. Postulated mechanism of the epoxidation with $PO_4[WO(O_2)_2]_4^{3-}$ as active catalytic species under phase-transfer conditions

W^{VI}-based epoxidation systems with H_2O_2 as oxidant have attracted the attention of industrial and research chemists because of their high reactivity for olefins, selectivity for the formation of epoxides and poor activity for the decomposition of the oxidant [112,121,122]. More specifically, the addition of a phosphorus source (*e.g.* phosphoric or phosphonic acids) to the peroxo species formed by WO_4^{2-} in the presence of H_2O_2 resulted in the formation of the W-based $PO_4[WO(O_2)_2]_4^{3-}$ complex [49,52,123], a highly effective catalyst for epoxidation reactions. Furthermore, the results obtained in this work demonstrated that also phosphinic acids (*e.g.* DPPA and BHPA) could obviously also be used as precursors of the polyperoxotungstatophosphate. Investigations on the mechanism of the epoxidation under Venturello's [50] or Ishii's [51,124] conditions have led to the conclusion that these catalyst systems, despite the fact that both differ on the catalysts precursors used, share the common polyperoxotungstatophosphate anion responsible for the epoxidation to take place [125-127]. Recently, based on the results of the investigations mentioned above, Wang et al. [128] provided a reaction scheme where a phosphotungstic quaternary ammonium salt with active oxygen is the catalyst responsible for the epoxidation. The active catalyst (see Figure 5) contains eight active oxygen atoms per molecule and only one active oxygen atom is consumed in each reaction step. Once deactivated, the complex must be regenerated by means of H_2O_2.

Based on these assumptions and the mechanism postulated by Noyori and coworkers for the epoxidation of olefins under phase-transfer conditions using an aminophosphonic acid

coordinated to a peroxotungstate catalyst and H_2O_2 as oxidant (see Figure 6), a catalytic cycle for the epoxidation of CHDD under phase-transfer conditions using H_2O_2 as terminal oxidant is proposed in Figure 39.

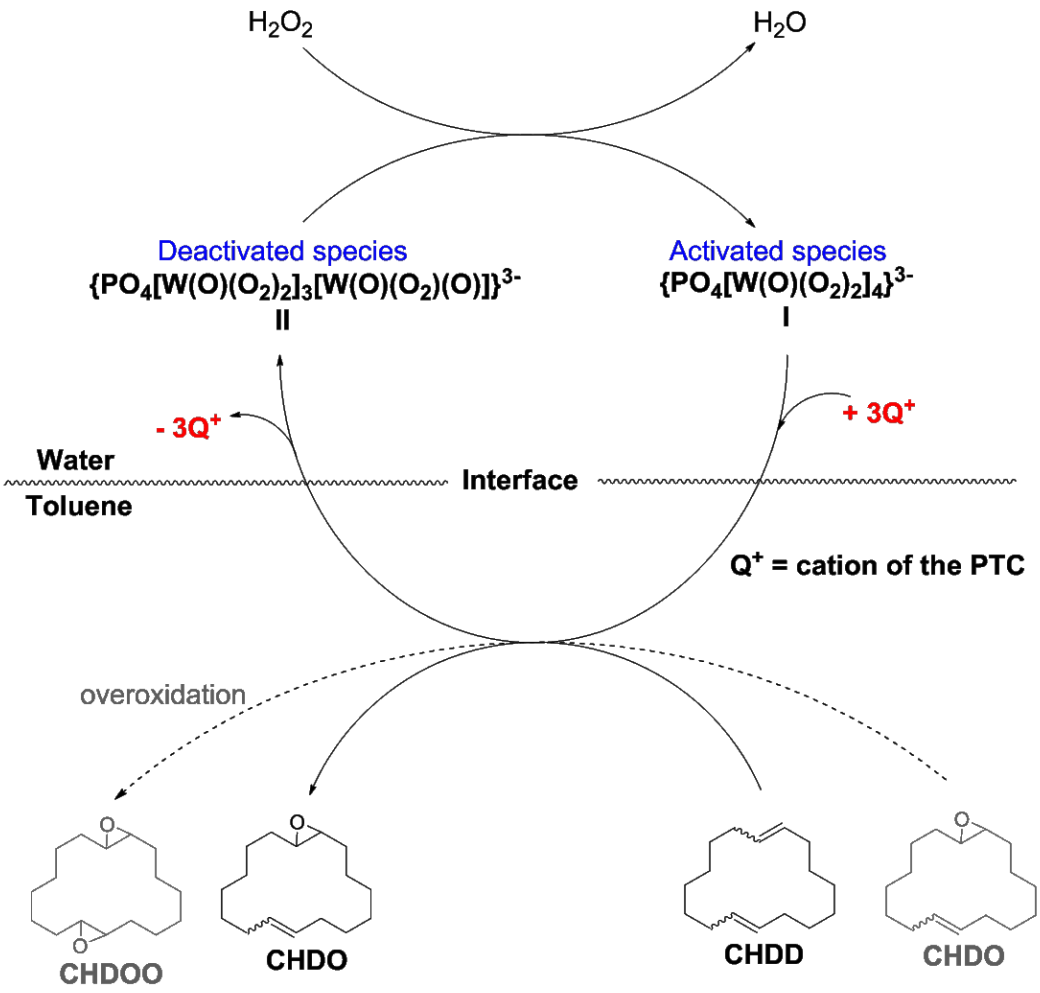


Figure 39. Reaction scheme proposed for the epoxidation of CHDD with polyperoxo complex under phase-transfer conditions

The active species are formed in the aqueous phase by mixing a tungstate precursor and a phosphorus source (e.g. phosphoric acid). The polyperoxotungstophosphate complex **I** is then extracted to the organic phase formed by toluene and CHDD by the cation $\mathbf{Q^+}$ of the PTC. Once in the organic phase, the complex transfers one of its active oxygen atoms to CHDD to form the monoepoxide CHDO. After the oxygen transfer, the deactivated species **II** are transferred back to the aqueous phase, where it is once again oxidized by H_2O_2 and the catalytic cycle starts again. If the concentration of CHDO is high enough, the consecutive oxidation to the corresponding diepoxide by an activated polyperoxotungstatophosphate complex can also take place.

Most probably, the epoxidation of CHDD with H_2O_2 is an example of an oxygen transfer reaction in which the W-containing catalyst is a peroxometal specie. Thus, the oxidation state of the W center of the polyperoxotungstophosphate does not change during the reaction [129].

4.2. Wacker-type oxidation of olefins

4.2.1. Wacker-type oxidation of α-olefins, internal and linear olefins

The $PdCl_2$/DMA copper-free catalyst system developed by Kaneda et al. [73] was systematically applied for the Wacker-type oxidation of several higher α-olefins. Due to its similarity with CHDD, 1-hexadecene was chosen as a model molecule for tests of this system with different Pd^{II} precursors. After the reaction, a sample of each reaction mixture was qualitatively analyzed using GC-FID; the chromatograms obtained are shown in Figure 40.

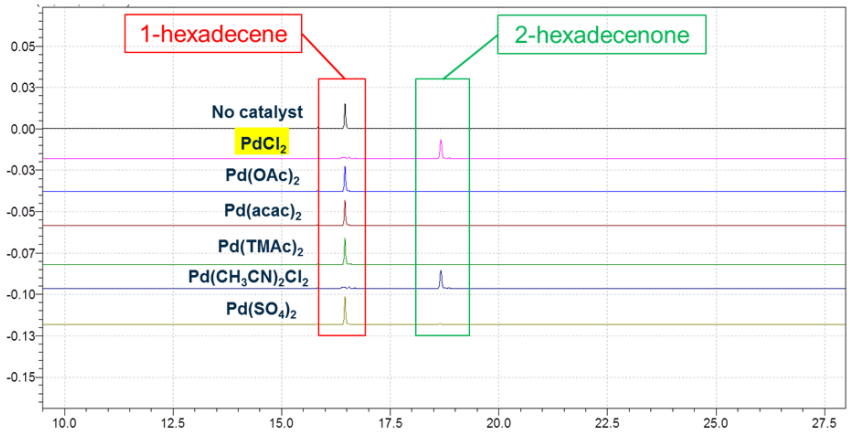
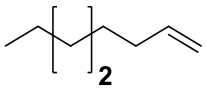
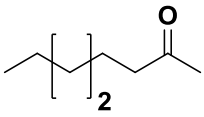
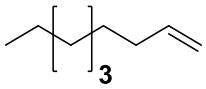
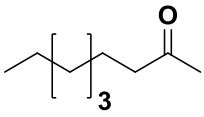
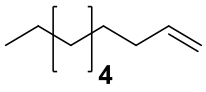
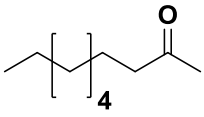
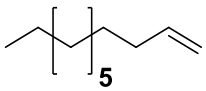
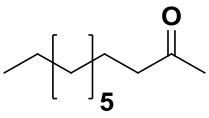
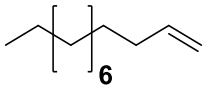
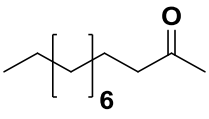
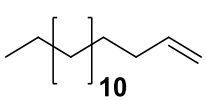
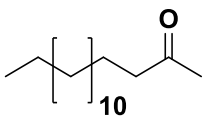


Figure 40. Test of different palladium (II) precursors for the Wacker-type oxidation of 1-hexadecene using the Kaneda catalyst system. Reaction conditions: 1 mol% catalyst, 0.55 mmol 1-hexadecene, 2.5 mL DMA, 0.2 mL H_2O, t = 2.5 h, T = 80°C, p_{O2} = 3 bar

Interestingly, only $PdCl_2$ successfully catalyzed the oxidation of 1-hexadecene, achieving full conversion and selectivity to the corresponding methyl ketone: 2-hexadecenone. During the addition, the nucleophilic attack of a molecule of water takes place at the carbon with the least number of hydrogen atoms (*i.e.* Markovnikov position) of the double bond and thus only the methyl ketone and not the corresponding aldehyde is formed. The need of palladium(II) species for the reaction to take place was confirmed with a blank test, in which no conversion of 1-hexadecene was observed under the same reaction conditions after 2.5 hours. Surprisingly other palladium catalysts (e.g. palladium(II) acetate, palladium(II) acetylacetonate, palladium(II) trimethylacetate and palladium(II) sulfate) did not show any

conversion of the α-olefin under the same conditions. Although this was not expected, there also might be an influence of the chloride ion in the reaction. When bis(acetonitrile)palladium(II) chloride was used as the catalyst, the same result as with $PdCl_2$ was obtained. This might be possible because the two molecules of acetonitrile coordinated to the palladium center leave as soon as the complex dissolves in the reaction solution and do not participate in the catalytic cycle; the only advantage of this complex is its higher solubility in the reaction medium DMA:H_2O at room temperature. However, the catalytic amounts of acetonitrile, which are present in the solution during the reaction, do not seem to have any effect, positive or negative, in the conversion of the olefin or selectivity of the methyl ketone.

Table 15. Oxidation of several α-olefins with Kaneda's catalyst system

Substrate	$PdCl_2$ [mol%]	t [h]	T [°C]	Product	Yield[a] [%]
 **1-octene**	1 mol%	2.5	80	 **2-octanone**	82
 **1-nonene**	1 mol%	2.5	80	 **2-nonanone**	86
 **1-decene**	1 mol%	2.5	80	 **2-decanone**	88
 **1-undecene**	1 mol%	2.5	80	 **2-undecanone**	87
 **1-dodecene**	1 mol%	2.5	80	 **2-dodecanone**	90
 **1-hexadecene**	1 mol%	2.5	80	 **2-hexadecanone**	88

Reaction conditions: 0.55 mmol of olefin, 2.5 mL DMA, 0.2 mL H_2O, T = 80°C, p_{O2} = 3 [bar]. [a] Determined by ^1H NMR spectroscopy using DFB as internal standard.

All of the ^{1}H and ^{13}C NMR spectra of the isolated products can be found in the Appendix section.

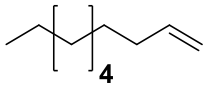
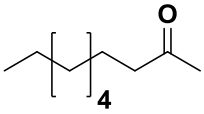
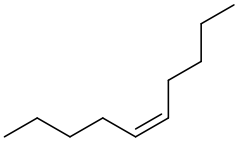
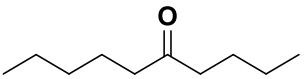
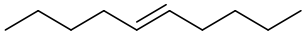
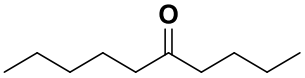
Based on the results obtained with 1-hexadecene and $PdCl_2$ as catalyst, a set of α-olefins from C_8 to C_{12} and C_{16} were oxidized under the same conditions and the product mixture was quantified using ^{1}H NMR. The results obtained are displayed in Table 15. As already proved with the qualitative experiments of the oxidation of 1-hexadecene with $PdCl_2$ and DMA as solvent, all of the α-olefins were successfully oxidized under these conditions. Conversions above 86% with full selectivity to the corresponding methyl ketone were achieved in all cases. Increasing the olefin's chain length does not seem to have a negative effect on the activity of the catalyst system since all of them present similar conversions. The slight difference in the conversion could have been caused by loss of product during the isolation procedure or by a measurement error of the GC method. Again 1-hexadecene was used as substrate, this time the conversion and selectivity were properly determined. This olefin was of particular interest for some reasons: a) it contains exactly the same number of carbons as CHDD and b) it was the only olefin insoluble in the reaction mixture at room temperature, just like CHDD. The low solubility of substrates such as higher olefins or other non-polar unsaturated compounds has been named to be one of the reasons for their low reactivity in Wacker-type reactions [62,130-133]. However, the low solubility of 1-hexadecene in the reaction mixture was not an impediment for the reaction to take place with a very good yield (88%), even slightly higher than the yield obtained when 1-octene, an α-olefin with half the size of 1-hexadecene, was used as the substrate under exactly the same conditions.

Several catalyst systems, including copper-free systems which use other ETMs as co-catalysts, have been successfully used for the Wacker-type oxidation of terminal olefins [22,134]. However, the application of the same systems for analogous internal olefins has been found to be problematic in most cases. For this reason, it was interesting to test internal olefins in the same catalytic system that successfully oxidized a number of terminal olefins. Additionally, internal olefins exist as both *cis*- and *trans*-isomers, which could eventually show different reaction rates. To evaluate if there is a difference in the reactivity of internal olefins and their isomers, *cis*-5-decene and *trans*-5-decene were oxidized under the same conditions as their 1-decene isomer; the result is shown in Table 16.

As expected, the activity of the Kaneda's catalyst system in the oxidation of higher, internal olefins was considerably lower compared to its activity for the oxidation of α-olefins. When *cis*-5-decene was treated under the same reaction conditions as 1-decene, the conversion decreased about 5.5 times. It is well known that, compared with the ready oxidation of α-

olefins, the Wacker-type oxidation of internal and cyclic olefins is extremely slow under these reaction conditions [62].

Table 16. Oxidation of terminal and internal olefins: *cis*- and *trans*-5-decene with Kaneda's catalyst system

Substrate	$PdCl_2$ [mol%]	t [h]	T [°C]	Product	Yield[a] [%]
 **1-decene**	1 mol%	2.5	80	 **2-decanone**	88
 **5-cis-decene**	1 mol%	2.5	80	 **5-decanone**	16
	5 mol%	20	80		73
 **5-trans-decene**	1 mol%	2.5	80	 **5-decanone**	-
	5 mol%	20	80		78

Reaction conditions: 0.55 mmol of olefin, 2.5 mL DMA, 0.2 mL H_2O, T = 80°C, p_{O2} = 3 [bar]. [a]Determined by ^1H NMR spectroscopy using DFB as internal standard.

Several strategies haven been followed to overcome this set of problems, *e.g.* increase of the catalyst concentration, longer reaction times, use of phase-transfer catalysis (tetraalkylammonium salts [135], polyethylene glycols [133] or cyclodextrins [136,137]), higher reaction temperatures or addition of co-solvents to increase the solubility of the substrate in the reaction mixture. The strategy followed in the present work was to increase 5 times the concentration of $PdCl_2$ and the reaction time to 20 h. To prevent the formation of undesired byproducts, the reaction temperature was kept constant. Under the new reaction conditions, the conversion of 5-*cis*-decene increased and 5-decanone was obtained in 73% yield, around 4.5 times higher than the yield obtained under the conditions used for the oxidation of α-olefins.

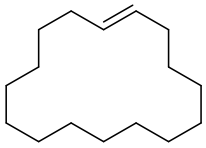
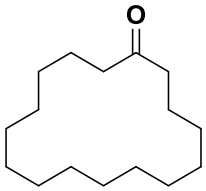
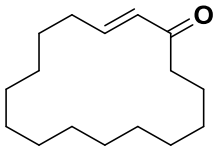
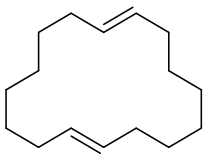
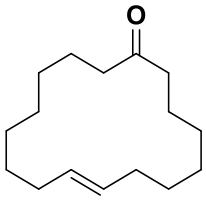
To evaluate if there is a difference in the reactivity of *cis* and *trans* isomers of internal olefins, 5-*trans*-decene was also tested as a substrate under the modified reaction conditions. Although it would be expected that, because of steric hindrance, a double bond with *cis* configuration could coordinate easier to the palladium center of the catalyst, the oxidation of *trans*-5-decene isomer resulted in 78% yield, slightly higher than the *cis* isomer. Nevertheless, by increasing the catalyst concentration and the reaction time, it was possible

to obtain similar results compared to the ones achieved with α-olefins using Kaneda's catalyst system. The 78% yield of 5-decanone obtained in the oxidation of 5-*trans*-decene is also comparable to the 80% isolated yield of 5-decanone reported by Kaneda et al. [73], especially because the water:DMA ratio used in this work was slightly higher (approx. 38% higher) than the amount of oxidant used in the present work.

4.2.2. Wacker-type oxidation of (Z/E)-cyclohexadecene

Since the use of the conditions described by Kaneda ([$PdCl_2$]=1-5 mol% in DMA:H_2O, 3 bar O_2 [73]) resulted in very good yields of methyl ketones in the Wacker-type oxidation of α-olefins and in good yields of 5-decanone when (Z/E)-5-decene was the substrate, it was decided to test the same system for the oxidation of (Z/E)-cyclohexadecene. The cyclic monoolefin was provided by Symrise. It was prepared via a selective monohydrogenation of CHDD. Nevertheless, the formation of undesired cyclohexadecane could not be avoided under the reaction conditions (5 wt% Pd/Al_2O_3, 1 wt% catalyst, 5 bar H_2, 50°C) and the highest purity of (Z/E)-cyclohexadecene after column distillation was 46% in cyclohexadecane.

Table 17. Comparison of the Wacker-type oxidation of (Z/E)-cyclohexadecene and CHDD under the same reaction conditions

Entry	Substrate	$PdCl_2$ [mol%]	Product	X_{CHDD} [%]	S [%]	Y [%]
1[a]		5 mol%		24	53	13
					17	4
2[b]		5 mol%		75	12	9

Reaction conditions: 0.55 mmol of olefin, 2.5 mL DMA, 0.2 mL H_2O, T = 80°C, p_{O2} = 3 [bar] [a] Determined by ^1H NMR spectroscopy using DFB as internal standard. [b] Determined by GC method using an internal standard.

The activity of the catalyst in the Wacker-type oxidation of (Z/E)-cyclohexadecene should not be affected by the presence of cyclohexadecane; on the other hand, the different solubility in the reaction medium could decrease the conversion of the substrate. The results obtained (see Table 17) were compared to the ones achieved for CHDD. Even at a relatively high concentration (5 mol%), the conversion of the substrate was only 24%, almost 3 times lower than the conversion obtained when (Z/E)-5-decene was treated under the same reaction conditions. The selectivity towards the desired monoketone was 53%, yielding 13%. Additionally, oxidation of the cyclic olefin at the allylic position also took place. Such behavior was already reported by Kaneda and coworkers in the Wacker-Oxidation of cyclohexene [73], whereas linear terminal or internal olefins resulted only in the corresponding ketone. The presence of methylene groups of cyclohexadecane in the reaction mixture made the quantification with the ^{1}H NMR method more complicated. Moreover, the substrate mixture was solid at room temperature and insoluble in the reaction mixture. This could have caused that some of the substrate was not in contact with the catalyst mixture during the reaction and could be an explanation for the low conversion of the substrate.

Interestingly, the activity of the catalyst increased when a second double bond was present in the C_{16} cyclic olefin. Under the same reaction conditions, the conversion of CHDD was 75%, three times higher than of the C_{16} ring with only one unsaturation. The conversion of CHDD was also comparable to that one of (Z/E)-5-decene under the same reaction conditions. Nevertheless, the selectivity towards the desired ketone was very low and only a yield of 9% was obtained.

4.2.3. Wacker-type oxidation of CHDD

The Kaneda catalyst system showed activity for the Wacker-type oxidation of CHDD (see Table 17); nevertheless, the selectivity for 8-CHD under these conditions was insufficient. Therefore, other Wacker-type oxidation catalysts and reaction conditions were also tested using CHDD as substrate. A couple of themhave already been successfully used for the oxidation of internal and cyclic olefins, sometimes resulting in higher yields. Such catalysts and the results of their application in the Wacker-type reaction are thoroughly discussed in the following sections.

4.2.3.1. Wacker-type oxidation of CHDD in different DMA-solvent mixtures with $Pd(OAc)_2$ and palladium(II) diamine complexes as catalysts

Although Kaneda and his coworkers reported that the application of $Pd(OAc)_2$ together with DMA resulted in only traces of ketones when used for the oxidation of internal olefins [73], it

was decided to test it as catalyst in the Wacker-type oxidation of CHDD. The results obtained with different catalyst concentrations are presented in Figure 41. The abbreviations of the legends used to classify the selectivity towards each product obtained after the reaction have the following meanings: 8-CHD = (Z/E)-8-cyclohexadecen-1-one, OXYG. PROD. = products with m/z 236, ISOM. CHDD = isomers of CHDD and UNIDENT. = unidentified peaks. The unidentified peaks appeared at higher retention times in relation to those of CHDD, 8-CHD and OXYG. PROD. and are most probably high-boiling compounds.

