UNIVERSIDADE TÉCNICA DE LISBOA

INSTITUTO SUPERIOR TÉCNICO

Development of more sustainable methodologies in organic synthesis

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Dissertação para obtenção do Grau de Doutor
em Química

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Janeiro 2011

Dedicated to Ariana and Dagmar

Acknowledgements

The work presented describes the beginning of my journey in scientific research. During this last four years I have learn that in professional, as such in our personal life the success only depends on our posture to failure.

I would like to thank all the persons that help me during this hard journey.

I want to thank my parents, my brother and sister and all my family. A special thanks to my mother and sister for the unconditional support during these last years.

I cannot find words to acknowledge the availability, the scientific advices and the commitment of the scientific supervisor of this work. Thereby I thank to Professor Carlos Afonso for the contribution on my scientific growth, but also the contribution for personal development.

To Ph.D. Luis Branco I thank all the support in the beginning of my scientific journey.

To Professor Cristiana Nunes I acknowledge the valuable collaboration, effort and patience.

I thank all my laboratory colleagues for the bad but also the good sheared experiences, I benefit from all: Ph.D. Željko Petrovski, Ph.D.Mariana Beija, Ph.D. Pedro Góis, Ph.D. Nuno Lourenço, Ph.D. João Rosa, Ph.D. Nuno Candeias, Ph.D. Gonçalo Carrera, Ph.D. Prashant Kulkarni, Graduate Joana Ferreira, Graduate Alexandre Trindade, Graduate João Nunes, M.S. Luís Gomes, Graduate Carlos Monteiro, M.S. Paulo Forte, Ph.D. Krassimira Guerra, Ph.D. Luís Frija, Master Catarina Rodrigues, Master Filipe Menezes, M.S. Jaime Coelho, M.S. Carolina Carias, Master Svilen Simeonov and undergraduate student Angelo Rocha. A special thanks to Master Carolina Marques and Ph.D. Raquel Frade for the extra support.

Last, but not least, I thank Fundação para a Ciência e Tecnologia and FEDER the financial support to this Ph.D. program with Ref. SFRH/BD/28242/2006.

Abstract

Ionic Liquids (ILs) are salts (contain only ions) with a low melting point, preferable liquids at room temperature. These types of compounds are used in organic chemistry manly as solvents, and the interest on their applications have been increasing exponentially in the last decade. In this work several ILs were synthesized and characterized. Different types of ILs were synthesized, such as Chiral Ionic Liquids (CILs) and Magnetic Ionic Liquids (MILs).

Some synthesized ILs were selected and an extensive study on the solubility of carbohydrates was performed. These ILs were based on the combination of tetraalkylammonium, tetraalkylphosphonium, 1-methyl-3-alkylimidazolium and dimethyl-tetraalkylguanidinium cations containing alkyl and ether pendant substituent groups, and anions consisted of chloride, dicyanamide, saccharine, acesulfame, acetate or thiocyanate. It was possible to achieve high solubilities values for different carbohydrates. It was also explored the possibility to extract carbohydrates from an aqueous phase using hydrophobic ILs. It was demonstrated that ILs are very efficient in the extraction, and also was observed some selectivity when a mixture of two carbohydrates were extracted, depending on the IL used.

Another approach to develop more sustainable methodologies in organic synthesis was explored by studding the olefin dihydroxylation in water. It was developed a simple, robust mild organocatalyzed and metal free dihydroxylation method. Several substrates were tested, and was demonstrated that this method is compatible a considerable range of organic functional groups.

Keywords: Ionic Liquids; carbohydrates; solubility; water; olefins; dihydroxylation.

Resumo

Líquidos Iónicos (LIs) são sais com um ponto de fusão baixo, preferencialmente líquidos à temperatura ambiente. Em química orgânica este tipo de compostos são usados maioritariamente como solventes, e o interesse na sua síntese, tal como na sua aplicação tem crescido exponencialmente na última década. Neste trabalho foram sintetizados vários LIs, incluindo LIs quirais e magnéticos.

