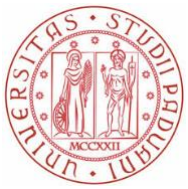

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DIPARTIMENTO DI SCIENZE CHIMICHE

CORSO DI LAUREA MAGISTRALE IN CHIMICA INDUSTRIALE

TESI DI LAUREA MAGISTRALE

Synthesis of menthol from citronellal over polymer supported catalyst

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Contents

1. Introduction

1.1 Menthol

Among the essential oils derived from different mint species, menthol is the most prevalent in both medicinal and cosmetical applications. In fact, menthol is used as the main flavour in oral care products, such as toothpaste and mouthwash, cigarettes, but also in chewing gums and candies. [1] Although it has been used for centuries, menthol, a cyclic monoterpene alcohol, was first isolated in 1771 by the Dutch botanist Hieronymus David Gaubius.

The menthol molecule comprises eight different isomers, resulting from the presence of three stereogenic centres which result in four pairs of optical isomers, (±)-menthol, (±)-isomenthol, (±)-neomenthol and (±)-neo-isomenthol (Figure 1), showing slightly different properties. Nevertheless, (-)-menthol is the sole isomer that exhibits the characteristic peppermint odour and cooling sensation on human skin and mucous membranes, which are commonly associated to menthol and mint.

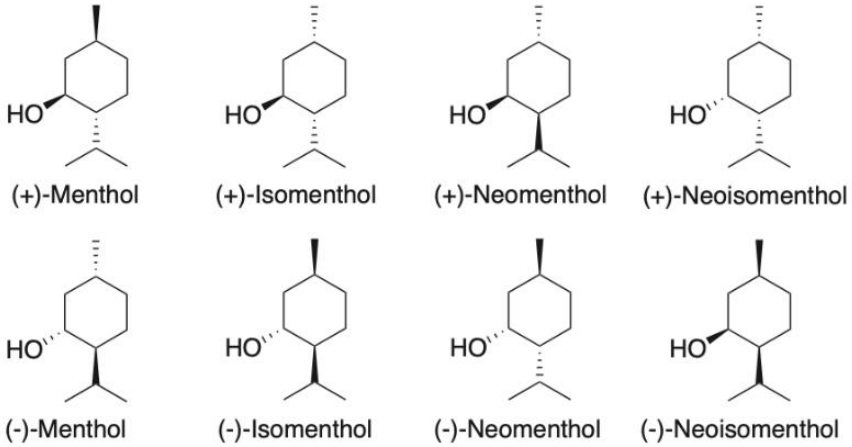

Figure 1. Isomers of menthol.

The remaining isomers, including isomenthol, neomenthol and neoisomenthol, are responsible for a rather unpleasant odour that reminds to earthy and musty notes.[2] With regard to human perception, the isomer that is mostly frequently perceived as fresh and minty is the L-(-)-menthol, due to the shape-sensitive chemoreceptors present in the human body. [3]

The physical properties are slightly different for enantiomers and the racemic mixtures. Notably, the boiling points display a similar range, with (-)-menthol boiling at 216.5°C, (-)-neomenthol at 211.7°C, (-)-isomenthol at 218.6°C. There is a difference of approximately 4°C among the boiling points of these compounds. [1] Accordingly, fractional distillation is the most used technique to obtain (-)-menthol from natural sources. Conversely, the melting points are remarkably different (Table 1).

Table 1. Physical properties of menthol isomers.

Isomer	**Boiling point (°C)**	**Melting point (°C)**
(-)-menthol	216.5	43.0
rac-Menthol	216.5	38.0
(-)-Isomenthol	218.6	82.5
rac-Isomenthol	218.6	53.6
(-)-Neomenthol	211.7	-15.0
rac-Neomenthol	211.7	52.0
(-)-Neoisomenthol	214.6	13.5
rac-Neoisomenthol	214.6	13.5

Menthol is white or colourless solid, with a density of 0.890 kg/dm^3 (25°C). It is soluble in water (455.5 mg/L at room temperature), but dissolves better in alcohol, diethyl ether and chloroform.[4]

The biological effects of menthol have been studied in detail, especially its ability to decrease the thresholds of cold and mechanical pain. Since many different stereoisomers are present, the properties of each isomer have been tested and some studies highlighted that only (-)-menthol shows analgesic effects.[4] Further investigations demonstrated that the reduction of pain sensation is attributable to the interaction of menthol with the voltage-gated Na^+ channels, which inhibits the perception of pain. On the other hand, the stimulation of cold receptors is linked to the inhibition of Ca^{2+} channels in neuronal membranes. Moreover, menthol thanks to its antifungal and antibacterial activities is widely used also as the additive in common medicine.

Because menthol and other essential oils have been used since ancient times for a variety of reasons, for a long time the only way to obtain (-)-menthol was the extraction from plants.

The industrial process of extraction of mint oil started in the second half of the 20th century and is based on the extraction of the aroma, followed by a fast crystallization from cornmint oil at -40°C. Finally, menthol is purified by recrystallization under strictly controlled conditions.

Menthol is currently the most in-demand flavour in the world, with an annual production of 34000 tonnes. Due to the increasing demand and the price volatility, some synthetic routes have been recently developed. [3]

1.2 Haarmann - Reimer Process

Considerable efforts have been made to achieve an efficient process to produce menthol from different precursors, easily available in nature and affordable. The first industrial process was developed by Haarmann & Reimer (Figure 2), a German company, later acquired by the Symrise AG. [1,3]

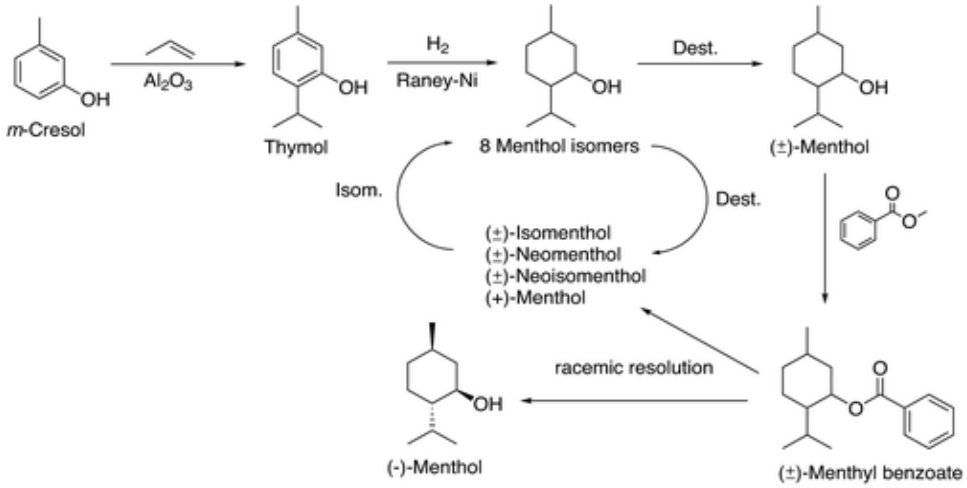

Figure 2. Haarmann - Reimer process.

The precursor used in this process is fossil-based m-cresol, which undergoes a Friedel-Craft alkylation with propene to obtain p-thymol. The intermediate is finally hydrogenated over Nickel or Cobalt catalysts to achieve menthol. However, the product is a racemic mixture, consisting in four menthol diastereomers, with >50% excess of the

thermodynamically favoured (±)-menthol. The mixture is treated with benzoic acid methyl ester in a transesterification reaction. The two enantiomers are separated by enantioselective crystallization by seeding the mixture with enantiopure (-)-methyl benzoate. This step is mandatory since (±)-menthol crystallize as the racemic mixture. This synthetic route allows to recover all the byproducts, to minimize wastes and maximize the yield of the whole process. Although the synthesis is efficient, the formation of the (±)-menthol diastereomers and their separation still represents critical aspects. A number of alternative options for the catalyst in the Haarmann - Reimer process have been recently proposed. The alkylation of the m-cresol can be achieved by using propene in the gas phase over acidic zeolite ZSM-5 with an overall selectivity for thymol of over 90%.[5,6] Moreover, the mesoporous Al-MCM-41 material was also reported as an effective catalyst at 290-350°C, especially when impregnated with zinc ions.[7] Thymol hydrogenation can be achieved with most of the common heterogenous metal catalysts, especially those containing nickel. Thymol reduction studies were carried out for decades, starting at the beginning of 19th century. Barney and al. explained how a nearly quantitative yield of menthol could be obtained by treating thymol with a hydrogenation catalyst to obtain a complex mixture of alcohols and ketones, specifically $dl-isomenthone \leftrightarrows enol \leftrightarrows dl-menthone$are in equilibrium in the solution. In this process, alcohols are dehydrogenated to the corresponding ketones under conditions that allow for the continuous removal of the desired intermediate dl-menthone. This allows the production of menthol and neomenthol through further hydrogenation and ensures the complete conversion. It must be noted that isomenthone hydrogenation leads to neoisomenthol and isomenthol, which are byproducts.[8] Further studies were conducted to identify an alternative to thymol, given the necessity to avoid the complicated separation of the undesired products.

1.3 Synthesis routes including citronellal

The most common and widely applied synthetic routes to synthetize menthol include citronellal in the overall reaction scheme. In fact, both BASF and Takasago processes require (+)-citronellal as the main intermediate for the reaction (Figure 3). [1,3,9]

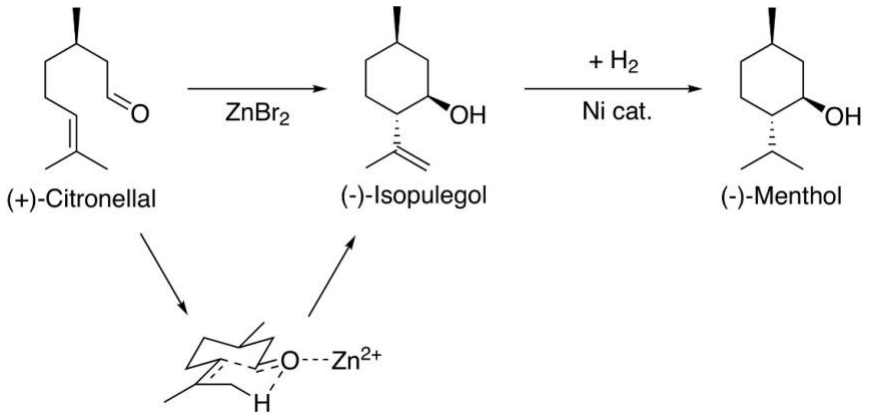

Figure 3. Use of citronellal as the intermediate for menthol production.

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Citronellal can be obtained with different precursors, mostly natural compounds easily available, such as myrcene for the Takasago process and geranial and neral for the BASF process. The key step is the isomerization of citronellal to isopulegol, which can be then converted to menthol by hydrogenation, as occurs in both Takasago and BASF processes. [3,4,10]

1.3.1 Takasago process

The Takasago International Corporation was the first company developing a process for the industrial production of menthol. Takasago patented in 1954 the process for menthol production from d-citronellal. D-citronellal was obtained with an overall yield of 35% from citronella oil extracted from plants. At that time, the production was around 300 tons. The advantage of using citronellal is the wider application of all the other components of citronellal oil in various processes (Figure 4). Moreover, because of the 80% of optical purity, d-citronellal was considered to be as a useful chiral starting material.

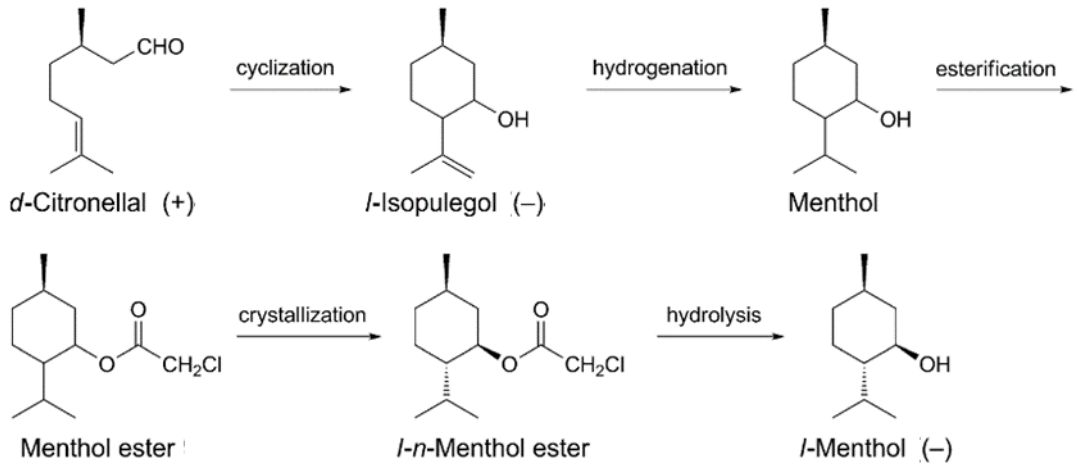

Figure 4. d-Citronellal process for the synthesis of (-)-menthol.

In less than 30 years, in 1972, Takasago started the production of menthol from thymol, which was obtained by m-cresol, a fossil-based reagent. The decision was taken in response to the significant increase of the global demand of menthol, which implied a wider use of d-citronellal, accounting approximately for half of the global consumption of natural citronella oil. However, this process was applied for less than a decade, since the prize volatility of petroleum-based materials was no more sustainable. As shown in Figure 5, thymol process requires to perform an optical resolution to obtain the desirable diastereoisomer, l-menthol. This was carried out by fractional crystallization from menthol ester to l-n-menthol ester. This allowed to successfully separate l-menthol by hydrolysis. [11]

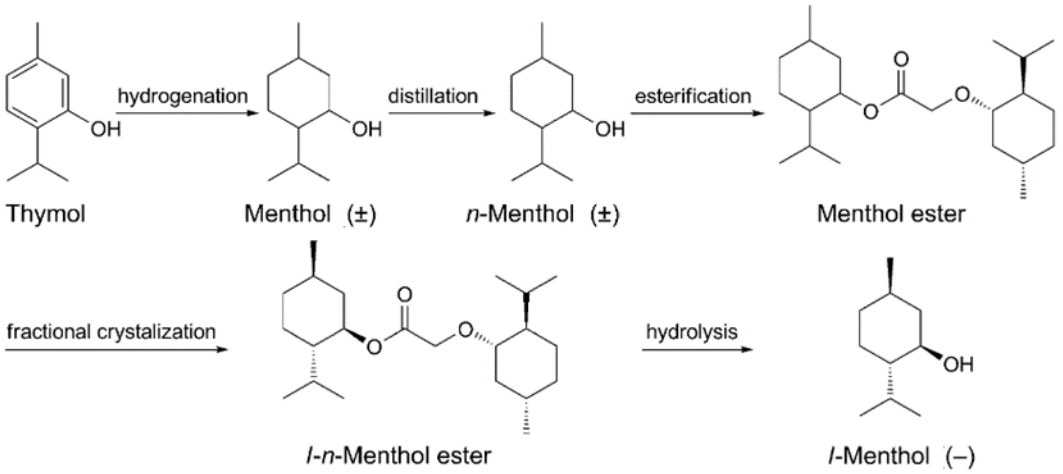

Figure 5. Thymol process for the synthesis of (-)-menthol.

In order to maximize the yield, the d-menthyl d-methoxyacetate remaining in the mother liquor was converted into dl-menthol with isomerization over Ni-catalysts, under high pressure conditions. Finally, with distillation, dl-n-menthol can be separated from iso-, neo-, and neoisomenthol.

Soon afterwards, a shortage of oil-based products brought to a high increase of m-cresol prize, making thymol more difficult to employ, forcing Takasago International Corporation to consider further possible starting materials.

Therefore, Takasago International Corporation started working on the exploitation of renewable sources as the starting material for the process, especially those found in nature, with low environmental impact and no need of special treatment. Thus, d-limonene and similar compounds have been tested as starting material, but, unfortunately, they cannot conveniently replace thymol. [10]

In 1983, Takasago International Corporation completed the asymmetric catalytic process using myrcene as the starting material, which is still currently used, although the process has been modified and improved throughout the years. [3,4]

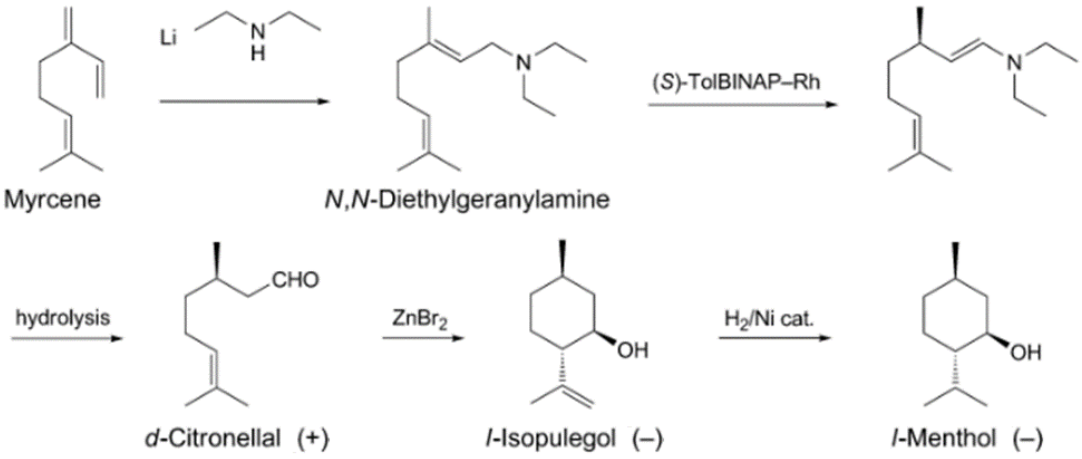

Figure 6. Takasago process for the synthesis of (-)-menthol using myrcene as starting material.

Nowadays, myrcene is used as the renewable starting material, as it can be easily isolated from gum rosin, wood rosin, toll rosin, tree sap, wood chips and the waste fluid of wood pulp.

The process (Figure 6) is based on the telomerization of myrcene with diethylamine to N,N-diethylgeranylamine, which is then isomerized to (+)-citronellal enamine, using rhodium BINAP catalyst. This is the key step of the process, which induces chirality in

the molecule with high selectivity. The enamine is hydrolysed to (+)-citronellal, which is cycloisomerized to isopulegol, that is finally hydrogenated to (-)-menthol. The organometallic catalyst Rh-BINAP (Figure 7) is crucial for the process and show a turnover number of 200,000.

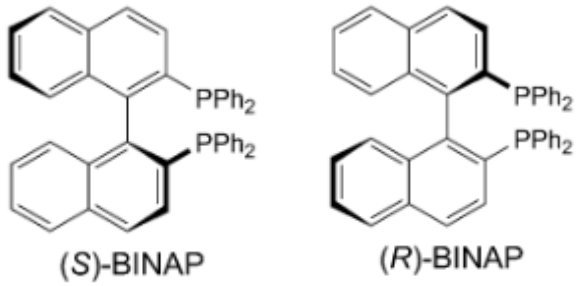

Figure 7. BINAP ligand.

The catalyst provides the chiral centre needed for the l-menthol synthesis. The other main improvement from previous processes can be observed in the cyclization of d-citronellal to l-isopulegol, obtained with $ZnBr_2$ with a selectivity of 92%. However, $ZnBr_2$ has been nowadays replaced by aluminum tris(2,6-diphenylphenoxide) (ATPH), increasing the overall selectivity to 99.5%.

1.3.2 BASF process

In 2005, BASF has submitted a patent application for the production of menthol starting from geraniol or nerol, or a mixture of both. The enantioselective hydrogenation of geraniol and nerol, or of a mixture of both, to (+)-citronellal was pursued using a chiral rhodium–(S,S)-Chiraphos catalyst in case of geranial and rhodium-(R,R)-Chiraphos catalyst when neral is used. In both cases (+)-citronellal is obtained with an enantiomeric excess above 87%. [3,12] This step is followed by cyclization of the resulting optically active citronellal to a mixture of optically active isopulegols, which are then hydrogenated to (-)-menthol over a Nickel catalyst. Remarkable chemo- and enantioselectivity can be achieved by combining the Chiraphos-ligand with CO-ligands, which avoids the hydrogenation of the carbonyl group and the trisubstituted double bond. This combination can also prevent any cis/trans isomerization between the geranial and neral isomers, which could occur under the hydrogenation conditions. According to the patent filed by BASF, the optimal starting material for the reaction is geraniol, particularly when it is of high purity. [12] The primary impurity present in the substrate is nerol. The enantioselective

hydrogenation is performed in the presence of a homogenous transition metal (Ru, Rh or Ir) catalyst and chiral ligands, typically a chiral diphosphine. The optically active citronellal obtained is typically cyclized in the presence of an acid catalyst. The resulting mixture comprises the four potential diastereoisomers of isopulegol (isopulegol, neo-isopulegol, iso-isopulegol and neoiso-isopulegol), depending on the chosen reaction conditions and catalyst. Other patents and academic investigations suggest the use of $ZnBr_2$ as active catalyst for the isomerization of (+)-citronellal to (-)-isopulegol. The final hydrogenation of (-)-isopulegol to (-)-menthol is carried out on the mixture of isomers and the optically active menthol is separated by crystallization in a further synthetic step [12-14].

Recently, a further approach for the synthesis of menthol has been reported and patented by BASF (Figure 8). It is based on the hydrogenation of geranial or neral to citronellol over a Ruthenium-BINAP catalyst, followed by the dehydrogenation to citronellal over mixed $ZnO/CaCO_3$. Nonetheless, the possible technological implementation of the process is still debated.

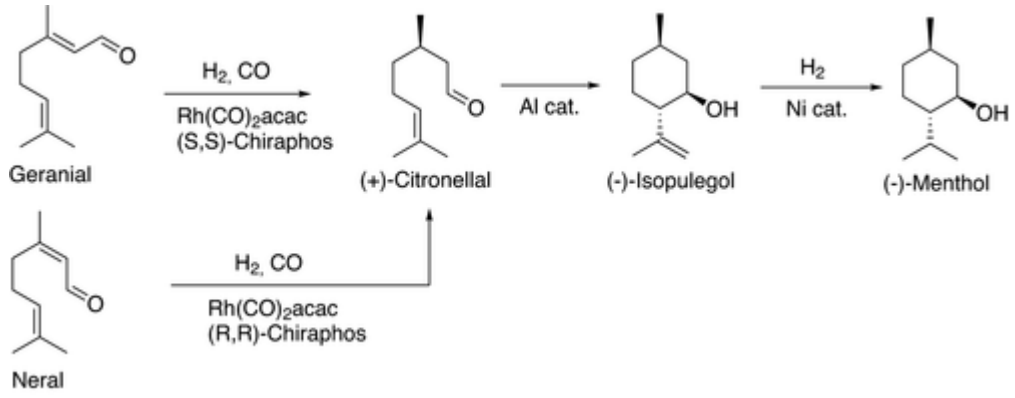

Figure 8. BASF process for the production of menthol.

1.4 Recent alternatives for menthol production

Since the most important step in the synthesis of menthol from citronellal is the cyclization of the latter substrate to isopulegol, several homogenous and heterogeneous catalysts have been studied to improve this specific step of the process. [15] To perform the cyclization of citronellal to isopulegol, both homogenous and heterogenous acid catalysts can be used. Mäki-Arvela et al. conducted some studies, highlighting that the acid sites needed to perform the cycloisomerazation are both strong Lewis acid sites

(LAS) and weak Bronsted acid sites (BAS).[9,17-19] To provide those acid sites, heterogenous catalyst, such as zeolites and resins, have been widely employed. Nevertheless, the catalytic material needs to be chosen carefully because strong acid sites can also promote side reactions. For example, it was observed that Amberlyst and Nafion favour cracking and etherification reactions, beside the dehydration of menthol. Among the materials tested, Al_2O_3 only containing Lewis acid sites, does not show any activity towards the isomerization of citronellal to isopulegol. Conversely, other zeolites such as H-MCM-41 and H-beta have shown successful results. In these cases, the activity has been attributed to the presence of both Lewis and Bronsted acid sites. [19,20]

Zeolites not only provide the acid sites for the reaction of cycloisomerization but can also be used as the support for metal nanoparticles active towards the hydrogenation. [22]

Homogeneous and heterogeneous Lewis acid catalysis showed promising results for the target reaction. For example. aqueous solutions of $ZnBr_2$ were successfully employed for the cycloisomerization of citronellal.[22] $ZnBr_2$ has also been employed as heterogenous catalyst. In this case, $ZnBr_2$ is supported on a material with high surface area and the resulting material is easy to use and shows a good selectivity towards the desired products. Although the leaching of the active material in solution during the reaction could represent a problem, the reported heterogeneous catalyst, reaching 94% of yield and 88% of diastereoselectivity, is not affected by leaching.[23] Further studies showed that the leaching of $ZnBr_2$ can be avoided using mesoporous supports (MCM-41, meso- Al_2O_3, HSM and Al-HSM were investigated), although no information on the lifetime of the material is reported. Corma and al. reported Sn-BEA zeolite as diastereoselective water-resistant heterogenous Lewis-acid catalyst for the isomerization of citronellal to isopulegol, suitable for both batch and fixed bed reactors and showing high conversions under both conditions (99% and 83% respectively). The catalyst is also less sensitive to humidity therefore it easier to be handled than other hygroscopic Lewis acid.[24]

Several studies have shown that Lewis acid sites are the most active towards the cycloisomerization. Different Lewis acids were investigated in citronellal cycloisomerization to isopulegol. Among those, $ZnBr_2$, $ZnCl_2$ and ZnI_2 have shown the best activity and selectivity towards the desired product. In particular, zinc halides mainly produce the desired isomer and only small fractions of neo-isopulegol and iso-isopulegol are observed. Neoiso-isopulegol is not detected, most probably due to its high instability. [22,25,26]

The catalytic performance of these Lewis acids supported on SiO_2 has been investigated in detail by Milone et al. They found that $ZnBr_2$ provides the highest activity and selectivity (86% selectivity). [22] $ZnCl_2$ showed lower selectivity and conversion than $ZnBr_2$, whereas the isomer ratio was similar. Although $FeCl_3$ and $SnCl_2$ are also active towards the cycloisomerization, the amount of produced (-)-isopulegol is much lower than with zinc halides. The isomer distribution, as well as the activity and the selectivity, strongly depends on the catalyst, according to this series: $ZnBr_2$>$ZnCl_2$>$FeCl_3$>$SnCl_2$. [25,26]

To study the effect of the counteranion on the catalytic activity, different zinc salts were deposited on SiO_2 and employed in the citronellal isomerization to menthol. Among $ZnBr_2$, $ZnCl_2$ and $Zn(NO_3)_2$, zinc bromide shows the highest activity and selectivity, according to previous investigations. $ZnCl_2$ shows a slightly lower activity and selectivity, as expected, but still in a similar range, whereas $Zn(NO_3)_2$ is the least active and selective catalyst. [26]

1.4.1 One Pot synthesis of Menthol

In recent years, there has been a growing interest in the one pot synthesis of menthol. According to Figure 9, the catalyst needs to be bifunctional, containing both acid sites, needed for the isomerization of citronellal to isopulegol, and a metal centre, promoting the hydrogenation from isopulegol to menthol. The exploitation of a bifunctional catalyst can also trigger several side reactions (Figure 9). As most of these byproducts have no practical exploitation, the selectivity has to be high, in order to maximise the production of the desired product. [18,27]

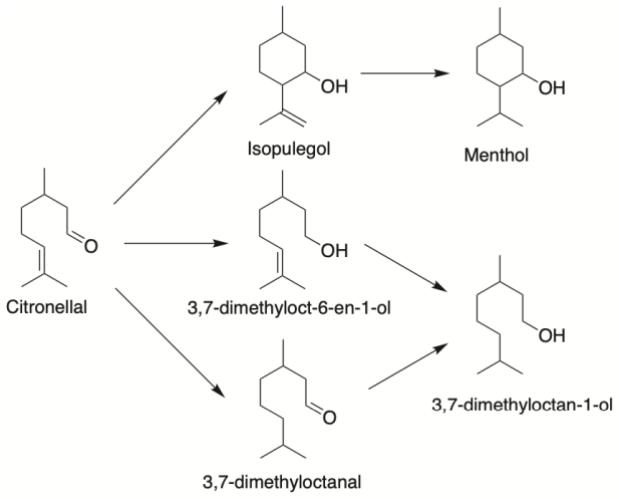

Figure 9. One-pot synthesis of menthol.