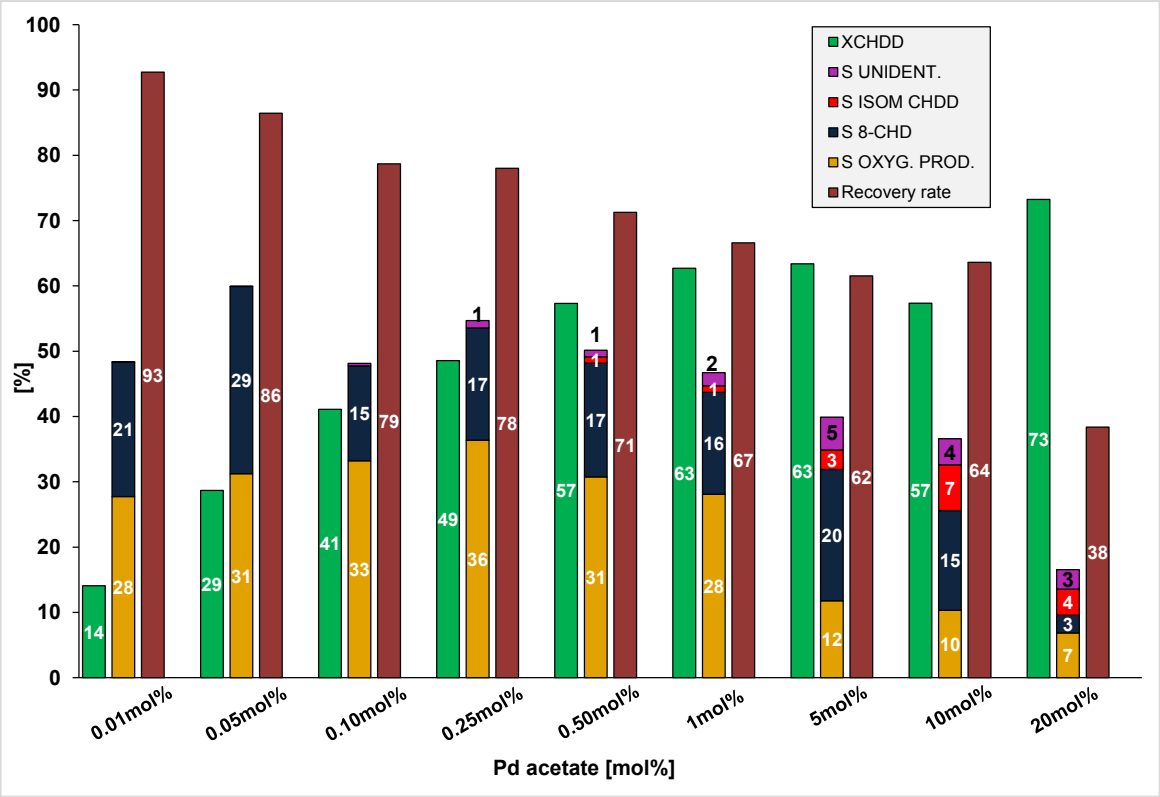


Figure 41. Wacker type oxidation of CHDD using $Pd(OAc)_2$ as catalyst in DMA. Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, p_{O2}=3 bar, t=15 h, T=90 °C.

Contrary to the results obtained by Kaneda in the oxidation of internal olefins, $Pd(OAc)_2$ catalyzed the Wacker-type oxidation in addition to other side-reactions, which resulted in the formation of undesired byproducts. A similar behavior was already reported by Skumov and coworkers [138] for the Wacker-type oxidation of dicyclopentadiene using $Pd(OAc)_2$ and benzoquinone in the presence of highly corrosive perchloric acid. Also, an inhibition effect of dicyclopentadiene and tricyclodecenone due to their complexation with the palladium center was demonstrated. The Wacker-type oxidation took place when $Pd(OAc)_2$ was used in small to high concentrations (0.01–20 mol%). The high activity shown by the $Pd(OAc)_2$-DMA system contrasts with other catalyst systems, which were reported to need a cocatalyst (e.g.

hydroquinone [139,140] and/or NPMoV [141]) or an additive (e.g. perchloric acid [138] or methanesulfonic acid [142]) for the reaction to take place.

Interestingly, when 0.01 and 0.50 mol% of catalyst were used, the highest selectivity towards 8-CHD was obtained at moderate CHDD conversion (see Figure 41). Such catalyst concentrations are relatively low for Wacker-oxidation conditions. As expected, the conversion of CHDD increased and the selectivity for 8-CHD decreased if higher concentrations of $Pd(OAc)_2$ were used. In addition, isomerization of CHDD and formation of diketones plus other oxygenated by-products also took place. The generation of by-products (*e.g.* ethers and other oxygenated products) was already reported by Balbolov and coworkers [142] when $Pd(OAc)_2$ was used as catalyst in the Wacker-type oxidation of CDT in methanol. The oxygenated species formed during the reaction, including ketones, showed an inhibitory effect. This would explain that, even with 20 mol% of catalyst, full conversion of CHDD was not achieved. Most probably, the oxygenated species formed during the reaction coordinate to the palladium center, shielding it and hinder the formation of the π-complex. Oligomeric derivatives as a result of the self-oxidative coupling of CHDD seem to be the major by-products. The same behavior was also found by Balbolov for the oxidation of CDT. This would explain why the recovery rate decreases when the concentration of $Pd(OAc)_2$ was increased and higher conversion of CHDD was achieved. Therefore, the best results were obtained with only 0.05 mol% $Pd(OAc)_2$ in DMA (X_{CHDD}=29%, $S_{8\text{-}CHD}$=29%, $Y_{8\text{-}CHD}$=8.4%). Higher yields were obtained by using higher concentrations of the catalyst; especially with 5 mol% $Pd(OAc)_2$, which yielded 12.6% of 8-CHD. Nevertheless, the amount of by-products was also higher, additionally to the low recovery rate after the reaction. Since the selectivity of $Pd(OAc)_2$ towards 8-CHD was not as high as expected, other approaches were investigated.

An active, selective, recyclable catalyst, which enables the O_2-coupled Wacker-type oxidation was still of high interest for the project. Concerning this matter, an interesting approach is the stabilization of Pd^0 species via complexation with ligands which are stable under Wacker conditions. Sigman et al. followed this strategy by using the $PdCl_2$ complex of (-)-sparteine [143] as catalyst in the oxidation of terminal olefins, including those with substituents at the allylic and homoallylic positions, under ambient oxygen pressure. The chemoselectivity of this catalyst showed to be extremely high for the oxidation of α-olefins but neither the formation of an internal ketone nor the isomerization of the double bond took place when 4-*cis*-decene was treated under this reaction conditions. For this reason it was decided not to investigate this approach. In a similar way, Sheldon and coworkers utilized bathophenanthroline disulfonate, a diamine bidentate ligand, to prepare a $PdCl_2$ complex

capable of stabilizing reduced Pd^0 under Wacker conditions. The usage of this complex as catalyst resulted in promising results in the Wacker-oxidation of terminal olefins. Although cyclopentene and cyclohexene were barely converted under these conditions, cyclooctene yielded 30% of the corresponding cycloalkanone [82].

These results and the high activity showed by $Pd(OAc)_2$ in the Wacker oxidation of CHDD, even at extremely low concentrations, encouraged the idea of testing $Pd(OAc)_2$ complexes of bidentate diamine ligands as catalysts for the oxidation of CHDD.

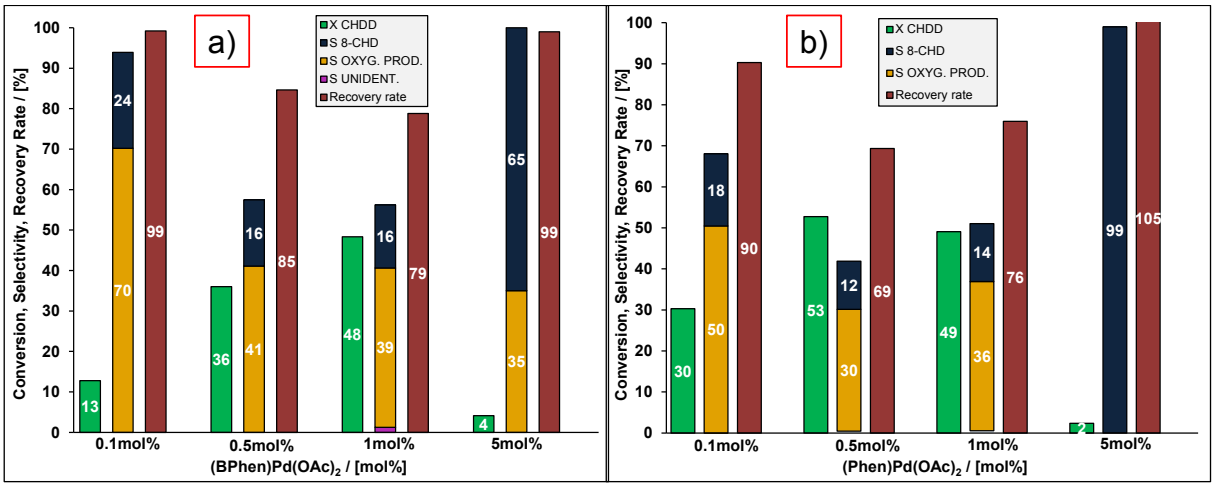


Figure 42. Wacker-type oxidation of CHDD using a) $(BPhen)Pd(OAc)_2$ or b) $(Phen)Pd(OAc)_2$ as catalyst in DMA. Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, pO_2 = 3 bar, t = 15 h, T = 90 °C

Since the goal was to test the complexes in DMA and not in water, no disulfonate groups were needed in the ligands used for the preparation of the complexes. Both catalysts were tested in different concentrations between 0.1 mol% and 5 mol% and in all cases conversion of CHDD took place. However, when 1 mol% of the BPhen (see Figure 42, a)) complex was used, it reached its highest activity. Interestingly, 48% of CHDD was converted but the selectivity of the complex towards 8-CHD was only 16%. Other oxygenated products, including the allylic ketone were formed. Such a mixture of products was also reported by Sheldon when cyclopentene and cyclohexene were treated under the same conditions. When lower concentrations of the catalyst were added, the conversion of CHDD decreased but the selectivity of the complex towards 8-CHD did not increase and again a mixture of oxygenated products was obtained. At a concentration of 5 mol%, the complex seems to lose its activity since only 4% of CHDD were converted. When 0.1 and 0.5 mol% of the phenanthroline complex were used, the conversion of CHDD was almost two times higher than with BPhen (see Figure 42, b)). Above these concentrations the results obtained were

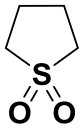
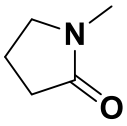
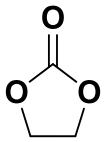
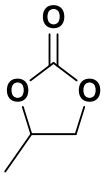
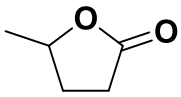
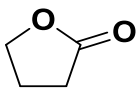
very similar. It could be that the absence of the phenyl groups in phenanthroline reduces the bulkiness of the ligand and increases the conversion of CHDD when low concentrations of the complex were used. However, the selectivity of the complex was not high, since other oxygenated byproducts than 8-CHDwere also formed in higher amounts. A trend towards lower recovery rates when the conversion increased was also observed. This was most probably caused by the formation of oligomers and other compounds which cannot be detected using a GC. Unlike bathophenanthroline, the highest conversion was obtained with 0.5 mol% of the phenanthroline complex. In conclusion, although the diamine bidentate complexes were able to partially convert CHDD, they were not effective since only low yields of 8-CHD were obtained.

For achieving a considerable progress in the Wacker oxidation, a notable aspect has been searching for suitable solvents and co-solvents which might enhance the activity of the catalyst system and the selectivity towards the desired product [144]. This approach also fits the use of eco-friendly reaction media instead of more dangerous and pollutant organic solvents, which are usually applied for this type of reactions.

As previously discussed, the $Pd(OAc)_2$-DMA system showed great activity, even at very low concentrations, when used for the oxidation of CHDD. In an attempt to take advantage of the benefits provided by using DMA as the reaction medium for the Wacker-type oxidation of internal and cyclic olefins, it was decided to add a co-solvent and run tests for 2 hours to evaluate if the selectivity for the target product might be increased (see Table 18); such strategy had already been followed by Grubbs and coworkers [145], although cyclic olefins were scarcely investigated. Most of the co-solvents selected were already used for Wacker oxidations: Escola et al. studied the Wacker-oxidation of 1-dodecene in several polar and unpolar solvents [146], among which the utilization of sulfolane resulted in the highest conversion of the α-olefin and yield of internal ketones. These findings agree with the high conversion of CHDD when sulfolane was used as co-solvent; however, no 8-CHD or oxygenated product was formed. Most probably condensation of CHDD took place to form oligomers or polymers, which were not detectable with GC-FID or GC/MS. NMP was successfully used by Kaneda [73] as the reaction's solvent for the Wacker-type oxidation of internal olefins. When it was used as a co-solvent for the oxidation of CHDD, no significant improvement was noticed. He et al. successfully used propylene carbonate and especially ethylene carbonate as solvents in the O_2-coupled Wacker oxidation of 1-dodecene [144]. The reaction turned to be highly selective, producing high to excellent yields of the corresponding methyl ketones when α-olefins were treated under these conditions. In addition, the activity of palladium in ethylene carbonate was as two times higher than in propylene carbonate. This

could explain why the conversion of CHDD was higher when ethylene carbonate was added as a co-solvent. Nevertheless, no substantial improvement was noticed with neither of the organic carbonates tested as co-solvents and only traces of 8-CHD were obtained. Additionally, GBL and GVL were investigated as co-solvents due to their environmentally friendly properties. GVL was recently named as a sustainable liquid, ideal for the production of carbon-based products, which possesses a high boiling point and it is water-soluble [147]. Its physical and chemical properties also qualify it as an excellent candidate for a green solvent [148,149]. GBL, having similar characteristics as GVL, was another solvent of choice [62].

Table 18. Effect of co-solvent on the Wacker-type oxidation of CHDD using $Pd(OAc)_2$ as catalyst

Entry	Co-solvent		$X^{[a]}_{CHDD}$ [%]	$S^{[a]}_{8\text{-}CHD}$ [%]	$Y^{[a]}_{8\text{-}CHD}$ [%]
1		sulfolan	45	0	0
2		*N*-methyl-2-pyrrolidone	17	20	3
3		ethylene carbonate	47	4	2
4		proyplene cabonate	23	3	1
5		γ-valero-lactone	18	13	2
6		γ-butyro-lactone	14	13	2

Reaction conditions: 0.55 mmol of CHDD, 1 mol% $Pd(OAc)_2$, 1 mL DMA, 1 mL co-solvent, 0.1 mL H_2O, p_{O2} = 10 bar, [a] determined by GC method using an internal standard

The use of lactams as co-solvents did not lead to any improvement. Although both experiments yielded only 2% of 8-CHD, the conversion of CHDD was slightly higher in the

DMA:GVL mixture. Therefore, it was concluded that the best results were obtained when $Pd(OAc)_2$ in DMA as sole solvent was applied as catalyst system. The O_2-coupled Wacker oxidation of CHDD did not need any additives to take place. Additionally, the concentration of the catalyst directly influenced the selectivity for the desired products.

4.2.3.2. Wacker-type oxidation of CHDD with $PdCl_2$ and palladium(II) diamine complexes as catalysts.

$PdCl_2$ together with a co-catalyst was the catalyst first used in the Wacker process (and Wacker-type oxidations) to transform an alkene into a ketone. However, a major drawback for oxidative palladium catalysis is the reduction of Pd^{II} into Pd^0 which can further precipitate and then is not able to be reoxidized, becoming inactive [28]; this problem was elegantly solved by Kaneda and his co-workers by using a $PdCl_2$-DMA copper-free catalyst system. DMA stabilizes Pd^0, which is readily reoxidized by O_2, and thus neither co-catalysts nor co-oxidants are needed. Although the O_2-coupled catalyst system works for linear internal olefins (including those with additional functional groups [150]), little has been done regarding the oxidation of macrocyclic olefins, *e.g.* CHDD.

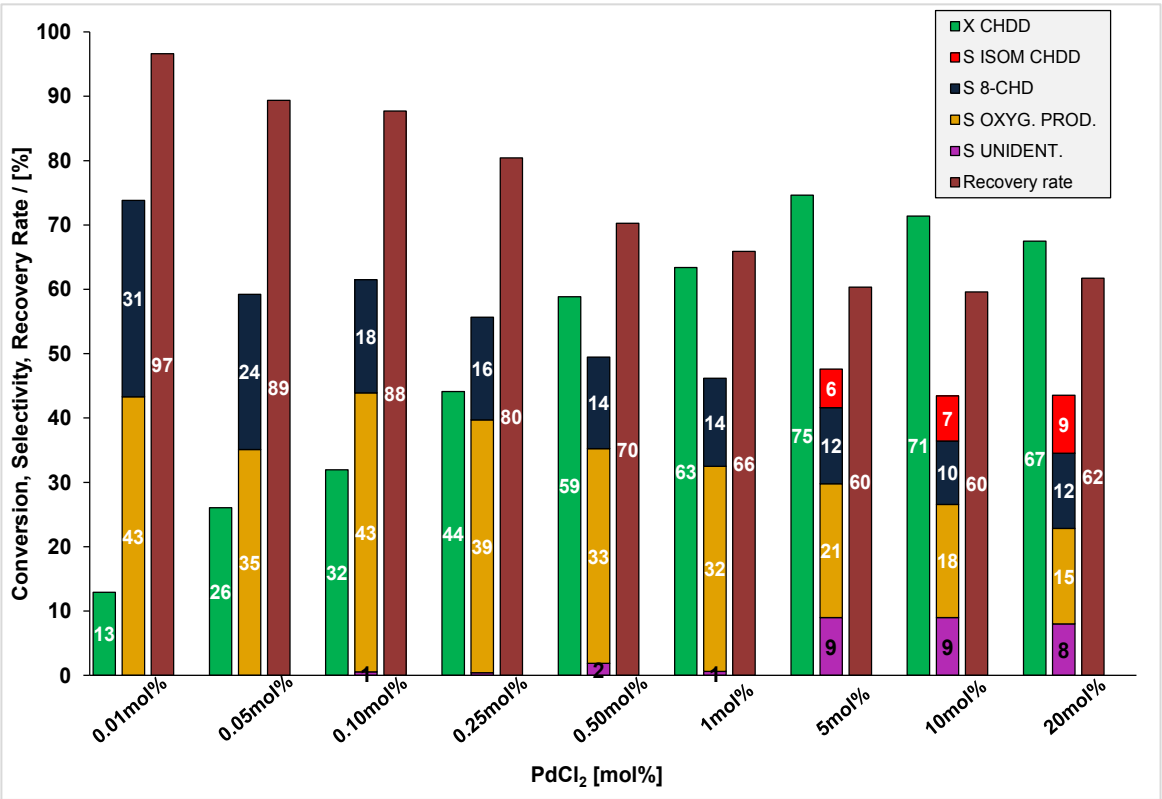


Figure 43. Wacker-type oxidation of CHDD using $PdCl_2$ as catalyst in DMA. Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, pO_2 = 3 bar, t = 15 h, T = 90 °C

For this reason, the Wacker-type oxidation of CHDD was also investigated. Several catalyst concentrations were investigated, the results obtained are presented in Figure 43. Kaneda's system showed activity, even at a low concentration of the catalyst. However, a number of by-products besides 8-CHD were formed. The allylic ketone was found among these by-products; Kaneda already reported the formation of such allylic ketones in the oxidation of cyclohexene [73]. In no case metallic palladium was found after the reaction time. Most probably, 3 bar O_2 was enough to reoxidize readily the reduced palladium during the catalyst's cycle. As expected, the conversion of CHDD increased when higher concentrations of $PdCl_2$ were used. However, the complete conversion of CHDD was not achieved, even when 20 mol% of catalyst were used. Remarkably, the highest conversion was achieved with 5 mol% of the catalyst. At this concentration 75% of CHDD was converted with a selectivity for 8-CHD of only 12%. A number of additional peaks with a m/z relation of 236 were identified using GC/MS, indicating the formation of oxygenated by-products. Isomerization of CHDD also took place at with 5 mol% and higher concentrations of the catalyst. Considering the relevance of preventing a loss of CHDD due to the formation of by-products, the best result was obtained with 0.05 mol% of $PdCl_2$ (X_{CHDD}=26%, $S_{8\text{-}CHD}$-=24%, $Y_{8\text{-}CHD}$=6%). Just as in the case of palladium(II) acetate-catalyzed Wacker-type oxidation of other cyclic olefins [142], it seems that higher-molecular species might be formed by condensation/cross-linking of CHDD which are not possible to detect with GC-FID or GC/MS. The lower recovery rates at higher CHDD conversions are another indicator of the formation of such compounds. By using $PdCl_2$ in DMA it was possible to convert CHDD even at very low concentrations of the catalyst. Nevertheless, the formation of a number of byproducts resulted in a very low selectivity of 8-CHD.

As an alternative approach to the Kaneda system bidentate diamine $PdCl_2$ complexes were investigated. Initially, the bathophenanthroline complex was tested in different concentrations (see Figure 44, a)). The highest conversion was achieved when 5 mol% (BPhen)$PdCl_2$ were used. The selectivity shown by the complex towards 8-CHD was in all cases rather low and even at the lowest conversion, the products obtained were a mixture of 8-CHD together with other oxygenated products. Again, at higher conversions of CHDD, the recovery rate was lower. (Phen)$PdCl_2$ showed a very poor solubility in the CHDD-DMA-H_2O reaction mixture, even after running both experiments.