Uma das aplicações dos LIs é a sua utilização na química dos açúcares. Neste trabalho foi feito um extenso estudo de solubilidade de vários açúcares em diferentes LIs. Estes LIs baseiam-se em diferentes catiões contendo substituintes alquilicos, ou com grupos éter presentes, em combinação com aniões orgânicos ou inorgânicos. Foi também explorada a possibilidade de extracção dos açúcares de um meio aquoso para vários LIs hidrofóbicos. Foi demonstrado neste estudo que os LIs são bastante eficientes nesta extracção, mas também pode haver uma selectividade na extracção de uma mistura de açúcares, dependendo do LI usado.

Tendo como objectivo o desenvolvimento de metodologias mais sustentáveis foi desenvolvido um método de dihidroxilação de olefinas em água. Para além deste método ser simples e robusto, não envolve metais. A estabilidade de diferentes grupos funcionais foi testada, e mostrou-se que este método é compatível com vários grupos funcionais.

Palavras-chave: Líquidos Iónicos; açucares; solubilidade; água; olefinas; dihidroxilação.

Abbreviations

AcOEt	Ethyl Acetate
AMPSO	N-(1,1-Dimethyl-2-hydroxyethyl)-3-amino-2-hydroxypropanesulfonic acid
ASBI	3-Allyl-1-(4-sulfobutyl) imidazolium
ASCBI	3-Allyl-1-(4-sulfurylchloridebutyl)imidazolium
BDMIM	1-Butyl-2,3-dimethylimidazolium
BF_4	Tetrafluoroborate
BMIM	1-Butyl-3-methyl imidazolium
BMPy	*N*-Butyl-*N*-methylpyridinium
BMPyr	1-*n*-Butyl-1-methyl Pyrrolidinium
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
C_{10}MIM	1-Decyl-3-Methyl-Imidazolium
C_{12}TMG	*N,N,N'N'*-Tetramethyl-*N,N*-didodecylguanidinium
$(C_3O)_4$DMG	*N,N,N',N'*-Tetra-(2-methoxyethyl)-*N,N*-dimethylguanidinium
C_6MPyr	1-*n*-Hexyl-1-methyl Pyrrolidinium
C_8MIM	1-Octyl-3-Methyl-Imidazolium
CAPSO	3-(Cyclohexyl amine) -2-hydroxy-1-propane-sulfonic acid
CIL	Chiral Ionic Liquids
DBSA	4-Dodecilbenzenesulfonic acid
DCM	Dichloromethane
(di-*h*)$_2$DMG	*N,N,N'N'*-Tetrahexyl-*N,N*-dimethylguanidinium
1,3-DMIM	1,3-Dimethylimidazolium
DMC	Dimethylcarbonate
DMF	N,N-Dimethyl Formamide
DMSO	Dimethyl Sulfoxide
E_a	Activation Energy
ee	Enantiomeric excess
EHS	Environmental, Health and Safety
EMIM	1-Ethyl-3-methyl imidazolium
GC	Gas chromatography
HMF	5-Hydroxymethylfurfural
HPLC	High Performance liquid chromatography

IL	Ionic Liquid
IS	Internal Standard
LCA	Life-cycle assessment
MIBK	Methyl isobutyl ketone
MIL	Magnetic Ionic Liquids
MOEOEMIM	1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium
MOPS	3-Morpholinopropane-1-sulfonic acid
mp	Melting point
MS	Mass spectroscopy
NDSA	Naphthalene-2,7-disulfonic acid
NIS	*N*-iodosuccinimide(NIS)
NMR	Nuclear Magnetic Resonance
nr	No reaction
NSA	Naphthalene-2-sulfonic acid
NTSA	Naftaleno-1,3,7-trisulfonic acid
$P_{6,6,6,14}$	Trihexyl(tetradecyl)phosphonium acetate
PESA	Pyridine-4-ethanesulfonic acid
PET	Poly(ethylene terephthalate)
ppm	parts per million
PSA	Pyridine-3-sulfonic acid
***p*-Ts**	*para*-Toluenesulfonyl
PTSA	*para*-Toluenesulfonic acid
Py	Pyridine
R	Universal Gas Constant (8,314)
R-CSA	(1R)-(+)-Camphor-10-sulfonic acid
rt	room temperature
S-CSA	(1S)-(+)-Camphor-10-sulfonic acid
T	Temperature (K)
TBDMS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
T_{dec}	Decomposition Temperature
TEA	Triethyl amine
T_g	Glass Temperature
TLC	Thin Layer Chromatography

TMSOTf	Trimethylsilyl triflate
VOC	Volatile Organic Compounds
η	Viscosity (Pa.s),
η_∞	Viscosity at infinite temperature

Index

1 Ionic Liquids Synthesis

In this chapter ILs synthesis, purification and characterization are discussed.