Recently, it has been studied the possibility of employing citral as the starting material for the synthesis of menthol. Using citral as the main reagent requires the hydrogenation of the double bond to obtain citronellal (Figure 10). Nonetheless, as citral can be easily retrieved, it represents an economic starting reagent. Of course, this additional step increases notably the number of possible side reactions. The concentration of byproducts not only depends on the type of catalyst but also on the solvent, the temperature and the hydrogen pressure used in the process. [1,9, 28]

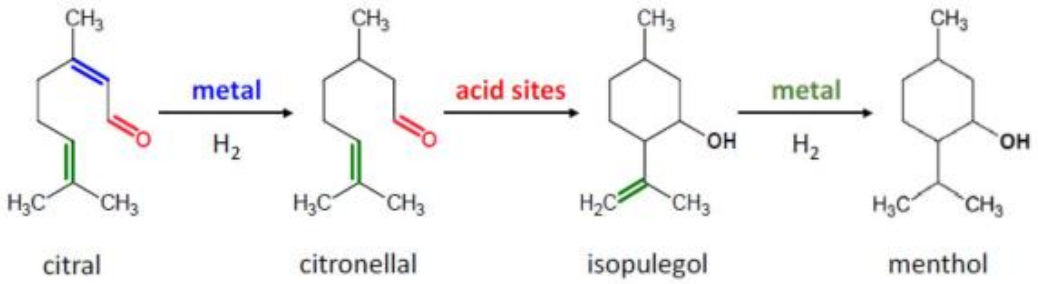

Figure 10. Simplified scheme of the one pot synthesis of menthol production from citral. [33]

Trasarti and al. reported for the first time the one pot selective synthesis of menthol starting from citral (Figure 10). As expected, the main disadvantage is represented by the byproducts produced under harsh hydrogenation conditions (Figure 11). In fact, citral hydrogenation can lead to 3,7-dimethyl-2,3-octanal and geraniol/nerol, depending on the catalyst. Nickel and palladium catalysts show a high selectivity towards C=C bond hydrogenation, whereas Trasarti et al. reported that other metals such as Cobalt and Iridium favour C=O hydrogenation, decreasing the overall selectivity and yield. [1, 28,29]

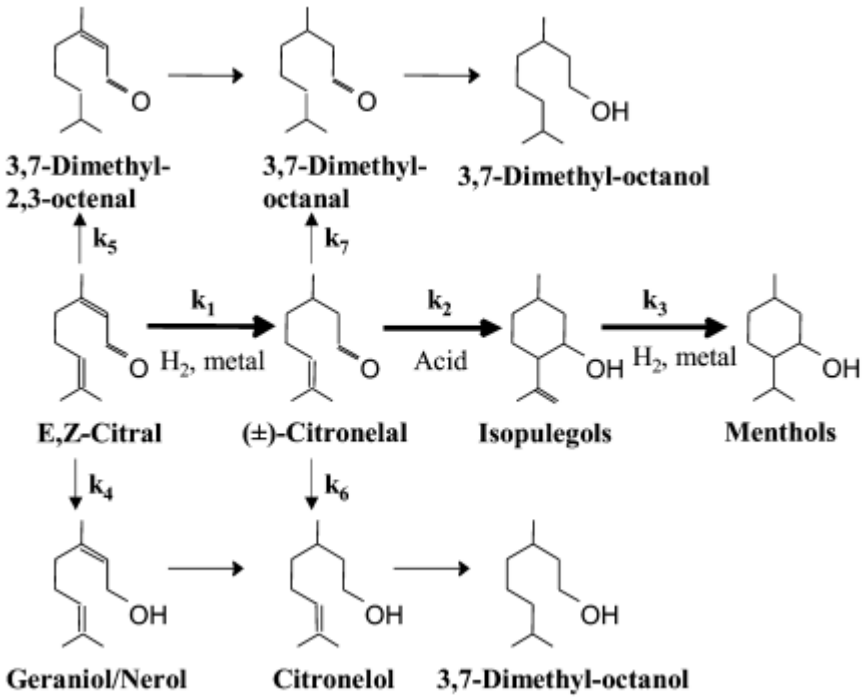

Figure 11. Reaction scheme for the one pot synthesis of menthol from citral.

Both citral and citronellal transformation are affected by the polarity of the solvent. Specifically, a hydrophobic solvent is preferable for both the conversion of citronellal and menthol yield. On the contrary, very hydrophobic solvent gave rise to a high amount of hydrogenation products. Defunctionalized products, particularly menthane and menthenes, were found predominantly in toluene. Tetrahydrofuran, 1,4-dioxane and cyclohexane have been reported most recently as solvents, as they enhance both the conversion and the selectivity towards the desired product. [9]

The effect of the temperature on the process is complex and, depending on the catalyst, different trends were observed. [9]

1.5 Polymer support

1.5.1 Resins

Most polymer supports are based on linear polymers, such as polystyrene, synthetized *via* free radical polymerization. The material consists in a mass of interpenetrating polymer random coils and appear as a glassy material the solid state, at room temperature. In this glass-like solid state, diffusion of even small particles is very small and these materials are able to interact with suitable solvents, sorbed solvents, which solvate the coils and allows backbone rotation to occur. This process is called 'plasticisation' and describes the change from a glassy-like solid material into a soft plastic material.

When a crosslinking agent is also polymerized, polymer chains result to be interconnected and the obtained material is insoluble in any solvent, although it can swell in suitable liquid media. These materials are commonly called “resins” or cross-linked polymers, isotropic materials often generated by the homo- or co-polymerisation of vinyl monomers. [30] Also in this case, the swelling is the result of the solvation of polymer coils but, due to the presence of crosslinks, dissolution does not take place.

Resins can be classified in several types according to their morphology which directly depends on the synthetic route and is essentially influenced by the crosslinking degree and the exploitation of a solvent unable to swell the polymer, thus called nonsolvent.

Gel-type resins generally consist of hard glassy transparent material obtained with a low amount of crosslinker, typically lower than 10%, and without any nonsolvent. The polymerization leads initially to a gel phase, then to a high degree of polymerization which leads to the syneresis of the material. At this point, part of the liquid phase is expelled from the polymer framework generating a glassy solid. This mechanism gives rise to a material with a low surface area in the dry state (<10 m^2/g). Nonetheless, it can be swollen in a suitable solvent, to develop an extensive porous system with high surface area and pores up to a few nm in size.

When a nonsolvent is present and a high crosslinking degree is used (typically higher than 12%), macrosynereris can occur. In this process, nuclei of gel phase initially formed become insoluble and expel the liquid phase. The polymerization continues around the nuclei formed and generates a gel phase around the inaccessible polymer spheres, creating a permanent porous system (size 20-60 nm). The well-developed porous system collapses at dry state and only macropores can be observed. Like gel-type resins, macroporous resins do swell in suitable solvent. Therefore, also the polymer matrix may be swollen to some extent. [31]

Gel-type resins swelling can be treated with the so-called “shrinking core model”, meaning that the swelling occurs from the outer to the inner part of the polymer matrix, in the presence of a suitable solvent (Figure 12).

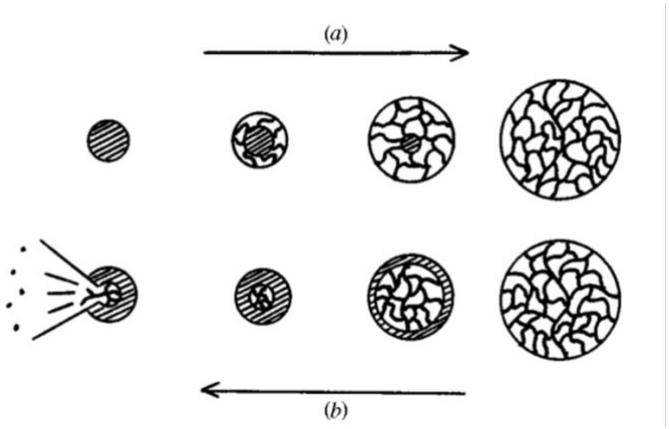

Figure 12. Solvent response of gel-type resins: (a) shrinking glass core to expanded gel in suitable solvent; (b) contraction of swollen gel on addition to a bad solvent resulting in bursting due to osmotic shock.

The network will swell to its elastic limit defined by the presence of a crosslinking agent. If a gel-type resin is swollen in a compatible solvent and the shrinking of the material, due to the presence of a "bad solvent", is induced, osmotic shocks can occur, causing the polymer matrix to burst. This is observed especially when a high level of stress is induced in the structure of the resin and, whether any microscopic flaws are present, e.g. cracks, fracturs may occur, causing the bursting.

Conversely, macroporous resins are much more tolerant to shear stress and osmotic pressure due to swelling and de-swelling process since it is not restricted in one direction as with gel-type resins. Therefore the "shrinking-core" effect is more difficult to observe (Figure 13). [32-35]

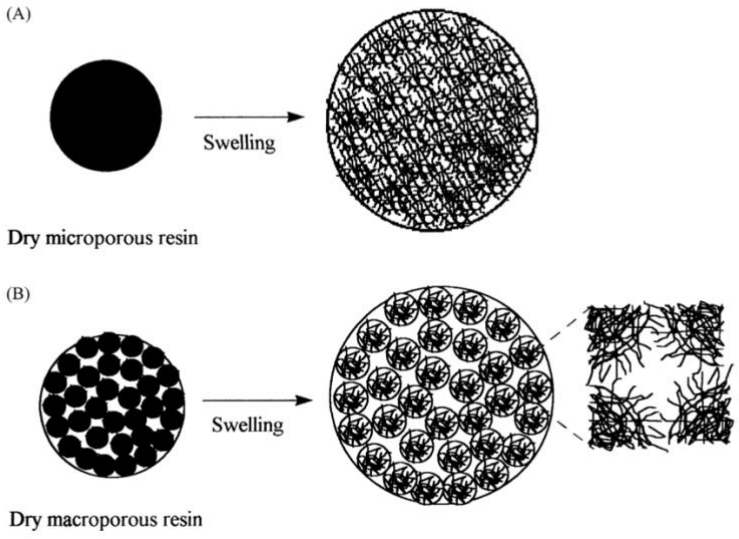

Figure 13. Schematic morphology representation of micropores in gel polymer (A) and macroporous polymer (B).

1.5.2 Resins applications

Resins can be applied as sorbents for organic compounds in water or air and are widely employed in catalysis. [36] To this end, resins are often functionalized to be able to exchange ions in the swollen state. Ion-exchange resins can be classified as cation or anion exchanges, depending on their ability to exchange cations or anions. These materials find applications mainly to replace Ca^{2+} with Na^{+} in the softening and deionization of water. Cation-exchange resins can also be employed as acid catalysts, when functionalized with strong acid groups. This kind of material is used to promote alkylation, condensation and hydration reactions. [37,38]

Polymers are also widely used as templating agents to control the growth of metal nanoparticles or inorganic materials. [39] The size of nanoparticles is affected by the porous system of the polymer matrix, especially in gel-type resins. [40-42] Therefore it is possible to employ such systems to prepare bifunctional materials bearing both acid sites and metal nanoparticles.

To this regard, the mesoporous polydivinylbenzene material developed by Zhang et al. appears very interesting for catalytic applications, due to its peculiar morphology. [36,43]

1.5.3 Polydivinylbenzene

In 2009 a novel superhydrophobic mesoporous material based on the radical polymerization of divinylbenzene was synthesized by solvothermal route by Zhang et al. [36,44]

The peculiar characteristics of the material were obtained by performing the radical polymerization of divinylbenzene under solvothermal conditions, reproducing the process usually employed for the synthesis of zeolites. The choice of the solvent was also fundamental since a suitable solvent, such as THF, can act as porogenic agent. Under these conditions, increasing of temperature of the synthesis results in a significant improvement of the porosity of the material. A sufficient reaction time is also needed in order to allow the complete polymerization of the monomer mixture. The dilution ratio is an important parameter as it affects for the formation of the porous system. In particular, the porosity of the material increases from a glassy non-porous solid to mesoporous materials, up to a macroporous morphology by increasing the solvent/monomer ratio.

The addition of a small amount of water acting as the non-solvent helps to control the properties of the material. The more water is added, the faster the syneresis is observed.

Under high dilution conditions, the ratio 10:1 (THF to water) allowed to obtain a mesoporous morphology.

The investigation of both the dry and swollen state of the material is essential to obtain a thorough description of the morphology and its properties. Inverse Size Exclusion Chromatography (ISEC) can be employed to determine the pore size distribution of the swollen polymer materials. This technique consists in the elution of standard solutes with well-known hydrodynamic size through a chromatographic column containing the swollen polymer. Depending on the retention time observed, it is possible to obtain information of the pore size and volume of the swollen material. By combining ISEC with a dry state characterization, such as nitrogen physisorption, it is possible to have a full understanding of the porous system and the surface area of the material. [36, 45]

Dry state characterization of pDVB shows that the specific surface area of the material is comparable to that of activated carbon. Remarkably, no micropores are present in the material and most of the pores are bigger than 4 nm. Polydivinylbenzene shows a type IV-isotherm nitrogen physisorption, demonstrating the presence of mostly mesopores.

As for other crosslinked polymer, the synthetic route influences the morphology of the material itself. The solvothermal route, combined with the use of a "good" solvent, allowed to suppress the segregation of highly cross-linked network during the polymerization. Thanks to the initial high dilution, it is possible to allow polymer chain growth and the formation of a gel phase, very similar to that generated in gel-type resins. Later, microsyneresis starts to occur and a phase separation is observed, along with the expulsion of some solvent droplets from the polymer, acting as the template for the further growing material. The resulting material is characterized by a high degree of both polymerization and cross-linking. [36, 46, 47]

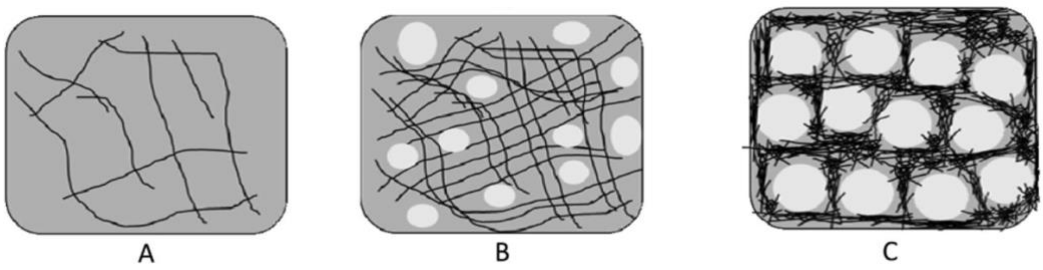

Figure 14. Schematic representation of the process of microsynerisis in highly diluted DVB polymerization. A- initial stages of polymer gel formation, B- start of phase separation, C- end of the polymerization.

Several studies were conducted on the swelling of the mesoporous material. When in contact with a suitable solvent such as THF, pDVB walls expand much more than a conventional polymer. [47] In fact, the phenomenon can be described as a restoration of the original shape of the pore walls, first deformed by the capillary forces in the drying process of the material.

1.5.4 Synthesis of polydivinylbenzene

Mesoporous polydivinylbenzene was synthetized according to the experimental procedure developed by Zhang et al. [36] The solvothermal synthesis is performed in a closed autoclave at 100°C, well above the boiling temperature of the solvent used (a water:THF mixture), starting from technical grade divinylbenzene (80% purity) as the monomer for the radical polymerization. [47] In order to start the polymerization, azobisisobutyronitrile (AIBN) is used as the radical initiator. The chemical structure the polymer is reported in Figure 15.

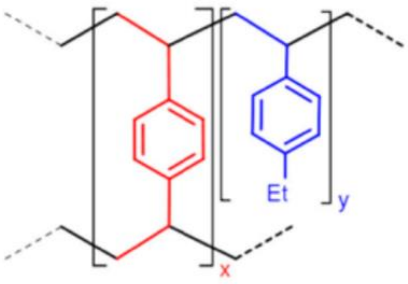

Figure 15. Sketch of the chemical structure of polydivinylbenzene, where x is 80 and y is 20. [48]

Ethylvinylbenzene is present in the technical grade divinylbenzene and is therefore polymerized into the final product. The material obtained is highly porous and its swelling properties allow an efficient mass transfer, making the material very promising for catalytic uses.[36] It is very important to carry out the polymerization under autogenic conditions for more than 24 hours. When carried out for less than 24 hours, the solvothermal process gives rise to compact materials, lacking porosity. Zhang et al. claim that the failure in the formation of a mesoporous structure might originate from the incomplete polymerization of DVB. Conversely, when the synthesis time reaches 24 hours or more, the nitrogen physisorption characterization shows the presence of a

mesoporous framework. [36] In this Thesis, the polymerization was carried out for 48 hours.

It is important to choose a solvent that allows the dissolution of the monomer. Accordingly, n-hexane cannot be used. The polymerization carried out in different solvents yields materials with different morphology, depending on the exploitation of a "good" or a "bad" porogenic solvent. A "good" solvent can interact favourably with the polymer chains and solvate them, whereas a "bad" solvent interacts hardly with a given polymer. When a "good" solvent was employed, syneresis was retarded due to the interaction between the solvent and the monomer. When a "bad" solvent was used, macrosyneresis was observed at an earlier stage of the polymerization, creating loosely packed microglobules. The SEM investigation of the polydivinylbenzene materials obtained with different solvents are reported in Figure 16. [47]

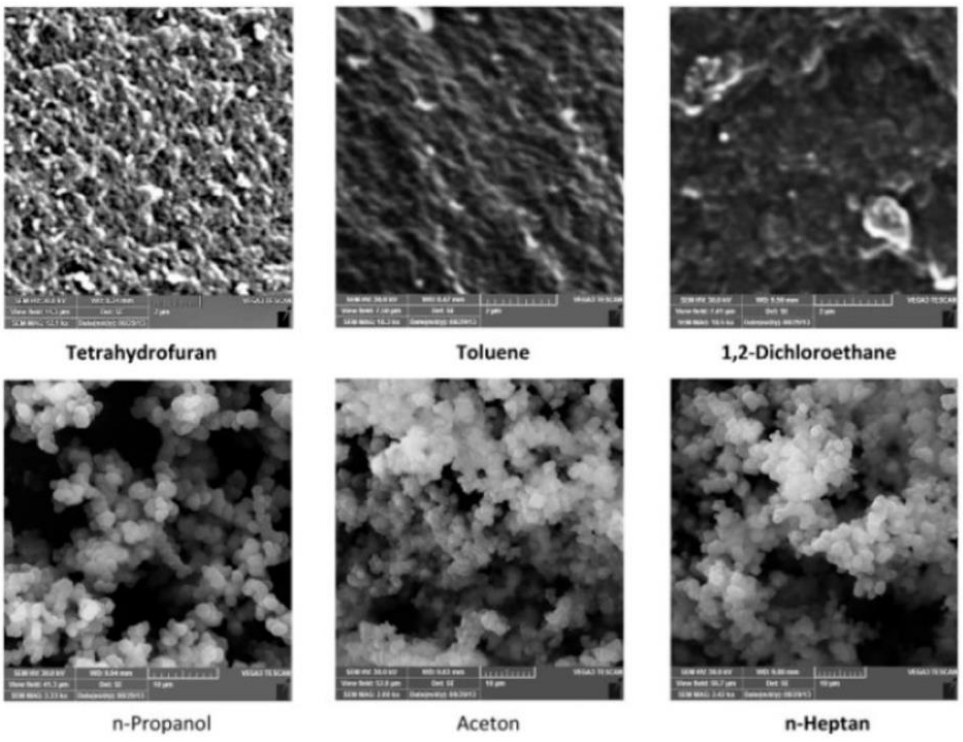

Figure 16. SEM micrographs of polydivinylbenzene prepared in the presence of different solvents.

Polydivinylbenzene synthetized in the presence of THF, toluene and 1,2-dichloromethane (DCM) shows a continuous matrix and, especially when THF is employed, pores are visible. Acetone, n-heptane and n-propanol are "bad solvents" and the surface shows microglobules rather that a uniform matrix, due to the early precipitation of the polymer

chains in the syneresis process. Both toluene and THF promote the formation of a highly porous structure when swollen, which is also able to undergo drying and re-swelling. [47]

Zhang et al. tested different temperatures for the polydivinylbenzene synthesis carried out in THF, to investigate further parameters influencing the morphology of the polymer. The sample synthetized at 60°C, a low solvothermal temperature, did not show any porous system. Conversely. increasing the temperature to 80-100°C showed beneficial effects in the morphology of the porous system obtained, specifically an improvement in the porosity. [36]

Despite the high dilution condition of the monomer with the porogenic solvent, the addition of a small amount of water as the non-solvent affects the syneresis process. [36,47] When the volumetric ratio THF to water is 10:1, at 100°C, the morphology of the polymer is mesoporous.

The solvent to monomer ratio significantly affects the morphology of the material (Figure 17). [48]

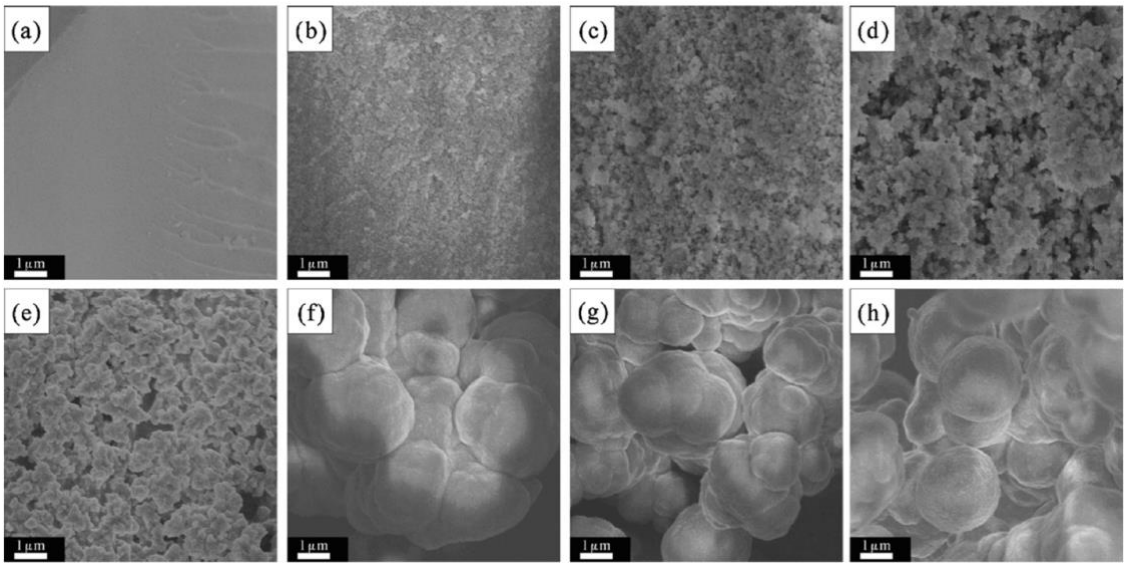

Figure 17. SEM characterization of pDVB synthetized with different ratio of monomer/solvent (m/v): a) 1:0.5, b) 1:1.25, c) 1:2.5, d) 1:5, e) 1:7.5, f) 1:10, g) 1:20, h) 1:40. [47]

The material does not present any porosity, when a low degree of dilution is employed (Figure 17a), whereas the material develops micropores and mesopores (Figure 17 b, c, d

and e) when a higher dilution ratio is tested. Macropores can also be observed when the solvent to monomer ratio reaches 1:20 and 1:40 (Figure 17 g and h).

The polydivinylbenzene employed in this Thesis was synthetized using a DVB:THF ratio of 1:10 g/mL. According to literature, the material obtained with this ratio value is characterized by pores of size between 40 and 80 nm. [47] Sterchele et al. investigated the morphology of pDVB obtained under these conditions at both the dry and the swollen state (Table 2 and 3). [34]

Table 2. Polydivinylbenzene characterization at dry state through nitrogen physisorption.

BET surface area (m^2/g)	Cumulative surface area in pores >4 nm (m^2/g)	Micropore volume (cm^3/g)	Total pore volume (cm^3/g)
1096	436	0.008	2.07

Table 3. Swollen state morphology of mesoporous polydivinylbenzene with ISEC in THF. [34]

Pore diameter (nm)	Pore volume (cm^3/g)	Pore wall surface area (m^2/g)
600	0.62	4.10
300	0.00	0.00
150	0.00	0.00
80.0	6.78	339
40.0	0.70	70.0
20.0	0.00	0.00
10.0	0.00	0.00
Total	8.10	413

According to Sterchele et al., the surface area of the material at the dry state and swollen state is similar (cumulative surface area in pores >4nm = 436 m^2/g, pore wall surface area=413 m^2/g). On the contrary, the pores volume is very different. At the swollen state the pore volume is 8.10 cm^3/g, whereas at the dry state is 2.07 cm^3/g (Table 2 and 3). Nonetheless, the pore volume at the dry state is still higher than the values observed macroreticular or hyper crosslinked polymers. This is due to the rigid structure of the

polymer, that does not collapse completely at the dry state and is restored when in contact with a solvent.

In this Thesis, pDVB has been used the support for $ZnCl_2$, the Lewis acid used for the cycloisomerization of citronellal to isopulegol. The obtained polymer material has been also functionalized with palladium nanoparticles, in order to provide the active sites for the hydrogenation of isopulegol to menthol.

2. Aim of the Thesis

The present Thesis work aims to the study of the reactivity of catalysts supported on mesoporous polydivinylbenzene in the one pot synthesis of menthol from citronellal under batch conditions.

The Thesis focuses on the optimization of the experimental set-up, in particular on the flushing operation and the sampling procedure. The development of an optimized procedure is essential to obtain reliable results from the catalytic tests.

The first part of this Thesis presents the development of the isomerization catalyst, consisting in zinc chloride deposited on the polymer support. Different catalysts, differing from the amount of active material and synthetic procedure will be tested in the cycloisomerization reaction of citronellal to isopulegol.

In the second part of the Thesis the one pot synthesis, combining the cycloisomerization of citronellal to isopulegol and the hydrogenation of isopulegol to menthol, is presented. The effect of the amount of hydrogenation catalyst is investigated by employing both the commercial catalyst Pd@C and a Pd catalyst supported on polydivinylbenzene.

Finally, a bifunctional catalyst containing both acid and redox function is presented.

3. Results and Discussion

3.1 Synthesis of mesoporous polydivinylbenzene

In this Thesis, three batches of polydivinylbenzene were synthetized (Paragraph 5.3). After the polymerization, polydivinylbenzene is obtained as a monolith of the same shape of the Teflon liner used for the synthesis (Figure 18).

Figure 18. Monolith of polydivinylbenzene after the polymerization.

The monolith is divided in fragments and let drying in an electric oven for two days at 110°C (Figure 19).

Figure 19. Dried polydivinylbenzene in fragments.

3.2 Deposition of $ZnCl_2$

Several studies have shown that Lewis acid sites are essential to promote the cycloisomerization of citronellal to isopulegol. Among the tested compounds, zinc halides have shown a remarkable activity and selectivity towards the diastereoisomer (-)-isopulegol, the desired product of the reaction. [22,25,26]

In this Thesis, polydivinylbenzene was employed as the support for the catalyst and $ZnCl_2$ was tested as the active material for the cycloisomerization reaction. In order to perform the deposition, polydivinylbenzene was swollen in THF for two hours (Figure 20).

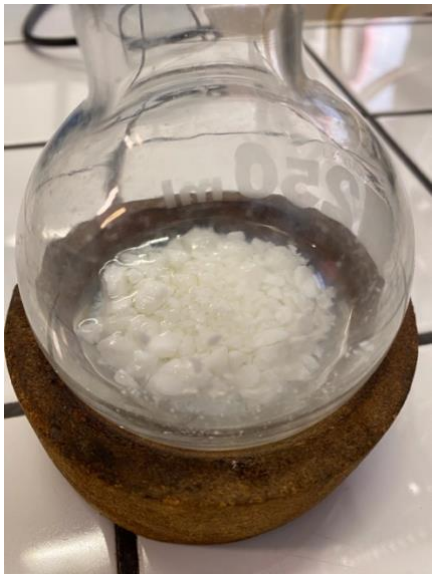

Figure 20. Polydivinylbenzene swollen in THF before the deposition of $ZnCl_2$.

THF was employed as the solvent to swell the resin. $ZnCl_2$ was dissolved in the smallest amount of water and the resin was left in contact with the resulting solution overnight at 60 rpm and room temperature. As $ZnCl_2$ is also soluble in THF, its precipitation is avoided during the metallation process. The solvent is finally removed by evaporation and the material is dried overnight in an electric oven at 110°C, to remove the solvent. The obtained catalyst shows a violet colour tending to brown (Figure 21). The catalyst is finally sieved to isolate the fraction with particles size 180-250 μm, which was used for the catalytic tests.

Figure 21. On the left, the catalyst after the deposition of $ZnCl_2$ and on the right the catalyst in the fraction 180-250 µm after the drying at 100°C.

3.3 Gas-Chromatographic determination of products

The one pot synthesis of citronellal to menthol requires the presence of both a cycloisomerization and a hydrogenation catalyst. Due to the presence of those catalysts under hydrogenation conditions, many byproducts can be possibly obtained (Figure 22). Therefore, it is important to develop a reliable analytical procedure to detect the possible byproducts, particularly the diastereomers of isopulegol and menthol.

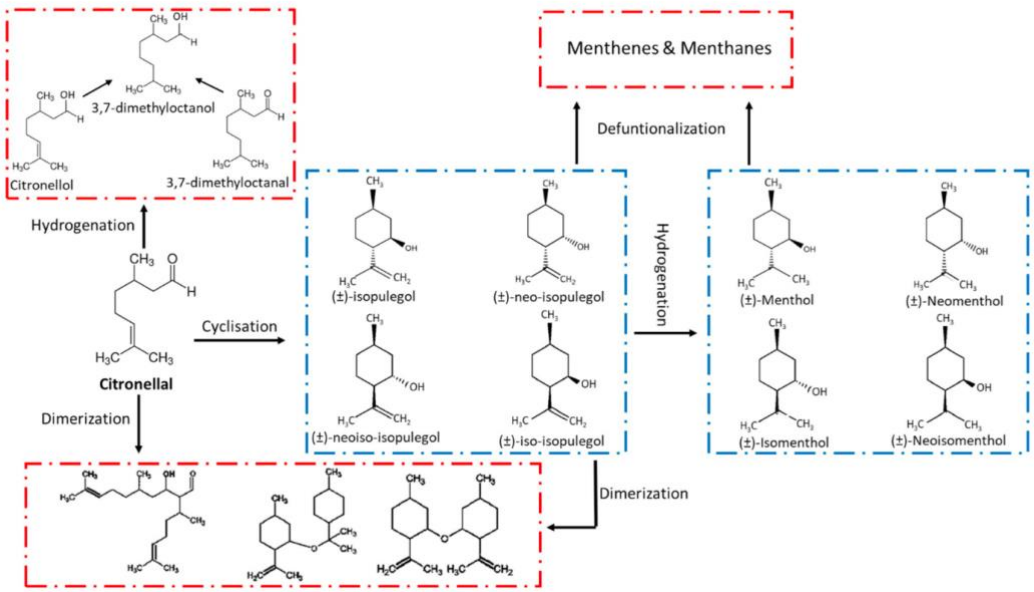

Figure 22. Reaction scheme of the one pot synthesis of menthol from citronellal. [27]

Since the boiling point of the products is in the range 216°C - 250°C and are dissolved in cyclohexane, gas-chromatographic analysis was employed as the main analytical technique for the reaction mixture.