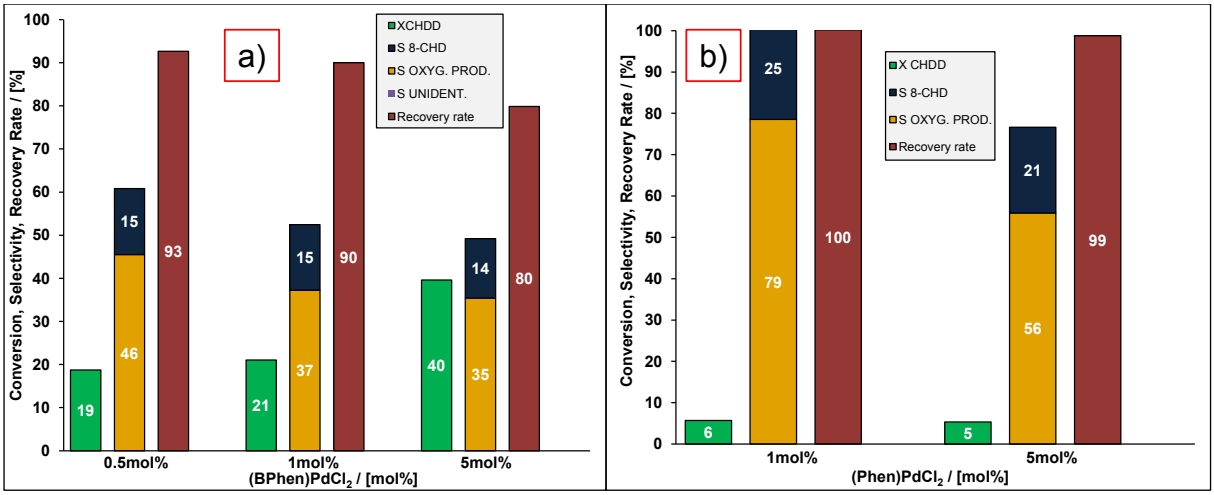


Figure 44. Wacker- type oxidation of CHDD using a) (BPhen)palladium(II) chloride or b) (phenanthroline)palladium(II) chloride as catalyst in DMA. Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, pO_2 = 3 bar, t = 15 h, T = 90 °C

It might be that only a small amount of the complex, most probably below 1 mol%, was dissolved in the reaction medium and resulted in low conversion of CHDD (see Figure 44). Nevertheless, the selectivity of the complex towards 8-CHD was below 25% in both cases. In conclusion, the $PdCl_2$ complexes of bidentate diamine ligands yielded very low amounts of 8-CHD and did not result in any improvement compared to $PdCl_2$.

Different results were obtained after testing $PdCl_2$, $Pd(OAc)_2$ and several analogous complexes. However, their effectiveness shown for the oxidation of α-olefins contrasted with their low selectivity towards the formation of 8-CHD. Subsequently, the influence of oxygen-containing ligands (β–diketones) was evaluated as a further opportunity to manage the activity of resulting palladium(II) complexes.

4.2.3.3. Wacker-type oxidation of CHDD with bis(β-diketonato)palladium(II) complexes

To evaluate the effect of ligands containing oxygen-donor atoms, it was decided to start with the acetylacetonate complex of Pd^{II}. Although a common ligand [151], the use of $Pd(acac)_2$ as a catalyst for the Wacker-type oxidation of cyclic olefins has not been known yet.

The results are presented in Figure 45. It can be noticed that the activity of the catalyst is significantly decreased in comparison to $PdCl_2$ or $Pd(OAc)_2$. Therefore concentrations of the catalyst below 1 mol% were not investigated. There are three possible explanations for the lower activity shown by this catalyst: a) an inhibition effect caused by DMA; a similar reaction system formed by $Pd(acac)_2$ as catalyst and TBHP as oxidant in acetic acid resulted in good

yields of the corresponding methyl ketone when 1-octene was used as the substrate [152]; when DMA was used as solvent no conversion took place, b) the acac ligand does not leave the palladium center so easily and it is more difficult, both for CHDD and for a molecule water molecule, to coordinate to the palladium center; a similar behavior of oxygenated species has already been reported by Skumov and coworkers [138] and discussed in this thesis.

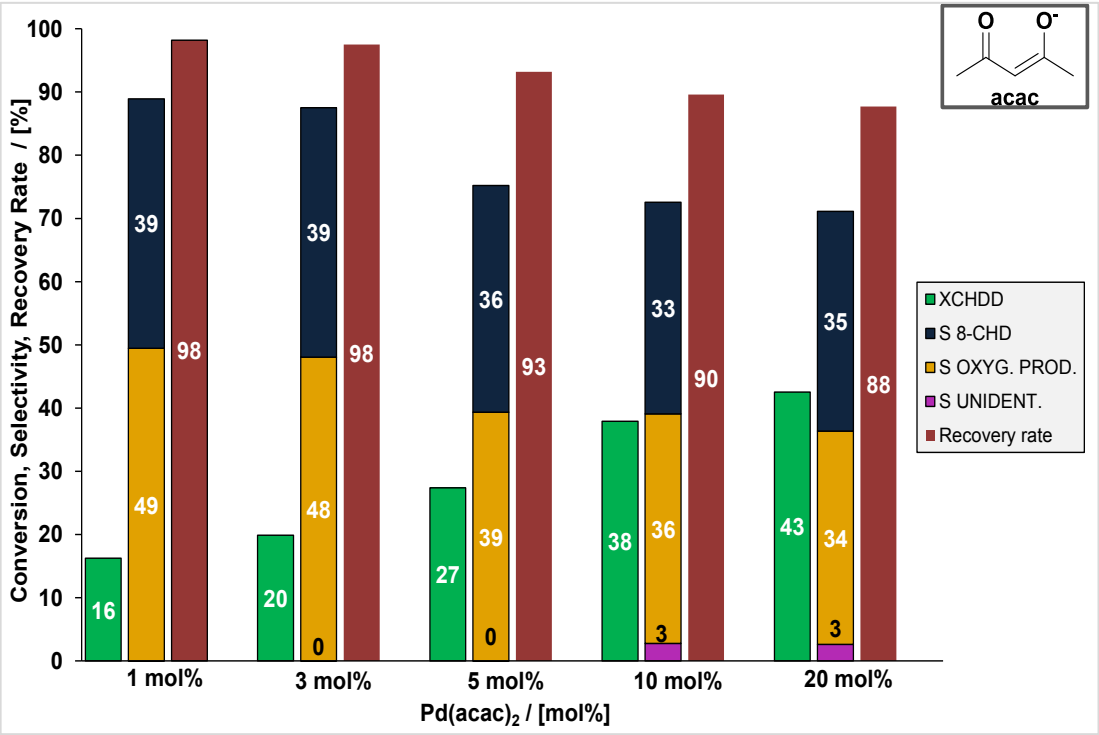


Figure 45. Wacker-type oxidation of CHDD using $Pd(acac)_2$ as catalyst in DMA. Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, pO_2 = 3 bar, t = 15 h, T = 90 °C

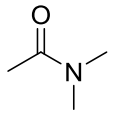
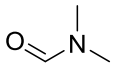
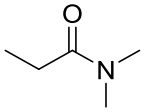
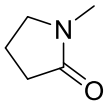
Finally it could be possible that, under the reaction conditions, CHDD acts as a bidentate ligand and coordinates to the palladium center, delaying the reaction to take place. Some diene complexes of palladium(II) have been reported to be formed already at room temperature [153,154].

On the other hand, the selectivity of $Pd(acac)_2$ towards 8-CHD was also higher than that of the other palladium complexes previously tested. Additionally, the recovery rates were also higher which means a lower loss of CHDD during the reaction via formation of oligomers. Of interest are the reactions with 1 mol% and particularly 3 mol% of catalyst, in which 20% of CHDD were converted with a 8-CHD selectivity of 39%. However, the selectivity of the complex towards 8-CHD decreased when higher concentrations of catalyst where used. Also, when the conversion of CHDD was above 38% (with 10 and 20 mol%), signals with a m/z relation of 250 and 252 were identified using GC/MS, indicating the formation of

diketones. Interestingly, the use of $Pd(acac)_2$ resulted in high yields of 8-CHD and oxygenated products without a significant undesired oligomerization of the starting material.

According to Kaneda, the stabilization of Pd^0 formed during the catalytic cycle in the Wacker-type oxidation of olefins in DMA might be attributable to the coordinating ability of the solvent [75]. This would implicate that the usage of DMA is essential for the O_2-coupled reoxidation of reduced palladium under copper-free conditions [150]. Therefore, three additional solvents containing an amide moiety were also investigated: DMF, DMPr and NMP.

Table 19. Wacker-type oxidation of CHDD in solvents containing an amide moiety

Solvent	X_{CHDD} [%]	$S_{8\text{-}CHD}$ [%]	$S_{Oxyg.\ Prod.}$ [%]	$S_{UNIDENT.}$ [%]	Recov. R. [%]	E_T^N [155],[156]
 **DMA**	20	39	47	1	97	0.377
 **DMF**	0	0	0	0	99	0.386
 **DMPr**	9	17	16	0	94	0.343
 **NMP**	61 11[a]	22 39	37 55	3 0	77 99	0.355

Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, pO_2 = 3 bar, t = 15 h, T = 90 °C. [a] reaction time was 5 h.

As seen in Table 19, the reactivity of $Pd(acac)_2$ was different in each of the investigated solvents. The polarity of the solvent influenced the solubility of both CHDD and the catalyst in the reaction medium. Moreover, it might have has an influence on the the conversion of CHDD. The so-called normalized solvent polarity parameter (E_T^N) correlates a certain solvent with the least polar solvent (tetramethylsilane) and the most polar solvent (water) at this scale. This parameter gives an immediate insight of a solvent's polarity [157] and has already been used to evaluate the influence of the polarity of a solvent for the Wacker oxidation of olefins [144].

DMF has been widely used as solvent in the Wacker oxidation of higher terminal and functionalized olefins [158,159]. However, its usage did not result in any conversion of

CHDD, most probably due to the low solubility of CHDD and $Pd(acac)_2$ in DMF, which was also the solvent with the highest E_T^N value. The solvent with the second highest E_T^N was DMA. In this solvent, 20% of CHDD were converted with 39% selectivity towards 8-CHD and 47% towards other oxygenated products. The recovery rate was 97%, which most probably means that no formation of high-boiling compounds took place. NMP has third highest E_T^N value. In this solvent, the conversion of CHDD was 61%, almost three times as high as the conversion in DMA. Nevertheless, the selectivity towards 8-CHD was only 22%. The recovery rate was also lower (77%) due to the oligomerization of CHDD. An additional experiment for a shorter reaction time in NMP was carried out. As expected, the conversion of CHDD decreased to 11% and the selectivity towards 8-CHD increased to 39%. Finally, DMPr was tested. This solvent has the lowest E_T^N value among the solvents tested that contain an amide moiety. The conversion of CHDD seemed to increase in less polar solvents. However, only 9% of CHDD were converted and the selectivity towards 8-CHD was only 17%. The highest CHDD conversions were achieved in DMA and NMP. According to the E_T^N values, these solvents have a medium polarity among the set of solvents containing an amide moiety that were tested (see Table 19). Probably, the optimal polarity of the solvent lies between the E_T^N values of 0.355 and 0.377. Interestingly, the highest conversion of CHDD took place in NMP, which contrasts with the results reported by Kaneda for the Wacker oxidation of *trans*-4-octene [73].

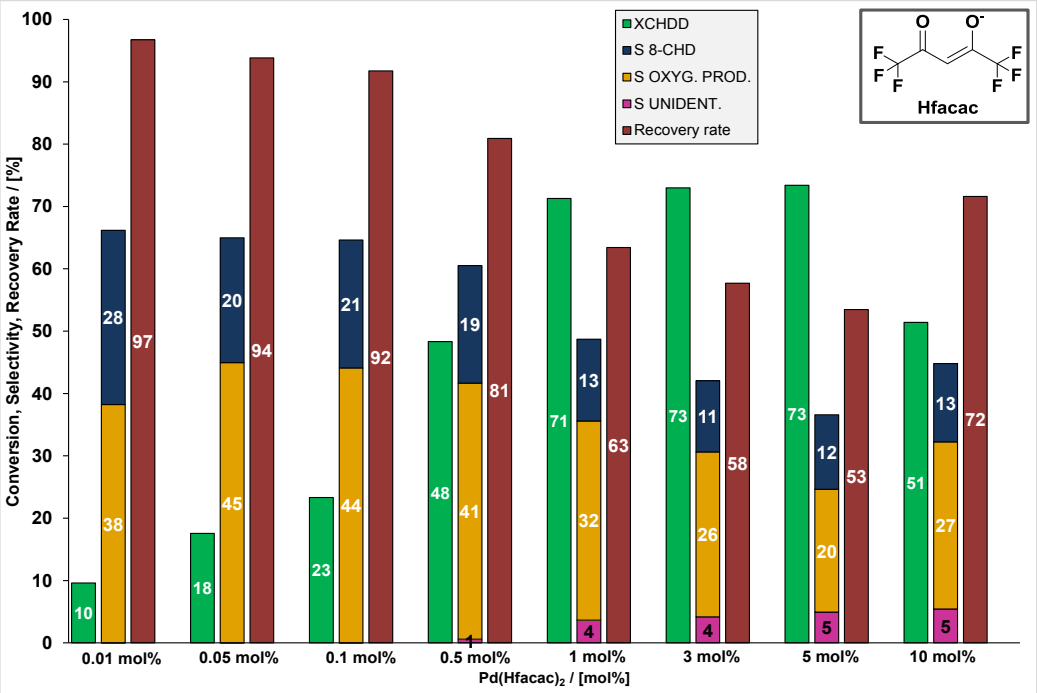


Figure 46. Wacker-type oxidation of CHDD using $Pd(Hfacac)_2$ as catalyst in DMA. Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, pO_2 = 3 bar, t = 15 h, T = 90 °C

Based on the interesting results obtained with $Pd(acac)_2$, it was decided to further investigate the usage of other bis(β-diketonato) complexes of Pd^{II} as catalyst. $Pd(hfacac)_2$, a strong Lewis acid, was chosen as the next complex to test. The results obtained using different catalyst concentrations are shown in Figure 46.

Recently, Stoltz reported that the use of $Pd(hfacac)_2$ for the oxidation of terminal olefins in a mixture of acetonitrile, acetic anhydride and acetic acid did not result in the formation of the corresponding methyl ketone [160]. However, it was of special interest to evaluate the effect of the fluorine atoms present in the ligand and if this could improve the selectivity of the complex towards 8-CHD. Surprisingly, a notorious increase in the conversion of CHDD in comparison to that of $Pd(acac)_2$ was noticed, even at low concentrations of the catalyst. This result differs with the ones reported by Mimoun in the Wacker oxidation of 1-octene in acetic acid [152]. The conversion obtained with both catalysts was almost identical (92% with $Pd(acac)_2$ and 94% with $Pd(hfacac)_2$) and the selectivity towards 2-octanone was 85% with both catalysts. Despite the interesting increase in the catalyst's activity, the selectivity of $Pd(hfacac)_2$ towards 8-CHD was lower than with $Pd(acac)_2$. Even low concentrations of the catalyst were used and low conversions of CHDD were achieved. Moreover, a number of additional byproducts were formed during the reaction when the conversion of CHDD was above 48%. As is the case for the other catalysts, the recovery rate was lower when the conversion of CHDD increased; most probably because of the formation of compounds which are not detectable with GC/MS. It can be concluded that the strongly electron-withdrawing CF_3 groups present in $Pd(hfacac)_2$ resulted in a high conversion of CHDD but a low selectivity towards 8-CHD. Therefore, no improvement was achieved in comparison to the results obtained by the usage of $Pd(acac)_2$ as catalyst.

It was found that the usage of $Pd(hfacac)_2$ as catalyst achieved a higher conversion of CHDD. Therefore a palladium(II) complex with a ligand containing only 3 atoms of F was prepared and used as catalyst (see Figure 47). Several concentrations of the complex were tested. At low concentrations such as 0.1 mol%, conversion of CHDD already took place. When higher concentrations of the catalyst were used, a higher conversion of CHDD was observed. However, when 0.1, 0.5 and 1 mol% of the catalyst was used, the conversions obtained with $Pd(tfac)_2$ were lower than those obtained with $Pd(hfacac)_2$. The selectivity towards 8-CHD with $Pd(tfac)_2$ was slightly higher. Interestingly, when 3, 5 and 10 mol% of the catalyst was used, the conversion of CHDD seemed to reach a maximum of 76-77% and selectivity towards remained constant. Only when 10 mol% of $Pd(tfac)_2$ was used, the selectivity was somewhat better, but still only 20% towards 8-CHD.

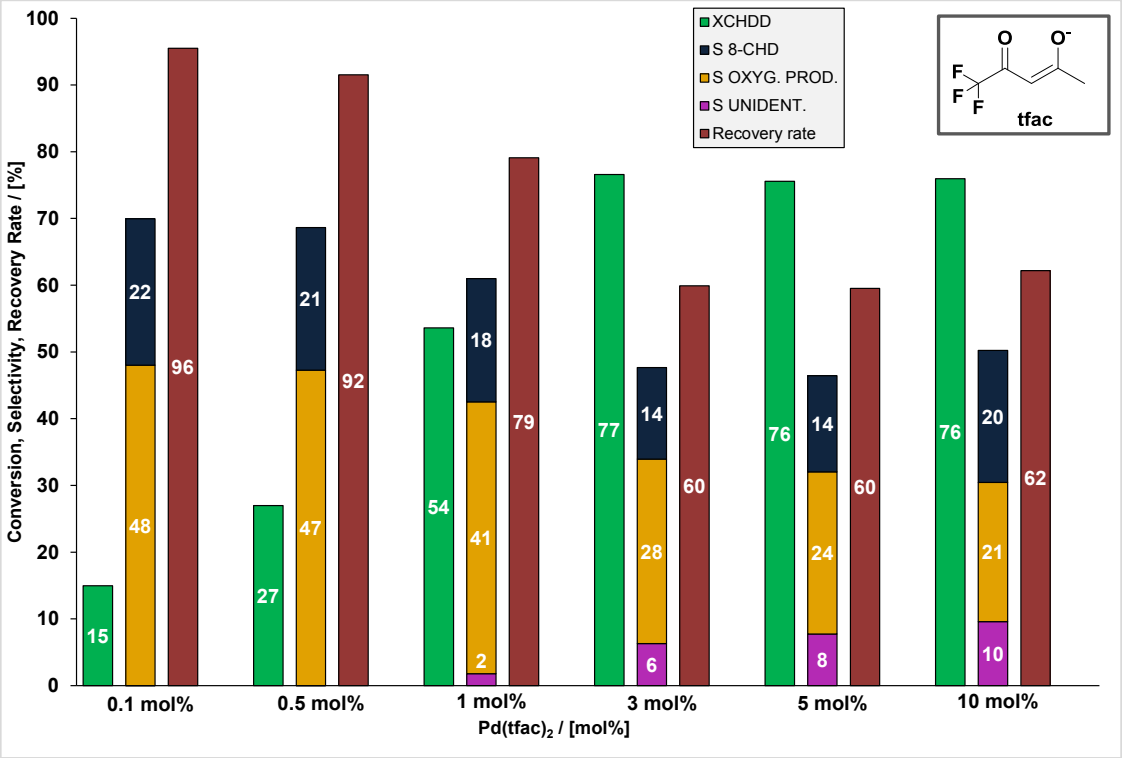


Figure 47. Wacker-type oxidation of CHDD using $Pd(tfac)_2$ as catalyst in DMA. Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, pO_2 = 3 bar, t = 15 h, T = 90 °C

Overall, the usage of $Pd(tfac)_2$ as catalyst resulted in slightly better results than those obtained with $Pd(hfacac)_2$.. Nevertheless, the usage of $Pd(acac)_2$ resulted in a higher selectivity towards 8-CHD.

Subsequently, the goal was to investigate if the bulkiness of the structure of the β-diketone could increase the selectivity of the catalyst towards 8-CHD. Therefore, $Pd(TMHD)_2$ was tested in different concentrations as a catalyst (see Figure 48). Such a Pd^{II} complex had not yet been tested in a Wacker-type oxidation. However, it has been reported as an efficient catalyst for Pd-catalyzed Suzuki, Heck and Sonogashira cross-coupling reactions. In all these cases, $Pd(TMHD)_2$ outperformed $Pd(acac)_2$ .Its efficiency as ligand has been attributed to the good balance existing between the steric and electronic properties of the ligand [161].

Overall, the conversion of CHDD obtained using different concentrations of $Pd(TMHD)_2$ as catalyst were similar to those obtained with $Pd(acac)_2$. However, the selectivity towards 8-CHD was slightly higher with $Pd(TMHD)_2$. A particularly interesting result was obtained using 5 mol% of catalyst, which provided 26% of conversion of CHDD with 43% selectivity towards 8-CHD and 41% selectivity towards other oxygenated products. The recovery rate was 96%, meaning almost no higher boiling by-products were formed. The use of lower catalyst

loadings resulted in lower conversion of CHDD and similar selectivity towards 8-CHD. On the other hand, higher concentrations of the catalyst resulted in higher conversions of CHDD and lower selectivity and recovery rate. Most probably, the presence of the *tert*-butyl groups in the ligand had a positive influence in the performance of the catalyst.

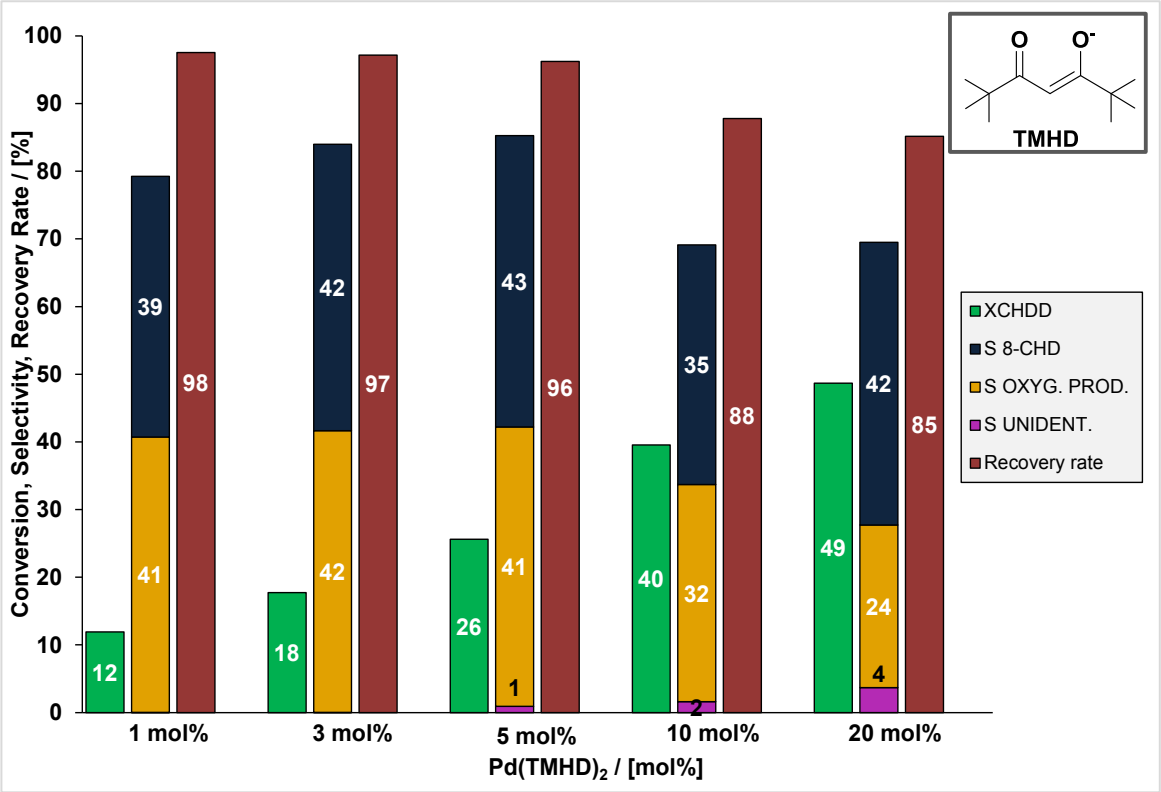


Figure 48. Wacker-type oxidation of CHDD using ($Pd(TMHD)_2$) as catalyst in DMA. Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, pO_2 = 3 bar, t = 15 h, T = 90 °C

The use $Pd(TMHD)_2$, a catalyst with a bulkier ligand than $Pd(acac)_2$, improved the selectivity towards 8-CHD in the the Wacker-type oxidation of CHDD. The influence of substituted acetylacetonate ligands has already been employed in the study of aryl aminations [162].