1.1 Introduction

1.1.1 Overview

Ionic Liquids (ILs) are a class of compounds with application in different scientific areas. Over 2000 new publications are reported producing a wide range of properties in an even wider range of salt structures. Therefore the synthetic methods applied to the preparation of ILs have become more sophisticated and capable of targeting more complex compounds. The goal in this chapter is to provide a comprehensive overview of the synthetic approaches currently available for different ILs, with special focus on guanidinium based ILs, Chiral Ionic Liquids (CILs) and Magnetic Ionic Liquids (MILs) that were the main ILs synthesized in this work.

1.1.2 Ionic liquids

Ionic Liquids (ILs) are liquids that consist exclusively or almost exclusively of ions, and have a melting point below the boiling point of water. In most cases possess a low viscosity and can be easily handled. The term ILs distinguish this type of compounds from the classic definition of molten salts, which have a very high melting point, high viscosity and are extremely corrosive compounds.[1] In the earlier days of ILs research, was tended to presume that ILs had very similar properties as a class, the ILs definition included being non-volatile, non-flammable, intrinsically "green", highly electrochemical stable, highly thermally stable, and comprising simple ionic species.[2] But it is now widely recognized that, in fact, they offer a very wide range of properties and one of the only properties that can be thought of as ubiquitous among ILs is ion conductivity.[3]

ILs are typically salts with nitrogen-, sulphur- or phosphorous-containing organic cations with alkyl chains (Figure 1.1.1), in combination with organic or inorganic anions (Figure 1.1.2).

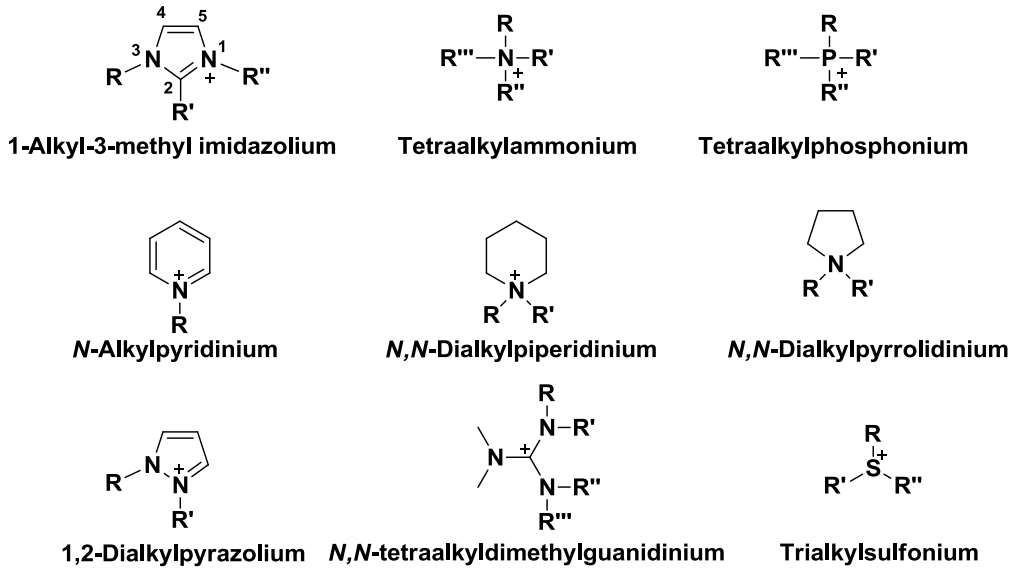


Figure 1.1.1 – Examples of some ILs organic cations.

Inorganic anions

- Halides **[X]**
- Hexafluorophosphate **[PF_6]**
- Tetrafluoroborate **[BF_4]**
- Chloroaluminates **[$AlCl_4$], [Al_2Cl_7]**
- Nitrate **[NO_3]**
- Metal complexes

Organic anions

- Alkyl sulphates **[RSO_4]**
- Alkylcarboxylates **[RCO_2]**
- *p*-Toluenesulfonate **[$CH_3C_6H_4SO_3$],** also known as tosylate **[OTs]**
- Trifluoromethylsulfonate **[CF_3SO_3]** also known as triflate **[OTf]**
- Bis(trifluoromethylsulfonyl)amide **[$N(SO_2CF_3)_2$]** also known as bistriflimide **[NTf_2]**
- Dicyanamide **[$N(CN)_2$],** or **[DCA]**

Figure 1.1.2 – Some examples of ILs anions.