To quantify the analytes, calibrations were performed for citronellal, isopulegol, menthol, citronellol, nerol and geraniol. The concentration of the standard solutions for the calibration ranges from 0.5 mg/mL to 4 mg/mL, since 4 mg/mL is the initial concentration of citronellal used for the test.

In order to confirm the nature of some peaks, GC-MS analysis was also employed.

3.4. Batch reactor

In this Thesis, the catalytic tests of cycloisomerization of citronellal to isopulegol and the one pot synthesis of menthol from citronellal were carried out using a batch reactor (Figure 23).

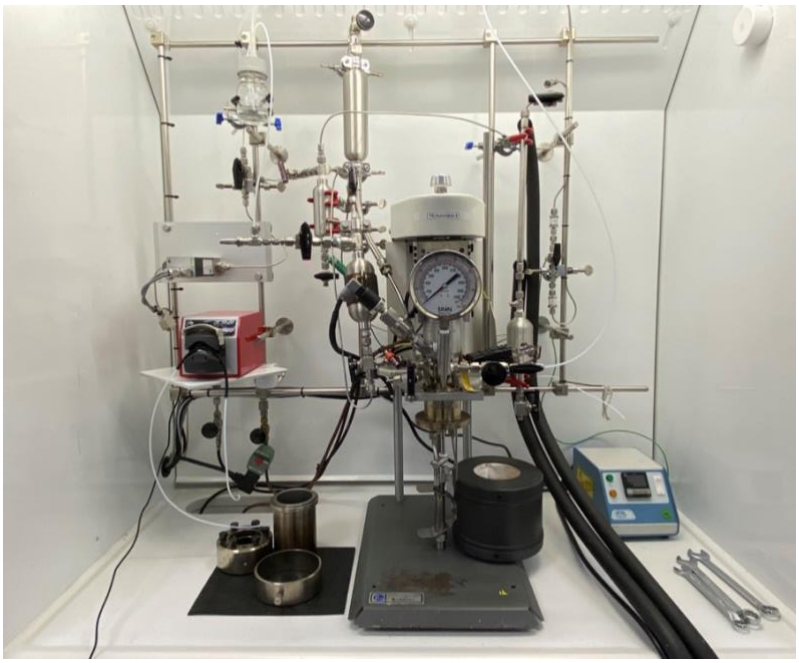

Figure 23. Batch reactor used for the catalytic tests.

The reagent solution was injected into the autoclave from the preheating chamber, which allows to preheat the solution to the temperature of the catalytic test. For the catalytic tests, 100 mL of a 4 mg/mL solution of reagent was used.

The preheating chamber is connected to the autoclave with the inlet-line and it can be opened on one side, to allow the injection of the reagent solution using a peristaltic pump.

The chamber is covered by a heating jacket that allows to rise the temperature of the reaction mixture before the injection of the reagent solution into the autoclave. The gas can flow inside the preheating chamber and the autoclave at a set pressure, corresponding initially to the gas tank pressure regulator, of both argon and hydrogen. The reactor is connected to a Parr controller, which allows to check in detail the reactions conditions such as temperature, pressure and to set the parameters inside the autoclave, such as the stirring rate.

The central device of the reactor is a stainless steel autoclave, that can be sealed with eight screws. Three different elements, a thermocouple, the stirrer and the injection/sampling line, can be found inside the autoclave (Figure 24).

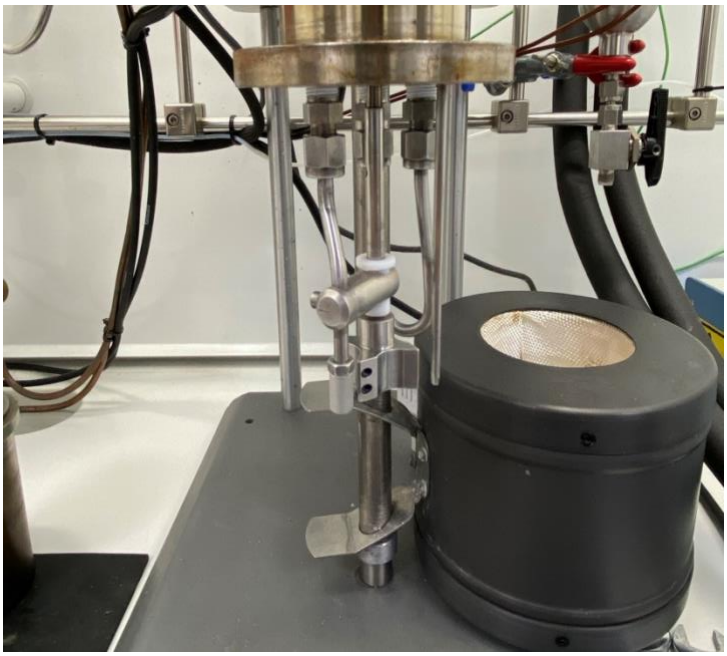

Figure 24. Details of the inner part of the reactor.

The sampling line is equipped with a filter that avoids the withdrawal of catalyst particles from the reaction mixture. The filter is screwed on to the sampling line, therefore it can be separated. After each experiment, the filter is removed and washed in an ultrasonic bath. Each of the other elements are washed with acetone and distilled water, then dried, before each experiment.

Before starting each experiment, it is important to check that all the bolt and nuts are tightened, especially around the autoclave and in correspondence of the preheating chamber.

As the tests are typically performed with polymer-supported catalysts, an *in situ* pre-treatment, consisting of two hours of swelling in the solvent of the reaction under test conditions, has to be carried out. Accordingly, the catalyst is weighted and transferred into the autoclave along with 50 mL of solvent (cyclohexane), i.e. half of the total volume of solvent needed for the test, and the reactor is sealed. In order to remove oxygen, the reactor is washed three times with 5 bar Ar. The autoclave is finally filled with 5 bar Ar. The temperature and stirring rate are set to the experiment values and the *in situ* pre-treatment of the catalyst is carried out for two hours. The autoclave is surrounded by a removable heating jacket and the temperature is measured with the thermocouple, immersed in the reaction mixture, connected to the reactor controller (Figure 25).

Figure 25. External reactor controller.

During the catalytic test, samples of the reaction mixture are withdrawn from the reactor using the sampling valve, connected to the sampling line. It is important to pay attention to possible losses of gas phase during the sampling procedure, when the valve is opened and a sample of the reaction mixture is collected in a vial. Despite the presence of the filter (Figure 24), the withdrawn sample appears opaque and is therefore further filtrated, with a 13 mm, 0.45 µm syringe filter. The collected sample is analyzed with GC. When the sample is withdrawn, a pressure drop of ca. 0.5 bar inside the reactor is observed and immediately restored. By restoring the pressure, the sampling line is emptied from the residual reaction mixture.

The catalytic test lasts normally for 3 hours and the sampling times is 0', 15', 30'. 60', 120' and 180'. This allows to precisely evaluate the catalytic performance by determining conversion (C), selectivity (S) and yield (Y), according to Equations 1-5.

$$C = \frac{n_{CAL,\in} - n_{CAL,END}}{n_{CAN,\in} \cdot 100} \quad (1)$$

$$C = \frac{n_{IP,\in} - n_{IP,END}}{n_{IP,\in} \cdot 100} \quad (2)$$

$$S = \frac{n_{desiredproduct}}{n_{CAL,\in} - n_{CAL,END} \cdot 100} \quad (3)$$

$$S = \frac{n_{desiredproduct}}{n_{IP,\in} - n_{IP,END} \cdot 100} \quad (4)$$

$$Y = \frac{n_{product}}{n_{reagent}} \cdot 100 \quad (5)$$

The selectivity is determined as the ratio between the moles of the target product ((-)-isopulegol or menthol) and the moles of reagent (citronellal and isopulegol) consumed during the reaction. The selectivity was determined for several products and byproducts, especially in the one-pot synthesis. The yield was calculated as the molar ratio between the considered product and the limiting reagent.

3.5 Selection of the reaction conditions

According to Plöβer et al., the nature of the solvent affects both the selectivity towards the desired product and the catalytic activity. [25] In fact, acetonitrile remarkably reduces the catalytic activity in the synthesis of menthol from citronellal, over Ru/H-BEA-150 catalyst. In contrast, toluene promotes the defunctionalisation of the reagent to menthane and menthene. [25] Despite the predominant presence of hydrogenation products, n-hexane and cyclohexane are desirable solvents because of the high solubility of hydrogen. In fact, hydrogen solubility decreases in the order n-hexane>toluene≈acetonitrile>dioxane. [9]

As to the temperature, citronellal hydrogenation to 3,7-dimethyloctanal and 3,7-dimethyloctanol is predominant at low temperatures, whereas the formation of defunctionalized products is mainly observed at high temperatures, generally over 70°C. In fact, 70°C has been identified as the temperature that allows more selectivity towards the main product.

Accordingly, in this Thesis, the standard reaction conditions employed were:

- Temperature: 70°C;
- Pressure: 10 bar of Argon or Hydrogen;
- 900 rpm;
- Isomerization catalyst: 300 mg, 2 hours swelling before the beginning of the test;
- Solvent: 100 mL of cyclohexane;
- Reagent: 400 mg of citronellal or isopulegol.

3.6 Blank and preliminary isomerization tests

To evaluate the reaction in the absence of the catalyst and to rule out the presence of catalyst residues in the reactor, a blank test was performed. The amount of citronellal during the test is reported in Figure 26. The detected traces of isopulegol and neo-isopulegol are present in the citronellal used as the reagent. The mass balance was determined by summing the amount of reagent and products detected with the chromatographic analysis.

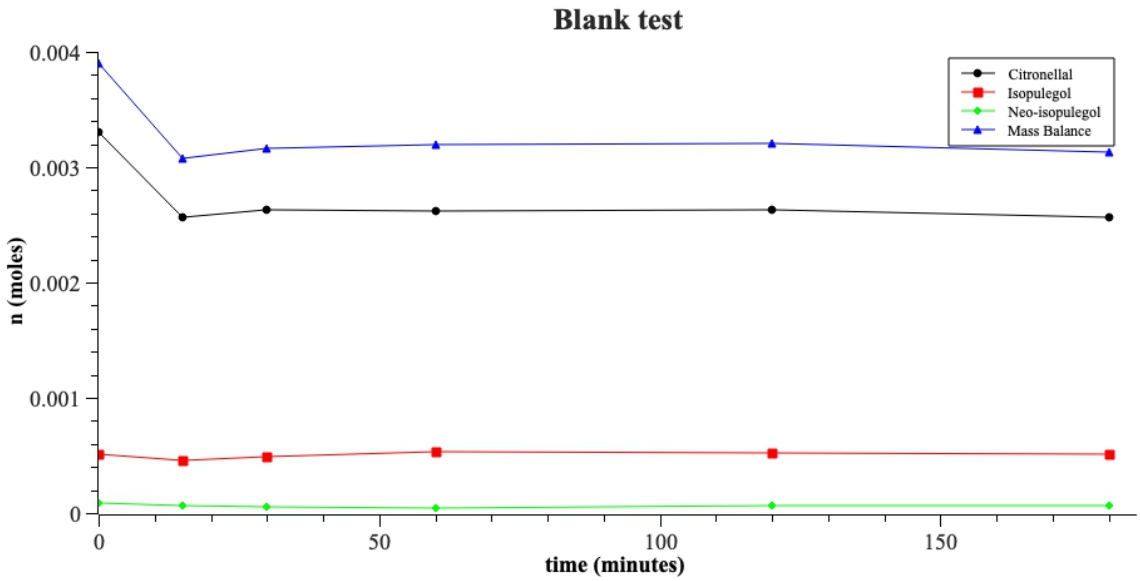

Figure 26. Blank test (70°C, 900 rpm, 10 bar Ar).

No significant conversion of citronellal was observed in blank test. Therefore, as expected, in the absence of catalyst, the reaction does not occur.

At the beginning of the test, the moles of citronellal present in solution are higher than expected from the amount reagent introduced into the reactor. The reagent solution is

injected in the apparatus and sampled from the autoclave from the same line. Since the concentration of the injected reagent solution is 8 mg/mL and is later diluted in the autoclave, the concentration of the first sample withdrawn is always higher than expected, due to the residues of the injection operations. For this reason, a "waste" sample is withdrawn to clean the sampling line, before to collect the samples used for defining the reaction profile.

A preliminary test to test the activity of Zn(5%)@HZSM-5 towards the cycloisomerization of citronellal to isopulegol, using 300 mg of Zn(5%)@HZSM-5, as cited in literature. The zeolite shows a SiO_2/Al_2O_3=80 and was synthetized according to the procedure reported by Tokarev et al. [50] The precursor of Zn employed is $Zn(NO_3)_2 \cdot H_2O$. The evolution of citronellal during the catalytic experiment is presented in Figure 27.

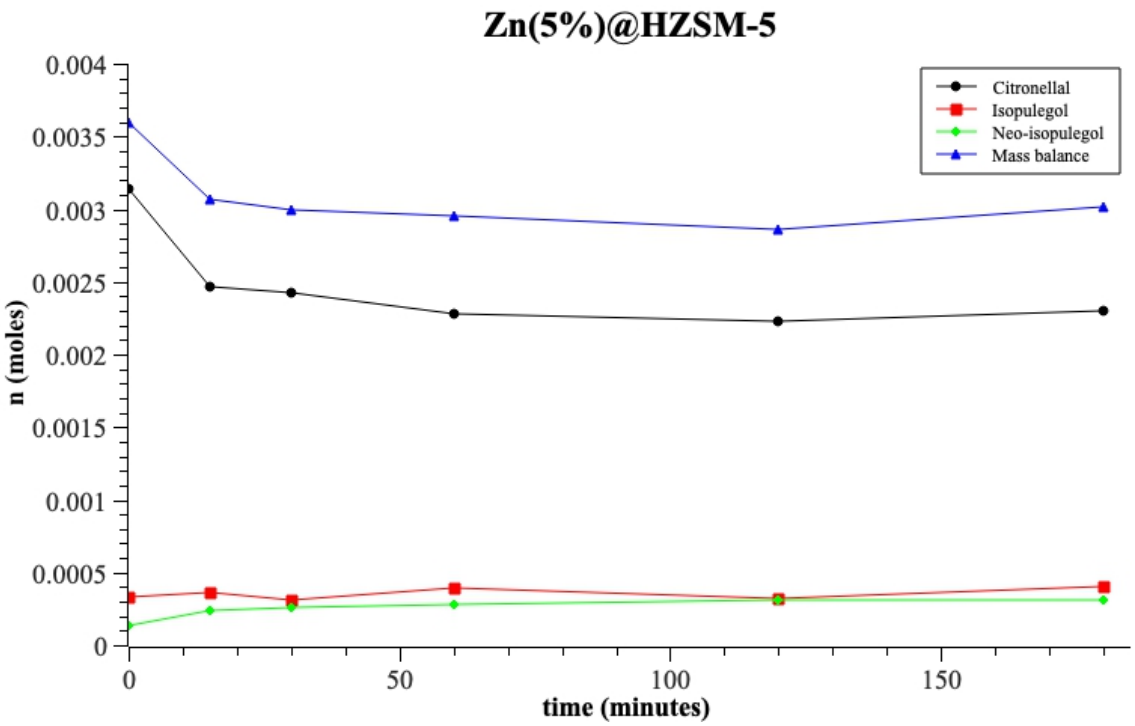

Figure 27. Zn(5%)@HSZM-5 preliminary test.

The amount of citronellal and isopulegol did not change significantly during the experiment and the small fluctuations can be ascribed to the sampling procedure. After the preliminary and the blank tests, the $ZnCl_2$(30%)@pDVB catalyst synthetized for the cycloisomerization of citronellal to isopulegol (Paragraph 5.4) was tested (Figure 28). As

the catalyst is based on a cross-linked polymer, it was *in situ* pre-treated according to the procedure reported in Paragraph 5.15.

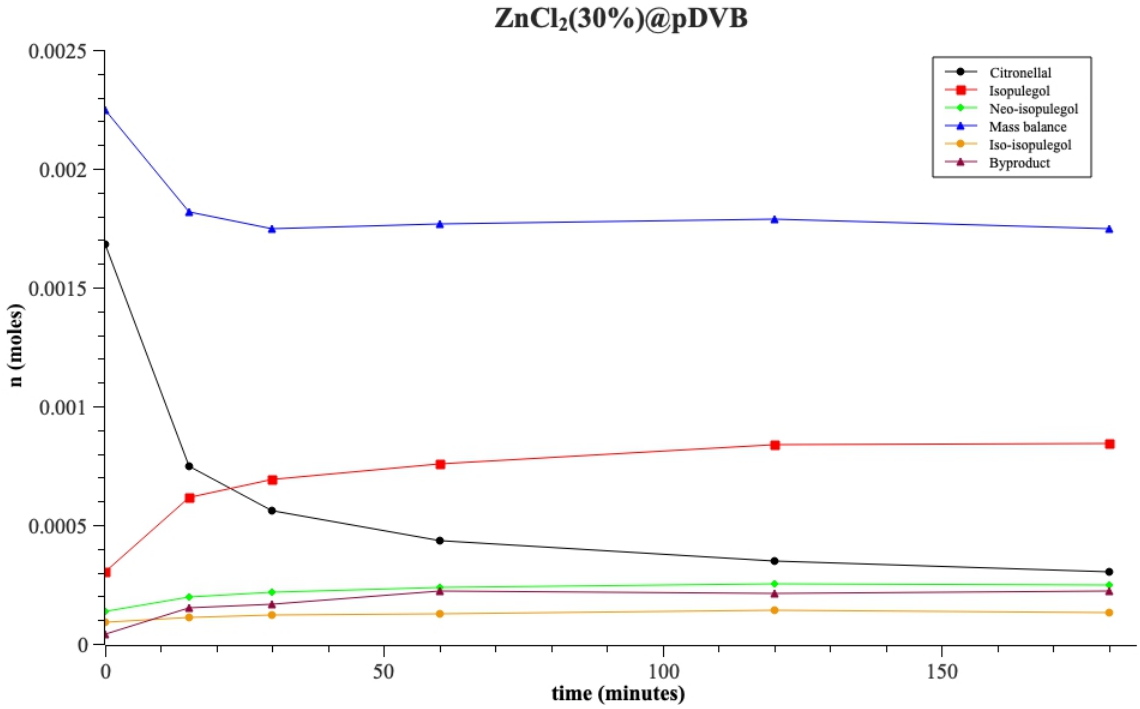

Figure 28. Catalytic test employing $ZnCl_2$(30%)@pDVB.

The catalyst $ZnCl_2$(30%)@pDVB is active in the cycloisomerization of citronellal to isopulegol. In particular, at 180' min 82% conversion is achieved, with 39% selectivity towards the desired product, (-)-isopulegol. Among the other products, neo-isopulegol and iso-isopulegol are the main byproducts. High molecular weight byproducts are also detected and will be discussed in Paragraph 3.11.

The preliminary test of isomerization also revealed a significant issue. In fact, it was possible to detect the loss of about 20 mL of solvent, over a total volume of 100 mL, during the catalytic test. A significant loss of solvent remarkably affects the concentration of the species in the reaction mixture determined from the GC analysis. To obtain reliable information about the reactivity of the catalysts is therefore essential to solve the issue of the loss of solvent (Paragraph 3.7).

3.7 Set-up Optimization

During the preliminary isomerization tests, it was detected a loss of solvent, that must be avoided, in order to precisely determine the concentration of species in the reaction mixture.

To address this issue, a series of experiments was designed to understand whether the solvent loss could be attributed to some leaching from the reactor or to some of the experimental actions taken during the test.

From the introduction of the solvent into the reactor to the recovery of the reaction mixture at the end of the test, the loss of solvent during the preliminary and black tests was ca. 20 mL.

Initially. the possible effect of the sampling procedure on the solvent loss was investigated. Since during the sampling procedure the pressure of the reactor decreases, in principle some solvent could be lost in the gas phase. Accordingly, a test without sampling was performed and a 22 mL of solvent were lost with respect the initial amount. Consequently, the solvent loss is not related to the sampling operations.

The flushing procedure was also considered. When the reactor is closed, the autoclave contains oxygen, which has to be removed as it can react with hydrogen and reaction substrates under catalytic conditions. Therefore a flushing procedure, consisting washing the autoclave with Ar, has been implemented. The flushing procedure is performed twice for each experiment: first inside the autoclave before the pre-treatment of the catalyst and also when the preheating chamber is filled with the reagent solution. After the flushing procedure, an overall loss of 5 mL was detected. However, this loss of solvent is significantly lower than that observed in the preliminary experiments.

Further investigations were performed to verify whether the solvent loss occurs only at the beginning of the test, or during the entire experiment. These control experiments were performed under the conditions normally used for the catalytic test (70°C and 10 bar Ar). The first experiment was performed using only the solvent instead of the reagent solution. An overall loss of 8 mL was detected: 5 mL were lost in the flushing procedure and 3 mL have been probably lost in the gas phase after opening the reactor or on the reactor component. The second test was carried out for 6 hours from the injection to the sampling, with no samples removed. As in the previous test, the preliminary tasks were performed. The detected loss was 8 mL and is associated to the flushing procedure and the

evaporation from the reactor components as in the previous test. On these basis, it appears that the issue due to the loss of solvent is not proportional to the length of the experiment.

A final experiment was performed by swelling 300 mg of $ZnCl_2$(30%)@pDVB catalyst in 100 mL of solvent for 2 hours. After recovering the catalyst by filtration, 90 mL of solvent were obtained. Therefore, the volume of solvent absorbed by the catalyst and the amount lost during the flushing procedure and the evaporation correspond to the total amount of cyclohexane lost during the preliminary experiments.

In conclusion, as the loss of reaction mixture is due to the absorption inside the catalyst, this issue does not significantly affect the kinetic experiments and the evaluation of the concentration of the analytes.

3.8 Design of the isomerization catalyst

In this Thesis, $ZnCl_2$ was employed as Lewis acid to perform the cycloisomerization of citronellal to (-)-isopulegol. The amount of zinc chloride deposited on polydivinylbenzene (Paragraph 5.4) was selected according to the investigation by Milone et al. [15,25,26]

3.8.1 The amount of $ZnCl_2$

The catalyst for the isomerization of citronellal was initially prepared according to a previous Thesis.[51] In particular, $ZnCl_2$ was deposited on a cross-linked polymer to obtain a catalyst, coded as $ZnCl_2$(30%)@pDVB, with a 30% w/w content of $ZnCl_2$.

The effect of the amount of $ZnCl_2$ was investigated by synthetizing two different catalyst, containing 30% and 10% w/w $ZnCl_2$ ($ZnCl_2$(30%)@pDVB and $ZnCl_2$(10%)@pDVB, respectively). The catalytic performance of $ZnCl_2$(30%)@pDVB catalysts are summarized in Figure 29 and Table 4.

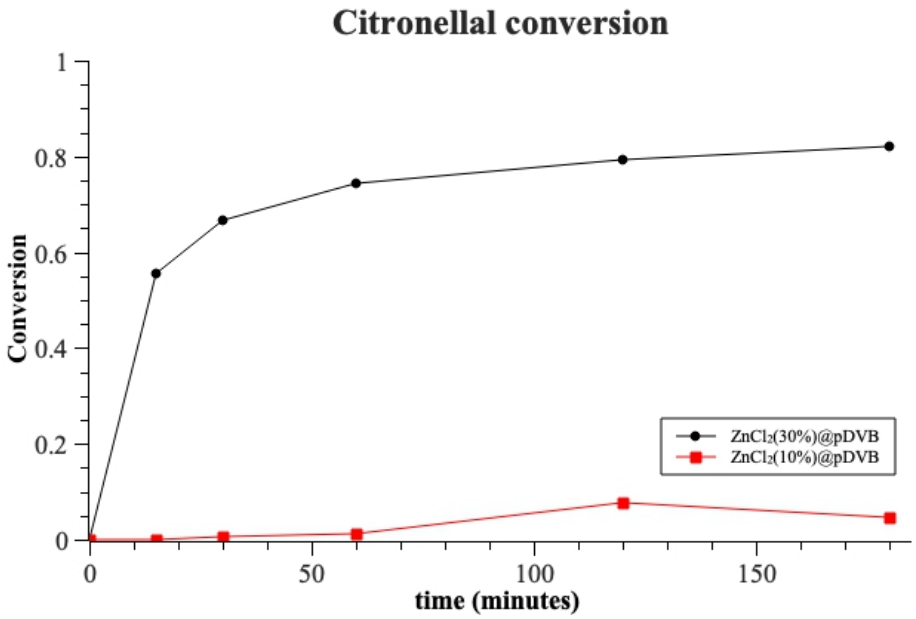

Figure 29. Citronellal conversion comparing $ZnCl_2$(30%)@pDVB and $ZnCl_2$(10%)@pDVB.

Table 4. Catalytic performances of $ZnCl_2$(30%)@pDVB and $ZnCl_2$(10%)@pDVB.

$ZnCl_2$(30%)@pDVB			**$ZnCl_2$(10%)@pDVB**		
t (minutes)	**C**	**S**	**t (minutes)**	**C**	**S**
0	0.00	0.00	0	0.00	0.00
15	0.55	0.23	15	0.00	0.00
30	0.67	0.28	30	0.00	0.00
60	0.74	0.33	60	0.00	0.00
120	0.79	0.39	120	0.08	0.00
180	0.82	0.39	180	0.06	0.00

The $ZnCl_2$(10%)@pDVB catalyst is not active in the isomerization of citronellal, whereas 82% conversion is obtained with $ZnCl_2$(30%)@pDVB at the end of the catalytic test, after reaching a plateau within the first hour. The selectivity of $ZnCl_2$(30%)@pDVB towards (-)-isopulegol increases during the test to reach 39% at the end of the test.

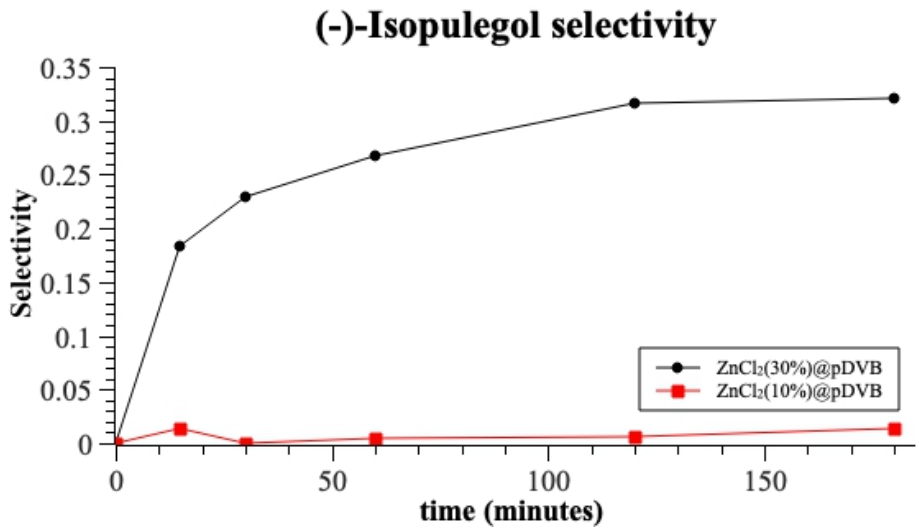

Figure 30. (-)-Isopulegol selectivity comparing $ZnCl_2$(30%)@pDVB and $ZnCl_2$(10%)@pDVB

3.8.2 Effect of H_2O on the synthesis of $ZnCl_2$(30%)@pDVB catalyst

$ZnCl_2$(30%)@pDVB is synthetized first by swelling the polymer in THF and then dissolving zinc chloride in the smallest amount of water possible (Paragraph 5.4). To investigate the possible role of water in the preparation of the catalyst, a catalyst with 30% $ZnCl_2$ w/w content was synthetized using THF instead of H_2O as the solvent.

The catalyst was prepared according to the experimental procedure described in Paragraph 5.4 and tested in the isomerization of citronellal, after the *in situ* pre-treatment designed for resin catalysts (Figure 31 and Table 5).

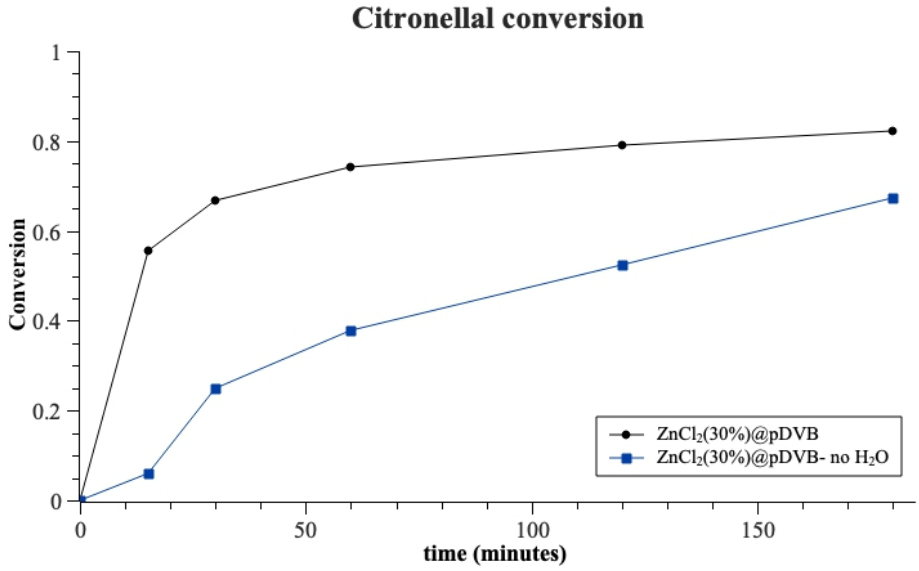

Figure 31. Citronellal conversion with $ZnCl_2$(30%)@pDVB and $ZnCl_2$(30%)@pDVB-no H_2O.