Therefore, the effect caused by bulkier β-diketonato complexes was further investigated by using the dibenzoylmethanato and butylmethoxydibenzoylmethanato complexes of Pd^{II} as catalysts (see Figure 49). Although the $Pd(dbm)_2$ and $Pd(bmdm)_2$ complexes had not yet been tested for Wacker-type oxidation of olefins, their use as catalyst resulted in the formation of 8-CHD and other by-products. The reactivity of $Pd(dbm)_2$ was higher than that of $Pd(acac)_2$. Interestingly, the terminal phenyl group substituents present in the ligands seem to increase the activity of the catalyst. With 1 mol% of the complex, the conversion of CHDD was 27% with 31% selectivity towards 8-CHD. When higher amounts of the catalyst were

used, the conversion of CHDD also increased and the selectivity towards 8-CHD remained constant.

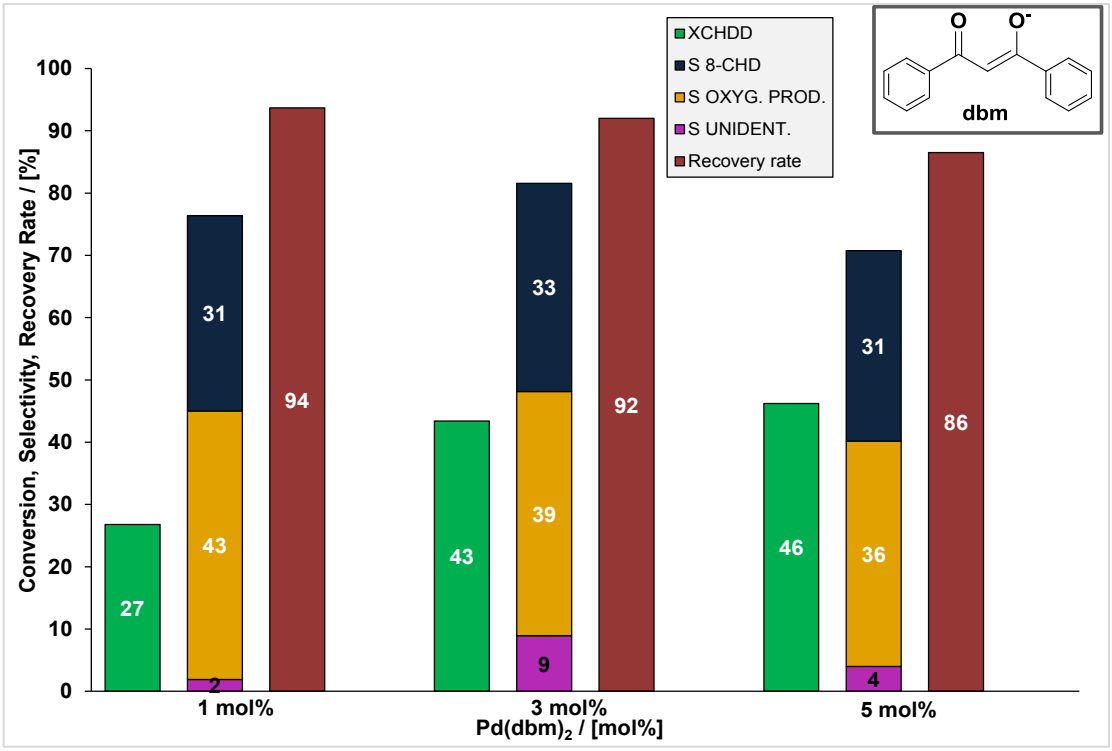


Figure 49. Wacker- type oxidation of CHDD using $Pd(dbm)_2$ as catalyst in DMA. Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, pO_2 = 3 bar, t = 15 h, T = 90°C

On the other hand, the recovery rate decreased as a result of this increase. Such behavior had been already observed with the other Pd^{II} catalysts tested in this thesis. Although $Pd(dbm)_2$ showed a higher reactivity, the selectivity towards 8-CHD was slightly lower than the one achieved with $Pd(acac)_2$ at similar conversions.

Subsequently, the use of $Pd(bmdm)_2$ as catalyst was investigated (see Figure 50). Although butylmethoxydibenzoylmethane has been already used to prepare complexes of Ir^{III} for their application on organic light-emitting diodes [163], its usage for the preparation of Pd^{II} complexes is not known. The conversion of CHDD obtained with different concentrations of $Pd(bmdm)_2$ was similar to the ones obtained with $Pd(acac)_2$. The structure of butylmethoxydibenzoylmethane contains a methoxy and a *tert*-butyl moiety at the *para* positions of the phenyl groups which increase the bulkiness of the ligand in comparison to dibenzoylmethane. Therefore, the decrease in the conversion of CHDD when $Pd(bmdm)_2$ was used might be due to a more difficult accessibility of CHDD to the palladium center. Using 1 mol% of the catalyst, only 13% of CHDD was converted and the selectivity towards 8-CHD was 39%. By using 3 mol% of $Pd(bmdm)_2$, the conversion of CHDD increased to 31%

and the selectivity towards 8-CHD slightly decreased to 37%. A drawback of this catalyst was its low solubility in the reaction medium. Therefore, there was no increase in the conversion of CHDD when 5 mol% of the catalyst was used. The results obtained with $Pd(bmdm)_2$ are comparable to those obtained with $Pd(acac)_2$. Additionally, using 5 mol% of $Pd(bmdm)_2$, both the conversion of CHDD and the selectivity towards 8-CHD were slightly higher.

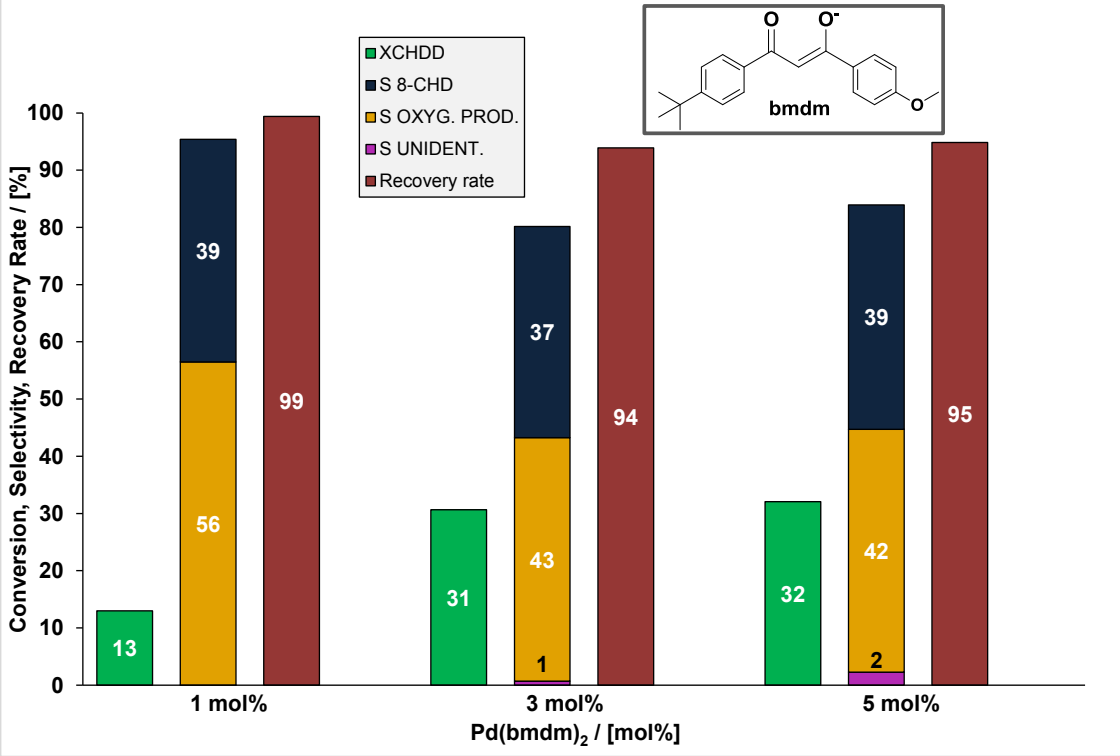


Figure 50. Wacker- type oxidation of CHDD using $Pd(bmdm)_2$ as catalyst in DMA. Reaction conditions: 0.55 mmol CHDD, 2.5 mL DMA, 0.2 mL H_2O, pO_2=3 bar, t=15 h, T=90 °C

In conclusion, the O_2-coupled Wacker-type oxidation of CHDD using a set of Pd^{II} catalysts in DMA was investigated. The goal was to obtain 8-CHD in a one-step reaction. Among the catalysts tested, $PdCl_2$ and $Pd(OAc)_2$ showed the highest reactivity. However, the selectivity of these catalysts towards 8-CHD was relatively low. The usage of diamine heterocyclic Pd^{II} complexes of $PdCl_2$ and $Pd(OAc)_2$ as catalysts lowered the conversion of CHDD and did not increase the selectivity towards 8-CHD. Subsequently, β-diketonato Pd^{II} complexes were tested as catalysts. Although these complexes showed a lower reactivity compared to $PdCl_2$ and $Pd(OAc)_2$, the selectivity towards 8-CHD was higher. Additionally, other by-products including ketones, α, β-enones and epoxides were identified. An experiment using $Pd(acac)_2$ as catalyst and $H_2{}^{18}O$ revealed that the oxygen atom incorporated into 8-CHD originates from water and not from O_2. The effect of the bulkiness of the β-diketonate Pd^{II} complexes on the selectivity towards 8-CHD was also investigated. Among these catalysts, particularly

promising results were obtained with $Pd(TMHD)_2$. Yet, the formation of undesired by-products could not be prevented.

4.2.3.4. Scale up experiment and oxidation using isotopically labeled water ($H_2{}^{18}O$) and molecular oxygen ($^{18}O_2$) with $Pd(acac)_2$ as catalyst

For a better identification of the oxygenated byproducts and its potential usefulness, a typical experiment under identical reaction conditions was performed on a higher scale. The results are shown in Table 20.

Table 20. Scale up of Wacker-type oxidation of CHDD using $Pd(acac)_2$-DMA

X_{CHDD} [%]	$S_{8\text{-CHD}}$ [%]	$S_{Oxyg.\ Prod.}$ [%]	$Y_{8\text{-CHD}}$ [%]	$Y_{Oxyg.\ Prod.}$ [%]	Recovery Rate [%]
43	32	33	14	14	85

Reaction conditions: 21.8 mmol CHDD, $Pd(acac)_2$ 5 mol%, 100 mL DMA, 8 mL H_2O, 90°C, t = 20 h, p_{O_2} = 3 bar, 800 rpm

The conversion of CHDD in the scale-up experiment with 5 mol% $Pd(acac)_2$ was almost two times higher than that of the smaller scale experiment using the same amount of catalyst. This was obviously caused by the longer reaction time. The increase in the conversion of CHDD had also a direct impact on the lower recovery rate. The isolated product mixture was distilled into 5 different fractions and analyzed using GC/MS.

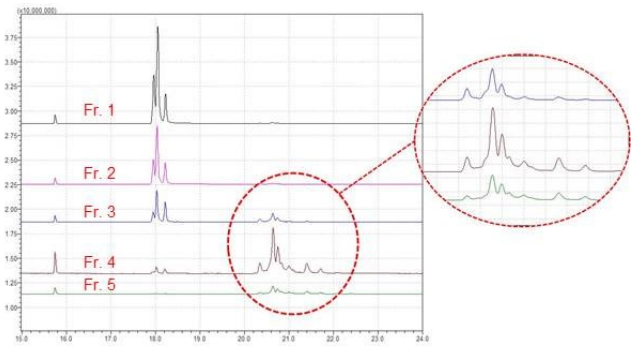
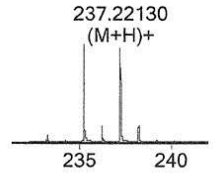
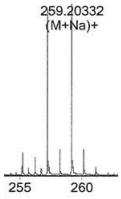
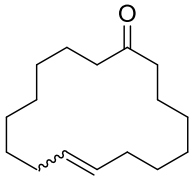


Figure 51. Gas chromatograms of the different fractions obtained after the distillation of the large scale experiment ___ Fr. 1, ___ Fr. 2, ___ Fr. 3, ___ Fr. 4, ___ Fr. 5.

Even though the separation of the different products by distillation was not possible, fraction 4 and 5 were mainly formed of 8-CHD (see Figure 51). Fraction 4 was analyzed using MS-ESI. The comparison between the theoretical and the measured mass of the products formed during the reaction is summarized in Figure 52.

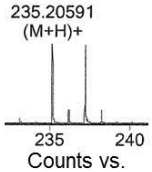


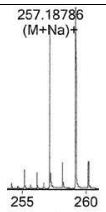


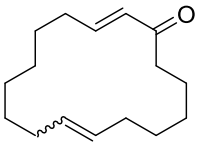


Chemical Formula: $C_{16}H_{28}O$
Exact Mass: 236,21

$[M+H]^+_{theo.}$= m/z 237.2213 | $[M+Na]^+_{theo.}$= m/z 259.2032

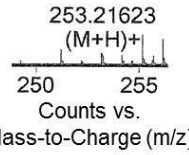


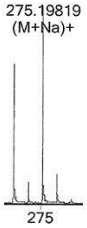


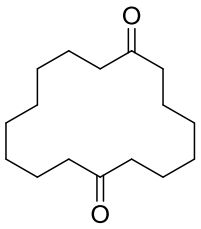


Chemical Formula: $C_{16}H_{26}O$
Exact Mass: 234,20

$[M+H]^+_{theo.}$= m/z 235.2056 | $[M+Na]^+_{theo.}$= m/z 257.1876

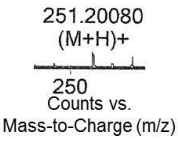


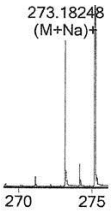


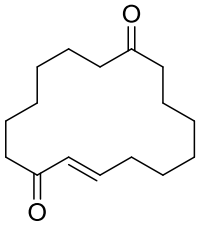


Chemical Formula: $C_{16}H_{28}O_2$
Exact Mass: 252,21

$[M+H]^+_{theo.}$= m/z 253.2162 | $[M+Na]^+_{theo.}$= m/z 275.1982







Chemical Formula: $C_{16}H_{26}O_2$
Exact Mass: 250,19

$[M+H]^+_{theo.}$= m/z 251.2006 | $[M+Na]^+_{theo.}$= m/z 273.1825

Figure 52. MS-ESI spectrograms of the products formed in the Wacker.type oxidation of CHDD with $Pd(acac)_2$.

Based on the high intensity of their peaks and the exactitude of the measurements, the formation of 8-CHD (peaks: $[M+H]^+$.= 237.2213, $[M+Na]^+$ 259.2033) as well as of the allylic ketone (peaks: $[M+H]^+$.= 235.2059, $[M+Na]^+$ 257.1879) were confirmed as the main products formed during the reaction. The formation of allylic ketones in the case of Wacker-oxidation has already been reported for cyclic alkenes [73,164]; a mechanism for the formation of this

side-product has not yet been proposed. On the other hand, although the peak intensity of the diketones is relatively small in comparison to the monoketones, their formation could also be possible.

In order to obtain additional information of the products formed during the reaction, Fraction 5 was analyzed using ^{1}H and ^{13}C NMR spectrometry. In Figure 53 the ^{1}H NMR spectrum of fraction 5 is presented. Based on these results, the formation of 8-CHD (δ 1.60, 1.62, 2.40, 2.42 ppm) and the allylic ketone (δ 2.87, 6.05, 6.74 ppm) can also be confirmed

The ^{13}C NMR spectrum of fraction 5 (see Figure 54) also confirmed the formation of 8-CHD (δ 212.7, 40.4, 23,5 ppm) and the allylic ketone (α,β-enone) (δ 201.9, 148.2 ppm). Additionally, the chemical shift typical for an oxirane ring (δ between 59-56 ppm) is also noticeable. The formation of an epoxide as one of the byproducts formed during the reaction was confirmed by comparing the ^{1}H NMR spectrum with the spectrum of a pure sample of CHDO (see Appendix section). To the best of our knowledge, no results related to the formation of epoxides as a product under conditions of a Wacker-type oxidation have been reported to date.

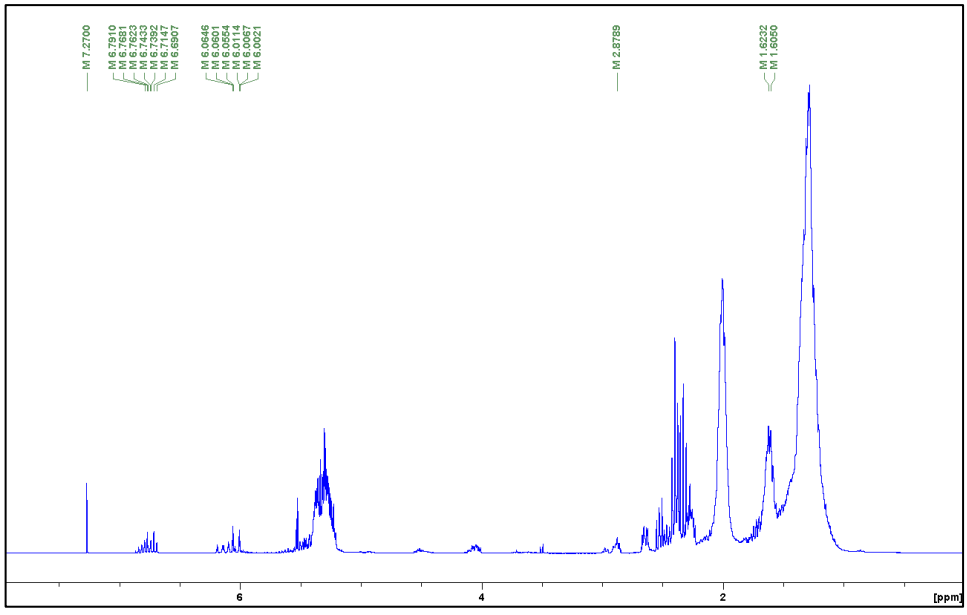


Figure 53. ^{1}H NMR spectrum of fraction 5 of the Wacker-type oxidation of CHDD with $Pd(acac)_2$ as catalyst in DMA.

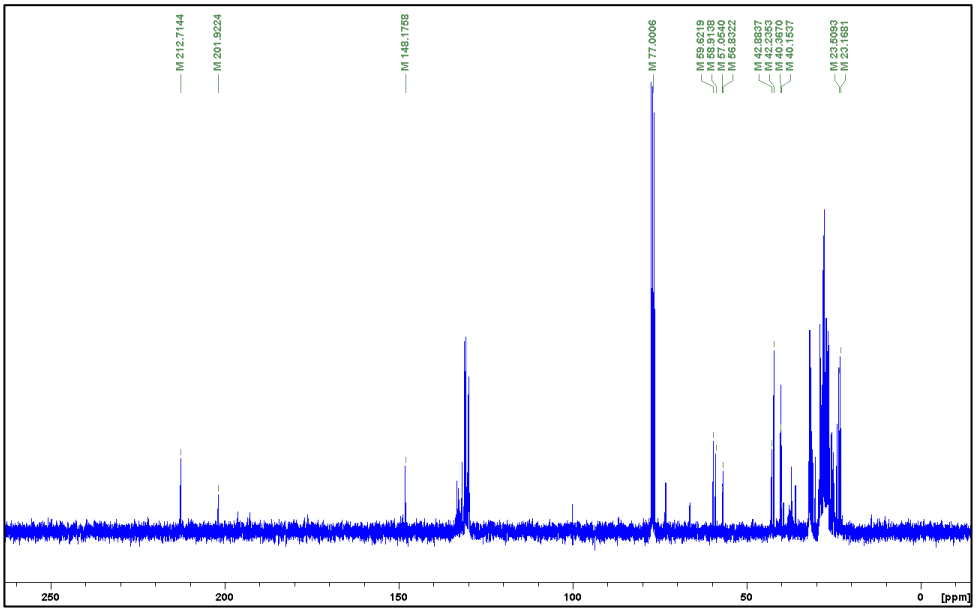


Figure 54. ^{13}C NMR spectrum of fraction 5 of the Wacker-type oxidation of CHDD with Pd(acac)$_2$ as catalyst in DMA.

Interestingly, the rearrangement of the epoxide in the presence of metal halides (e.g. magnesium iodide, sodium iodide and lithium chloride) or acidic or basic catalysts is widely used for the preparation of ethers, alcohols, aldehydes and ketones [165,166]. In this way, the epoxides formed as by-products during the Wacker-type oxidation could be further converted into 8-CHD in a separate reaction.