Different ILs notations or abbreviations have been employed in the literature. For example 1-ethyl-3-methylimidazolium cation is commonly denoted as [C2C1IM], [EMI], [EMIM], [emim] or [EtMeIm]. In this work 1-alkyl-3-methylimidazolium cations are denoted as [C_nMIM], where the *n* is the number of carbon atoms in the linear alkyl chain. Two exceptions, for 1-butyl-3-methylimidazolium cation that is denoted as [BMIM] and for 1-ethyl-3-methylimidazolium cation that is denoted as [EMIM]. Similarly [C_nPyr] is used for 1-alkyl-pyrrolidinium cations, and [C_nPy] is used for 1-alkyl-pyridinium cations. For tetraalkylammonium or tetraalkylphosphonium cations the C denoting the carbon atom is often dropped, for example [$P_{4,4,4,14}$] denotes tributyl(tetradecyl)phosphonium cation.

1.1.3 Green chemistry

The twenty century chemistry has changed the way of living in many areas, for example the development of pharmaceutical industry, transportation, clothing, etc, have improved the life quality of public in general. But still chemical industry is often viewed, by the general public, as causing more harm than good. A major reason is that the industry is perceived as being polluting and causing significant environmental damage. During the history several industrial accidents have emphasize this idea of chemical industry. The challenge for the chemical industry in the twenty first century is to continue to provide the benefits in an economically viable manner, but without the adverse environmental side effects.[4] During the early 1990s the US Environmental Protection Agency (EPA) coined the phrase Green Chemistry[4] "To promote innovative chemical technologies that reduce or eliminate the use or generation of hazardous substances in the design, manufacture and use of chemical products." Since then, Green Chemistry has been recognized as a methodology to achieve sustainability. In 1998 Paul Anastas described twelve principles, that can be summarize[5]:

1. Prevention

It is better to prevent waste than to treat or clean up waste after it has been created.

2. Atom Economy

Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. Less Hazardous Chemical Syntheses

Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. Designing Safer Chemicals

Chemical products should be designed to effect their desired function while minimizing their toxicity.

5. Safer Solvents and Auxiliaries

The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6. Design for Energy Efficiency

Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. Reduce Derivatives

Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. **Catalysis**
   Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. **Design for Degradation**
    Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. **Real-time analysis for Pollution Prevention**
    Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. **Inherently Safer Chemistry for Accident Prevention**
    Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Unfortunately, these 12 principles do not explicitly include a number of important concepts highly relevant to environmental impact, for example the inherency of a product or process, the need for life cycle assessment, or the possibility of heat recovery from an exothermic reaction. For this reason, Anastas and Zimmerman subsequently proposed a set of 12 Principles of Green Engineering[6] that concerns engineering quality and safety specifications, but also considers environmental, economic, and social factors. Latter on Poliakoff *et al.* suggest a condensed 24 Principles of Green Chemistry and Green Engineering, with the mnemonic "IMPROVEMENTS PRODUCTIVELY"[7] (Figure 1.1.3).

Principles of Green Chemistry	**Principles of Green Engineering**
P-Prevent wastes	**I-**Inherently non-hazardous and safe
R-Renewable materials	**M-**Minimize material diversity
O-Omit derivatization steps	**P-**Prevention instead of treatment
D-Degradable chemical products	**R-**Renewable material and energy inputs
U-Use safe synthetic methods	**O-**Output-led design
C-Catalytic reagents	**V-**Very simple
T-Temperature, Pressure ambient	**E-**Efficient use of mass, energy, space and time
I-In-Process Monitoring	**M-**Meet the need
V-Very few auxiliary substances	**E-**Easy to separate by design
E-E-factor maximize feed in product	**N-**Networks for exchange of local mass and energy
L-Low toxicity of chemical products	**T-**Test the life cycle of the design
Y-Yes it's safe	**S-**Sustainability through product life cycle