Table 5. Catalytic performances of $ZnCl_2$(30%)@pDVB and $ZnCl_2$(30%)@pDVB-no H_2O.

$ZnCl_2$(30%)@pDVB			**$ZnCl_2$(30%)@pDVB- no H_2O**		
t (minutes)	**C**	**S**	**t (minutes)**	**C**	**S**
0	0.00	0.00	0	0.00	0.00
15	0.55	0.23	15	0.06	0.03
30	0.67	0.28	30	0.25	0.05
60	0.74	0.33	60	0.38	0.12
120	0.79	0.39	120	0.53	0.29
180	0.82	0.39	180	0.67	0.25

The conversion of citronellal obtained with the catalyst and $ZnCl_2$(30%)@pDVB-no H_2O reaches 67% at the end of the experiment, significantly lower than 82% obtained with $ZnCl_2$(30%)@pDVB (Figure 31). It appears that the presence of water during the synthesis allows to obtain a more active catalyst, that outperforms over the whole test the corresponding material obtained without water. This behaviour is particularly evident at the beginning of the catalytic test. In fact, after 15 minutes, 55% and 6% conversion have been obtained for $ZnCl_2$(30%)@pDVB and $ZnCl_2$(30%)@pDVB-no H_2O, respectively. Interestingly, the $ZnCl_2$(30%)@pDVB-no H_2O catalyst does not reach a plateau value within three hours of reaction. It could be useful in future investigations to study the catalytic performance of the latter material for longer reaction times.

The evolution of the selectivity of $ZnCl_2$(30%)@pDVB and $ZnCl_2$(30%)@pDVB-no H_2O catalysts during the catalytic test is presented in Figure 32.

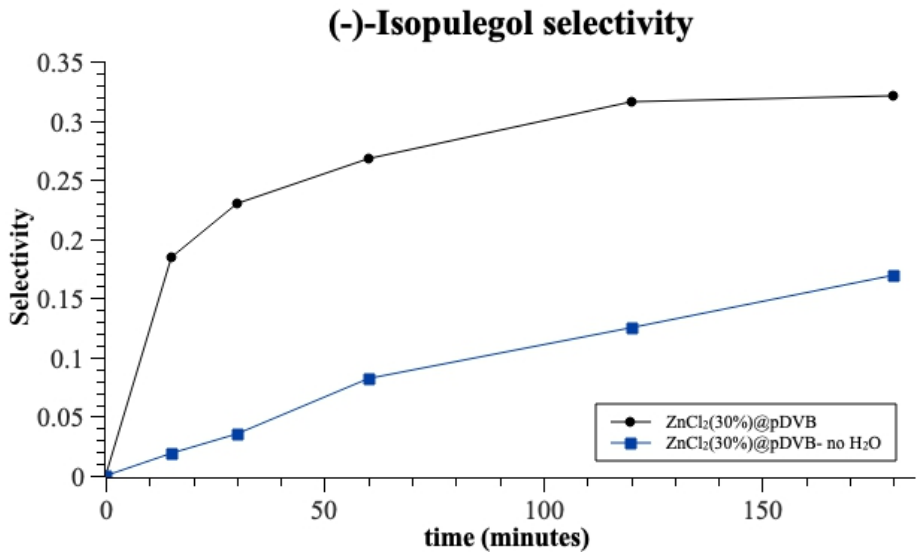

Figure 32. (-)-Isopulegol selectivity comparing $ZnCl_2$(30%)@pDVB and $ZnCl_2$(30%)@pDVB-no H_2O.

The catalyst synthetized with water outperforms $ZnCl_2$(30%)@pDVB-no H_2O in selectivity over the entire experiment. In spite a plateau value is obtained with $ZnCl_2$(30%)@pDVB, this material shows a selectivity remarkably higher than that of $ZnCl_2$(30%)@pDVB-no H_2O (39% and 25%, respectively). Interestingly, the isopulegol diastereoisomers ratio (isopulegol:neo-isopulegol:iso-isopulegol; neoiso-isopulegol is not observed, according to its low stability) is similar for both the catalysts, 78:16:2 and 75:20:5 for $ZnCl_2$(30%)@pDVB and $ZnCl_2$(30%)@pDVB-no H_2O respectively. [25] This indicates that the higher selectivity of the catalyst prepared in the presence of water is due to the formation of a remarkably lower amount of byproducts, different from the undesired isopulegol diasteroisomers.

On these basis, it can be speculated that the preparation of the catalyst without water could lead to the formation of stronger acid sites, promoting the formation of a number of byproducts, with the consequent decrease of the selectivity, with respect $ZnCl_2$(30%)@pDVB catalyst.

The activity of $ZnCl_2$ towards the cycloisomerization of citronellal to isopulegol was demonstrated. Nonetheless, the potential effect of the counteranion of Zn^{2+} and of chloride ions on the catalytic activity was also preliminarily investigated by testing catalysts obtained by depositing $Zn(NO_3)_2$ and $MgCl_2$ on polydivinylbenzene. The catalytic results are presented in Appendix 1 and 2, respectively.

3.9 Catalyst deactivation and optimization of the pre-treatment procedure

After carrying out the preliminary tests discussed in Paragraph 3.6, the catalyst $ZnCl_2$(30%)@pDVB was tested in the citronellal conversion to (-)-isopulegol but the conversion did not follow the same trend observed during in the preliminary tests. Instead, citronellal starts being converted after 60' from the beginning of the experiment (Figure 33).

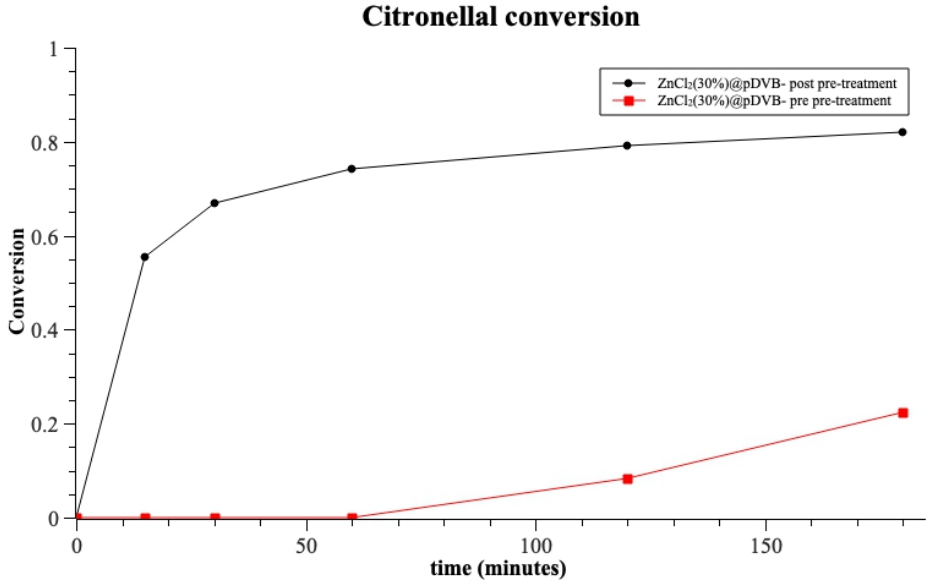

Figure 33. Citronellal conversion of $ZnCl_2$(30%)@pDVB before (red curve) and after (black curve) the thermal pre-treatment.

The catalyst used for the test was prepared two months before the catalytic experiment. The red curve shows the conversion of citronellal, reaching 22% after three hours. In all the preliminary tests, the conversion was about 80%. Due to the polar nature of the Lewis acid phase and the microporous morphology of the polymer support, the deactivation of the catalyst due to ageing could be reasonably associated to the absorption of moisture, reducing the strength of the acid sites. Accordingly, the catalyst was dried in an electric oven at 110°C overnight to remove the absorbed water. The conversion of the dried catalyst turned out to be 85%, comparable to that obtained in the preliminary tests (Figure 33).

In view of this result, the catalysts were systematically dried overnight before the catalytic test.

To better understand the catalytic behaviour of $ZnCl_2$(30%)@pDVB, the reaction mixture was also analysed with ICP-OES to ascertain the presence of Zn species, leached from

the material during the test and possibly acting as homogeneous catalysts. The catalyst $ZnCl_2$(30%)@pDVB used in the preliminary catalytic experiment without any pre-treatment released about 8% of the total amount of Zn at the end of the test (Table 6).

Table 6. Leaching of Zn analysed by ICP-OES.

Catalyst	Leaching (Zn)
Preliminary $ZnCl_2$(30%)@pDVB	8.0%
$ZnCl_2$(30%)@pDVB- post pre-treatment	0.2%
$ZnCl_2$(30%)@pDVB- no H_2O	2.0%
$ZnCl_2$(10%)@pDVB	0.5%

Interestingly, the exploitation of the thermal pre-treatment resulted not only in the restoration of the catalytic activity, but also in the significant reduction of Zn leaching to 0.2%.

The same analysis was also performed on the other catalysts discussed in Paragraphs 3.8.1 and 3.8.2, namely $ZnCl_2$(10%)@pDVB and $ZnCl_2$(30%)@pDVB-no H_2O. The leaching of Zn from the catalyst containing 10% $ZnCl_2$ w/w is 0.5%, similar to that observed for the pretreated $ZnCl_2$(30%)@pDVB catalyst. It is important to note that, in spite of this, the catalyst was not active. On the contrary, leaching of the poorly active catalyst $ZnCl_2$(30%)@pDVB-no H_2O is 2%. These outcomes suggest that the amount of Zn leached from the catalysts increases with the content of water present in the catalyst. Remarkably, it also appears that the observed catalytic performance is not due to the leaching of Zn species from the catalysts, as the catalyst with the lowest activity (Preliminary $ZnCl_2$(30%)@pDVB) shows the highest level of leaching and catalysts with the same leaching level ($ZnCl_2$(30%)@pDVB- post pre-treatment and $ZnCl_2$(10%)@pDVB) are featured by remarkably different catalytic activity.

3.10 Hot Filtration test

The results of the ICP-OES analysis of the reaction mixture at the end of the catalytic tests reveal the leaching of Zn from the catalysts and suggests that this is not relevant for the observed performance. To definitely rule out a possible contribution of the homogeneous species to the catalytic performance of the materials, a hot filtration test was performed. This test consists in the recovery of the reaction mixture at the end of the catalytic test and in its exploitation in a subsequent test: in case active homogeneous species are present, a significant conversion of the considered reagent is observed. The hot filtration test (Paragraph 5.16) was carried out using 301.2 mg of $ZnCl_2$(30%)@pDVB and 401.2 mg of citronellal. The experiment was performed by adding the reagent solution to the catalyst, swollen for two hours in 50 mL of cyclohexane under the standard experimental conditions. To perform the hot filtration, the entire solution was removed from the autoclave at 70°C and transferred to the preheating chamber after 15 minutes from the beginning of the experiment. The solution was heated to 70°C in the preheating chamber while the autoclave was opened and thoroughly cleaned, to remove any residual catalyst. The autoclave was sealed again, and the previously filtered reaction mixture was injected. The mixture was sampled at 30, 60, 120 and 180 minutes.

The hot filtration test (Figure 34) clearly shows that both the conversion of citronellal and the formation of products stop after the removal of the solid catalyst by hot filtration. These results indicate that the observed performance is only due to active sites present on the surface of the solid catalyst and there is no significant contribution from homogeneous species.

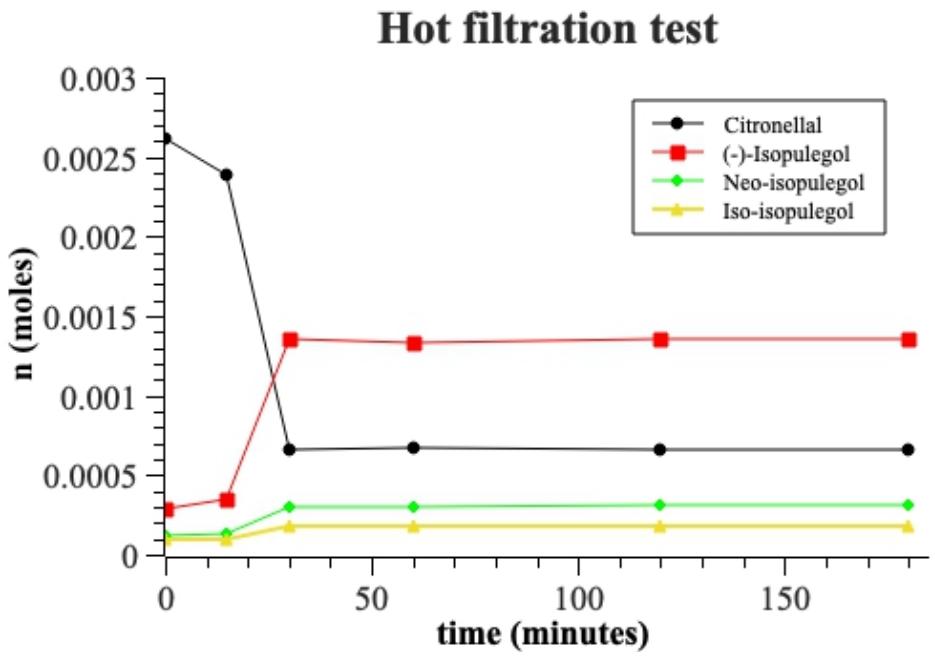

Figure 34. Hot Filtration test using 301.2 mg $ZnCl_2$(30%)@pDVB in the isomerization of citronellal to (-)-isopulegol.

3.11 Cycloisomerization byproducts

During the cycloisomerisation reaction, the $ZnCl_2$(30%)@pDVB catalyst produced high molecular weight byproducts with a retention time of 59'-62' in the gaschromatographic analysis. According to Mäki-Arvela et al. and Plöβer et al., dimers of citronellal and isopulegol can be obtained in the presence of Lewis acids, under the reaction conditions used for the cycloisomerization (Figure 35). [13,16]

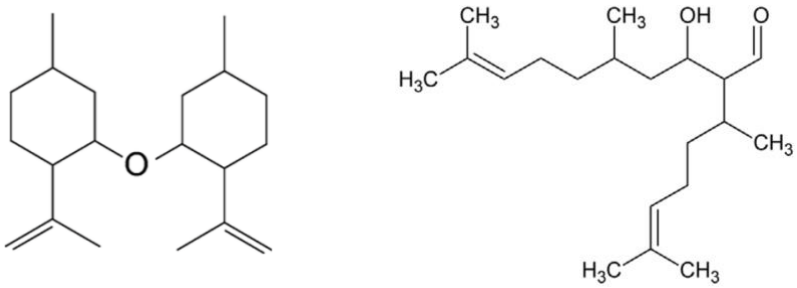

Figure 35. Products of dimerization of isopulegol, on the left, and dimer of citronellal on the right.[16]

Due to their high molecular weight, these products were observed at the end of the chromatographic run, when the temperature reached 280°C. The obtained products could be the result of the dimerization of citronellal and isopulegol, acting as reagent and intermediate in the isomerisation, respectively. Although the byproducts reported in Figure 35 are those mainly discussed in the literature, the obtained chromatograms clearly indicate the presence of several high molecular weight species. To better understand the nature of these byproducts, the samples of reaction mixture were also analysed with GC-MS. The GC-MS analysis revealed the presence of four distinct m/z ratios, 309, 339, 429 and 451, associated to the main peaks in the interval of retention time 59-62'. These findings differ from those previously reported in the literature, which indicated the presence of two m/z ratios 292 and 309. Oligomers were also formed, according to the signals with m/z ratio 429 and 451. In spite of this, the high molecular weight species could not be further analysed and their selectivity was expressed by assigning the area of the signals in the 59-62'range to the most abundant byproduct, with 309 m/z ratio.

Table 7. Selectivity toward high molecular weight byproducts.

$S_{Byproducts}$	0	15	30	60	120	180
$ZnCl_2$(30%)@pDVB	0.00	0.08	0.09	0.13	0.13	0.13
$ZnCl_2$(10%)@pDVB	0.00	0.00	0.00	0.00	0.00	0.00
$ZnCl_2$(30%)@pDVB-no H_2O	0.00	0.00	0.04	0.07	0.08	0.11

The catalytic results show that $ZnCl_2$(30%)@pDVB and $ZnCl_2$(30%)@pDVB-no H_2O produces a significant amount of heavy byproducts (13% and 11% selectivity, respectively), whereas no byproducts were observed with the catalyst with a lower content of $ZnCl_2$, $ZnCl_2$(10%)@pDVB (Table 7).

3.12 Characterization of the catalyst for the isomerization of citronellal

The morphology of the isomerisation catalysts was characterized with Transmission Electron Microscopy (TEM). The support as prepared shows the mesoporous morphology with pores of 5-50 nm, according to literature. [36, 47,48]

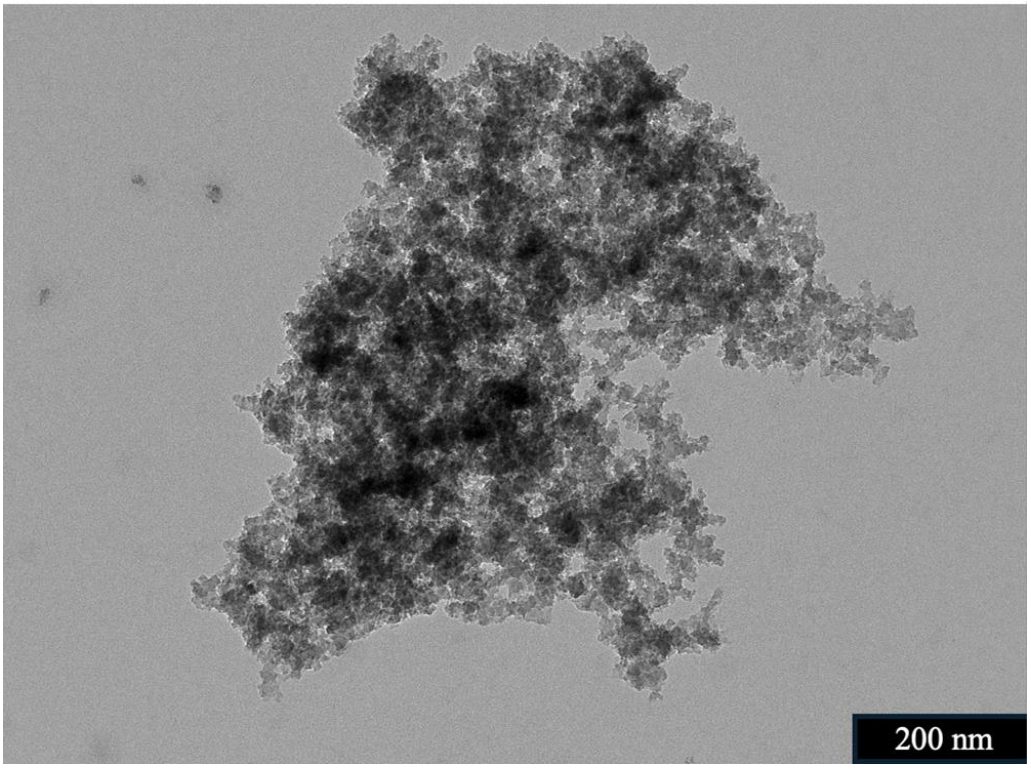

Figure 36. TEM characterization of polydivinylbenzene.

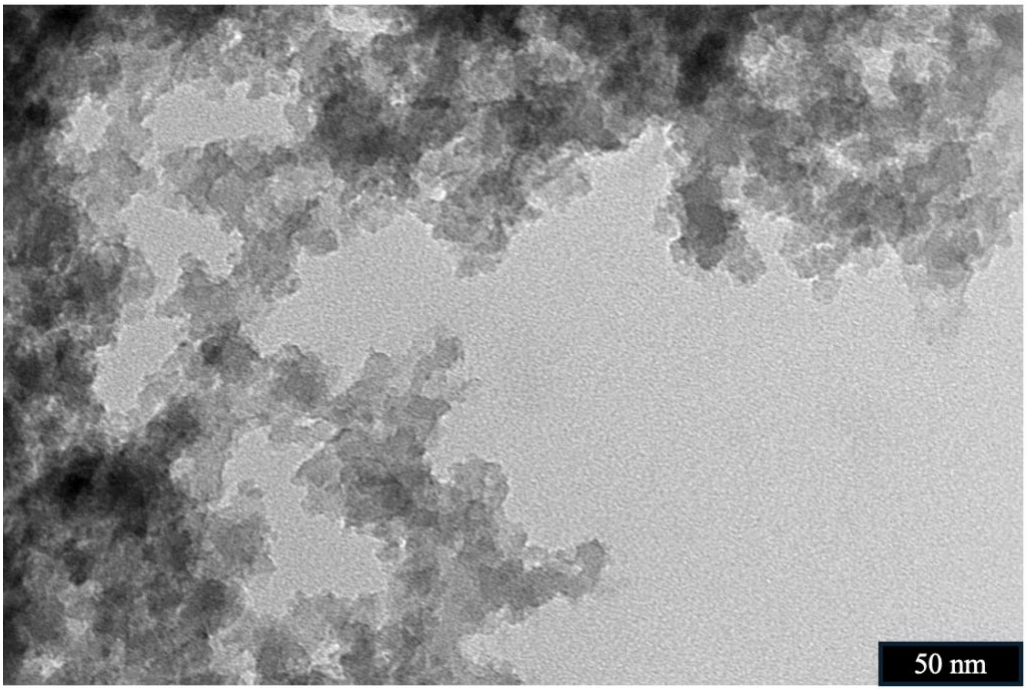

Figure 37. TEM characterization of polydivinylbenzene.

Conversely, the TEM characterisation of $ZnCl_2$(30%)@pDVB catalyst revealed, on the surface of the polymer support, the presence of large crystals of $ZnCl_2$, several tens of nanometres in size (Figures 38, 39 and 40).

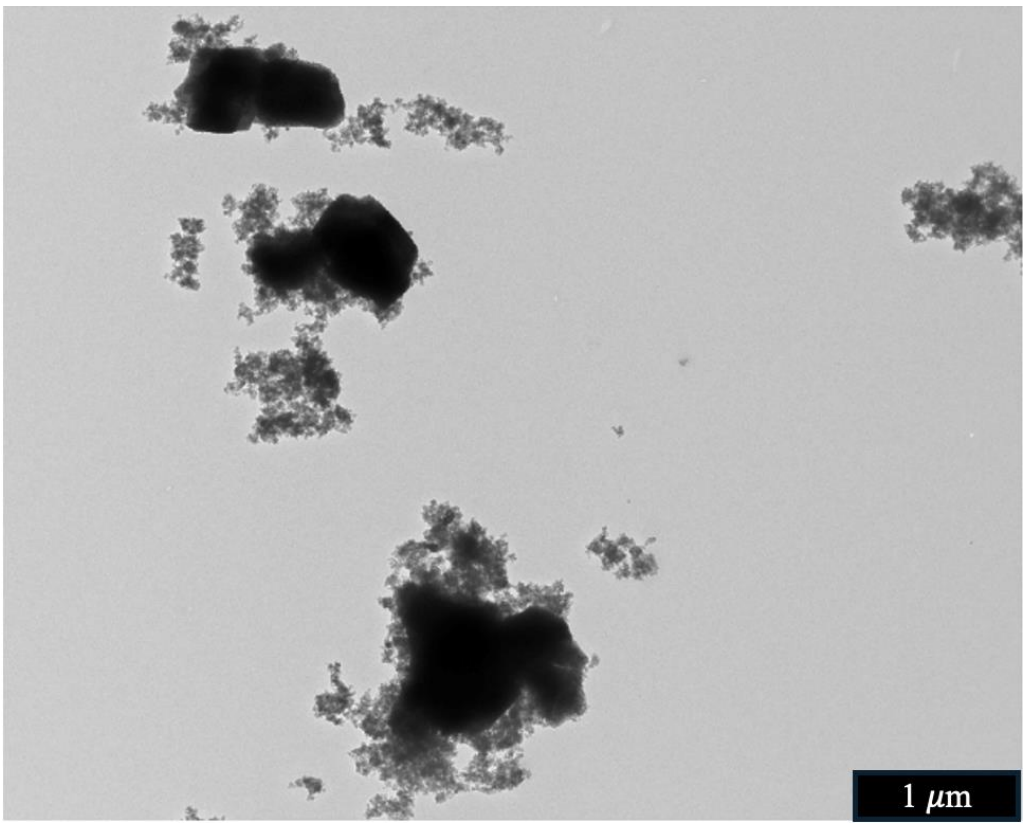

Figure 38. TEM characterization of $ZnCl_2$(30%)@DVB.

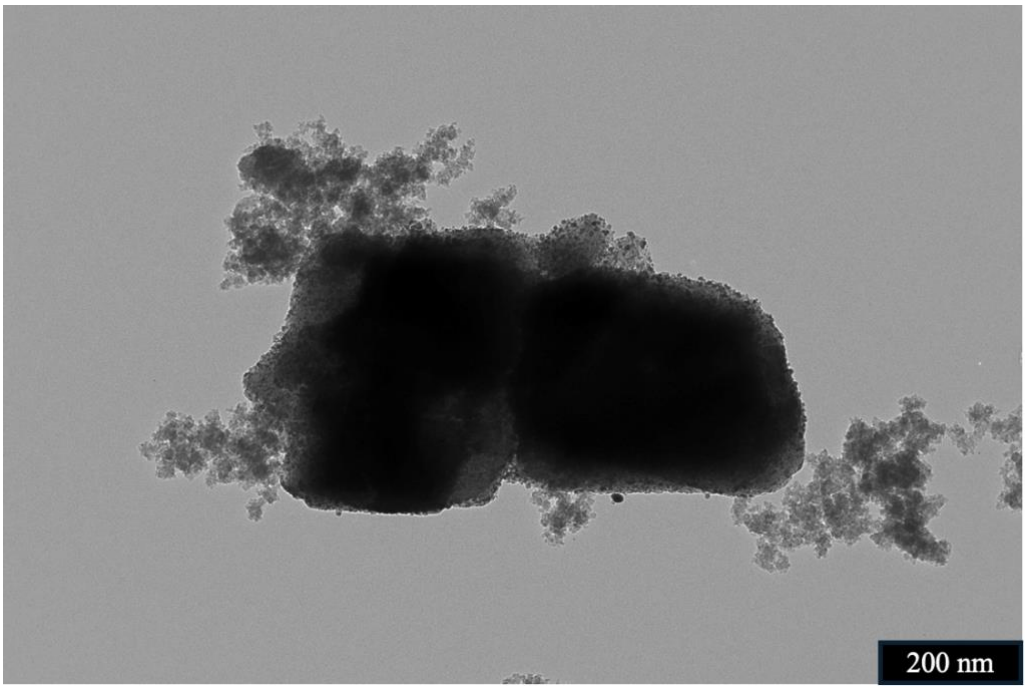

Figure 39. TEM characterization of $ZnCl_2$(30%)@DVB.

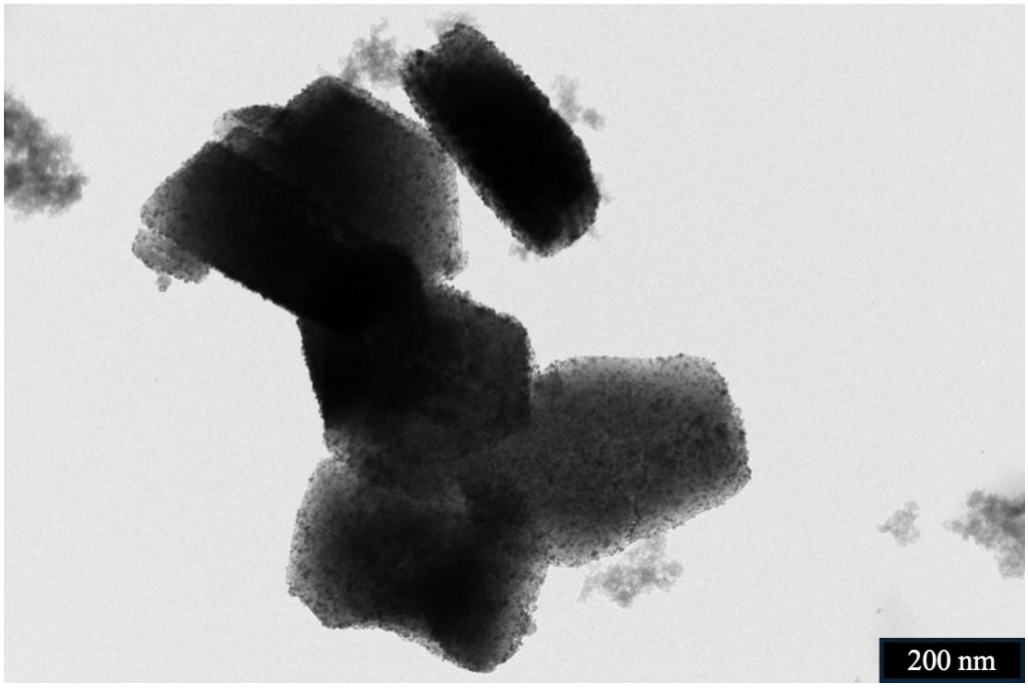

Figure 40. TEM characterization of $ZnCl_2$(30%)@DVB.