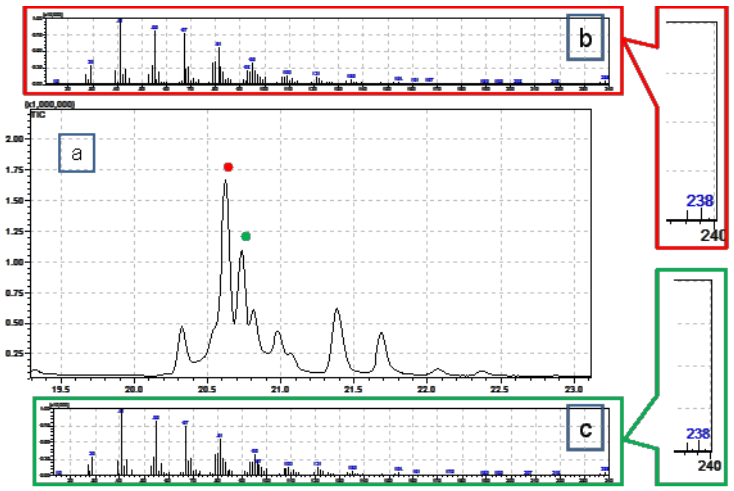


Figure 55. Results obtained from the Wacker-type oxidation of CHDD using 10 mol% Pd(acac)$_2$ as catalyst and $H_2{}^{18}O$ as reagent. a) chromatogram showing the products, b), c) mass spectrum corresponding to the two isomers of 8-CHD.

It is well known that water acts as the nucleophile in the Wacker-type oxidation of olefins, whereas the role of O_2 is to act as the terminal oxidant of the catalytic cycle [167]. Kaneda

and co-workers reported the formation of ^{18}O-labeled ketone with 99% selectivity when *trans*-4-octene was treated with ^{18}O-labeled water using the $PdCl_2$-DMA system [73]. This confirmed that the oxygen atom incorporated into the internal ketone comes from water and not from O_2. In an attempt to clear out if water played the same role in the Wacker-type oxidation of CHDD with $Pd(acac)_2$, two different experiments were carried out. The first experiment was run under 3 bar of $^{16}O_2$ using $H_2{}^{18}O$ as oxidant.

GC-MS analysis confirmed that the use of ^{18}O-labeled water and 3 bar of $^{16}O_2$ provided exclusively ^{18}O-labeled 8-CHD (see Figure 55). This result was supported by those obtained from the MS-ESI analysis (see Figure 56).

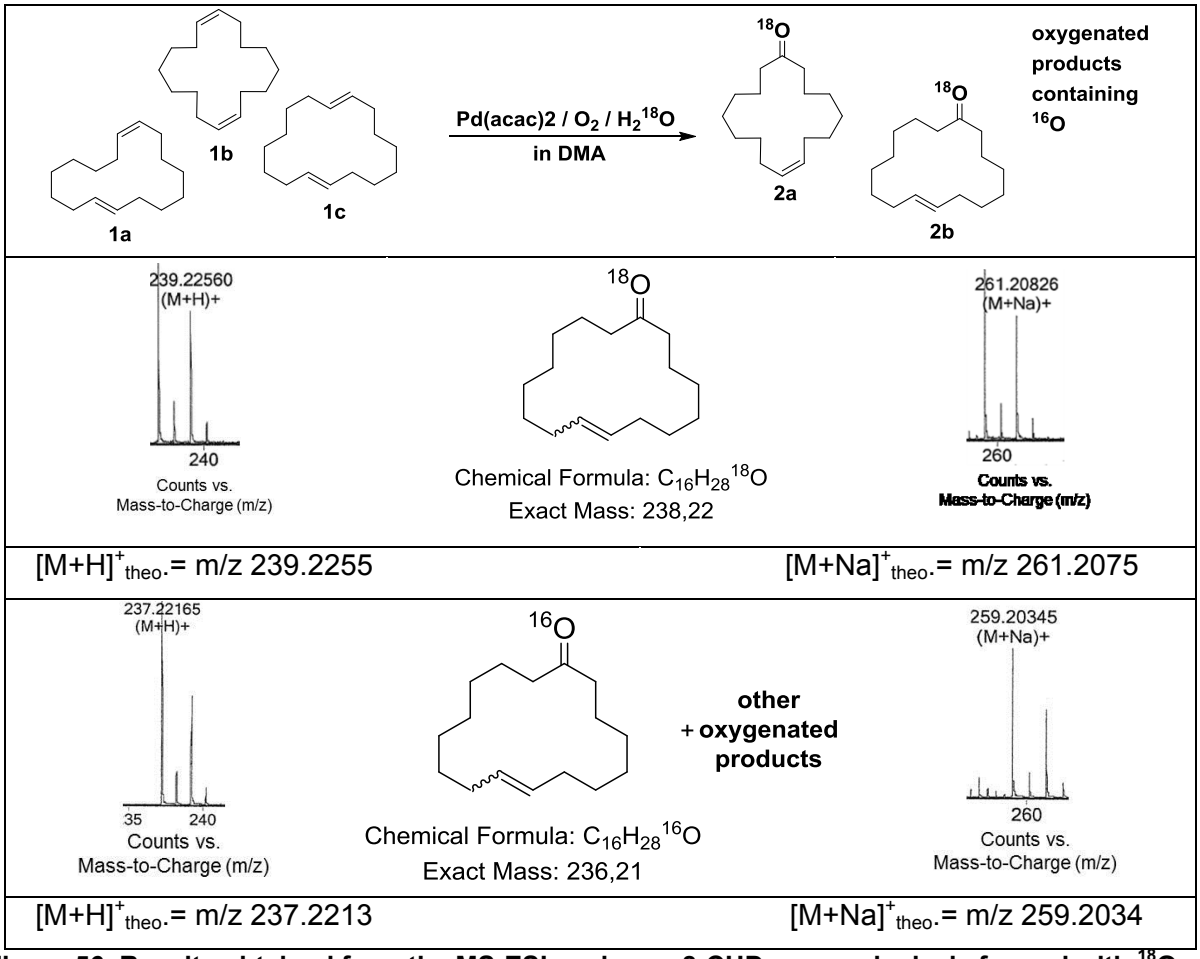


Figure 56. Results obtained from the MS-ESI analyses. 8-CHD was exclusively formed with ^{18}O-labeled water.

It was confirmed that water acts as the nucleophile and that the O atom incorporated into the ketone is derived from water and not from O_2 (peaks: $[M+H]^+$.= 239.2256, $[M+Na]^+$ 261.2082) in the formation of 8-CHD (see Figure 56, 2a and 2b). The α,β-enone formed as an allylic oxidation product did not contain an ^{18}O atom and is most probably result of a reaction which follows another mechanism. The formation of allylic oxidation product was already reported

by Kaneda and coworkers for the oxidation of cyclohexene using $PdCl_2$-DMA [73]; however, these results was not further discussed or clarified. A possible explanation could be a palladium(II)-catalyzed radical reaction involving the formation of an allylic hydroperoxide, which is then further oxidized to the α,β-enone. Both Pd^{II} and Pd^0 complexes are known to form peroxospecies in the presence of O_2 [168-170]. Since the experiment was run under 3 bar of $^{16}O_2$, the formation of $H_2{}^{16}O$ as a product of the reoxidation of Pd^0 to Pd^{II} is also a possibility. As the reaction advances, the concentration of unmarked water in the reaction mixture can increase and act as the oxidant in the Wacker oxidation of CHDD.

The second experiment was carried out using $H_2{}^{16}O$ and 3 bar of ^{18}O-labeled O_2. Due to low conversion of CHDD, an additional experiment under 6.5 bar of ^{18}O-labeled molecular oxygen was carried out; a part of the chromatogram showing the product mixture is presented in Figure 57.

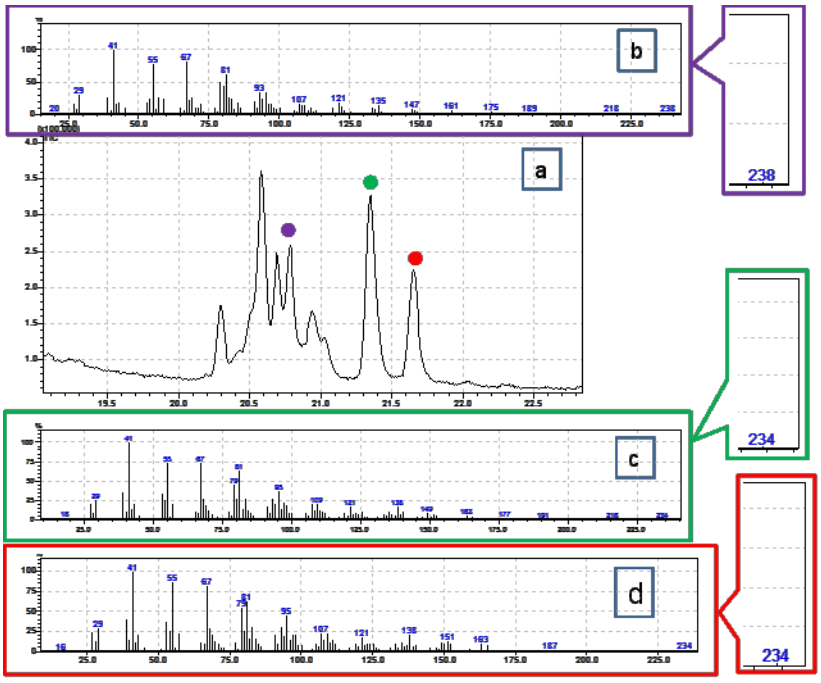


Figure 57. Results obtained from the Wacker-type oxidation of CHDD using 10 mol% $Pd(acac)_2$ as catalyt and $H_2{}^{16}O$ and $^{18}O_2$. a) part of the chromatogram showing the products. Mass spectrum of b) ^{18}O-oxygenated product, c) and d) allylic oxidation products.

The mass spectrum of the two peaks corresponding to the isomers of 8-CHD (not shown) showed the formation of ^{16}O-labeled ketone; in this way, it was confirmed that the O-atom incorporated into the ketone comes from a water molecule. Although one of the oxygenated byproducts did incorporate an ^{18}O-labeled atom, the GC-MS showed that only ^{16}O was incorporated to the α,β-enones. Nevertheless, these results must be proved, as the yield of the products was relatively low.

A reaction mechanism for the Wacker-type oxidation of olefins in DMA under copper-free conditions has not yet been proposed. Kaneda and co-workers did not disclose any mechanism for the system formed by $PdCl_2$ and DMA. However, it is believed that DMA is responsible for the stabilization of zerovalent palladium species, *i.e.* acts as a Lewis base and coordinates to the palladium center during the reaction. It is possible that zerovalent Pd formed during the catalytic cycle is held by DMA in a coagulated state that is small enough to allow reoxidation faster than the aggregation of Pd^0 that results in the formation of the "so-called" palladium black. Takehira and co-workers also proposed that Pd species are stabilized by the coordination of amides (e.g. DMA and N,N-diethylacetamide) in the Wacker-type oxidation of cyclopentene [79]. The formation of Pd(II) complexes of DMA, in which the oxygen atom of DMA coordinates with the palladium center has already been reported [171]. Likewise, the stabilization of reduced palladium through the coordination of a ligand has also been reported for diamine bidentate ligands like 2,2'-bipyridine or phenanthroline [172-174]. Additionally, bis-ligated Pd^0 species are highly sensitive toward oxidation to Pd^{II} in the presence of O_2 [175]. Interestingly, the usage of solvents (e.g. ethylene carbonate [176] or DMSO [177-179]) that can coordinate to the Pd center and form a complex has a similar effect on O_2-coupled oxidation reactions with palladium.

Although the elucidation of the reaction mechanism did not take part of the goals of this thesis, a reaction mechanism based on experimental work and mechanistic studies concerning the O_2-coupled reoxidation of Pd^0 stabilized by bidentate ligands [77,180,181] that lack additional co-oxidants is presented in Figure 58.

In accordance to the suspected mechanism: firstly, one molecule of acetylacetonate (acac) dissociates from the palladium center followed by binding of one equiv. of CHDD and water, respectively (see Step **(1)** in Figure 58). The deprotonation of the coordinated water would lead to an intramolecular *syn* attack (see Step **(2)** – **(3)**). The assertion of a *syn* mechanism has been reported in the past by Henry [69]. The formation of the product in Step **(4)** would also result in the formation of Pd^0. The coordination ability of DMA might be the explanation to the stabilization of Pd^0, preventing its aggregation and the formation of inactive palladium "black". It might be possible that the effectiveness of DMA as solvent is associated with its palladium-coordination ability. Perhaps it facilitates the redox reaction between Pd^{II} and Pd^0. The reaction between molecular oxygen and a $(DMA)_nPd^0$ complex (see Step **(5)**) would result in the formation of peroxopalladium(II) species [181]. Subsequent protonolysis of peroxopalladium(II) species in Step **(6)** would result in the formation of the Pd^{II} catalyst and H_2O_2 [181]. If H_2O_2 is formed during the catalytic cycle, it could either act as a reoxidant of Pd^0 or react with palladium to generate a reactive oxygen species capable of oxidizing CHDD

[180]. Dissociation of the coordinated DMA and further binding of 2 equiv. of acac would result in the formation of $Pd(acac)_2$ (see Step **(7)**).

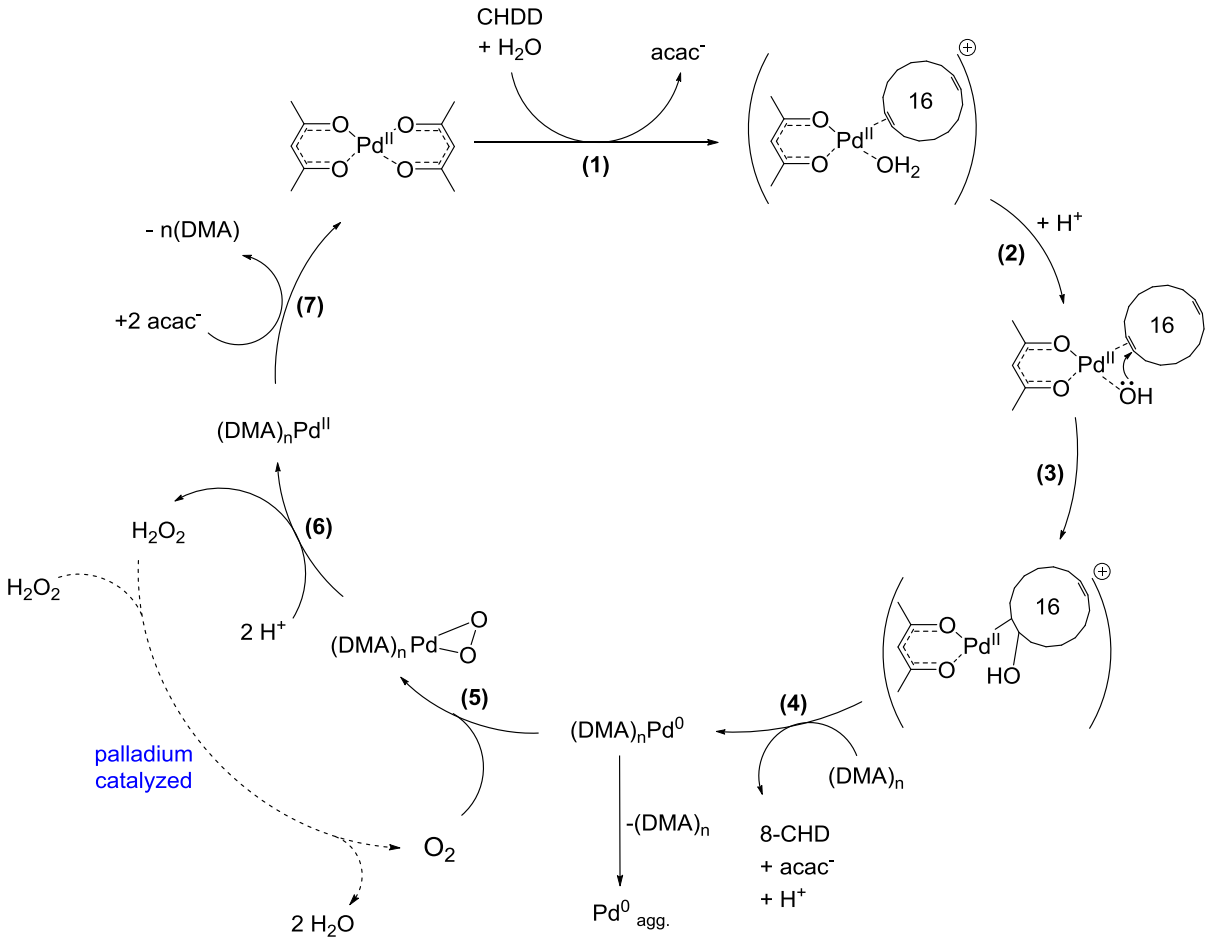


Figure 58. Suspected catalytic cycle for the Wacker oxidation of CHDD with $Pd(acac)_2$ in DMA

The experiments with $H_2{}^{18}O$ confirmed the nucleophilic attack by water and its role in the formation of 8-CHD. However, it is not clear if the nucleophilic addition step follows a *syn* or an *anti* mechanism (see Figure 59). In the past, two different mechanisms have been proposed for the hydroxypalladation step in the Wacker reaction. Henry proposed a *syn* mechanism [69] in which one molecule of water should be bound *cis* relative to CHDD. Bäckvall postulated an *anti* mechanism in which a water molecule outside the coordination sphere attacks the coordinated olefin [182].

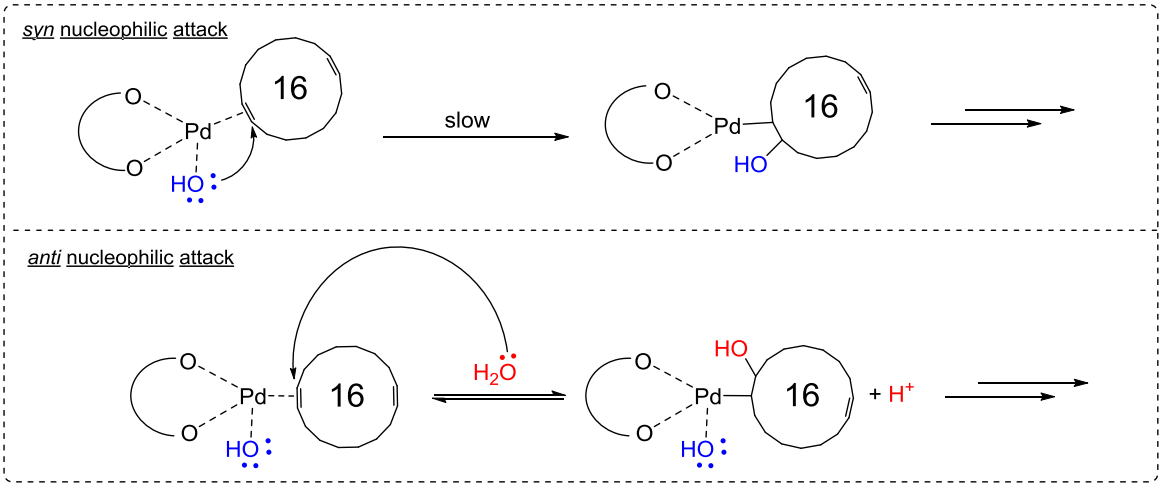


Figure 59. Possible modes of the nucleophilic attack of water on the coordinated CHDD

Although the mechanism followed by our system was not investigated, the experiment with isotopically labeled water proved that the oxygen incorporated into 8-CHD originated from water and not from molecular oxygen. This supports the results obtained by Kaneda and coworkers in the oxidation of olefins using $PdCl_2$ in DMA.

5. Overall Summary and Outlook

5.1. Selective monoepoxidation of CHDD

The selective epoxidation of CHDD in a biphasic liquid system was studied using a catalyst composed by a polyperoxo complex and a quaternary ammonium salt as PTC. The peroxotungstatophosphate was formed *in situ* by adding and stirring phosphoric acid and a W^{VI} precursor in water. The purpose of the PTC was to extract the active peroxotungstatophosphate species from the aqueous into the organic phase, formed of CHDD and toluene, where the reaction took place. Once the oxidation had taken place, the reduced catalyst was extracted back into the aqueous phase, where it was again oxidized by H_2O_2. Thus, the presence of H_2O_2 was essential for the catalytic cycle. A major drawback of this approach was the inevitable formation of the diepoxide as a product of the oxidation of the double bond present in CHDO. In an attempt to overcome this problem, a set of phosphonic and phosphinic acids were used as precursors of the peroxotungstatophosphate. The influence of the structure (cation and anion) of a set of PTCs in the epoxidation was also studied. In all cases, sodium tungstate was used as W^{VI} precursor and 0.5 equiv. of H_2O_2 were added as oxidant.

The use of Aliquat 336 as PTC and phosphoric (or phosphonic) acid(s) showed different catalytic activity. Clearly, using phosphoric acid resulted in the highest conversion of CHDD. Nevertheless, the selectivity towards the desired monoepoxide was relatively low and formation of diepoxide took place from the beginning of the reaction. Although the conversion was slightly lower, using aminomethylphosphonic acid resulted in higher selectivity towards CHDO. After 180 min, a CHDD conversion of 40% with 90% selectivity towards CHDO was achieved. The use of hydroxymethylphosphonic acid or phenylphosphonic acid resulted in lower conversion of CHDD with a similar selectivity towards the monoepoxide after 180 min of reaction time. The usage of PTC-B, a quaternary ammonium salt containing the same cation as Aliquat 336 and hydrogensulfate as anion, changed the activity again. The usage of phosphoric acid resulted in the highest CHDD conversion. Similarly, the results obtained with aminomethylphosphonic acid were basically the same as the ones obtained with Aliquat 336. Surprisingly, the activity shown by hydroxymethylphosphonic acid and phenylphosphonic acid increased and resulted in 46% and 47% CHDD conversion, respectively; nevertheless, the selectivity with hydroxymethylphosphonic acid was slightly higher. No further improvement in the activity of the catalyst was noticed when phosphinic acids (e.g. diphenylphosphinic and bishydroxymethylphosphinic acid) were tested. Additionally, CHDD was not converted using diphenylphosphinic acid at the standard temperature. Thus, the

temperature was elevated to 80°C. Nevertheless, the conversion of CHDD after 180 min was only 24%. For comparison, bishydroxymethylphosphinic acid was also tested at 60°C and 80°C. Although the latter showed a higher activity during the reaction, both resulted in 45% conversion of CHDD and 88% selectivity towards CHDO after 180 min. In case of employement of PTC-C, which contained longer alkyl chains and also hydrogensulfate as anion, both CHDO and the CHDOO were formed. Using PTC-C, phosphoric acid showed again the highest conversion of CHDD (53%) but also the lowest selectivity towards CHDO (82%). Among the phosphonic acids, hydroxymethylphosphonic acid resulted in the highest conversion of CHDD (48%) with 86% selectivity towards CHDO. aminomethylphosphonic acid and phenylphosphonic acid resulted in slightly lower conversions of CHDD.