Figure 1.1.3 – 24 Principles of Green Chemistry and Green Engineering, with the mnemonic "IMPROVEMENTS PRODUCTIVELY"[7]

Organic solvents are widely used in a variety of unit operations including extraction, recrystallization and dissolution of solids for ease of handling. The key role that solvents play in the chemical industry is that of reactant solvent allowing the homogenization of a reactant

mixture, speeding up reactions through improved mixing, and in addition reducing energy consumption.[4] Many industrial processes use volatile organic compounds (VOCs) as solvents because of their ease of removal by evaporation, although these volatile compounds can be released from many sources in the chemical process resulting in VOC emissions to the atmosphere. The total elimination of volatile organic solvents from all chemical processes is a worthy goal, but the pursuit of this goal must be subject to some caution. Alternative organic solvent-free processes may have poor heat and/or mass transfer and/or viscosity limitations, which could result in excessive energy use or the production of less pure products, needing large amounts of organic solvents in subsequent purification steps.[8] The solvent choice has to be wisely, and depends on many factors, such as ease of recycle, ability to handle, low flash point materials, price and performance. Over the last years chemistry research into the use of greener and alternative solvents has grown enormously.

To consider a solvent as "green" several factors have to be consider and is not ease to compare among different solvents. Therefore in the last years have been developed a few methods to quantify or qualify the "greenness" properties of a solvent. For example, Fischer and co-workers have developed a chemical assessment method based on EHS (environmental, health and safety) criteria[9] that aims to identify potential hazards of chemicals. Another method, the life-cycle assessment (LCA) method, evaluates the environmental burdens of a product, process, or activity, quantify resource use and emissions, and assess the environmental and human health impact.[9] Unfortunately, assessment tools used in this study could not yet be applied to alternative solvent technologies such as supercritical fluids or ILs due to the lack of data regarding to industrial production, recycling, and disposal processes as well as EHS characteristics. [9-10]

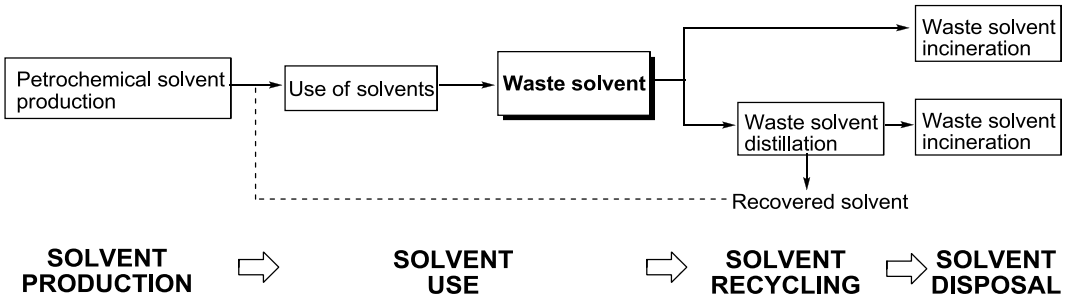


Figure 1.1.4 – System model of the solvent assessment using the life-cycle assessment method[9].

ILs have been considered as green solvents. The reason behind that consideration is that ILs have negligible vapour pressures and do not emit volatile organic compounds. However it is noteworthy that greenness for a specific process is a relative concept and application of ILs provides a potential alternative for green process, but greenness for a specific process depends

on its environmental impact, and use of ILs cannot guarantee a green process.[11] Synthesis of ILs, like preparation of other chemicals can cause severe environmental impact,[12] due to use of several organic solvents, energy consuming processes and so on. It is essential to reduce or eliminate the use and generation of hazardous substances for preparation of ILs by simplifying their synthesis procedures, using renewable raw materials and improving their atom efficiency. Green synthesis of ILs is as important as the improvement of their properties.[9, 11]

Recent research on the toxicology and degradability of ILs[13] show that not all ILs are eco-friendly as expected. Although ILs can reduce air pollution, it is possible to cause water and soil pollution, by accidental spills or effluents. Therefore, the greenness of ILs should be assessed for their specific applications on entire basis including their synthesis and recovery using for example, the life-cycle assessment method (quantification of emissions and resource use over the whole life-cycle of a solvent).[9]