Beside larger $ZnCl_2$ crystals, smaller crystallites (ca. 10 nm) surrounded by the cross-linked polymer, can be also recognized.

For sake of comparison, the catalyst with 10% w/w $ZnCl_2$ ($ZnCl_2$(10%)@pDVB), resulting poorly active in cycloisomerisation, was also characterized (Figures 41 and 42).

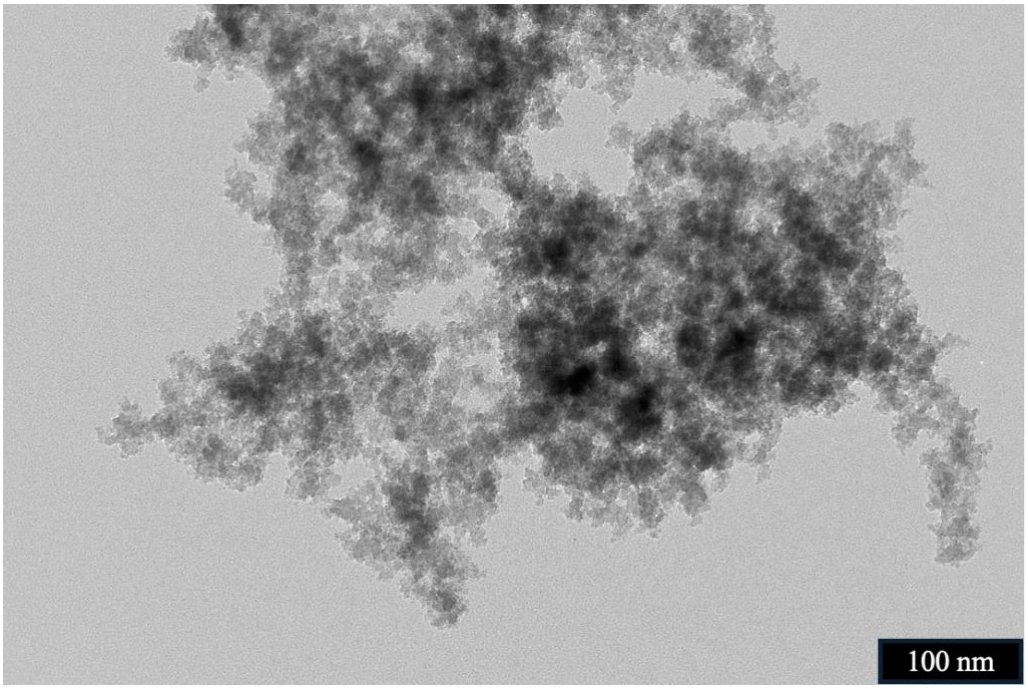

Figure 41. TEM characterization of $ZnCl_2$(10%)@pDVB.

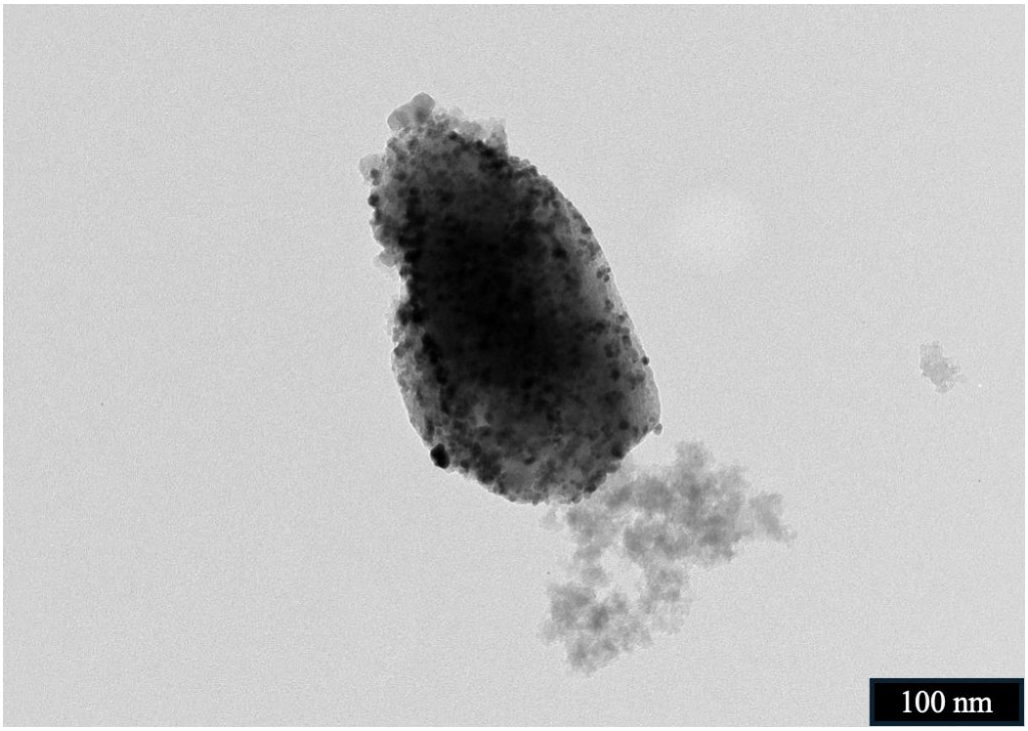

Figure 42. TEM characterization of $ZnCl_2$(10%)@pDVB.

The morphology of $ZnCl_2$(10%)@pDVB appears very similar to that of the active catalyst $ZnCl_2$(30%)@pDVB and consist in large $ZnCl_2$ crystals and smaller crystallites surrounded by the polymer support. This characterization does not allow to address the different catalytic performance of the materials to a clear morphological feature.

Conversely, the TEM characterization of the catalyst synthesised without using water (*$ZnCl_2$(30%)@pDVB- no H_2O*) appears different and particularly large crystals cannot be recognized (Figures 43 and 44).

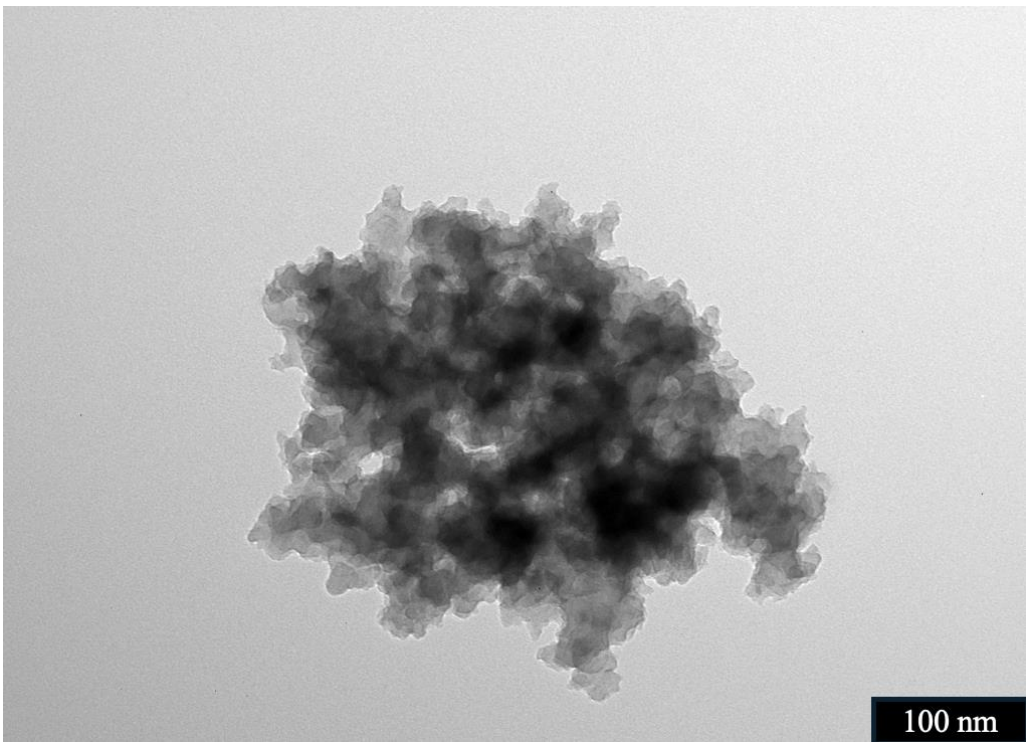

Figure 43. TEM characterization of $ZnCl_2$(30%)@pDVB – no H_2O.

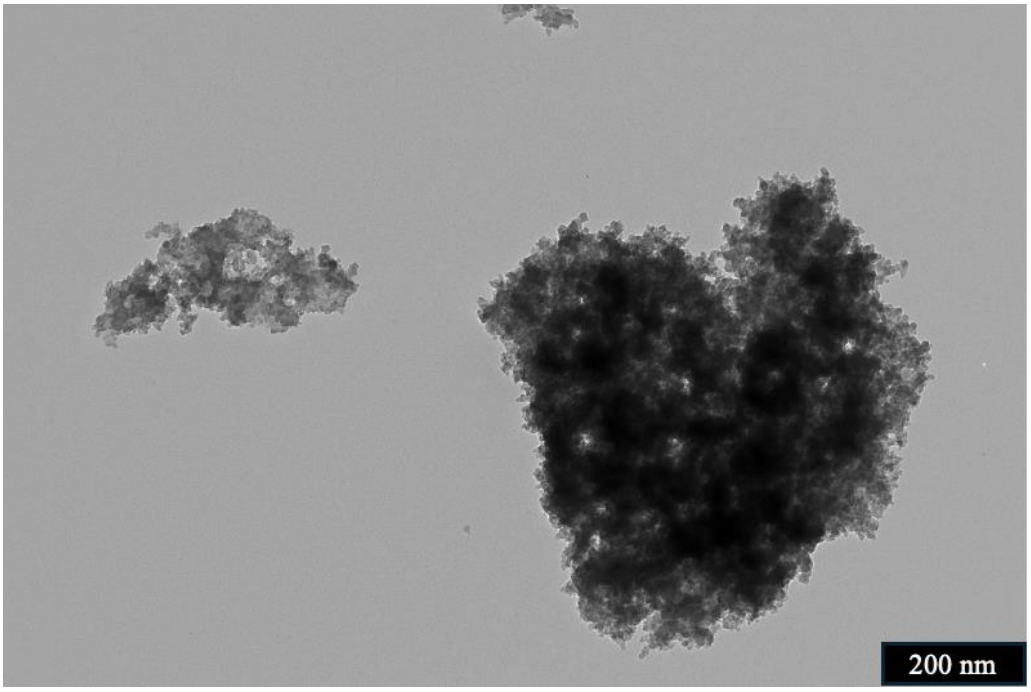

Figure 44. TEM characterization of $ZnCl_2$(30%)@pDVB- no H_2O.

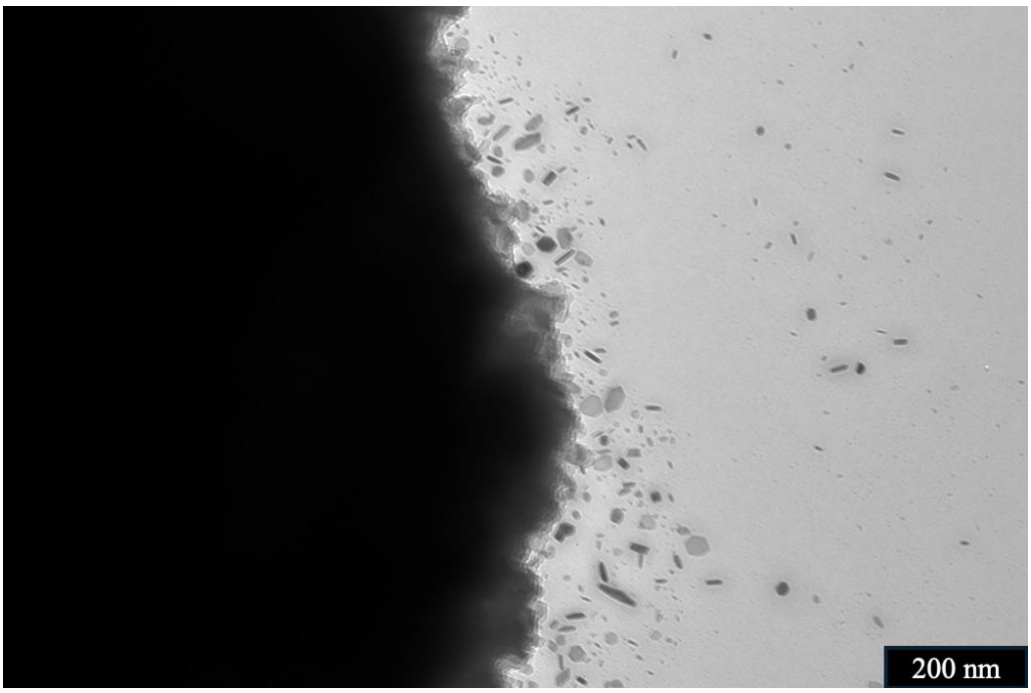

Figure 45. TEM characterization of $ZnCl_2$(30%)@pDVB- no H_2O.

In the sample prepared without water is possible to recognize both the texture of the polymer support and the presence of small crystallites, similar to those observed in the samples prepared using water as the solvent.

On the basis of the morphological features of the materials, the small crystallites, that are observed in any active catalyst ($ZnCl_2$(30%)@pDVB, $ZnCl_2$(30%)@pDVB- no H_2O), are likely the active sites of the catalysts. Conversely, the large crystals are probably negligible for the catalytic activity, as they are found both in the active catalyst $ZnCl_2$(30%)@pDVB and in the poorly active catalyst $ZnCl_2$(10%)@pDVB, but cannot be recognized in the active catalyst $ZnCl_2$(30%)@pDVB- no H_2O.

The solid state morphology of $ZnCl_2$(30%)@pDVB and $ZnCl_2$(30%)@pDVB without H_2O have been investigated with nitrogen physisorption (Table 8).

Table 8. BET surface area analysis of $ZnCl_2$(30%)@pDVB and $ZnCl_2$(30%)@pDVB no H_2O.

	$ZnCl_2$(30%)@pDVB	**$ZnCl_2$(30%)@pDVB- no H_2O**
BET surface area (m^2/g)	348	1050

The results show a specific surface area of 1050 m^2/g for the catalyst synthesised without water. This value is very similar to the 1089 m^2/g reported by Sterchele et al. for the polydivinylbenzene support as prepared: [34] this clearly indicates that the $ZnCl_2$ phase of the catalyst must have a very high specific surface area, approximately of the same order of magnitude of the polymer support. Conversely, the surface area obtained for $ZnCl_2$(30%)@pDVB is 348 m^2/g. This result is in agreement with the presence of large $ZnCl_2$ crystals in the sample revealed with TEM characterization (Figures 39 and 40).

3.13 One Pot Synthesis of menthol from citronellal

The one pot synthesis of menthol from citronellal is promoted by a bifunctional catalyst, bearing both redox and Lewis acid sites, or by the physical mixture of two different catalysts with distinct functionalities. The first step of the process is the cycloisomerisation of citronellal to (-)-isopulegol, followed by hydrogenation of the latter to menthol. As $ZnCl_2$ catalysts supported on polydivinylbenzene are active in the cycloisomerisation of citronellal, it is essential to select a catalyst for the selective hydrogenation of (-)-isopulegol, in the presence of the residual citronellal, thus avoiding the formation of 3,7-dimethyloctanal (DMA) and of the further hydrogenation byproduct, 3,7-dimethyloctanol. By hydrogenation of citronellal, citronellol can also be obtained from the reduction of the formyl group of DMA, whereas 3,7-dimethyloctanal can be produced by the further reduction of citronellol. The possible reaction of hydrogenation of citronellal and its products of isomerization and reduction are summarized in Figure 46. [21]

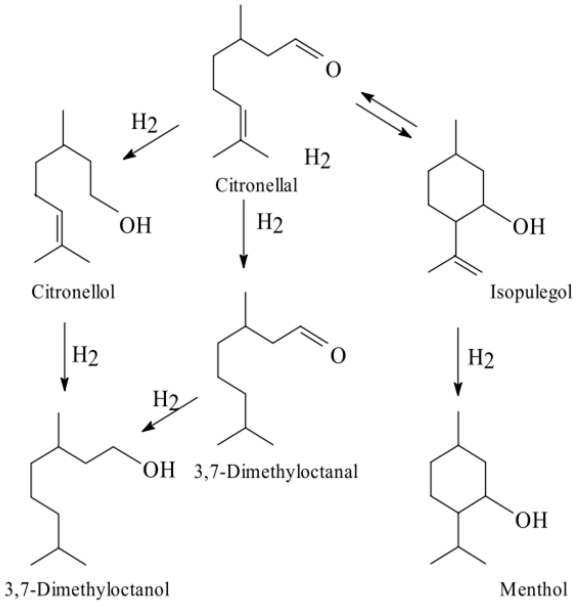

Figure 46. Reaction scheme of the one pot menthol synthesis from citronellal.

3.14 Effect of the amount of the hydrogenation catalyst

A number of hydrogenation catalysts have been reported in the one pot reaction, with nickel and palladium demonstrating high levels of both activity and selectivity towards menthol. Given the higher activity palladium, it is typically deposited on the support in smaller amounts than nickel. [9] The rate of hydrogenation of the molecules present in the reaction mixture is influenced by the amount of hydrogenation catalyst used, as well as the activity of the catalyst itself. It should be noted that the amount of active sites increases with the amount of catalyst. This makes easier the reduction of the double bond of (-)-isopulegol to obtain menthol, but also may decrease the selectivity towards the desired product, due to the formation of hydrogenation by-products such as 3,7-dimethyloctanal and citronellol.

3.14.1 Pd@C

The one pot synthesis of menthol from citronellal has been initially studied by using a physical mixture of a commercial palladium on activated carbon catalyst, Pd(5%)@C, with $ZnCl_2$(30%)@pDVB. As the isomerisation catalyst requires *in situ* pre-treatment, both catalysts were suspended in cyclohexane as for the cycloisomerization tests (Paragraph 5.15). In this initial part of the investigation, the effect of the amount of Pd@C on the conversion of citronellal and on the yield of isopulegol and menthol was studied. The amount of the isomerisation catalyst was maintained constant (0.3 g, as for cycloisomerization tests), whereas the amount hydrogenation catalyst was modified. The conversion of citronellal with different physical mixtures Pd(5%)@C - $ZnCl_2$(30%)@pDVB are reported in Figure 47 and Table 9.

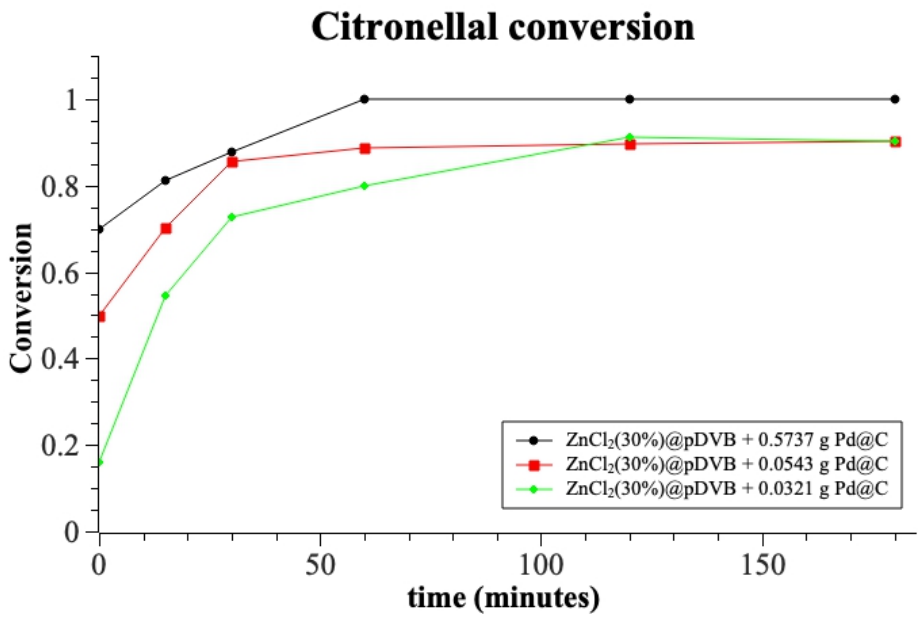

Figure 47. Citronellal conversion using 0.3 g $ZnCl_2$(30%)@pDVB and Pd(5%)@C 0.5757 g, 0.0543 g and 0.0321 g.

Table 9. Citronellal conversion using $ZnCl_2$(30%)@pDVB and Pd(5%)@C 0.5757 g, 0.0543 g and 0.0321 g.

C	0’	15’	30’	60’	120’	180’
$ZnCl_2$(30%) @pDVB+ 0.5737 Pd@C	0.70	0.81	0.88	1.00	1.00	1.00
$ZnCl_2$(30%) @pDVB + 0.0543 Pd@C	0.49	0.70	0.86	0.89	0.90	0.90
$ZnCl_2$(30%) @pDVB + 0.0321 Pd@C	0.16	0.55	0.73	0.80	0.91	0.90

As expected, the conversion increases with the amount of Pd(5%)@C catalyst. In particular, by using 0.57g of hydrogenation catalyst, 70% conversion of citronellal is achieved immediately after the injection of the reagent solution, whereas 49% and 16% conversion values are obtained by reducing the amount of Pd(5%)@C catalyst by 10 and 18 times. At the end of the test, similar performances are observed with different amount of hydrogenation catalyst: the complete conversion of citronellal is obtained with the highest amount of Pd(5%)@C, whereas 90% conversion is observed with 0.054 and 0.032 g of catalyst.

However, the high conversion of citronellal at the beginning of the test obtained with the highest amount of Pd(5%)@C mainly produces the undesired product of hydrogenation dimethyloctanal (71% yield, Figure 48 and Table 10).

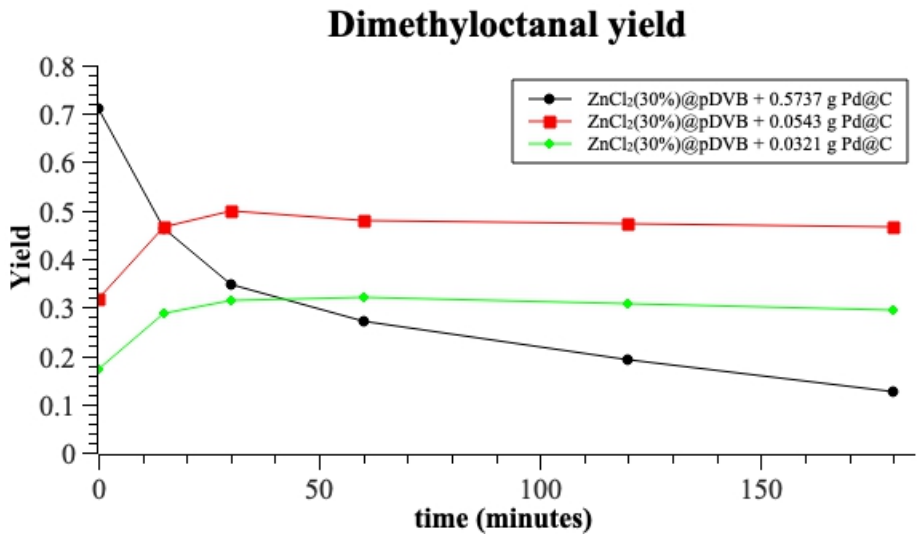

Figure 48. Dimethyloctanal yield using 0.3 g $ZnCl_2$(30%)@pDVB and Pd(5%)@C 0.5757 g, 0.0543 g and 0.0321 g.

Table 10. Dimethyloctanal yield using $ZnCl_2$(30%)@pDVB and Pd(5%)@C 0.5757 g, 0.0543 g and 0.0321 g.

DMA Y	0’	15’	30’	60’	120’	180’
$ZnCl_2$(30%) @pDVB + 0.5737 Pd@C	0.71	0.46	0.35	0.27	0.19	0.13
$ZnCl_2$(30%) @pDVB + 0.0543 Pd@C	0.32	0.47	0.5	0.48	0.47	0.47
$ZnCl_2$(30%) @pDVB + 0.0321 Pd@C	0.17	0.29	0.32	0.32	0.30	0.29

As expected, by reducing the amount of the hydrogenation catalyst, the yield of DMA at the beginning of the test decreases accordingly (32% and 17% yield with 0.054 and 0.032g, respectively). As shown in Figure 48 (red and green curves), by reducing the amount of hydrogenation catalyst, the DMA profiles stabilize and remains constant from 30’ until the end of the three hours experiment. Interestingly, the DMA yield decreases during the test, when the highest amount of Pd(5%)@C is used. This means that under

these conditions DMA is consumed by side reactions, that are in principle its acid catalysed condensation with the alcohols formed during the process and the reduction of formyl and C=C groups. By reducing the amount of Pd(5%)@C catalyst and keeping constant that of $ZnCl_2$(30%)@pDVB, the DMA yield reaches a plateau value (47% and 29% for 0.054 g and 0.032 g, respectively), the observed decrease of the DMA yield over the test with 0.57 g of Pd(5%)@C is most probably due to the hydrogenation side reactions (forming DMA and 2,7-dimethyloctanol), rather than to those of condensation. This hypothesis is indirectly confirmed also by the plateau values observed for the DMA yield with 0.054 g and 0.032 g of Pd(5%)@C: the value of the yield decreases with the amount of catalyst, according to milder hydrogenation conditions. The yield of (-)-isopulegol significantly changes with the different hydrogenation conditions, whereas the yield of menthol is poorly affected (Figures 49, 50 and Tables 10, 11).

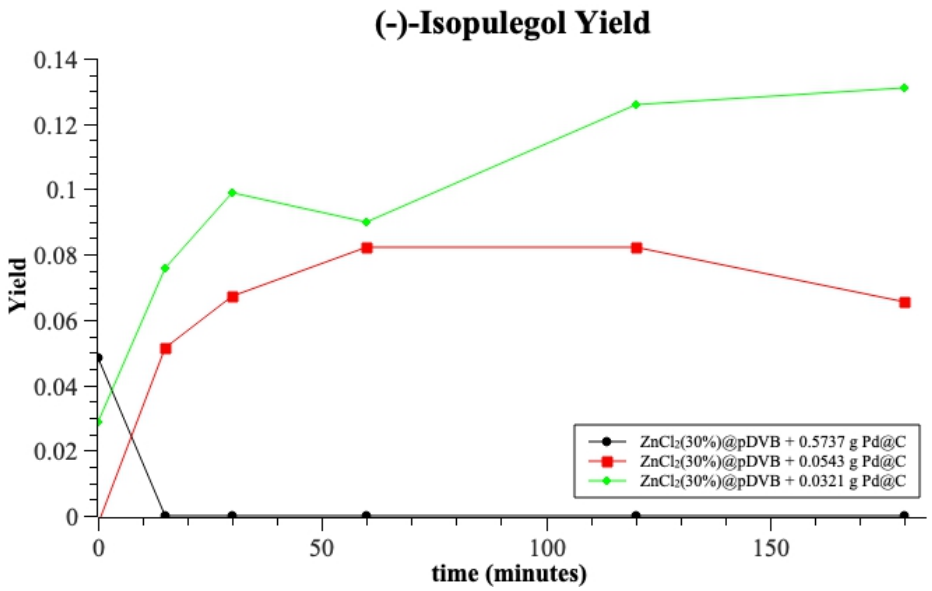

Figure 49. (-)-Isopulegol yield using 0.3 g $ZnCl_2$(30%)@pDVB and Pd(5%)@C 0.5757 g, 0.0543 g and 0.0321 g.

Table 11. (-)-Isopulegol yield using $ZnCl_2$(30%)@pDVB and Pd(5%)@C 0.5757 g, 0.0543 g and 0.0321 g.

IP Y	0’	15’	30’	60’	120’	180’
$ZnCl_2$(30%) @pDVB + 0.5737 Pd@C	0.05	0.00	0.00	0.00	0.00	0.00

$ZnCl_2$(30%) @pDVB + 0.0543 Pd@C	0.00	0.05	0.07	0.08	0.08	0.07
$ZnCl_2$(30%) @pDVB + 0.0321 Pd@C	0.03	0.08	0.10	0.10	0.13	0.13

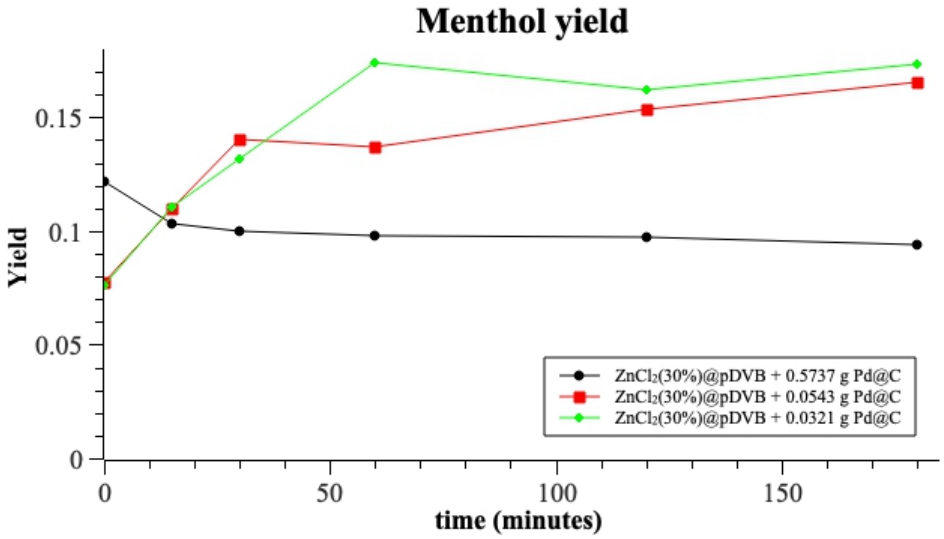

Figure 50. Menthol yield using 0.3 g $ZnCl_2$(30%)@pDVB and Pd(5%)@C 0.5757 g, 0.0543 g and 0.0321 g.