In order to learn more about the influence of their structure, a set of experiments using different PTCs was done. Phosphoric acid was chosen as the precursor of the peroxotungstatophosphate because it showed the highest activity among the phosphor-containing acids. Interestingly, the three PTCs with one methyl group in its structure resulted in the highest conversion of CHDD. Among them, the one with chloride as anion (PTC-A) resulted in the highest conversion of CHDD (55%) and lowest selectivity towards CHDO (78%). The substitution of one alkyl chain for a methyl group slightly decreased the conversion after 180 min. Interestingly, when the length of the four alkyl chains present in the cation of the PTC was shortened to C_4, no conversion took place. However, by increasing the length of the alkyl chains to C_{18}, the reaction took place.

5.2. Wacker-type oxidation of CHDD

The Wacker-type oxidation of CHDD with different Pd^{II} complexes was studied. The O_2-coupled copper-free method proposed by Kaneda and coworkers consisting of $PdCl_2$ in DMA [73] was successfully applied to the oxidation of α-olefins to the corresponding methyl ketone. However, this catalytic system showed a lower activity in the oxidation of *cis*- and *trans*-5-decene. When the catalyst concentration was increased, the corresponding internal ketones were obtained in good yields. The application of Kaneda's method ($PdCl_2$-DMA) in the oxidation of CHDD resulted in the formation of the target product 8-CHD, even at low catalyst concentrations. However, the selectivity towards 8-CHD was rather low and a number of by-products were also formed. Similar results were obtained using $Pd(OAc)_2$ in DMA. Further screening of palladium(II) chloride and acetate complexes of bidentate (di)amine as catalyst decreased the conversion of CHDD and did not improve the selectivity towards 8-CHD.

Interestingly, the use of Pd^{II} complexes of β-diketones in DMA, resulted in lower CHDD conversions but higher selectivity towards 8-CHD. An experiment using $Pd(acac)_2$ as catalyst and $H_2{}^{18}O$ as oxidant under 3 bar of $^{16}O_2$ confirmed that the O atom incorporated into 8-CHD is derived from water and not from O_2. Also a number of oxygenated byproducts such as α,β-enones, ketones and epoxides were formed during the reaction. Nevertheless, these byproducts could potentially be of some use for the fragrance industry. An experiment using $H_2{}^{16}O$ as oxidant under 6.5 bar of $^{18}O_2$ resulted in the incorporation of labeled-O into only one of the byproducts; however, the possibility that the O atom incorporated into the byproducts comes from O_2 cannot be discarded. Other solvents containing an amide moiety (*e.g.* DMF, DMPr and NMP) and with different polarities were also investigated. Although the activity of $Pd(acac)_2$ increased in NMP, the selectivity towards 8-CHD was lower. The catalytic activity and selectivity towards 8-CHD varied in dependance on which β-diketone complex of Pd^{II} was used. The use of $Pd(hfacac)_2$ as catalyst drastically increased the catalytic activity but also lowered the selectivity towards the target product. The usage of $Pd(tfac)_2$ resulted in similar results.

On the other hand, the use of catalysts containing bulkier β-diketones increased the selectivity towards 8-CHD. Interestingly, with 20 mol% of $Pd(TMHD)_2$ CHDD underwent 49% conversion to give 8-CHD in 42% selectivity. When lower amounts of this catalyst were used the conversion of CHDD decreased but the selectivity remained constant. This could mean that a radical oxidation as parallel reaction might take place and that the formation of the by-products follows another mechanism. Similarly, CHDD was oxidized using other bulky β-diketonato Pd^{II} complexes like $Pd(dbm)_2$ and $Pd(bmdm)_2$. The usage of $Pd(dbm)_2$ showed a higher reactivity and lower selectivity towards 8-CHD compared to those obtained using $Pd(acac)_2$. Interesting results were obtained with $Pd(bmdm)_2$. With 3 mol% CHDD underwent 31% conversion to give 8-CHD in 37% selectivity. The low solubility of this complex in the reaction medium might be the reason why almost the same results were obtained using 5 mol% of the catalyst. A number of oxygenated by-products were formed during the Wacker-type oxidation of CHDD using β-diketonato Pd^{II} complexes. Nevertheless, these compounds could be further transformed into valuable products or directly have applications in the fragrance industry.

Although the Wacker-type oxidation of cyclic olefins is not as facile as that of terminal olefins, the previously undescribed O_2-coupled oxidation of CHDD into the macrocylic monoketone 8-CHD was possible using Pd^{II} catalysts in DMA. Especially interesting results were obtained using β-diketonato Pd^{II} complexes. This was the first time that such a systematic study of the Wacker-type oxidation of a macrocyclic olefin such as CHDD was done and the results of

this thesis provide the basis for a one-step reaction and constitute an alternative to the two-step epoxidation route.

5.3. Outlook

The results obtained in the epoxidation of CHDD provided interesting insights regarding the role of the structure of the PTC and the precursors of the polyperoxotungstophosphate. Although the reaction medium is formed by an aqueous and an organic phase, the isolation of the product and unconverted substrate in addition to the isolation of the catalyst can be extremely difficult. An interesting alternative would be the immobilization of the catalyst for its further isolation and reusability for the preparation of CHDO on higher scales. Recently, the immobilization of tungsten species on covalently linked phosphoramides resulted in materials capable of catalyzing the epoxidation of several olefins [183]. However, macrocyclic olefins similar to CHDD have not been tested using such materials as catalyst yet. The leaching of the catalytic species could be an additional problem to be solved. Another interesting approach would be the use of metal oxides as heterogeneous catalysts for the epoxidation of CHDD using H_2O_2 or TBHP. This would provide the possibility of running the oxidation in a continuous fashion.

The results of the O_2-coupled Wacker-type oxidation demonstrated that a one-step approach under copper-free conditions using water and molecular oxygen as oxidants for preparing 8-CHD is possible. Of special interest would be the identification of the oxygenated byproducts generated during the oxidation, especially with β-diketonato complexes, for its potential use in the fragrance industry. The usage of these complexes improved the results obtained with $PdCl_2$ and $Pd(OAc)_2$ and their corresponding diamine complexes. Further investigations of the reaction parameters could still improve the selectivity of these catalysts towards 8-CHD. The employement of other Pd^{II} complexes and oxidants (e.g. TBHP) other than water or oxygen would also be an interesting alternative. The TBHP-mediated Wacker-type oxidation of internal olefins using the $PdCl_2$ complex of 2-(4,5-dihydro-2-oxazolyl)quinolone (Quinox) disclosed by Sigman and coworkers would be an interesting approach. In the proposed mechanism [184], the O atom incorporated into the ketone originates from tBHP, which acts as a nucleophile and follows a *syn*-peroxypalladation mechanism. The electronic disparity between the quinolone and oxazoline moieties of the ligand seems to be crucial for the efficiency of the catalyst [185]. Therefore, the bulkiness of TBHP in comparison to that of water could improve the selectivity towards 8-CHD. The oxidation of (Z/E)-cyclododecene using this method gave a 76% yield of cyclododecanone [186].

6. References

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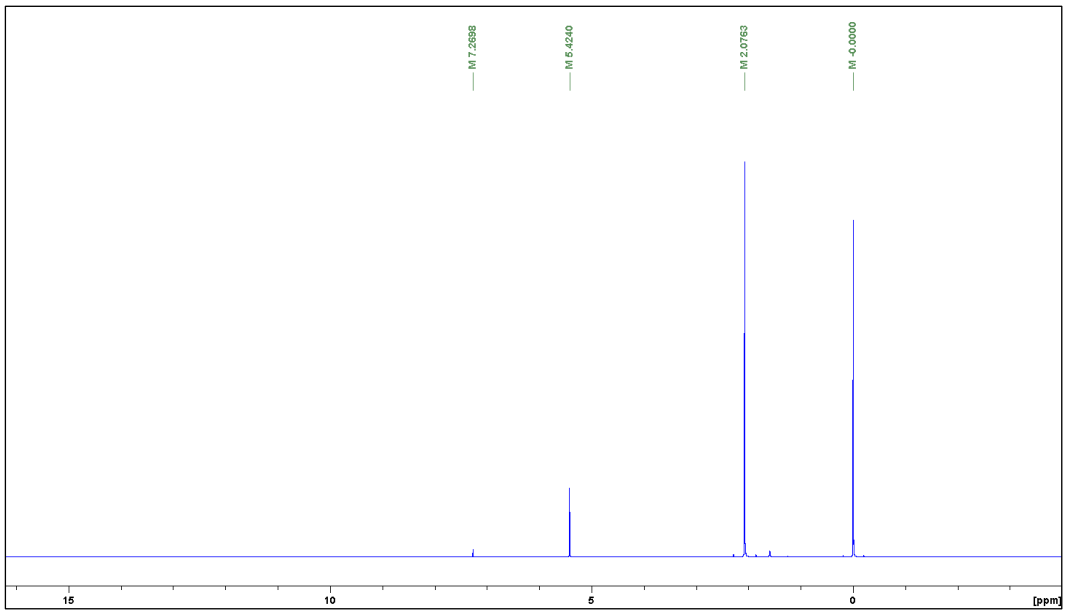
7. Appendix

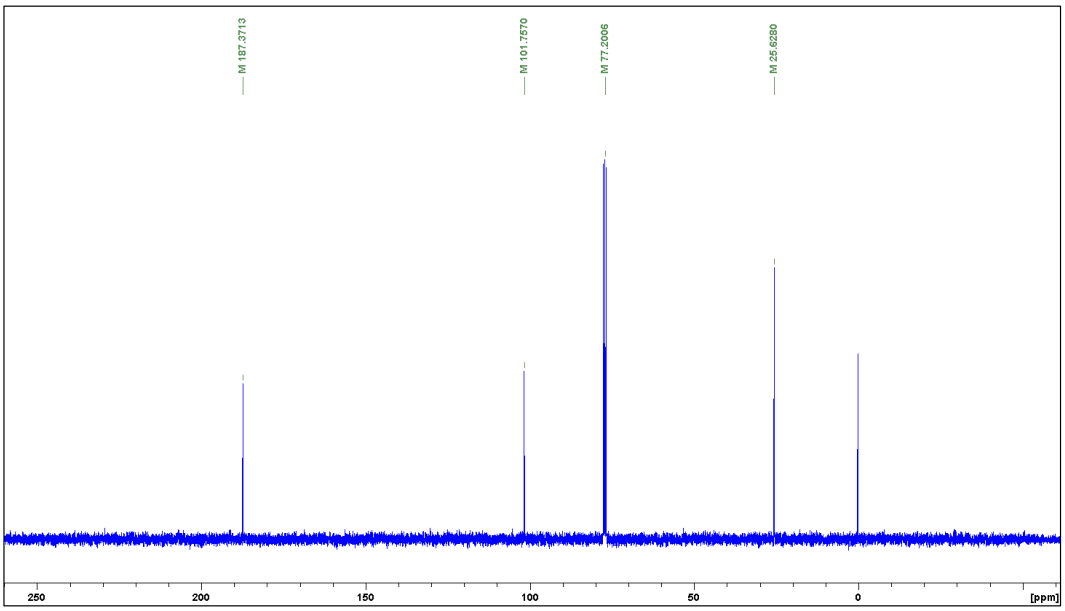
NMR Spectra of the palladium(II) complexes

Palladium(II) acetylacetonate

^{1}H NMR spectrum

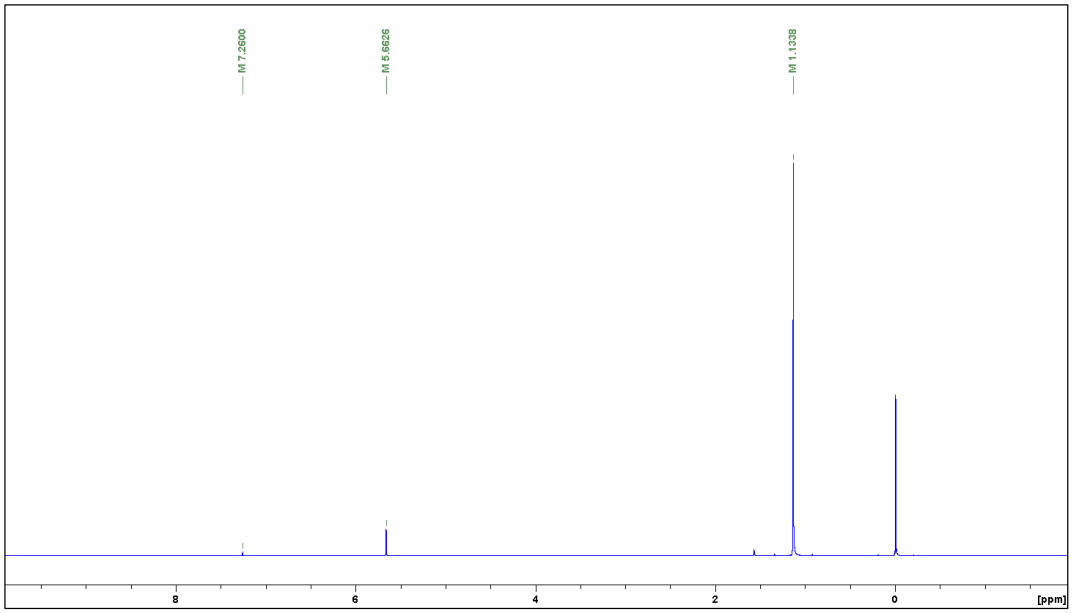


^{13}C NMR spectrum



Palladium(II) tetramethylheptanedionato

^{1}H NMR spectrum



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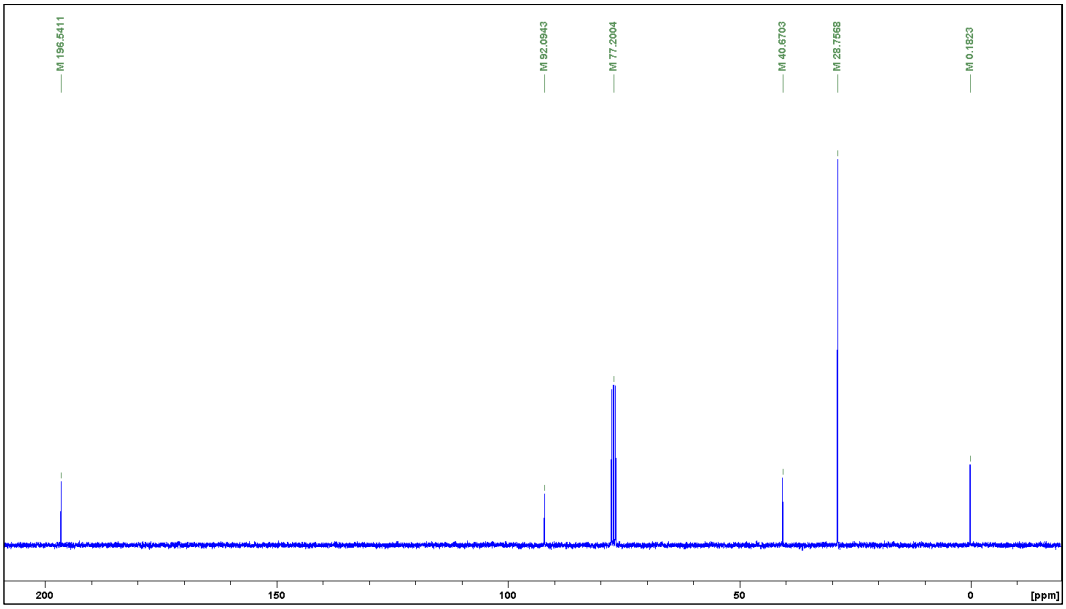
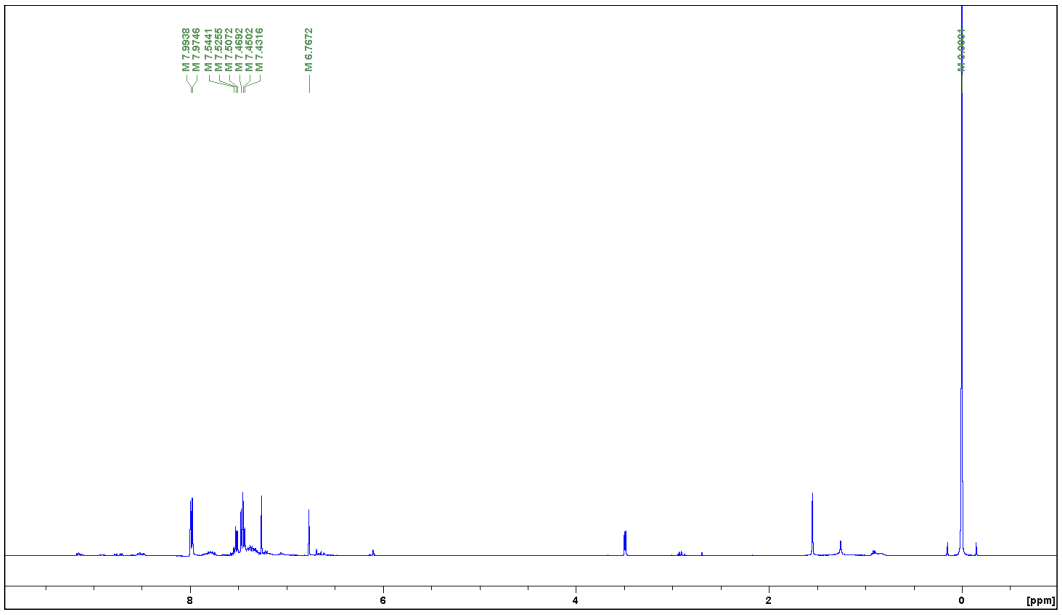


Palladium(II) dibenzoylmethanato

^{1}H NMR spectrum



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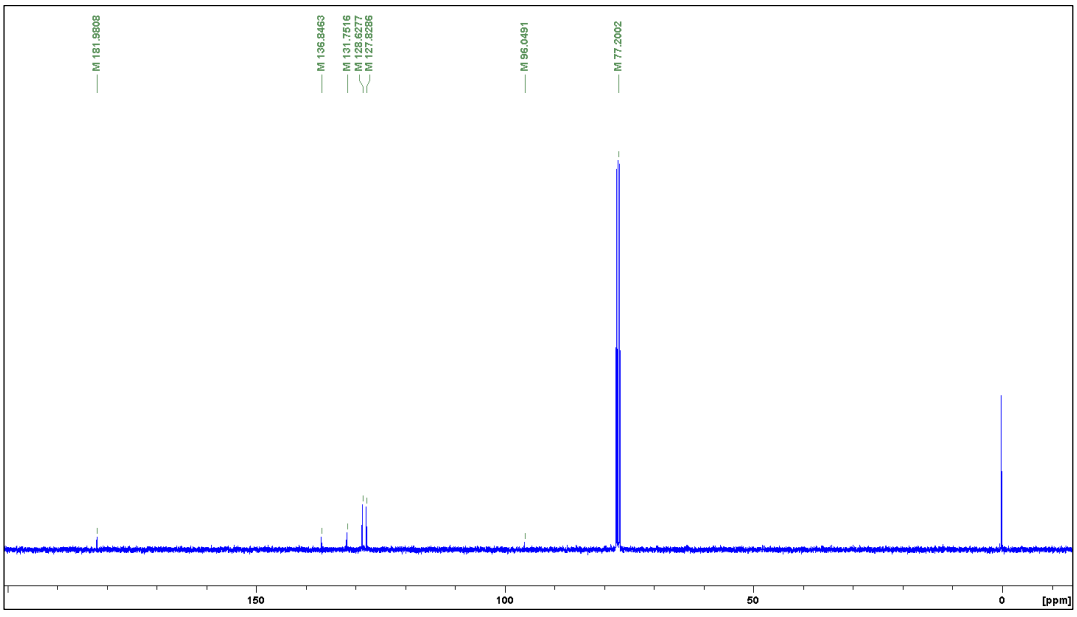
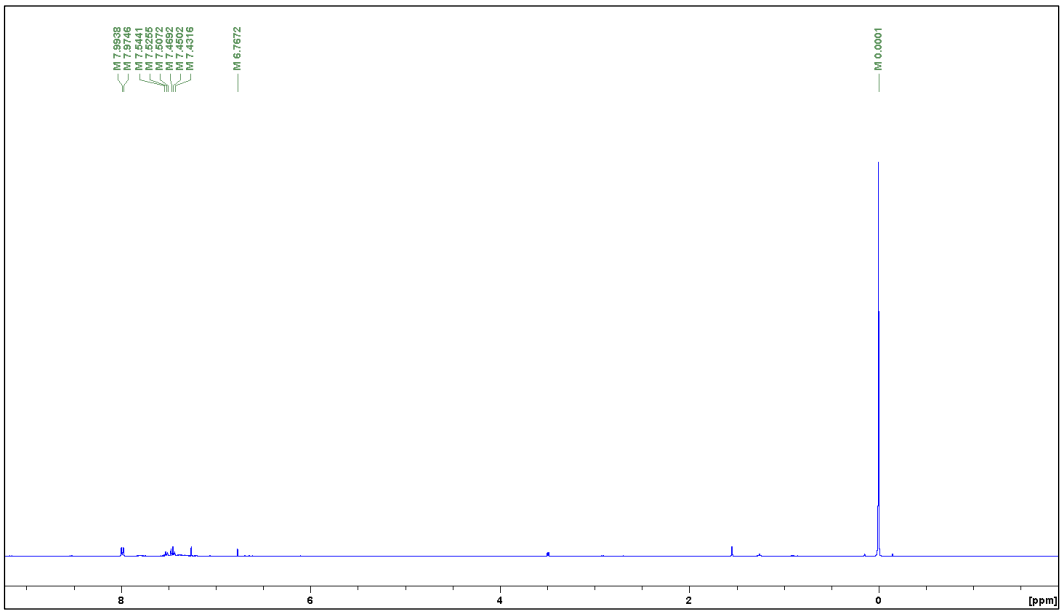