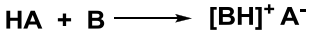
1.1.3.1 Ionic Liquids History

Probably the first description of a IL was made in 1914, by Walden *et al.*,[14] where the preparation of ethylammonium nitrate (melting point of 12 °C) was describe. Progress was subsequently low, being the next significant step made in 1951 by Hurley and Wier.[15] They have prepared several quaternary ammonium salts, reporting them as electrolytes for the electro deposition of aluminium. In 1967, Swain *et al* [16]described the use of tetrahexylammonium benzoate as a solvent for electrochemistry and kinetic investigations. It was only in 1975 that these type of compounds were rediscovered by Osterryoung and Wilkes[17] and again applied in electrochemistry. In 1981 Knifton[18] reported the use of phosphonium or ammonium bromide to synthesize ethylene glycol from synthesis gas. A year later Wilkes *et al.*[19] reported dialkylimidazolium chloroaluminate melts as a new class of room-temperature ILs for electrochemistry, spectroscopy, and synthesis. Since then the research publications increased exponentially. This growing interest in ILs is due to some of their properties: liquid over a broad temperature range, non-flammable, non-explosive, non-coordinating, not very corrosive, low vapour pressure, miscibility or non-miscibility with water and other solvents, dissolving ability, polarity, viscosity, density, electric conductivity, high electrochemical stability, that can be tuned by an appropriate choice of the anion and the cation.[20] Although, it should be mentioned that these properties are not intrinsically of all known ILs, it is just to give an idea of the possible advantages of this type of compounds. In addition to some advantages offered by their physical properties, when used as solvents ILs usually can afford higher reaction rates, yields and better selectivity when compared to some conventional organic solvents.[21] But, as previous point out,

ILs can be quite toxic solvents[22], and their applications on green chemistry context have to be used with quite precaution.

1.1.3.2 Synthetic Methodologies

Since early 2000s the number of known ILs has increased exponentially. Is relatively easy to discover a new IL, but to determine its usefulness as a solvent, or in some other application, requires a much more substantial investment in determination of physical and chemical properties. The simplest method for the formation of ILs is the protonation of suitable starting material. For example the synthesis of protic ILs can be achieved by the proton transfer from a Brønsted acid to a base that can accept a proton, this is a Brønsted base (Scheme 1.1.1).[23]



Scheme 1.1.1 – Formation of a protic IL.

Unfortunately this type of ILs has limited applications, due to the possibility of decomposition through deprotonation, so more complex methods are generally required.[21] The synthesis of ILs can generally be divided into two sections: the formation of the desired cation and the anion exchange (Figure 1.1.5).

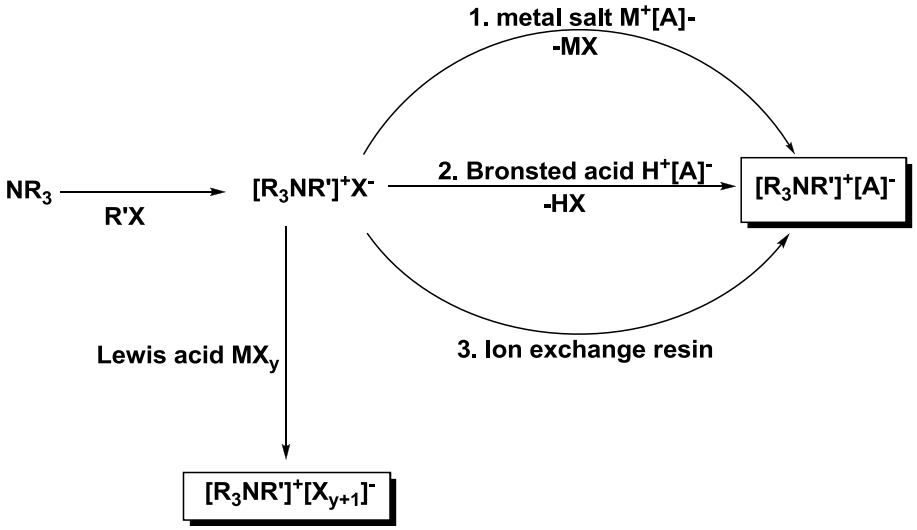


Figure 1.1.5 – Different synthesis paths for the preparations of ILs.[21]