Table 12. Menthol yield using $ZnCl_2$(30%)@pDVB and Pd(5%)@C 0.5757 g, 0.0543 g and 0.0321 g.

MNT Y (%)	**0'**	**15'**	**30'**	**60'**	**120'**	**180'**
$ZnCl_2$(30%) @pDVB + 0.5737 Pd@C	0.12	0.10	0.10	0.10	0.10	0.10
$ZnCl_2$(30%) @pDVB + 0.0543 Pd@C	0.08	0.11	0.14	0.14	0.15	0.17
$ZnCl_2$(30%) @pDVB + 0.0321 Pd@C	0.08	0.11	0.13	0.17	0.16	0.17

The amount of menthol obtained with different amounts of Pd(5%)@C catalyst ranges from 9% and 17% over the whole test. Nevertheless, with reduced amounts of Pd(5%)@C (i.e. 0.054 g and 0.032 g), the menthol yield increases over time, whereas under harsh hydrogenation conditions (0.5737 g Pd(5%)@C) the menthol yield decreases from the

value obtained at the beginning of the test. In fact, under mild hydrogenation conditions, the rate of the hydrogenation reactions is sufficiently low to make possible the cycloisomerization of a significant amount of citronellal to (-)-isopulegol. Accordingly, (-)-isopulegol accumulates in the reaction mixture and can be hydrogenated to menthol, especially for longer reaction times. The profile of isopulegol yield is clearly a bell-shaped curve, as expected for a reaction intermediate, when 0.054 g of hydrogenation catalyst are used, whereas by further reducing the amount of Pd(5%)@C to 0.032 g the reaction conditions are so mild that the (-)-isopulegol yield still increases at the end of the test (Figure 49). Conversely, under harsh hydrogenation conditions (0.5737 g Pd(5%)@C), (-)-isopulegol can accumulate in the reaction mixture only at the beginning of the test, because it is quickly reduced to the desired product and citronellal is rapidly consumed to form DMA and further hydrogenation side products (Figure 48). The minor decrease of menthol yield with respect to the value obtained immediately after the injection of the reagent solution is reasonably due to the aldolic condensation of the desired product with citronellal and/or DMA.

In spite the menthol yield is roughly similar with different amounts of Pd(5%)@C, using the highest amount is not recommended, not only due to the high cost of palladium catalysts. In fact, smaller amounts of the hydrogenation catalyst make possible to obtain low amounts of hydrogenation byproducts (2,7-dimethyloctanal, 2,7-dimethyloctanol and citronellol). Moreover, the significant amount of the intermediate (-)-isopulegol, present in solution after 180 minutes tests, can be in principle converted to menthol for longer reaction times. Therefore, the most promising experiment among those with different amounts of hydrogenation catalyst is that that with the physical mixture of 0.3 g $ZnCl_2$(30%)@pDVB and 0.0321 g Pd(5%)@C. The detailed reaction profile for this test is presented in Figure 51 and Table 13.

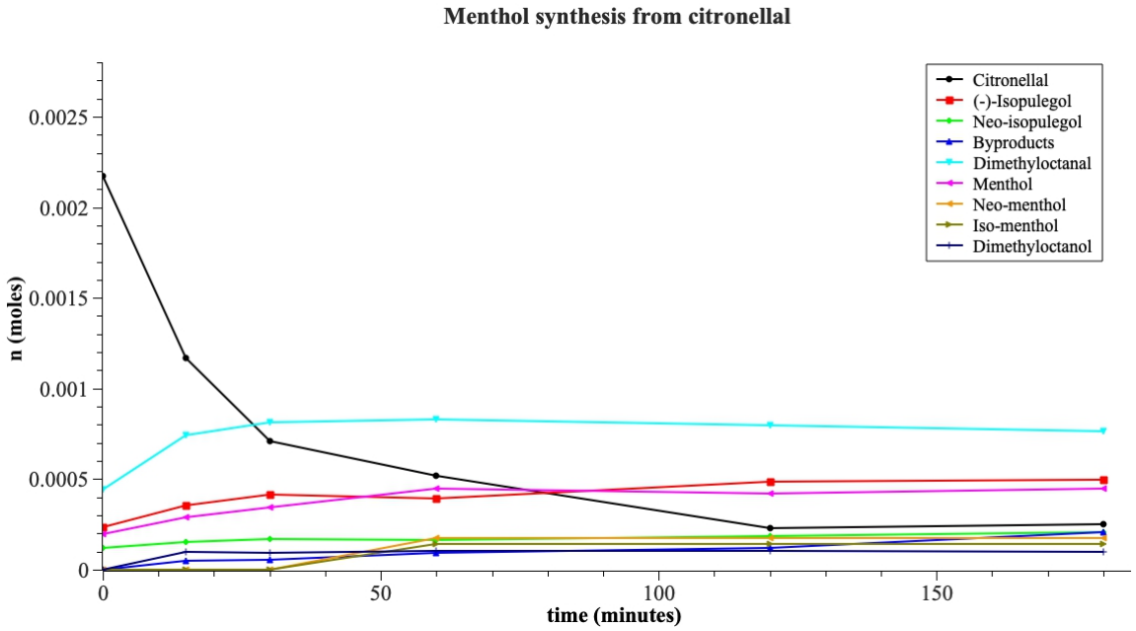

Figure 51. Menthol synthesis from citronellal using 0.3 g $ZnCl_2$(30%)@pDVB and 0.0321 g Pd(5%)@C.

Table 13. N (moles) of reagent consumed and products formed in the one pot menthol synthesis from citronellal using 0.3 g $ZnCl_2$(30%)@pDVB and 0.0321 g Pd(5%)@C.

n (moles)	0’	15’	30’	60’	120’	180’
CAL	2.17E-03	1.17E-03	7.09E-04	7.09E-04	2.30E-04	2.30E-04
DMA	4.44E-04	7.42E-04	8.15E-04	8.30E-04	7.98E-04	7.63E-04
IP	2.34E-04	2.34E-04	4.15E-04	4.15E-04	4.15E-04	4.99E-04
NIP	1.18E-04	1.52E-04	1.69E-04	1.69E-04	1.69E-04	2.07E-04
Byproducts	0.00E+00	4.72E-05	4.72E-05	9.13E-05	1.21E-04	2.09E-04
MNT	1.98E-04	2.87E-04	3.42E-04	4.50E-04	4.19E-04	4.49E-04
N-MNT	0.00E+00	0.00E+00	0.00E+00	1.76E-04	1.72E-04	1.76E-04
I-MNT	0.00E+00	0.00E+00	0.00E+00	1.44E-04	1.40E-04	1.43E-04
DMO	0.00E+00	9.71E-05	9.38E-05	1.02E-04	1.02E-04	9.91E-05

In detail, after 15 minutes, half of the citronellal reagent was converted into (-)-isopulegol, neo-isopulegol and dimethyloctanal. Iso-isopulegol was not observed and the ratio of

IP:NIP was 70.7:29.3 by the end of the test. It is noteworthy that, despite the absence of iso-isopulegol, iso-menthol (I-MNT) was produced. Three different diastereoisomers of menthol were identified: menthol, the main and desired product, neo-menthol (N-MNT), obtained from the reduction of neo-isopulegol, and iso-menthol. The ratio MNT:N-MNT:I-MNT is 58.4:23.0:18.6. This indicates that iso-isopulegol was generated during the process but was quickly hydrogenated to the final products. Under these mild reaction conditions, a residual amount of dimethyloctanol is formed by hydrogenation of dimethyoctanal. Additionally, high molecular weight by-products are also formed: this is reasonable by taking into the account the mild hydrogenation conditions, making available significant amount of aldehydes (citronellal and DMA) for the Lewis acid catalysed condensation sidereactions.

Remarkably, after 60 to 120 minutes the consumption of citronellal and the formation of the products are interrupted, suggesting the deactivation of both the acid and reduction catalysts.

3.14.2 Deposition of palladium nanoparticles on polydivinylbenzene

After verifying the possibility to achieve a catalytic system for the one pot conversion of citronellal to menthol with a physical mixture of $ZnCl_2$(30%)@pDVB and Pd(5%)@C, a bifunctional catalyst consisting in Pd nanoparticles supported on the $ZnCl_2$(30%)@pDVB isomerization catalyst. To start this investigation, before to prepare a bifunctional catalyst, a Pd catalyst supported on polydivinylbenzene has been prepared to be used in a physical mixture with the $ZnCl_2$(30%)@pDVB isomerization catalyst. Taking into the account the high activity of Pd(5%)@C observed in the one pot tests (Paragraph 5.15) the loading of Pd of the polymer catalyst was set to 1% w/w.

The experimental procedure developed in this investigation is based on a previous Thesis on the same topic.[52] Pd(II) was loaded into the resin support by incipient wettness. (Figure 52).

Figure 52. Palladium acetylacetonate ($Pd(acac)_2$) solution in DCM used for the preparation of Pd@(1%)@pDVB by incipient wettness.

The obtained material shows a light-yellow hue with a greyish tint. The solid material has been treated with a methanol solution of $NaBH_4$ to reduce the Pd(II) precursor. After washing and drying, the catalyst appears as a heterogeneously coloured grey-black solid (Figure 53).

Figure 53. Pd(1%)@pDVB after reduction.

The catalyst was tested in the one pot menthol synthesis in a physical mixture with the cycloisomerisation catalyst $ZnCl_2$(30%)@pDVB. As for the one pot tests with Pd(5%)@C, the catalysts mixture has been swollen *in situ* in cyclohexane for two hours before the test. The test was performed as reported for the one pot tests with Pd(5%)@C (Paragraph 5.15) and the reaction mixture was sampled at 0', 15', 30', 60', 120' and 180'. The amount of both $ZnCl_2$ (30%)@pDVB and Pd(1%)@pDVB catalysts was ca. 0.3 g. The results of the catalytic experiment are presented in Figure 54 and Table 14. Further details on the catalytic test are provided in Table 15.

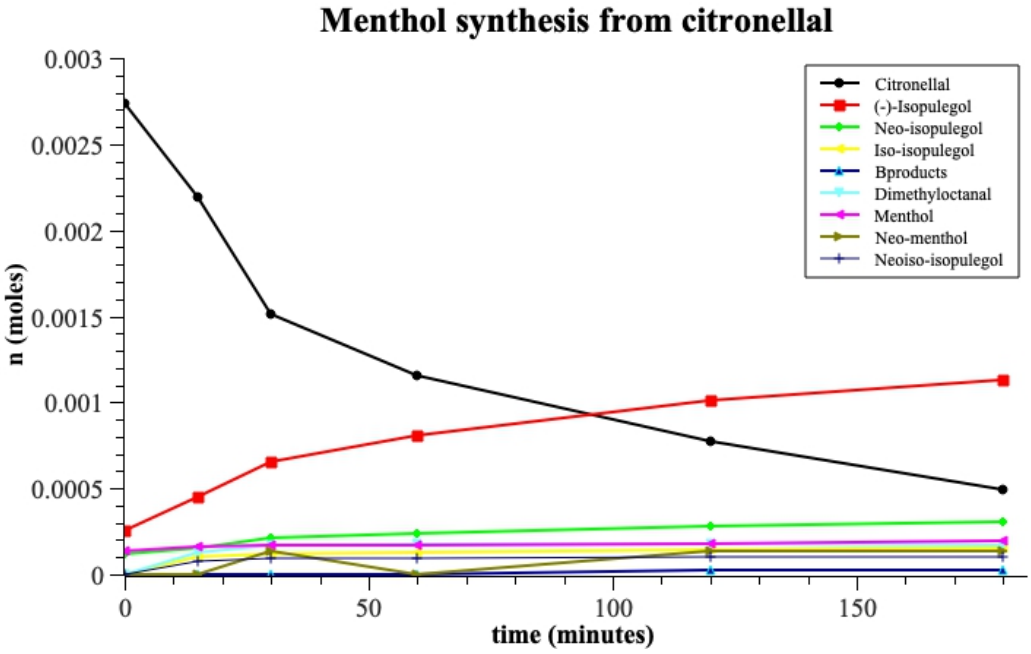

Figure 54. Menthol synthesis from citronellal using a physical mixture of $ZnCl_2$(30%)@pDVB and Pd(1%)@pDVB.

Table 14. moles of reagent consumed and products formed in the one pot menthol synthesis from citronellal using a physical mixture of $ZnCl_2$(30%)@pDVB and Pd(1%)@pDVB.

n (moles)	0’	15’	30’	60’	120’	180’
CAL	2.74E-03	2.19E-03	1.51E-03	1.16E-03	7.73E-04	4.95E-04
DMA	0.00E+00	1.30E-04	1.73E-04	1.75E-04	1.79E-04	1.72E-04
IP	2.59E-04	4.53E-04	6.57E-04	8.10E-04	1.01E-03	1.13E-03
NIP	1.15E-04	1.52E-04	2.10E-04	2.35E-04	2.83E-04	3.10E-04

IIP	0.00	1.03E-04	1.21E-04	1.27E-04	1.44E-04	1.54E-04
Heavy byproducts	0.00	0.00	0.00	0.00	2.63E-05	2.87E-05
MNT	1.40E-04	1.60E-04	1.68E-04	1.70E-04	1.81E-04	1.92E-04
N-MNT	0.00	0.00E+00	1.32E-04	0.00	1.33E-04	1.37E-04
N-IIP	0.00	7.93E-05	9.29E-05	9.42E-05	9.97E-05	9.90E-05

Table 15. Citronellal conversion, (-)-isopulegol, menthol and dimethyloctanal yield.

	0'	**15'**	**30'**	**60'**	**120'**	**180'**
$C_{Citronellal}$	0.00	0.2	0.45	0.58	0.72	0.82
$Y_{(-)\text{-isopulegol}}$	0.13	0.22	0.32	0.40	0.50	0.55
$Y_{menthol}$	0.07	0.08	0.08	0.08	0.09	0.09
$Y_{Dimethyloctanal}$	0.00	0.06	0.09	0.09	0.09	0.08

The one pot synthesis of menthol from citronellal promoted with a physical mixture of $ZnCl_2$(30%)@pDVB and Pd(1%)@pDVB is more complex than that obtained in similar tests using Pd(5%)@C. At the end of the experiment, 82% conversion of citronellal has been achieved. This value is comparable to that observed in the isomerisation experiments (Paragraph 3.8), with a yield towards (-)-isopulegol of 55%. In this experiment, both the amount of consumed citronellal and formed (-)-isopulegol increase steadily over time, rather than reaching a plateau. This means that the hydrogenation conditions are milder than those observed in the previous one pot experiment with Pd(5%)@C. Notably, DMA, obtained in small amount, 8% yield at the end of the three hours experiment, is the only byproduct obtained from the reduction of citronellal, whereas dimethyloctanol is not detected. The main product of the test is the intermediate (-)-isopulegol (55% yield), with the concentration increasing over time. In addition to (-)-isopulegol, neo-isopulegol, iso-isopulegol and neoiso-isopulegol were also observed. In spite of its high instability, neoiso-isopulegol (NIIP) has also been detected. The IP:NIP:IIP:NIIP ratio is 66.7:18.4:9.11:5.86. In this test, only two diastereoisomers of menthol are detected: menthol and neo-menthol, deriving from the reduction of neo-isopulegol. The yield towards menthol never exceeds 9%, with a yield of menthol of 9% after 180 minutes of the catalytic experiment. Similarly to the one pot tests with Pd(5%)@C, the hydrogenation of the intermediate to menthol apparently stops: in this case after the initial stage of the test, suggesting the deactivation of the catalyst. High molecular weight by-

products are present, but in trace amounts only. This means that, under the test conditions, the rate of aldolic condensation is particularly low and the main alcohol product progressively accumulates in the reaction mixture during the test. The Pd(1%)@pDVB catalyst was characterised with TEM. Figures 55 and 56 show irregular of palladium nanoparticles in the range 10-15 nm.

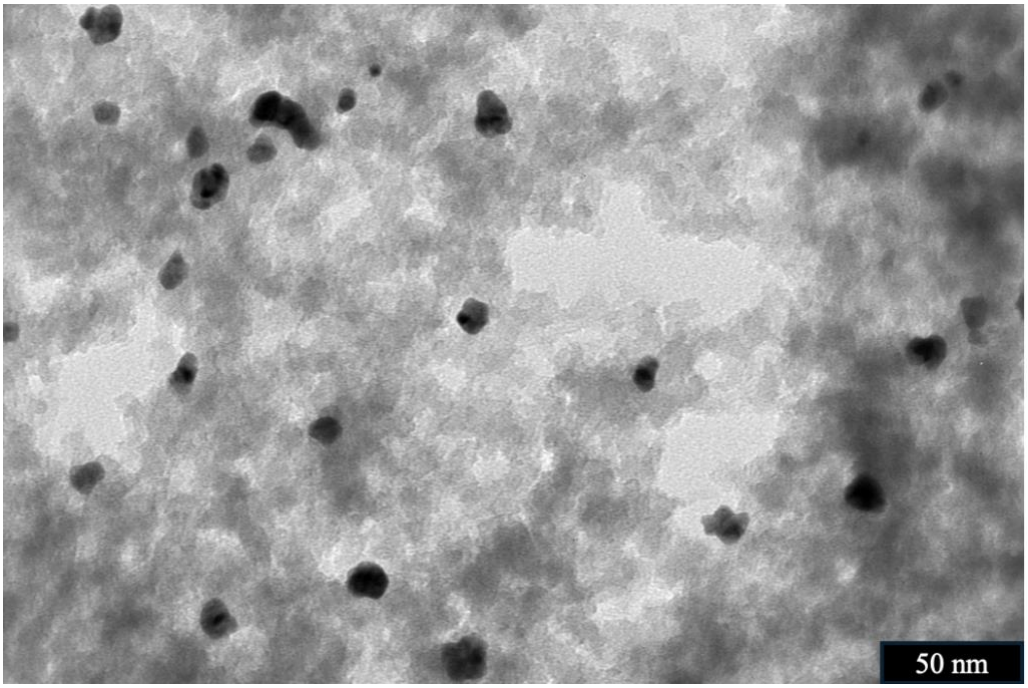

Figure 55. TEM characterization of Pd(1%)@pDVB.

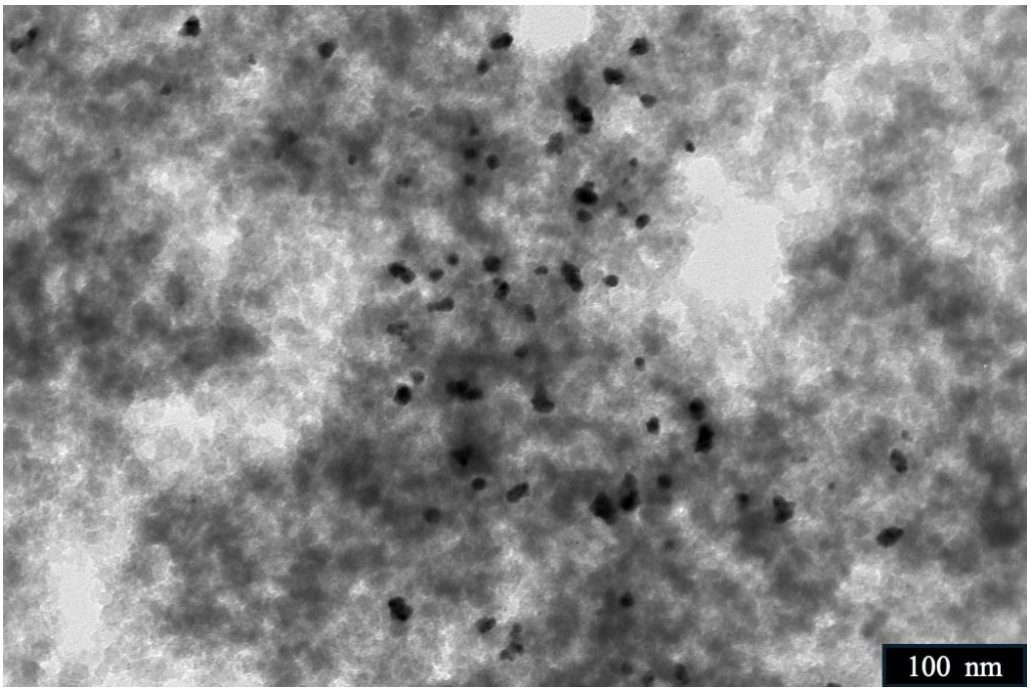

Figure 56. TEM characterization of Pd(1%)@pDVB.

Low magnification TEM show the presence of agglomerates of nanoparticles irregularly distributed within the polymer support.

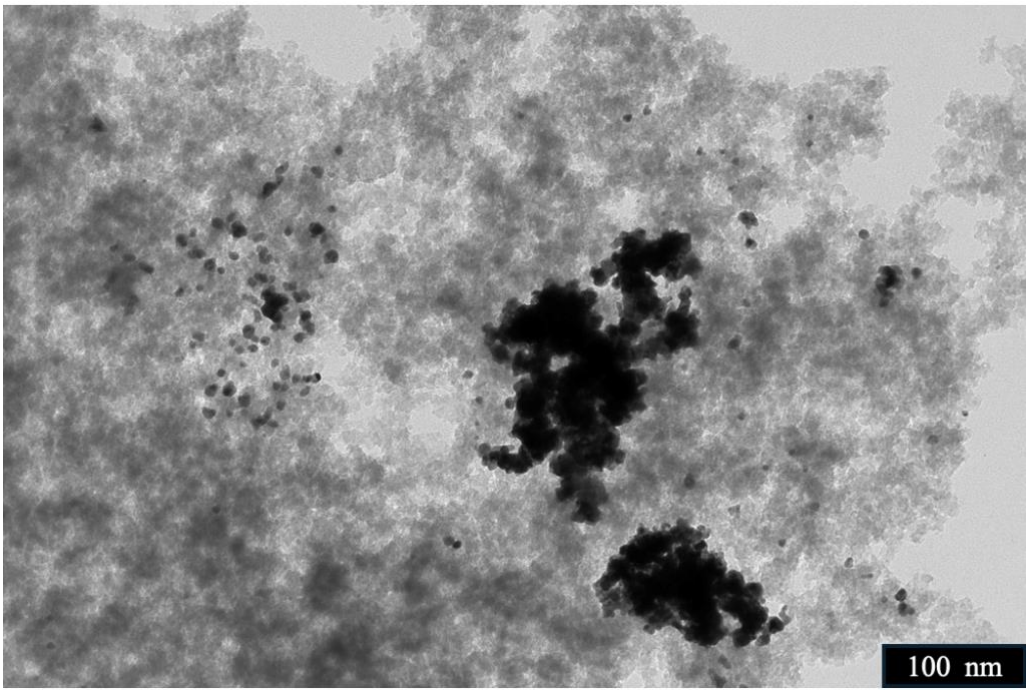

Figure 57. TEM characterization of Pd(1%)@pDVB.

3.15 Synthesis of the bifunctional catalyst

The preliminary investigation on the one pot synthesis of menthols promoted by a physical mixture of a cycloisomerisation and a hydrogenation catalyst, especially supported on the same material, was a key step towards the synthesis of a bifunctional catalyst, containing both Lewis acid sites and metal nanoparticles.

The synthetic protocol of the bifunctional catalyst has to be carefully designed. The results of the one pot tests (Paragraphs 3.14.1-3.14.2) suggests a content of $ZnCl_2$ of 30% w/w, whereas a 1% w/w of Pd is expected to be suitable to obtain the desired product, avoiding the excessive formation of byproducts. Given the significantly lower amount of palladium to be deposited with respect to zinc chloride, it is straightforward to synthesize the cycloisomerisation catalyst, that can be later used to absorb a solution of palladium (II) and obtained the nanostructured Pd phase, by chemical reduction. This approach is expected to avoid that the Pd nanoparticles are covered with $ZnCl_2$, becoming unavailable for the hydrogenation reaction.

Two different reduction strategies were implemented to obtain the Pd nanoparticles (Paragraph 5.5).

A palladium acetate solution in DCM was added to a batch of the cycloisomerisation catalyst, previously swollen for two hours in dichloromethane. For the loading of Pd(II),

it is essential to swell the resin with a solvent able to dissolve the palladium precursor, without dissolving the zinc chloride deposited on the catalyst. The catalyst was left to stir overnight in a rotavapor and finally the solvent was evaporated. The material obtained after metallation with Pd(II) precursor is presented in Figure 58.

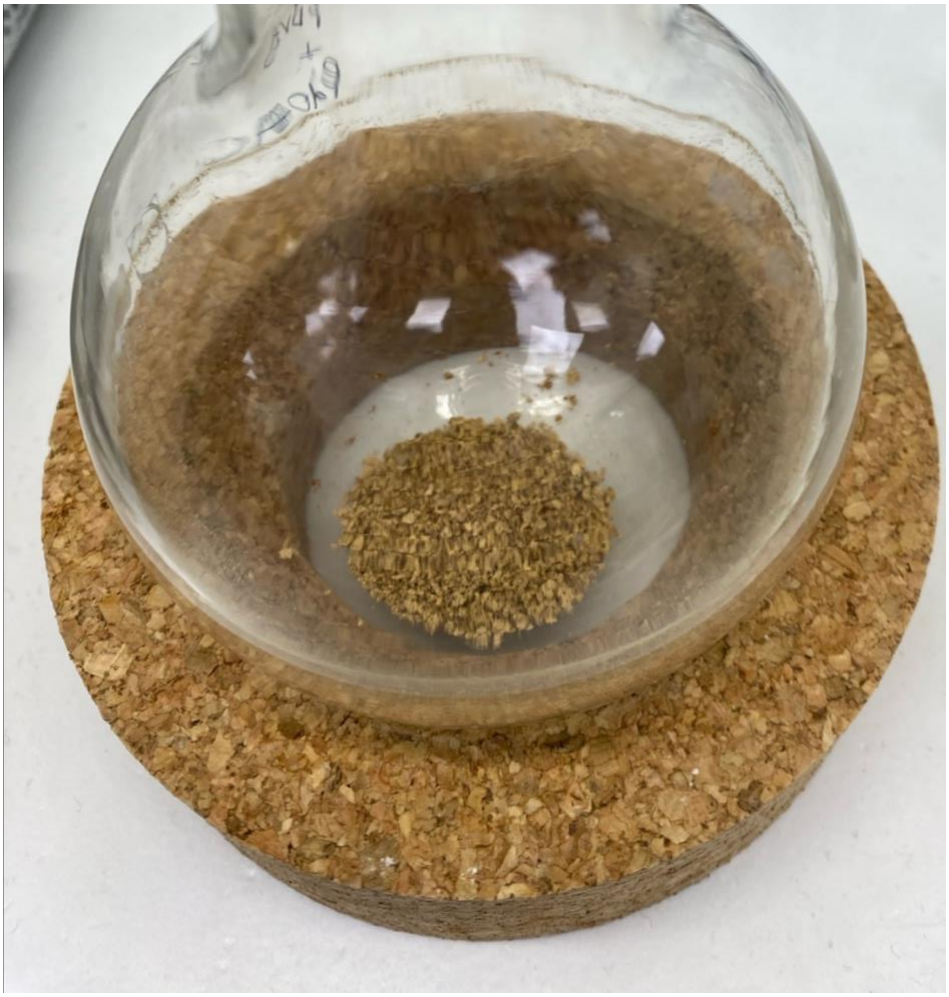

Figure 58. $ZnCl_2$(30%)@pDVB metalated with palladium before the reduction.

The material was transferred into a glass reactor equipped with a water condenser, a mechanical stirrer and a thermocouple (Figure 59).