Palladium(II) butylmethoxydibenzoylmethanato

^{1}H NMR spectrum



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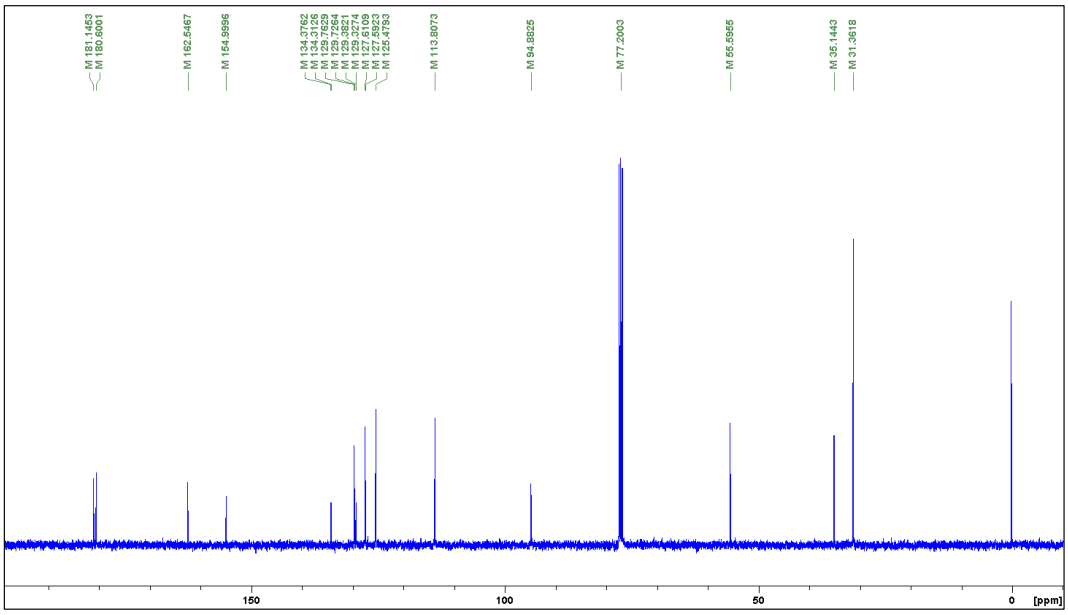

Palladium(II) trifluoropentanedionato

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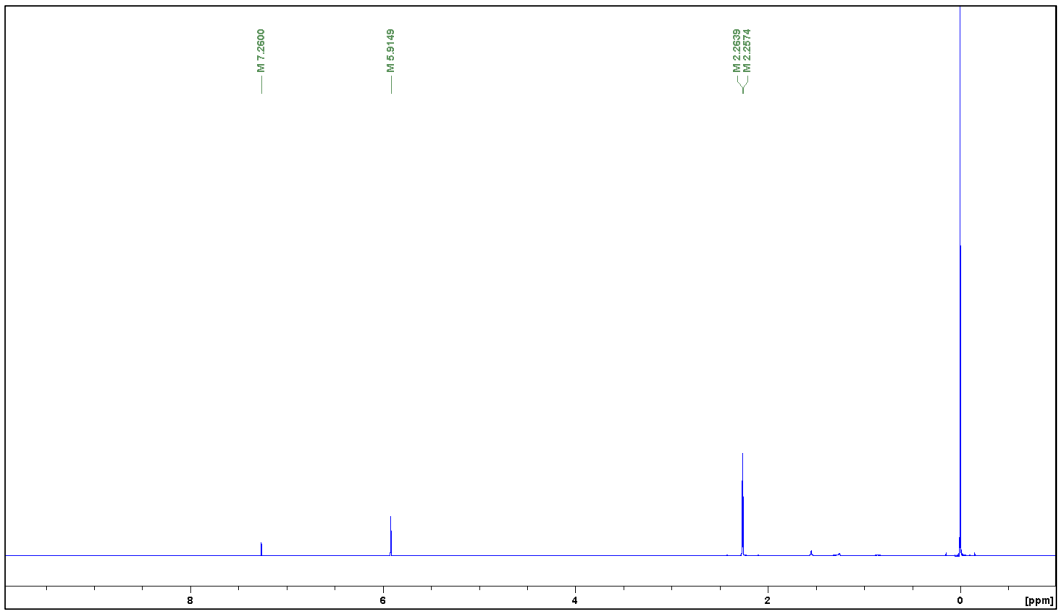

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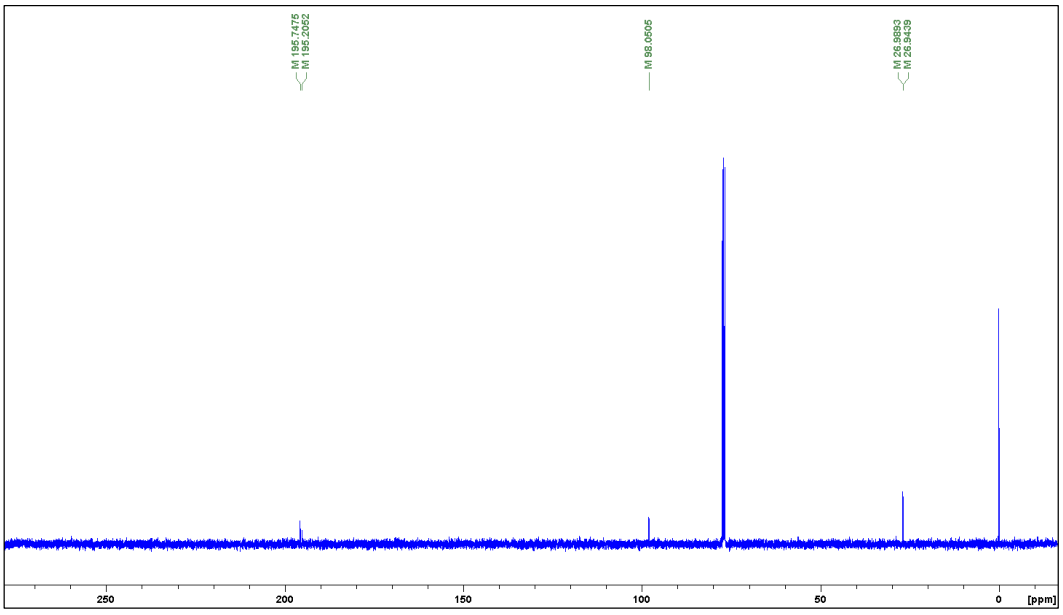
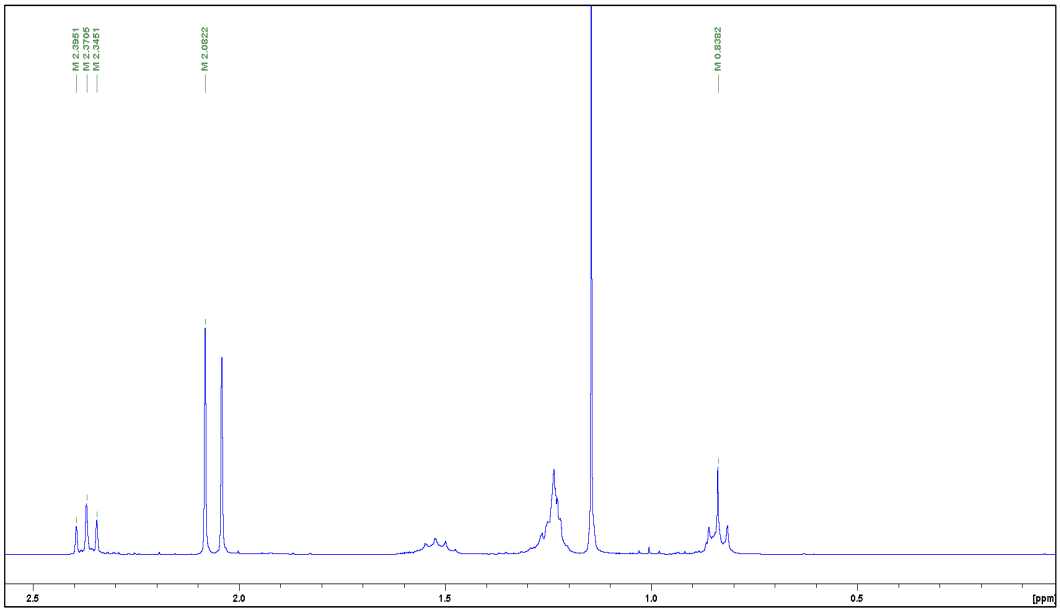


NMR spectra of methyl and internal ketones

2-octanone

^{1}H NMR spectrum



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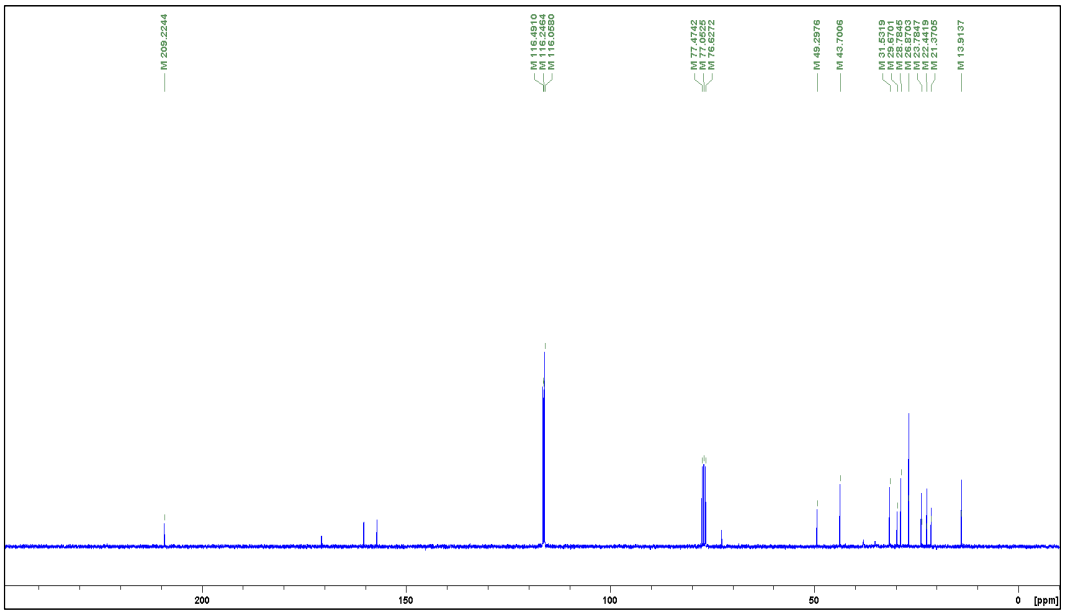

2-nonanone

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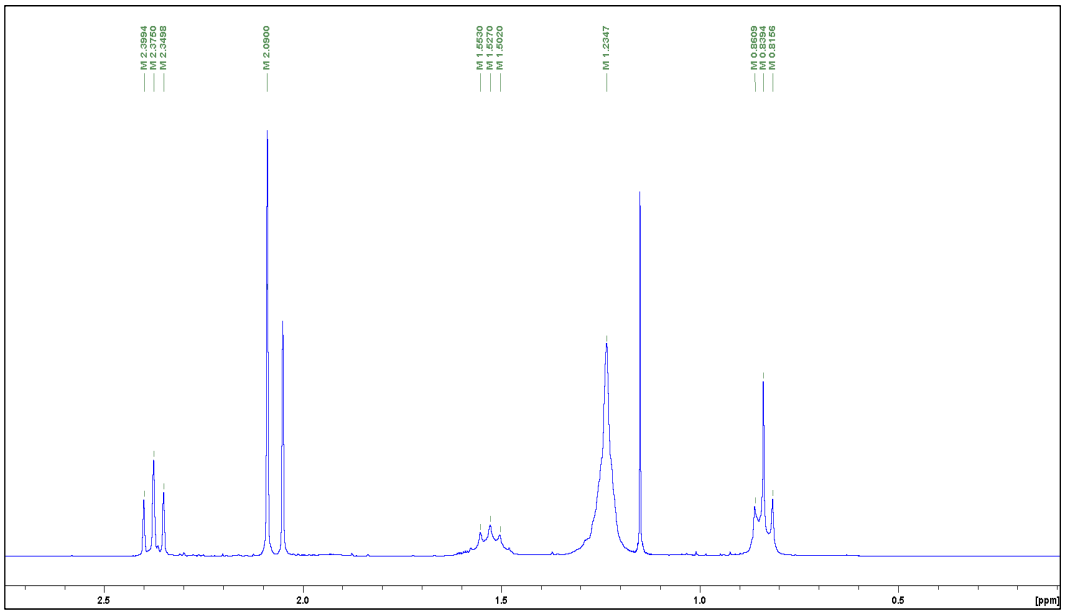

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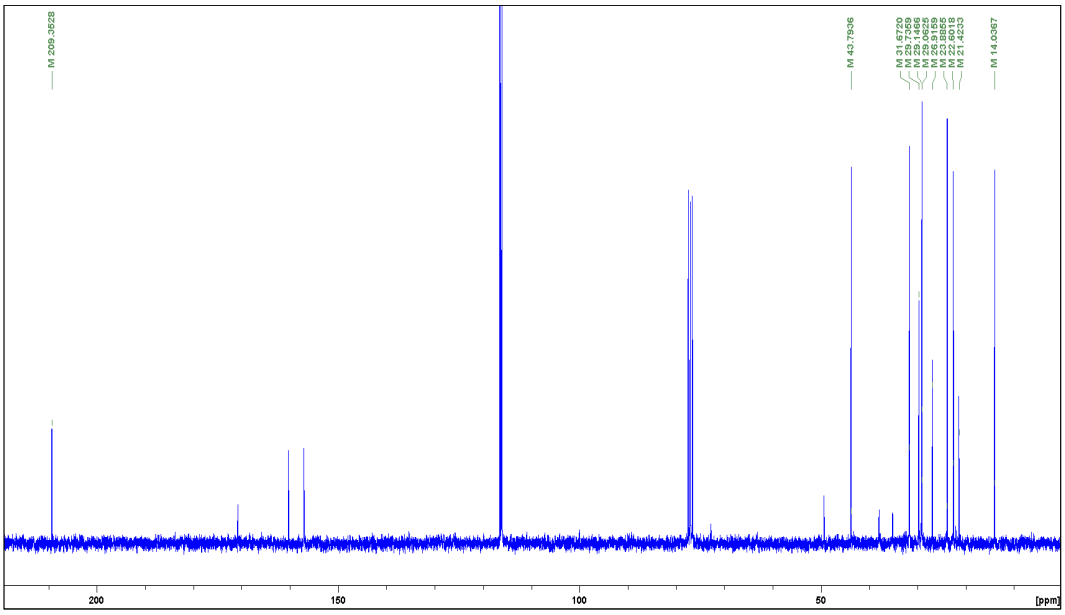
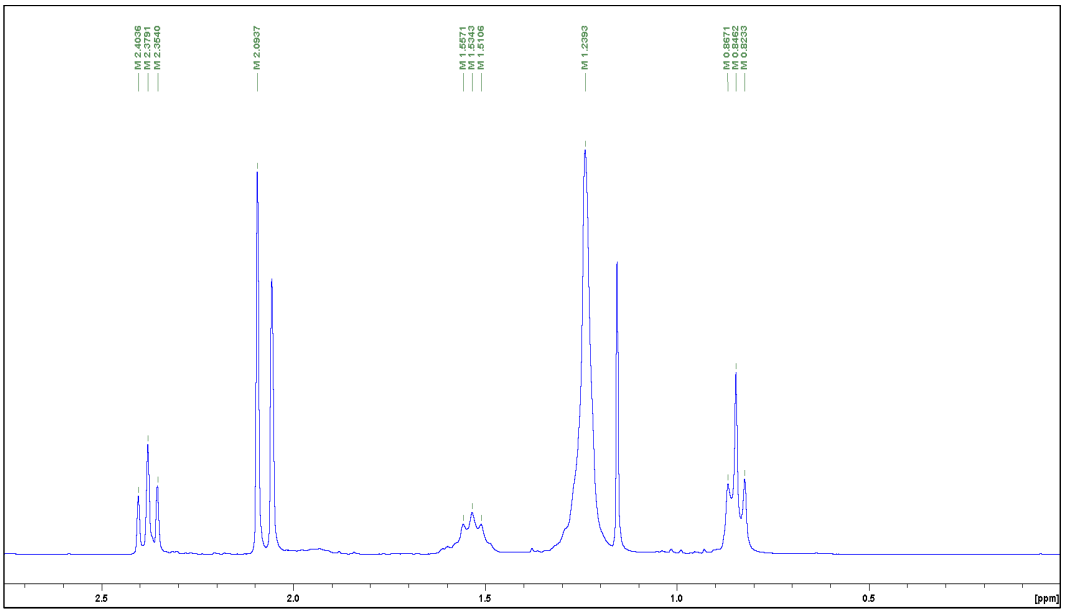


2-decanone

^{1}H NMR spectrum



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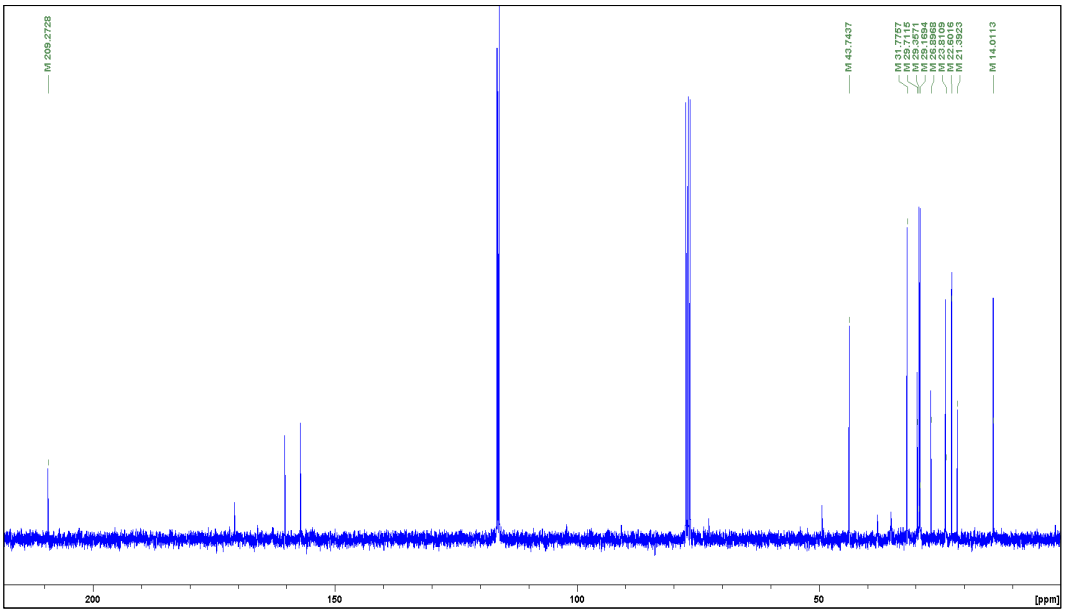
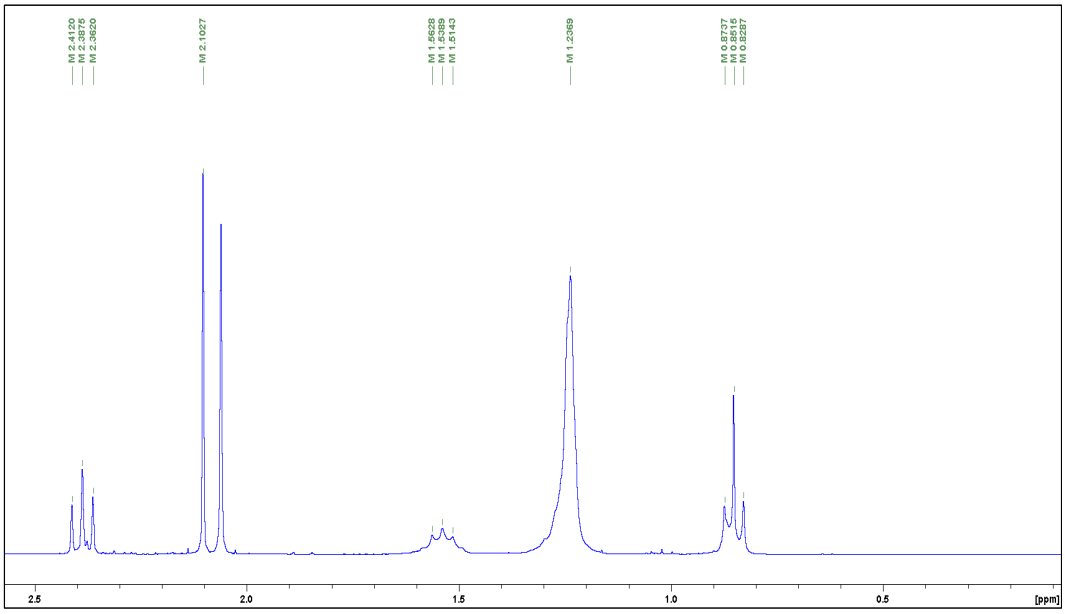