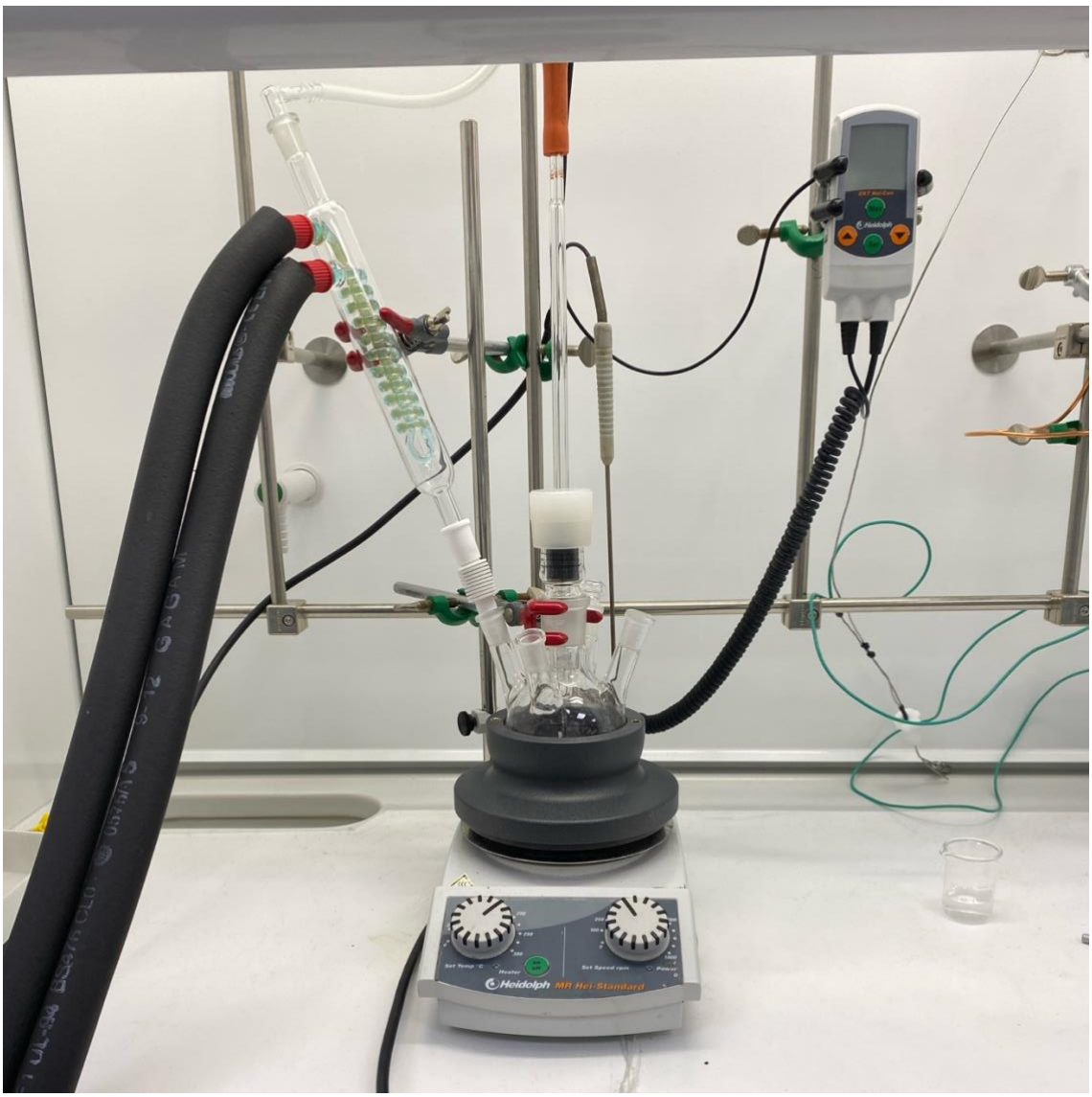

Figure 59. Experimental apparatus used for the reduction of the first batch of bifunctional catalyst, consisting in a glass reactor, a cryostat, a mechanical stirrer and a thermometer.

The catalyst was swollen in cyclohexane under argon atmosphere for two hours. Subsequently, the solid was treated with H_2 for 4 hours (at 30°C, 90 rpm and 30 mL/min of hydrogen). The flask was finally removed from the reactor, the solvent was removed using a rotavapor and the reduced catalyst was dried in an electric oven at 110°C overnight.

The catalytic test was performed according to the procedure used for the one pot experiments (Paragraph 5.15), using ca. 300 mg of bifunctional catalyst, coded as $ZnCl_2$(30%)Pd(1%)@pDVB-1. The results of the catalytic test are reported in Figure 60 and Table 16.

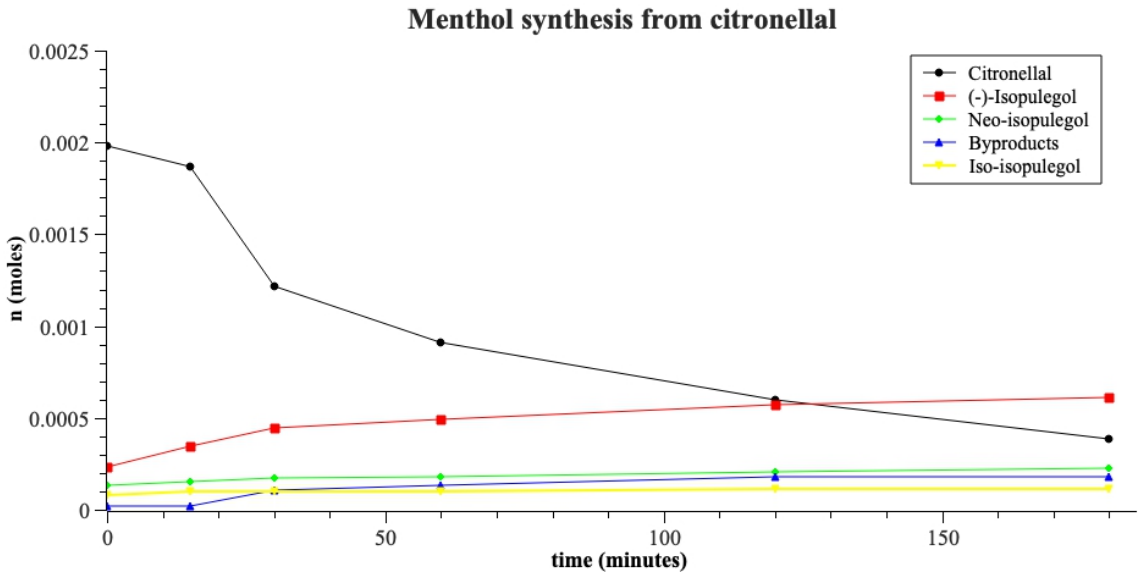

Figure 60. Menthol synthesis from citronellal using 0.2965 g of $ZnCl_2$(30%)Pd(1%)@pDVB-1.

Table 16. Citronellal conversion and (-)-isopulegol yield.

	0’	15’	30’	60’	120’	180’
C	0.00	0.05	0.38	0.54	0.7	0.81
$Y_{(-)\text{-isopulegol}}$	0.11	0.18	0.22	0.25	0.29	0.31

The catalytic test carried out with the bifunctional catalyst did not yield any menthol. As detailed in Table 16, citronellal was converted in (-)-isopulegol, neo-isopulegol and iso-isopulegol. These were present in the final reaction solution in a ratio IP:NIP:IIP of 64.6:23.7:11.7. The conversion of citronellal was slower than that observed in previous experiments. In fact, only 5% of the citronellal was converted in the first 15 minutes, to reach 81% of citronellal conversion after 180 minutes. This value is comparable to that observed in the other cycloisomerisation experiments discussed in Paragraph 3.8. The yield of (-)-isopulegol reaches a maximum of 31% after 180 minutes. As neither the absence of both menthol nor the hydrogenation byproducts were formed during the reaction, it is possible to conclude that the hydrogenation catalyst was either inactive or became inactive at an early stage of the reaction. A detailed characterization of the catalyst is needed to explain the observed behaviour: particularly useful could be the measurement

of the actual content of Pd of the bifunctional catalyst and the amount of Zn leached in the reaction mixture at the end of the test.

A second batch of bifunctional catalyst, coded as $ZnCl_2$(30%)Pd(1%)@pDVB-2 was prepared by *in situ* reduction of the $ZnCl_2$(30%)@pDVB catalyst after loading the Pd(II) precursor (Paragraph 5.6). In particular, a palladium acetate solution in DCM was added to a batch of the cycloisomerisation catalyst, previously swollen for two hours in dichloromethane. As for the batch 1 of bifunctional catalyst, it is essential to swell the resin in a solvent able to dissolve palladium acetate without solubilizing zinc chloride. The catalyst was left to stir overnight in a rotavapor and finally the solvent was evaporated. The catalyst was transferred to the autoclave and swollen in 50ml of cyclohexane to perform the reduction at 60°C, with 10 bar of hydrogen and 900 rpm for 18 hours. The catalyst was left in the autoclave for 18 hours, before the reagent solution was injected. The experiment was carried out according to procedure reported in Paragraph 5.15. The results of the catalytic test are reported in Figure 61 and Table 17.

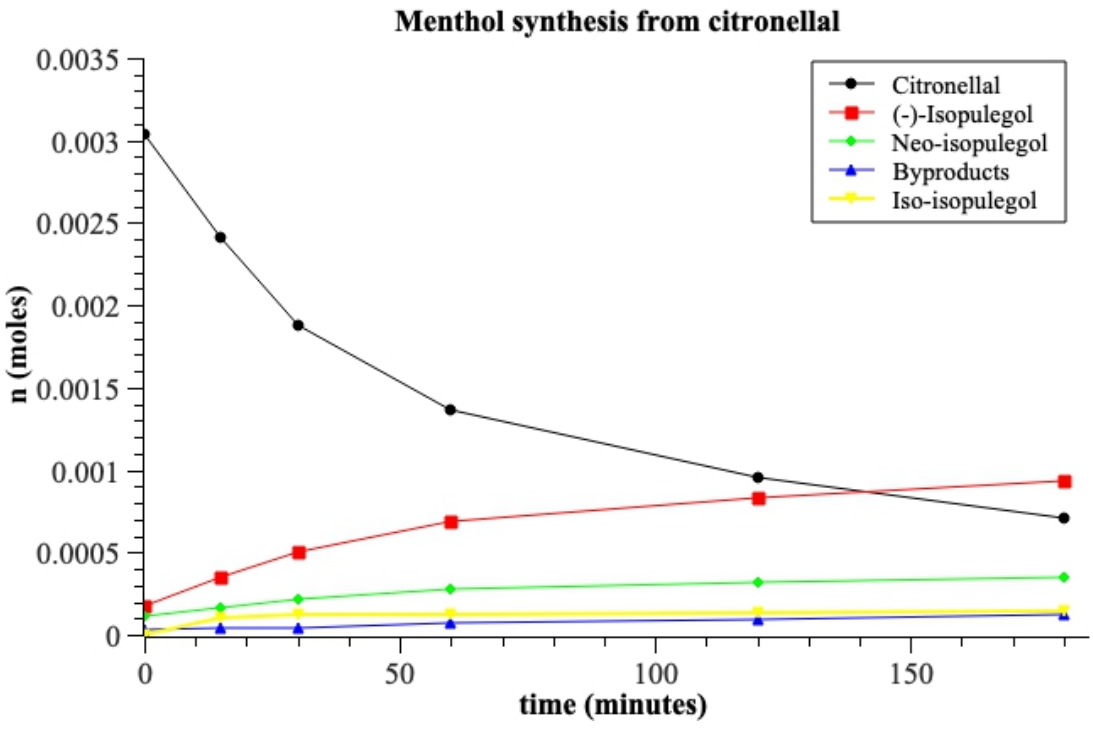

Figure 61. Menthol synthesis from citronellal using ca. 0.3 g of $ZnCl_2$(30%)Pd(1%)@pDVB-2.

Table 17. Citronellal conversion (%) and (-)-isopulegol yield (%).

	0’	15’	30’	60’	120’	180’
C	0	0.17	0.35	0.53	0.67	0.75
$Y_{(-)\text{-isopulegol}}$	0.13	0.22	0.32	0.40	0.50	0.55

Similarly to the test with $ZnCl_2$(30%)Pd(1%)@pDVB-1, no menthol was produced also with $ZnCl_2$(30%)Pd(1%)@pDVB-2. The only detected products were isopulegol and its diastereoisomers, as well as a high molecular weight byproduct. However, it should be noted that the conversion obtained at 180’ is 75%, which is lower than observed in the test with $ZnCl_2$(30%)Pd(1%)@pDVB-1 catalyst. It is worth noting that the yield towards (-)-isopulegol is high, reaching 55% at the end of the experiment. Furthermore, the ratio of the diastereoisomers of isopulegols IP:NIP:IIP is 65.3:24.7:10.1, in agreement with the catalytic test with $ZnCl_2$(30%)@pDVB catalyst.

Similarly to the test with $ZnCl_2$(30%)Pd(1%)@pDVB-2 catalyst, neither menthol, or dimethyloctanal or further hydrogenation byproducts were produced, supporting the possible deactivation or poisoning of the catalyst. To shed a light on this issue, a further TEM characterisation was performed on $ZnCl_2$(30%)Pd(1%)@pDVB-2 catalyst (Figures 62-64).

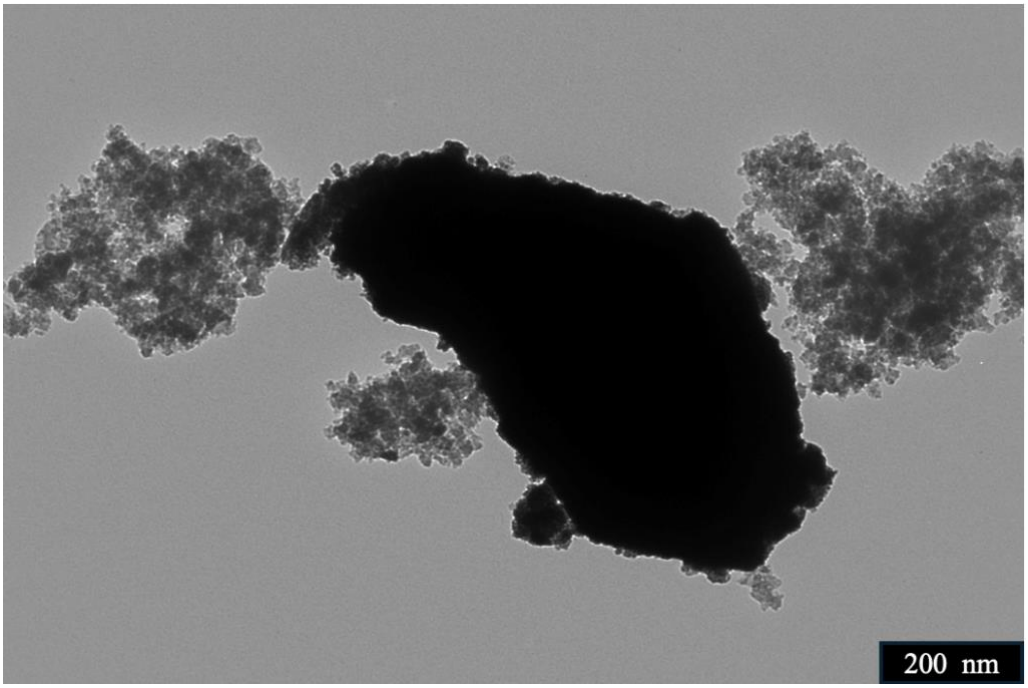

Figure 62. TEM characterization of $ZnCl_2$(30%)Pd(1%)@pDVB-2.

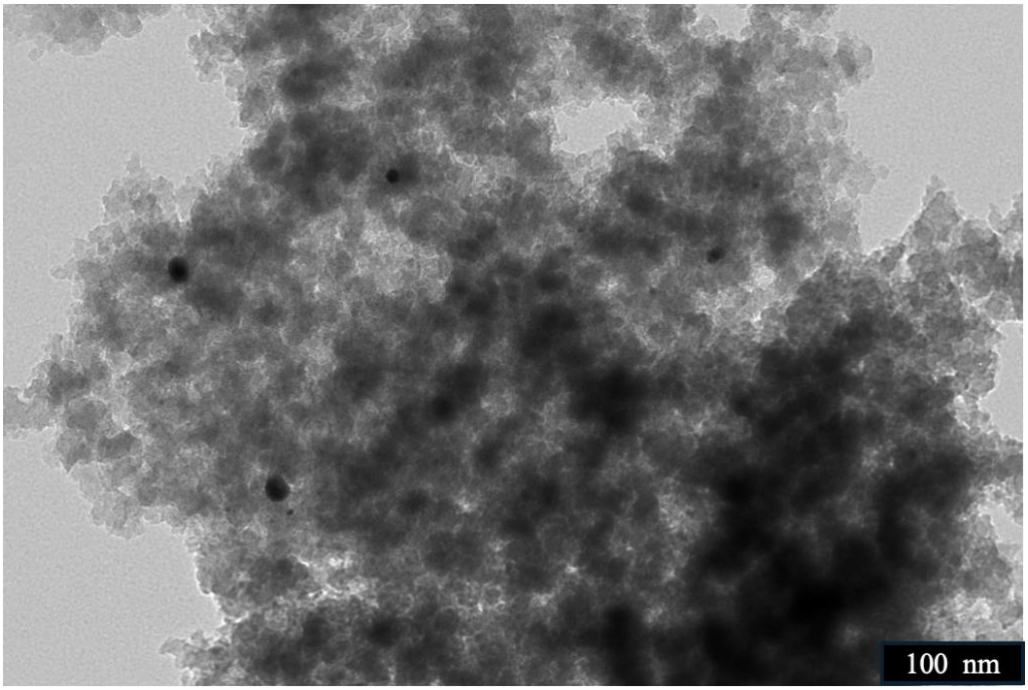

Figure 63. TEM characterization of $ZnCl_2$(30%)Pd(1%)@pDVB-2.

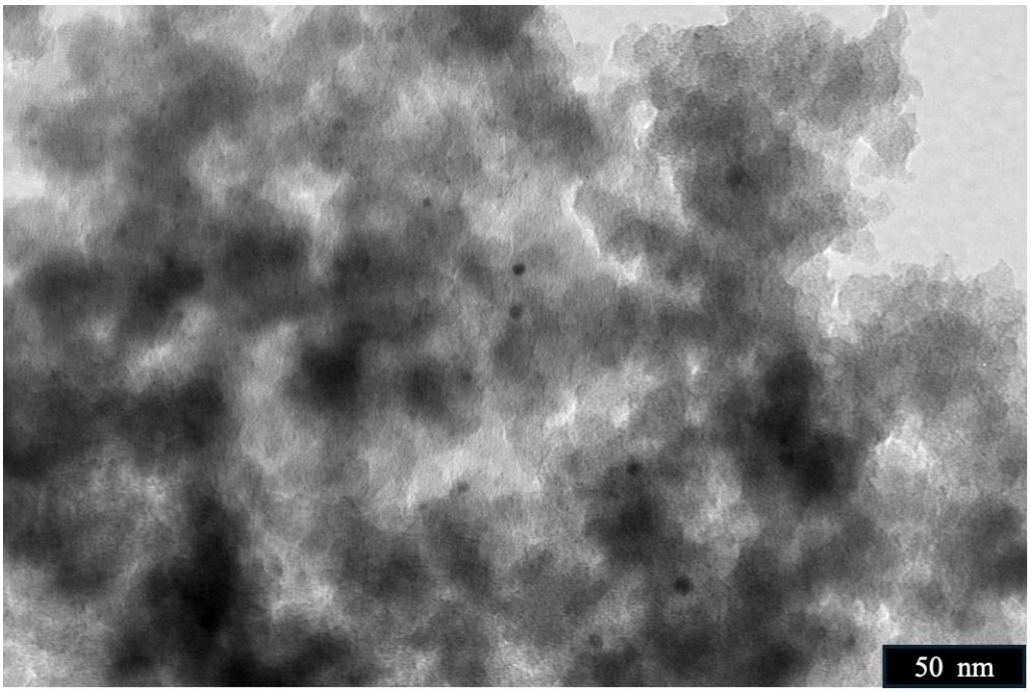

Figure 64. TEM characterization of $ZnCl_2$(30%)Pd(1%)@pDVB-2.

TEM characterization of $ZnCl_2$(30%)Pd(1%)@pDVB-2 catalyst shows the copresence of large $ZnCl_2$ crystals and smaller crystallites as observed for the cycloisomerisation catalyst $ZnCl_2$(30%)@pDVB (Figure 38-40). This suggests that the preparation of palladium nanoparticles did not significantly affect the morphology of the $ZnCl_2$ phase. Moreover, 1-3 nm palladium nanoparticles can be clearly recognized in the catalyst (Figures 63 and 64), indicating that the metallation procedure was effective.

4. Conclusions

This Thesis investigates the one pot synthesis of menthol from citronellal, based on the cycloisomerisation of citronellal to isopulegol and its subsequent hydrogenation.

The first part of the Thesis is focused on the role of Lewis acid sites in the cycloisomerization process. The investigation has shown that is possible to obtain an effective and selective catalyst for the isomerization of citronellal to (-)-isopulegol, with an heterogeneous catalyst obtained by depositing $ZnCl_2$ on mesoporous polydivinylbenzene. The results indicate that the content of $ZnCl_2$ of the catalyst must be 30% w/w and that the synthesis has to be performed in the presence of a small amount of water. The synthetic protocol allows to obtain a distinctive $ZnCl_2$ morphology consisting in large crystals and small crystallites, probably representing the active sites. The investigation of the effect of the amount of $ZnCl_2$ ($ZnCl_2$(10%)@pDVB) reveals that the catalyst is not active when a 10%w/w of acid component is employed. When $ZnCl_2$ is precipitated on polydivinylbenzene from a solution without H_2O, the resulting isomerization catalyst shows a reduced activity, increasing during the experiment and a lower selectivity towards (-)-isopulegol. TEM characterisation interestingly reveals that small $ZnCl_2$ crystallites, recognized in the active catalyst $ZnCl_2$(30%)@pDVB were not present.

The one pot synthesis of menthol using different amounts of the hydrogenation catalyst, in a physical mixture with the isomerization catalyst, was examined. Several experiments with Pd(5%)@C showed that the amount of hydrogenation catalyst remarkably affects the overall rates of reduction of citronellal to 3,7-dimethyloctanal and to 3,7-dimethyoctanol over the cycloisomerization of citronellal to isopulegol. Therefore the amount of catalyst has to be low and carefully selected in order to promote the hydrogenation reactions only after the cycloisomerization of citronellal. With respect to commercial Pd(5%)@C, Pd(1%)@pDVB appeared less effective towards the hydrogenation of (-)-isopulegol, although the formation of menthol, and its diastereoisomers was observed, with only a small amount of byproducts, such as DMA and DMO.

Interestingly, ICP-OES analysis of the reaction mixtures at the end of the tests and a hot filtration test demonstrated that the observed catalytic properties can be attributed only to active species present in the solid catalyst, ruling out any possible effect of soluble species leached out from the catalyst.

Finally, a bifunctional catalyst bearing both $ZnCl_2$ and palladium nanoparticles was tested. However, it appeared inactive towards the hydrogenation: only citronellal isomerization occurred, with the production only of (-)-isopulegol and its diastereoisomers as main products of the reaction. In spite the morphology of both Pd nanoparticles and $ZnCl_2$ crystallites did not suggest particular issues during the synthesis, menthol was not obtained and further studies are needed to rationalize the result.

This investigation successfully demonstrated that polydivinylbenzene can be employed as the support for the cycloisomerization of citronellal to isopulegol. The huge surface area and the wide porosity of the polymer support can be further exploited not only for the development of bifunctional catalysts for the synthesis of menthol from citronellal, but more generally to promote one pot processes.

Appendix 1 Synthesis of $Zn(NO_3)_2$ supported on polydivinylbenzene

According to Milone et al., the counterion of the Lewis acid ion can significantly affect the activity and selectivity of the catalyst in the synthesis of menthol from citronellal. [25] In particular, it has been reported that zinc bromide is the most active and selective catalyst among the compounds $ZnBr_2$, $ZnCl_2$ and $Zn(NO_3)_2$. The second most active and selective catalyst is zinc chloride, which is slightly less active. Zinc nitrate demonstrated a lower activity and selectivity than the other Lewis acid.

The catalyst was synthetized using the same experimental procedure employed for the deposition of zinc chloride on the polymer support (Paragraph 5.9). The amount of $Zn(NO_3)_2$ was selected in order to achieve the same amount of Zn that was deposited on $ZnCl_2$(30%)@pDVB.

$Zn(NO_3)_2$@pDVB is synthetized first by swelling the polymer in THF and then dissolving zinc nitrate in the smallest amount of water possible (Paragraph 5.9). The catalyst was prepared by following the experimental procedure described in Paragraph 5.9 and once dried in the electric oven, it was observed to have a yellow-brownish colour (Figure 65). The catalyst was tested in the isomerization of citronellal, performing the *in situ* pre-treatment designed for resin catalysts.

The performance of $ZnCl_2$(30%)@pDVB, the most promising catalyst for the isomerisation reaction, prepared in this Thesis (Paragraph 5.4), have been reported as the reference in Figure 66 and Table 18, along with $Zn(NO_3)_2$@pDVB.

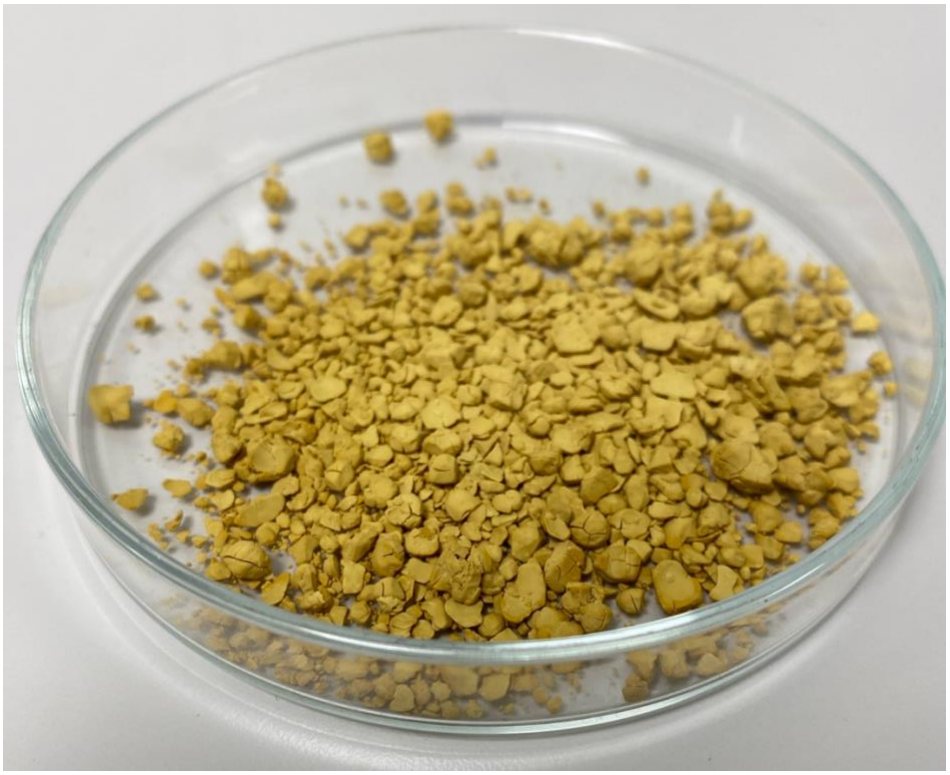

Figure 65. $Zn(NO_3)_2$ catalyst.

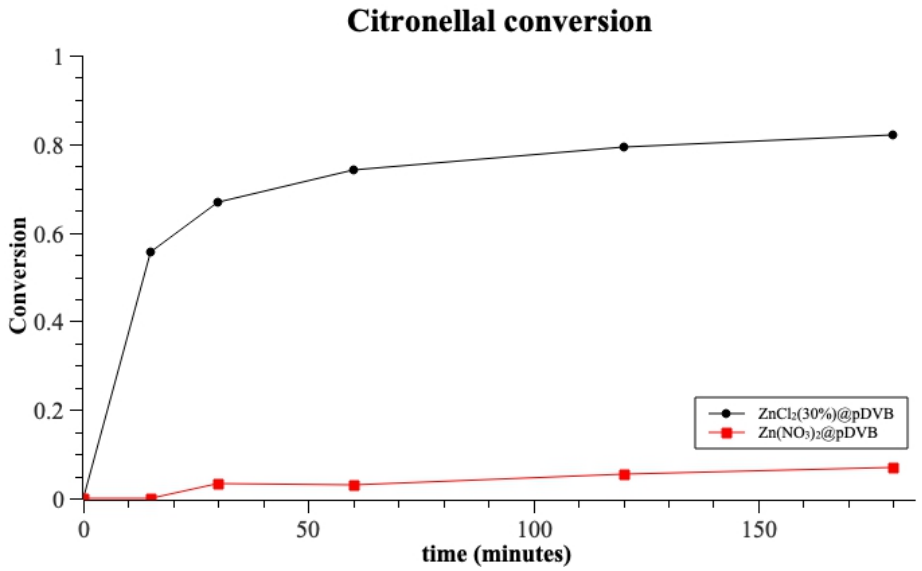

Figure 66. Citronellal conversion using $ZnCl_2$(30%)@pDVB and $Zn(NO_3)_2$@pDVB as catalyst.

Table 18. Citronellal conversion using $ZnCl_2$(30%)@pDVB and $Zn(NO_3)_2$@pDVB as catalyst.

$ZnCl_2$(30%)@pDVB		**$Zn(NO_3)_2$@pDVB**	
t (minutes)	**C**	**t (minutes)**	**C**
0	0.00	0	0.00
15	0.55	15	0.00
30	0.67	30	0.03
60	0.74	60	0.03
120	0.79	120	0.06
180	0.82	180	0.07

The catalyst $Zn(NO_3)_2$@pDVB is inactive in the cycloisomerisation of citronellal. In contrast to what was reported in literature by Milone et al. using $Zn(NO_3)_2$, the conversion of citronellal in presence of $Zn(NO_3)_2$@pDVB as isomerization catalyst was very low, reaching 7% at the end of the three hours experiment. [25]

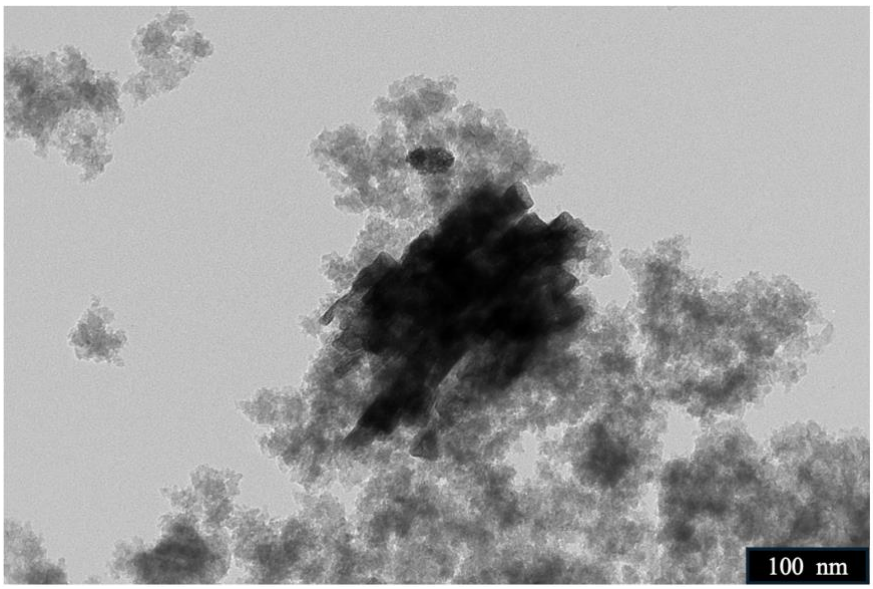

Figure 67. TEM characterization of $Zn(NO_3)_2$@pDVB.