2-undecanone

^{1}H NMR spectrum



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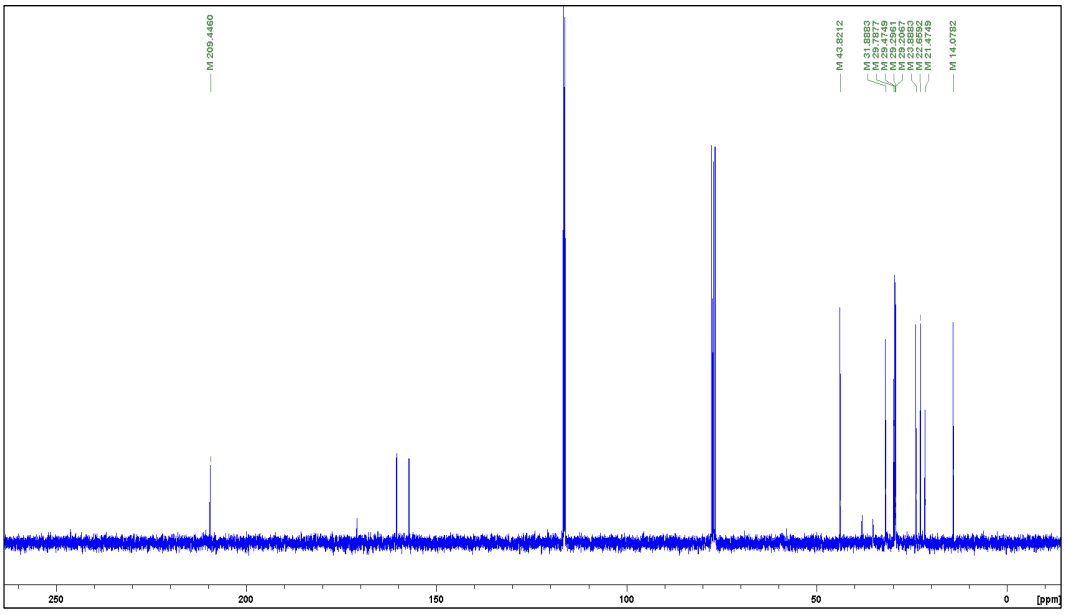
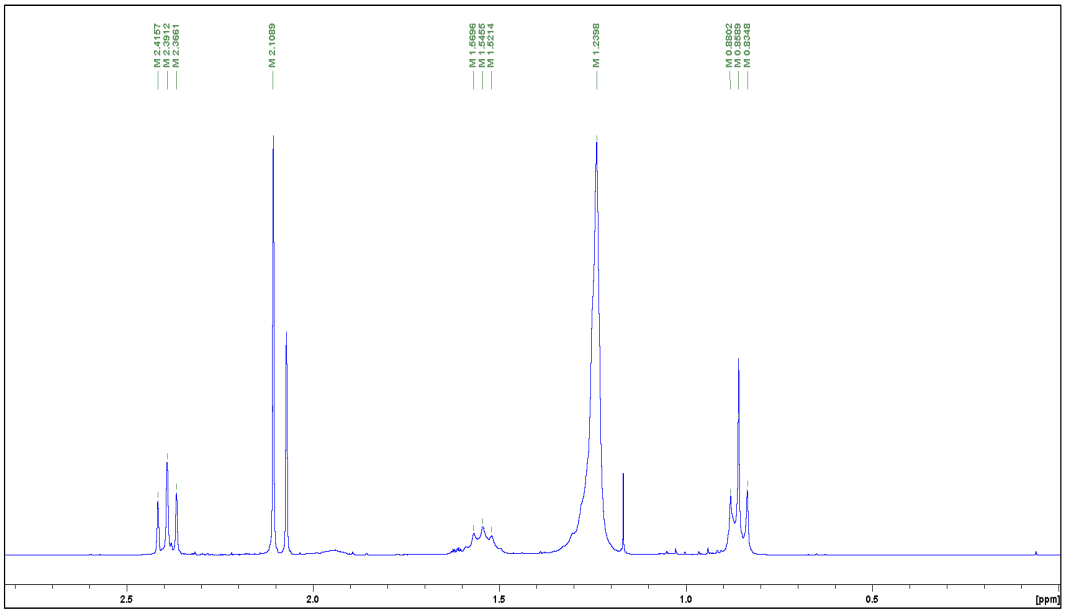
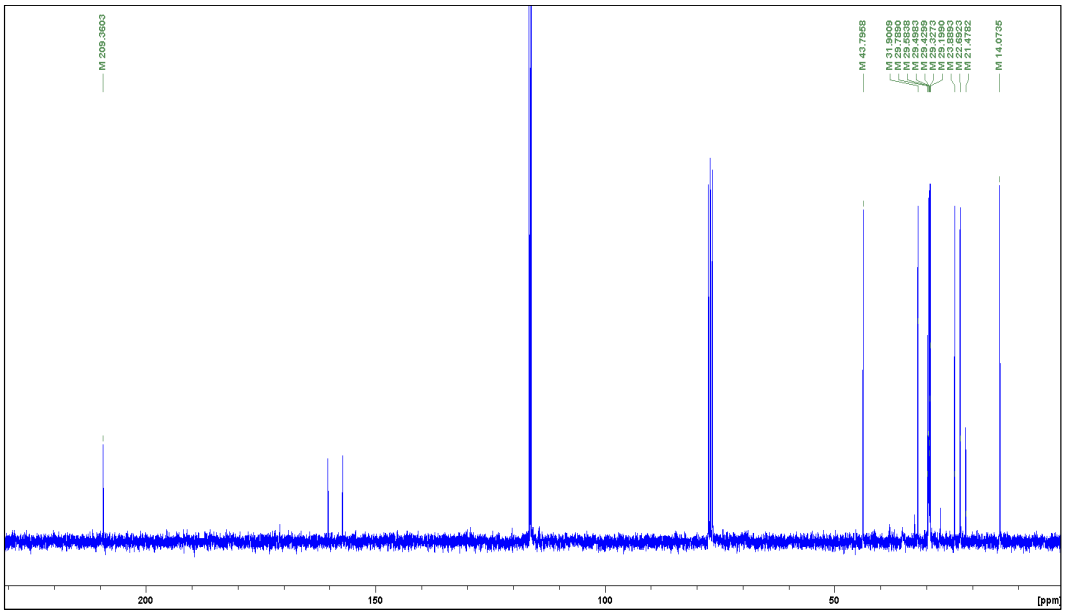


2-dodecanone

^{1}H NMR spectrum

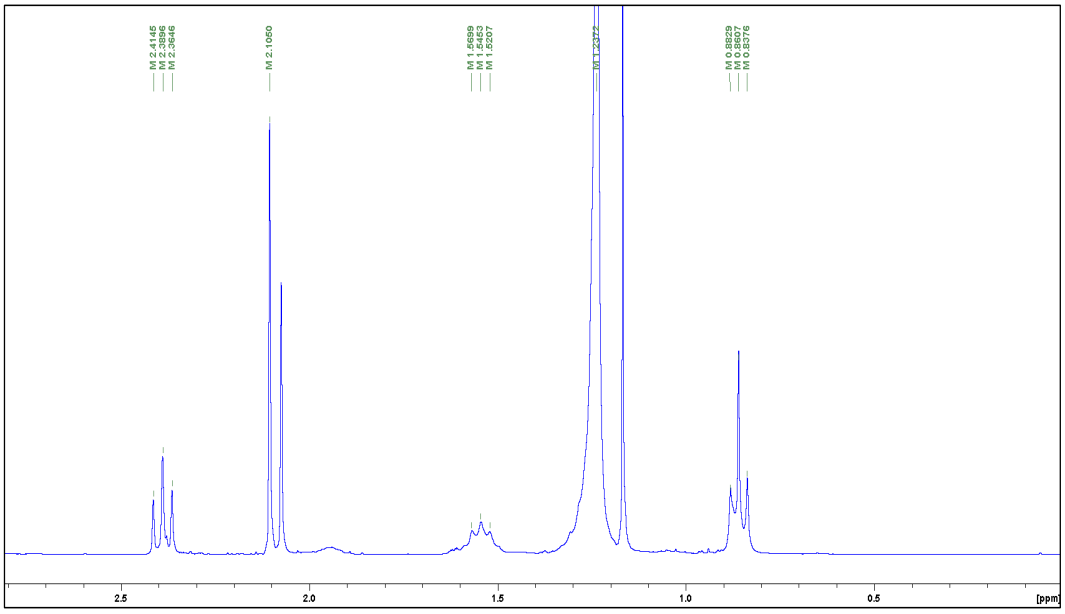


^{13}C NMR spectrum

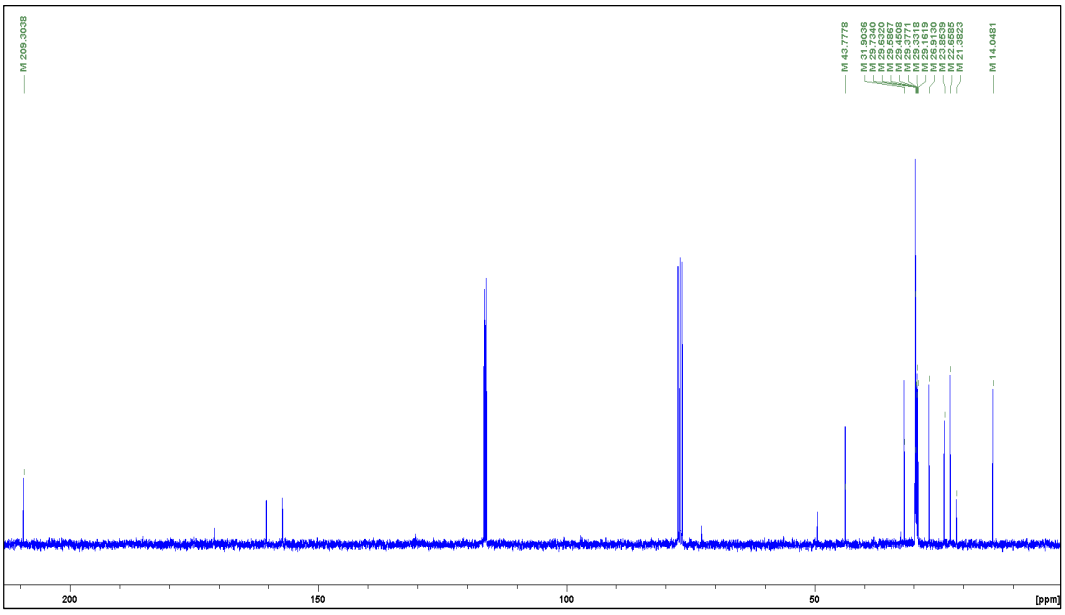


2-hexadecanone

^{1}H NMR spectrum

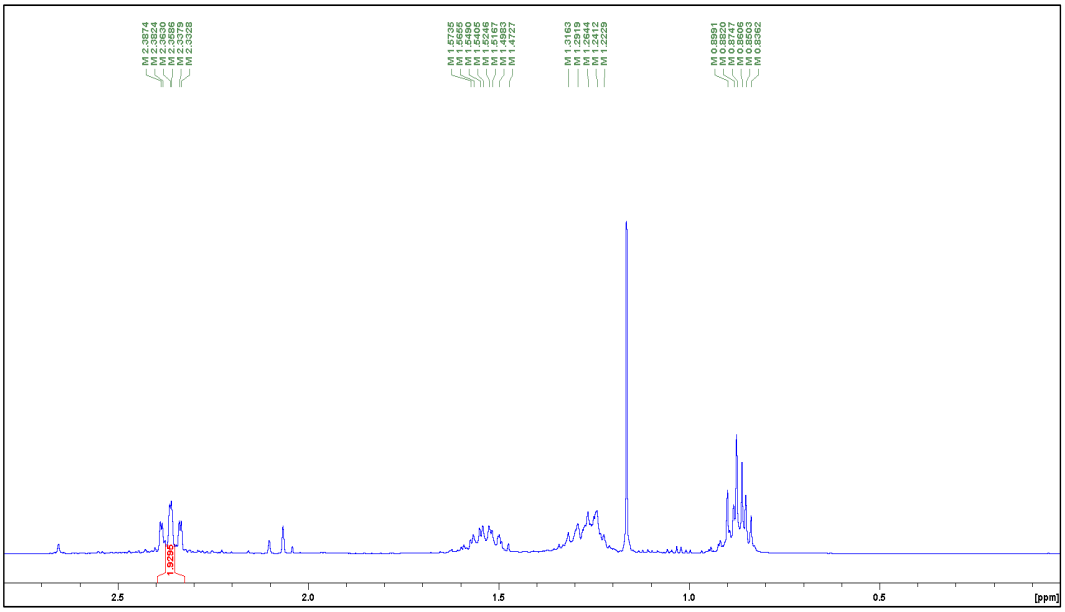


^{13}C NMR spectrum

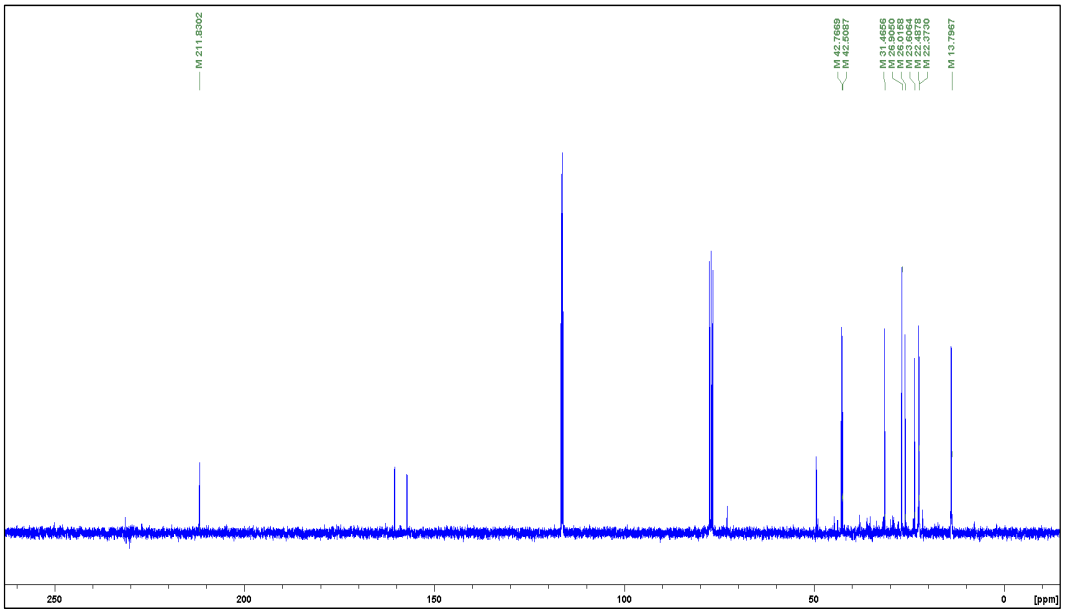


5-decanone from *cis*-5-decene

^{1}H NMR spectrum



^{13}C NMR spectrum



5-decanone from *trans*-5-decene

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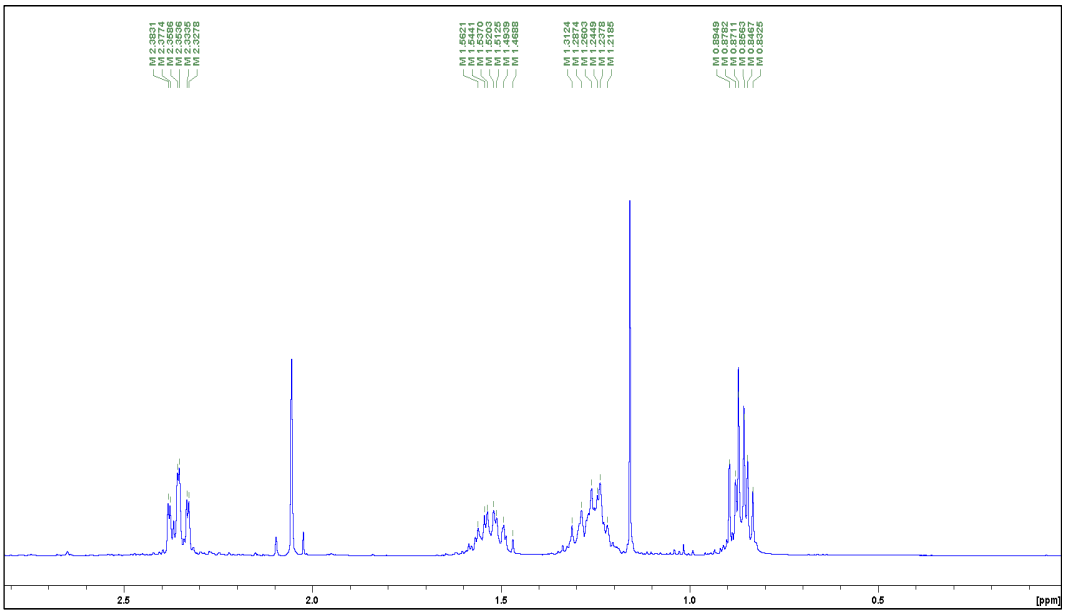
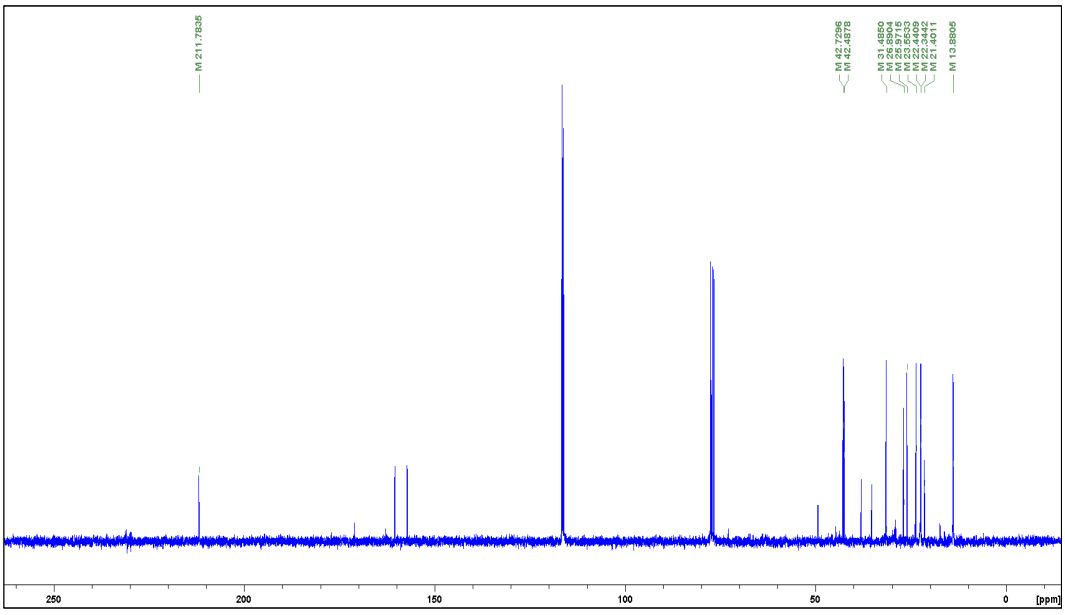
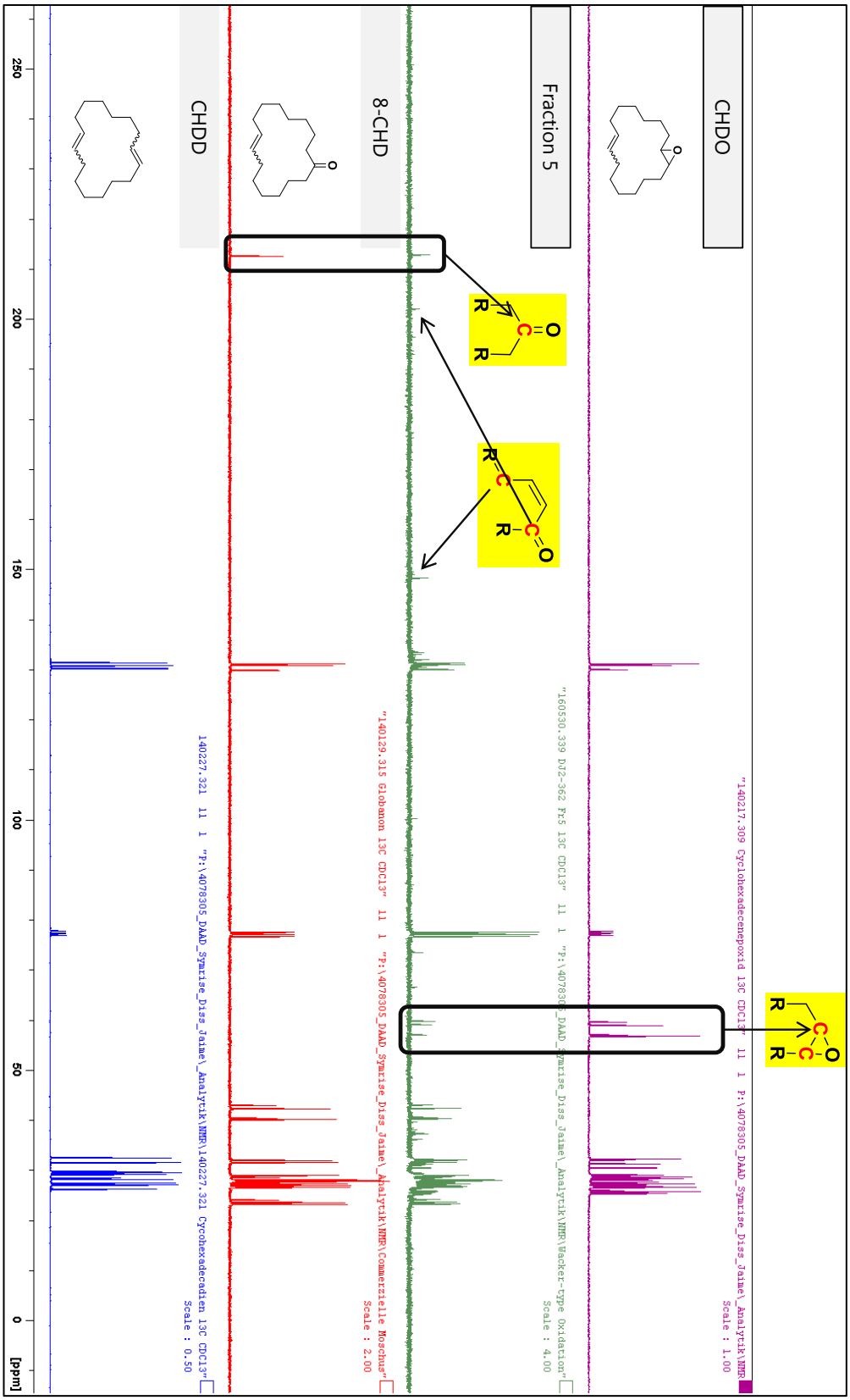


^{13}C NMR spectrum



Large scale experiment of the Wacker oxidation of CHDD with $Pd(acac)_2$

Fraction 5 compared to CHDD, CHDO and 8-CHD



List of Publications

Poster presentations:

Diego Jaime, Andreas Martin, Johannes Panten, Peter Esser, Angela Köckritz, Study of the selective epoxidation to a fragrance intermediate under phase-transfer conditions, 11th internation Congress on Catalysis and Fine Chemicals, Lyon (France), 2016

Patents:

Diego Jaime, Andreas Martin, Angela Köckritz, Herstellung von 17-Oxabicyclo[14.1.0]heptadec-8-en, EP 16186941.7