TEM characterisations of $Zn(NO_3)_2$@pDVB shows the presence of dark and organised areas on the texture of the cross-linked polymer, which may be associated with the deposition of $Zn(NO_3)_2$ on the surface of the material (Figure 67). However, the morphology of $Zn(NO_3)_2$@pDVB turn out to be different from that of $ZnCl_2$(30%)@pDVB (Figures 37-39) and remarkably no small crystallites can be recognized.

Appendix 2 Synthesis of $MgCl_2$

To ascertain the role of chlorides in the reaction, magnesium chloride ($MgCl_2$) was deposited on polydivinylbenzene (pDVB) and the material was tested in the cycloisomerisation reaction of citronellal to isopulegol. Similarly to $Zn(NO_3)_2$ reported in Appendix 1, the amount of magnesium chloride deposited on the resin was determined in order to obtain the same amount of chloride ions loaded in $ZnCl_2$(30%)@pDVB.

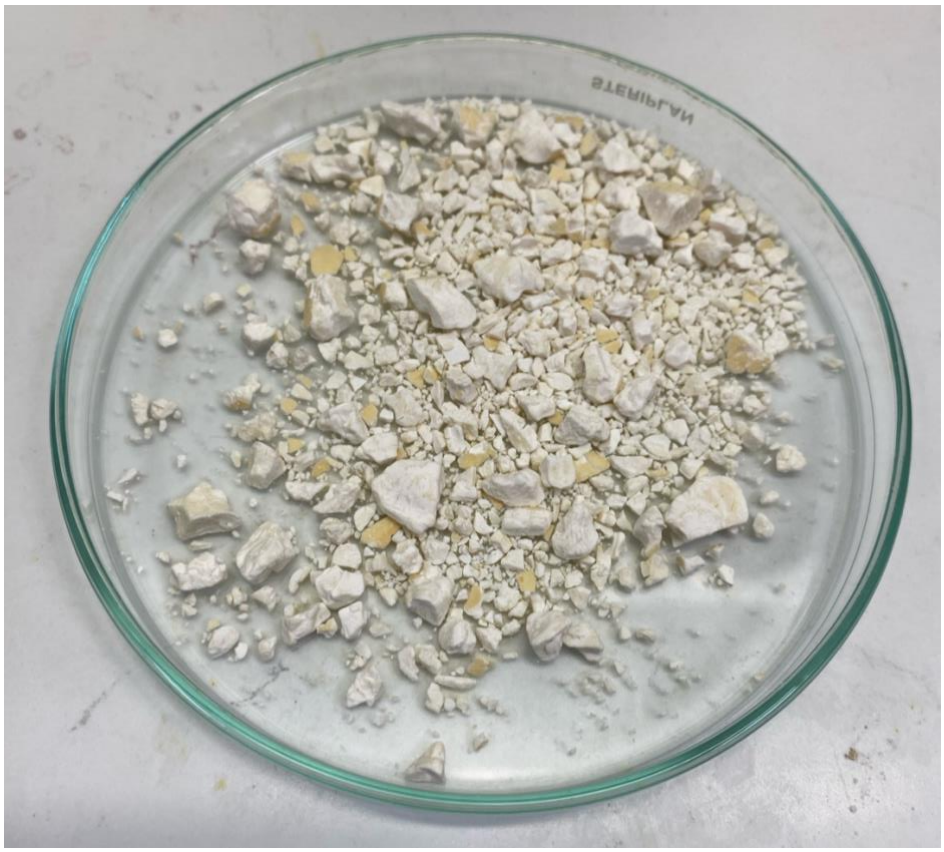

Figure 68. $MgCl_2$@pDVB catalyst.

The material was synthetized following the same experimental procedure (Paragraph 6.10) applied for the other catalytic material but using methanol instead THF to dissolve $MgCl_2$ (Figure 68). The result of the test of cycloisomerization of citronellal with $MgCl_2$@pDVB catalyst are reported in Figure 69. No conversion of citronellal was observed.

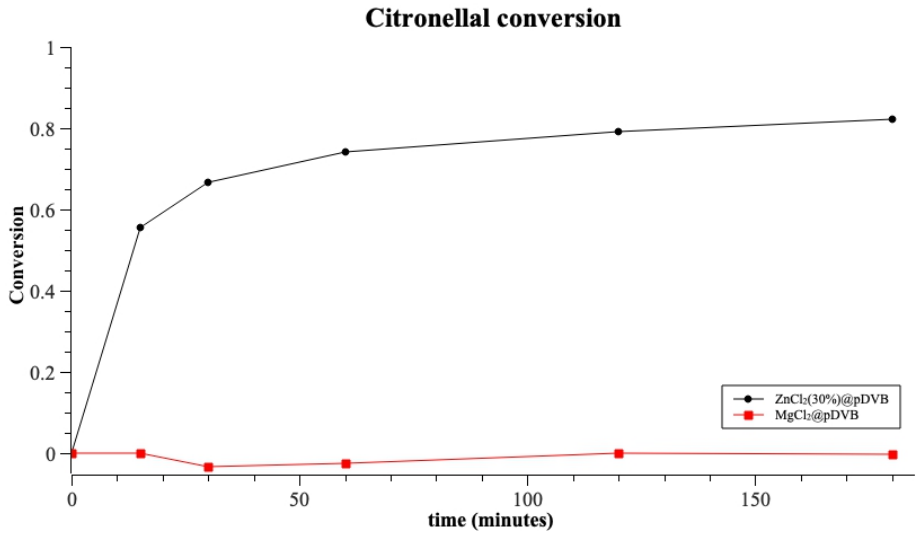

Figure 69. Citronellal conversion using $ZnCl_2$(30%)@pDVB and $MgCl_2$@pDVB as catalyst.

5. Experimental section

5.1 Reagents and solvents

Solvents and reagents used during the thesis work are reported in Table 19.

Table 19. Reagents and solvents employed.

Reagent	Formula	Density [g/mL]	PM [g/mol]	Producer
Divinylbenzene (80%)	$C_{10}H_{10}$	0.914	130.19	Sigma-Aldrich
Tetrahydrofuran for HPLC (≥99.9%)	C_4H_8O	0.888	72.11	Sigma-Aldrich
Methanol	CH_3OH	0.7910	32.04	Sigma-Aldrich
Neutral Alumina	Al_2O_3	-	101.96	Merck
Potassium iodide	KI	-	166.00	Sigma-Aldrich
Sodium molybdite	Na_2MoO_4	-	205.92	Sigma-Aldrich
Cyclohexane	C_6H_{12}	0.779	84.16	Thermoscientific
Dichloromethane	CH_2Cl_2	1.3250	84.93	Sigma-Aldrich
(±)-Citronellal	$C_{10}H_{18}O$	0.855	154.25	Sigma-Aldrich
(-)-Isopulegol	$C_{10}H_{18}O$	0.912	154.25	Sigma-Aldrich
Palladium acetate	$Pd(O_2CH_3)$	-	224.49	Sigma-Aldrich
Palladium (II) acetylacetonate	$Pd(C_5H_7O_2)$	-	304.54	Sigma-Aldrich
Palladium, 5% m/m, on activated carbon	Pd/C	-	-	Sigma-Aldrich
Zinc chloride	$ZnCl_2$	-	136.28	TCI
Hydrogen	H_2	-	2.02	
Argon	Ar	-	39.948	

5.2 Equipment

The equipments used are reported in the following Table 20.

Table 20. Equipments employed in the thesis work.

Equipment	Model
Gas-Chromatography	6890N Agilent Technology
GC-MS	6890N Agilent Technology and 5973Net work mass selective detector
DB-1 column	30 m (length) x 250 µm (diameter) x 0.5 µm (internal film thickness)
ICP-OES	PerkinElmer Optima 5300 DV
TEM	JEOL JEM-1400Plus
Nitrogen Physisorption	Micrometrics 3Flex-3500

5.3 Synthesis of mesoporous polydivinylbenzene

Mesoporous polydivinylbenzene was synthetized from divinylbenzene by radicalic polymerisation under solvothermal conditions. 6 g of technical divinylbenzene (80% purity) have been added to 60 mL of purified THF and 6 g of deionised water in a Teflon liner of 70 mL of volume.

165 mg of azobisisobutyronitrile (AIBN) have been weighted and added to the solution, which has been stirred for 4 hours. The Teflon liner was inserted into a steel autoclave, that has been sealed and put into a preheated stove at 100 °C for 48 hours. The polymer was obtained in the form of a white monolith, then broken into rough pieces and dried in a ventilated over at 110 °C for 48 hours. This procedure was repeated twice, and the amounts of used reagents are reported in Table 21.

Table 21 Amount of reagents weighted for the polydivinylbenzene syntheses. All the reactions were carried out with 60 mL of THF.

Batch	**DVB (g)**	**H_2O (g)**	**AIBN (mg)**
1	5.964	5.9864	167.0
2	6.0275	6.0247	165.8
3	6.0187	6.0301	166.0

5.4 Synthesis of $ZnCl_2$@pDVB

In a round bottomed flask, polydivinylbenzene has been added and swollen in 30 mL of purified THF. The mixture was left under orbital stirring for 2 hours at 60 rpm and room temperature. $ZnCl_2$ was dissolved in 10 mL of H_2O and added to the round flask. The amount $ZnCl_2$ allows to obtain a catalyst with a 30% w/w content of zinc chloride.

In Table 22, the mass of resin and zinc chloride deposited in every batch has been reported.

The suspension was left under stirring in a rotavapor overnight at 60 rpm. The solvent was removed *via* evaporation and the catalyst removed from the evaporating flask was dried in oven overnight at 110°C.

Table 22 Details on the deposition of $ZnCl_2$ on pDVB.

Batch (date)	Mass pDVB (g)	Expected mass $ZnCl_2$ (g)	Mass $ZnCl_2$ weighted (g)
1 (29.1)	2.5280	1.2640	1.3000
2 (13.2)	0.9806	0.4908	0.5510
3 (15.2)	0.4550	0.2275	0.2300
4 (14.3)[a]	0.7400	0.0740	0.0755
5 (9.4)[b]	0.3900	0.1950	0.2093
6 (7.5)	1.5625	0.7812	0.7805
7 (24.6)	2.0440	1.0220	0.9988

a: preparation of a catalyst with a 10% w/w content of $ZnCl_2$.

b: zinc chloride has been dissolved in THF and no water was employed in the deposition.

5.5 Metallation of the catalyst with palladium acetate

$ZnCl_2$@pDVB was weighted and swollen in 20 mL of dichloromethane at 60 rpm for 2 hours. A precise amount of palladium precursor, $Pd(OAc)_2$ has been dissolved in 10 mL of dichloromethane and added to the mixture. The amount of precursor used for the synthesis was determined in order to obtain 1% w/w catalyst. In Table 23, the mass of the catalyst before metallation and the precursor are reported for each synthetized batch.

Table 23. Details on the deposition of palladium on $ZnCl_2$@pDVB using palladium acetate as precursor.

Batch	Mass catalyst (g)	Expected mass $Pd(OAc)_2$ (g)	Mass $Pd(OAc)_2$ weighted (g)
1 (15.4)[a]	0.8029	0.0082	0.0168
2 (16.5)[b]	0.3155	0.0063	0.0074

a: the mixture is left under stirring in the rotavapor overnight at room temperature, 60 rpm. The solvent is removed *via* evaporation in the rotavapor at 100 mbar, and the catalyst is treated for the reduction as described in Paragraph 6.6.

b: the mixture is left under stirring for 2 hours under the same conditions of batch n. 1, then the solvent is removed *via* evaporation in the rotavapor at 100 mbar, and the catalyst is treated for the reduction as described in Paragraph 6.6.

5.6 Preparation of the catalyst by hydrogenation in the liquid phase

The catalyst Batch 1 (Paragraph 6.5) was transferred into a reactor for the reduction, swollen in 50 mL cyclohexane under inert atmosphere with 5 bar Argon for two hours. The reactor is composed by a 5-neck round bottom flask, surrounded with a heating mantle: one neck is equipped with a stirrer, to allow the mixing of the solution, the flux of hydrogen is connected to the second neck e and the third one is equipped with a cryostat. The other two necks are closed. A thermometer is connected to the apparatus to control the temperature. The reduction is performed at 30°C, 90 rpm and a 30mL/min flux of hydrogen for four hours. The catalyst was removed from the 5-neck round bottom flask poured into a round flask. The solvent was removed *via* evaporation in the rotavapor. The catalytic material was placed onto a watch glass and dried in oven at 110°C overnight. The final product appears as a dark brown-black powder.

Batch 2 was reduced *in situ* in the autoclave where the experiment is carried out (Paragraph 6.14). The catalyst was transferred into the autoclave for the menthol synthesis and swollen with 50 mL of cyclohexane. The autoclave was washed three times with 5 bar Argon at room temperature. The autoclave was pressurized with 10 bar of hydrogen and the sample was let to react overnight at 60°C, under magnetic stirring at 900 rpm. After18 hours, the catalyst was immediately used for a catalytic test of menthol synthesis (Paragraph 5.15).

5.7 Metallation of polydivinylbenzene with palladium acetylacetonate

28.2 mg of $Pd(acac)_2$ were dissolved in 9 mL of dichloromethane. The amount of palladium acetylacetonate was calculated in order to obtain 1% content of Pd deposited on the support. The yellowish solution was poured drop by drop on 1.0258 g of polydivinylbenzene in a round bottomed flask. While dripping the solution, the support was stirred by hand in order to uniformly treat the whole amount of solid sample. The round bottomed flask was closed and stored in a refrigerator for 72 hours. At the end of the procedure, the obtained sample appears slightly grey and swollen.

5.8 Reduction of palladium with $NaBH_4$

15 mL of methanol were carefully poured into a becher containing 0.2538g of sodium borohydride. The solution was dripped onto polydivinylbenzene swollen with palladium acetate precursor solution. As soon as the solution enters in contact with the material, the solid sample becomes dark-grey. The mixture was let to react for three hours in the round flask. The material was recovered by gooch filtration and washed with 250 mL of MeOH, in portions of 30 mL each. The catalyst was dried for 24 hours in an electric oven at 110°C.

5.9 Synthesis of $Zn(NO_3)_2$@pDVB

In a round flask, 1.02 g of polydivinylbenzene were suspended in 26.07 g of purified THF. The mixture was left to stir in a rotavapor 2 hours at 60 rpm and room temperature in order to allow the proper swelling of the resin.1.1363 g of $Zn(NO_3)_2 \cdot 6\ H_2O$ were dissolved in the smallest amount of H_2O (6.08 g). The watch glass was cleaned with purified THF (9.87 g) and added to the round flask. The amount of $Zn(NO_3)_2 \cdot 6\ H_2O$ weighted was calculated to obtain the same amount of Zn in moles as in the catalyst containing $ZnCl_2$@pDVB.

The suspension was left to stir overnight at 60 rpm and then the solvent was removed and the catalyst was placed in the stove to remove any trace of solvent.

5.10 Synthesis of $MgCl_2$@pDVB

1.5240 g of polydivinylbenzene were swollen in a round flask with 13.11 g of methanol for two hours. 1.1527 g of $MgCl_2$ were dissolved in 5.1477 g of water and 13. 5192 g of methanol, and the resulting solution was transferred into the flask containing the methanol suspension of polydivinylbenzene. The round flask was connected to a rotavapor and left under stirring overnight at 60 rpm and room temperature.

The solvent was removed by evaporation in a rotavapor at 110 mbar and the catalyst was dried in an electric oven at 110°C for 24 hours.

5.11 Preparation of the solution for the ICP analysis

The reaction mixture obtained from the catalytic tests were moved to a round flask treated in order to remove the solvent via evaporation in a rotavapor. 10 mL of hydrochloric acid 37% was added to the organic solution remaining and transferred into a 250 mL volumetric flask. Several rinsings with deionised water were performed in order to remove any metal trace from the round flask, where the reaction mixture was poured. Then, the solution was diluted in the volumetric flask with deionised water to 250 mL.

5.12 Purification of THF from peroxides

A chromatographic column filled with 25 cm of neutral alumina was used to purify THF from peroxides. The solvent was poured into the alumina column, let flow through the column and collected at the end. The solvent was stored in a closed bottle, to minimize the exposure to air. The procedure was repeated twice.

To verify the removal of peroxides, 10 mL of purified THF were treated with 2 mL of a 0.13 g/L Na_2MoO_4 solution and 3 mL of a 10 g/L KI solution. The solution turned yellow in 5 minutes, therefore the quality of the purification was not confirmed. The purification was repeated a third time, then the solution was tested again until the quality of purification was confirmed.

When the Na_2MoO_4 solution was not available, it was replaced with the same amount of acetic acid.

5.13 Preparation of the samples for nitrogen physisorption

The samples reported in Table 24 were tested with nitrogen physisorption.

Ca. 100 mg of sample were loaded into a weighted sampling tube. The tube containing the sample was weighted in order to exactly determine the weight of the sample. The sampling tube was then connected to the vacuum pump, degassed and filled with argon. The procedure was repeated three times per each sample. The samples were heated at 150°C overnight in the pretreatment apparatus. The sampling tube was removed from the vacuum pump, weighted and moved to the Nitrogen Physisorption equipment.

Table 24. Details of sample preparation for nitrogen physisorption analysis.

	m tube (g)	m material (g)	m tube+material (g)	m tube+ material post pretreatment (g)
$ZnCl_2$@pDVB	38.9193	0.12644	39.0305	39.0196
$ZnCl_2$@pDVB no H_2O	38.9815	0.1263	39.0079	38.9994
pDVB	39.0030	0.1182	39.0812	39.0762
$Zn(NO_3)_2$@pDVB	39.4523	0.1276	39.5856	39.5687
$ZnCl_2$@pDVB post reaction	39.2234	0.1263	39.0079	39.2736

5.14. Description of the Reactor for the synthesis of menthol

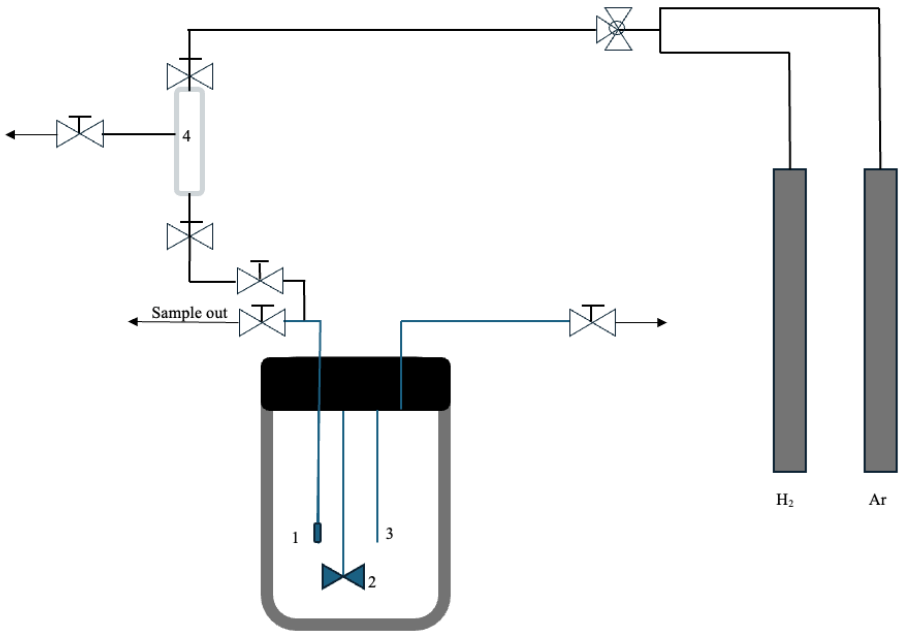

Figure 70. Scheme of the experimental set-up used for the one pot synthesis of menthol.

The batch reactor consists in a stainless steel autoclave and a removable heating jacket. The autoclave blocked to the central body of the reactor with a clamp, closed with screws. Finally, the clamp is blocked with a further clamp, tightened with a single screw.

Inside the reactor there are:

- a sampling line (Figure 70, 1), equipped with a filter, which allows both injection and sampling of the experimental mixture;
- a stirrer (Figure 70, 2) which allows a homogeneous mixing of the solution and a rather homogenous temperature distribution inside the autoclave;
- a thermocouple (Figure 70, 3) for the on-line measurement of the temperature inside the reactor.

These elements are connected to a central controller that measures pressure and temperature and allows to set the rpm inside the reactor. The temperature can also be tracked by a computerized software.

At the beginning of the test, the catalyst and the solvent are transferred inside the autoclave for the *in situ* pretreatment of the catalyst. In order to perform the swelling of the catalyst, half of the solvent needed for the experiment is added to the autoclave, along with the catalyst, before sealing the reactor.

The reactor is filled with argon and the proper conditions of temperature and stirring rate are set. The gases are fed into the reactor from two tanks, which are positioned in suitable lockers and connected via a three-via valve. The three-via valve allows to select the gas to be injected. The flow rate can be controlled by manual valves located before and after the preheating chamber and before the autoclave.

The reactor is equipped with a preheating chamber (Figure 70, 4) that is connected to the autoclave with an injection line. The preheating chamber is needed in order to inject the reactant solution into the autoclave containing the pretreated catalyst. The flow can be redirected outside the preheating chamber thanks to mechanical valve. In this part of the apparatus, the preheating valve can also be opened, allowing the injection of solutions. Around the preheating chamber, a heating jacket is placed to increase the temperature of the solution before the injection into the autoclave. There is no thermocouple inside the preheating chamber, so the temperature measured is related to the heating jacket.

After the injection, the solution is sampled from the sampling line, closed with a mechanical valve. The valve is opened just for the time needed to withdraw the samples. After each sampling, the gas flow is opened in order to restore the pressure inside the reactor. This procedure also allows to empty the sampling line from the residual reaction mixture.

To carefully release the pressure inside the reactor, an outlet line is also present and controlled by a double mechanical valve.

To cool down the autoclave, the reactor is equipped with a cooling line on the main body of the reactor itself. The cooling system is managed with a centralised controller.

5.15 Procedure for the catalytic test

Before each catalytic test, the catalyst was dried overnight at 110°C in an electric oven. 300 mg of catalyst were transferred into the autoclave with 50 mL of cyclohexane. The autoclave is washed three times with 5 bar Argon at room temperature. The autoclave is finally filled with Argon at 5 bar. The stirrer is turned on at 900 rpm and the heating is set up at 70 °C. The temperature is increased until 70°C are reached. The cooling system is also turned on to better control the temperature. When the experimental conditions are reached, specifically 5 bar of Argon, 70°C and 900 rpm, the system is let to equilibrate for two hours before the injection of the solution. In the meantime, a solution of 400 mg of citronellal or isopulegol is prepared in 50 mL of cyclohexane in a volumetric flask. The preheating chamber is isolated closing the valve above and below it and the valve on the side is opened so that the pressure inside the chamber can be decreased and the gas can be fluxed outside. The outgoing gas is let to flow into a 100 mL bottle filled with water and the chamber is open when no bubbling is observed. When the chamber is open, a peristaltic pump is used in order to introduce the reagent solution inside the preheating chamber, carefully controlling the flow rate to avoid the liquid to spill out. When the injection is over, the preheating chamber is closed again and argon is let to flow inside, through the inlet valve above the chamber. The chamber is closed, and oxygen is removed from the chamber by opening the side valve. The procedure is carried out for two minutes. The chamber is sealed and the heater is turned on. Since no thermocouple is present inside the preheating chamber, heating is carried out for 15 minutes in order to reach the thermal equilibrium with the reactor. The valves are opened and the solution is injected inside the autoclave. The experiment conventionally starts in this moment. 8 mL vials are used to collect samples from the sampling line. The vial needs to be weighted before and after the sampling procedure in order precisely determine the weight of the sample. Right after the injection, at time 0', a first sample of waste is removed from the sampling line and then the actual 0' sample is collected.

Samples are always collected at the same reaction times: 0', 15', 30', 60', 120' and 180'.

After the sampling, the injection valve is opened again to restore the pressure inside the reactor and to remove all the solution from inside the sampling line.

At the end of the experiment, after 3 hours, the heater is turned off, the heating jacket surrounding the autoclave is removed, the temperature is set to 20°C and the temperature is decreased by the cooling system. When the room temperature is reached, the gas tank is closed and the gas is expelled through the preheating chamber getaway. The outlet line is opened and the pressure is released also from the reactor. The autoclave is opened, the solution is filtered with a 12-25 μm paper filter using a funnel, into a 100 mL bottle. The catalyst is dried overnight at 110°C in the electric oven, and the solution is stored for further analysis.

Each sample of reaction mixture withdrawn during the test is transferred from the vial into a 1 mL syringe and filtered through a 13 mm, 0.45 μm syringe filter into a GC vial. The reagent solution prepared with 400 mg of citronellal in 50 mL of cyclohexane is also tested before being injected inside the preheating chamber. Since the concentration is 8 mg/mL, the sample is diluted 1:2 in cyclohexane in a GC vial and analyzed.

Table 25. Detailed amount of catalyst employed in the catalytic experiments described.

EXPERIMENT	**Zn(5%) @ HZSM-5**	**$ZnCl_2$@pDVB (Content)**	**Pd(5%) @C**	**Pd(1%) @pDVB**	**Pd(1%)$ZnCl_2$(30%) @pDVB**
Zn(5%)@HZSM-5	0.3025	-	-	-	-
$ZnCl_2$(30%)@pDVB	-	0.3037 (30%)	-	-	-
$ZnCl_2$(10%)@pDVB,	-	0.3124 (10%)	-	-	-
$ZnCl_2$(30%)@pDVB- no H_2O	-	0.301 (30%)	-	-	-
$ZnCl_2$(30%)@pDVB- post pre-treatment	-	0.2962 (30%)	-	-	-
$ZnCl_2$(30%)@pDVB (Hot Filtration Test)	-	0.3012 (30%)	-	-	-
$ZnCl_2$(30%)@pDVB and Pd(5%)@C	-	0.2752 (30%)	0.5737	-	-
$ZnCl_2$(30%)@pDVB and Pd(5%)@C	-	0.29 (30%)	0.0543	-	-
$ZnCl_2$(30%)@pDVB and Pd(5%)@C	-	0.3015 (30%)	0.068	-	-
$ZnCl_2$(30%)@pDVB and Pd@(1%)@pDVB	-	0.2983 (30%)	-	0.2937	-

$ZnCl_2$(30%)Pd(1%)@pDVB-1	-	-	-	-	0.2946
$ZnCl_2$(30%)Pd(1%)@pDVB-2	-	-	-	-	0.2900

5.16 Hot Filtration test

In the hot filtration test, 301.2 mg of catalyst were weighted and swollen in 50 mL of cyclohexane at 70°C, 900 rpm , 5 bar of argon for 2 hours. In the meantime, 401.2 mg of citronellal were mixed in 50 mL of cyclohexane. The solution was injected in the preheating chamber, oxygen was removed flushing Argon for 2 minutes with the outlet valve opened, then the valve was closed, the solution was heated to 70°C and, after two hours from the start of the catalyst pretreatment, the reagent solution was injected with 10 bar of argon. Samples were removed at 0' and 15' from the sampling valve, then the solution was completely removed from the autoclave, filtered in a 12-25 μm paper filter, and injected in the preheating chamber, where the temperature was restored. In the meantime, the autoclave was opened, completely washed with acetone and closed. The operation required 15 minutes, then the solution was injected again, and at 30' the third sample was taken. The sampling procedure continued until the end of the experiment, so at 60', 120', 180'. At the end of the experimental procedure, the reactor was cooled down, the pressure was decreased, and the autoclave was opened. The solution was stored for further analysis and the reactor was cleaned.

5.17 GC calibration and analysis

The liquid samples obtained during the reaction were analysed with a Gas-chromatograph equipped with a FID detector. In order to precisely determine the concentration of the compounds, calibrations were performed before starting the experiments. 4 mg/mL, 2 mg/mL, 1 mg/mL and 0.5 mg/mL standard solutions of the most important compounds, namely citronellal, (-) – isopulegol and menthol, were used for the calibration. The response factors were determined the values of chromatographic areas vs. the concentration of the samples. The response factor was considered to be the same for the diasteroisomers of isopulegol and menthol.

The temperature program used for the analysis starts from 110° C, increases 0.40°C/min until 130°C, then 13 °/min. When 280 °C are reached, the temperature is held for 10'. The column employed is a DB-1 column, 30 m (length) x 250 µm (diameter) x 0.5 µm (internal film thickness).

Some of the samples were also analyzed with a Gas-chromatograph coupled with Mass Spectrometer employing the same column and temperature program.

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