1.1.3.2.1 Cation Synthesis

Quaternization

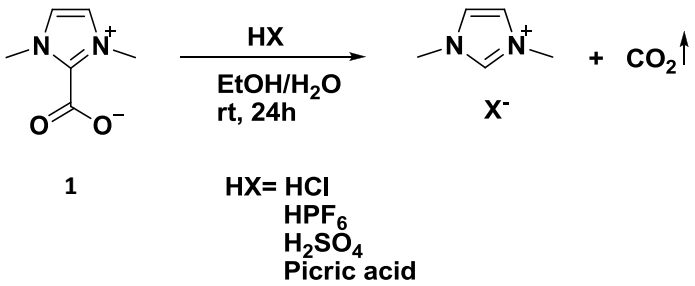
The cation formation can be achieved by protonation with a free acid, as mentioned before, or by quaternization of an amine or a phosphine, most commonly with a haloalkane (Figure 1.1.5). The alkylation process has some advantages, since a wide range of cheap haloalkanes are available, and the substitution reactions generally occur smoothly at reasonable temperatures.[21]

The reaction may be carried out with chloroalkanes, bromoalkanes, or iodoalkanes, with the reaction conditions required becoming steadily more gentle in the order Cl → Br → I, as expected for nucleophilic substitution reactions. Fluoride salts cannot be formed in this manner. [21] Another advantage of the alkylation process is that usually the halide salts are denser than the solvents, so removal of excess solvent and starting material can be achieved simply by decantation. Furthermore, the halide salts formed can easily be converted into salts with other anions, by a metathesis reaction (please see section 1.1.3.2.2, page 17). Unfortunately the production of high purity materials by this method can be problematic due to contamination by residual halide, when the anion exchange is accomplished. The presence of halides in the resulting ILs can drastically change the physical properties,[24] and may result in catalyst poisoning and deactivation.[25] Therefore, various synthetic strategies have been devised to synthesize halide free ILs.

Halide free synthesis

MacFarlane *et al.*[3] divided the direct syntheses of halide free ILs into three groups: a) synthesis via *N*-heterocyclic carbene intermediates, b) phosphorus based direct reactions with imidazoles and c) sulfur-based direct reactions with imidazoles.

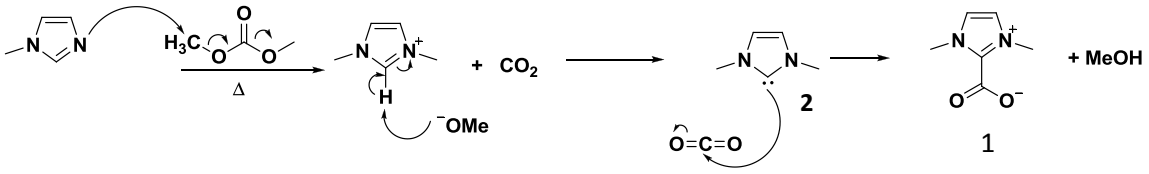
Rogers *et al*. [26] has recently reported the formation of ILs *via* reaction of the zwitterionic 1,3-dimethylimidazolium-2-carboxylate **1** (Scheme 1.1.2) with protic acids.[26] In an ethanolic solution compound **1** was treated with various acids (HPF_6, H_2SO_4, HCl, HNO_3, picric acid), leading to decarboxylation and formation of the 1,3-dimethylimidazolium salt and evolution of gaseous CO_2.



Scheme 1.1.2– 1,3-dialkyllimidazolium-2-carboxylate

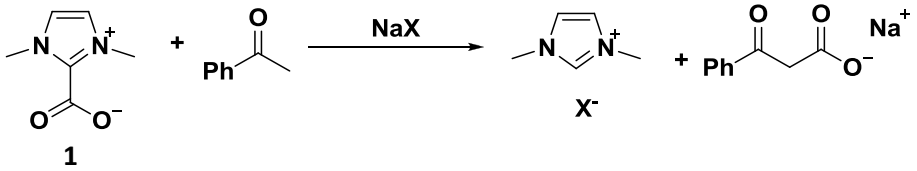
The synthesis of the zwitterionic 1,3-dimethylimidazolium-2-carboxylate **1** is achieved by reaction of dimethyl carbonate (DMC) with *N*-methylimidazole at high temperatures. The proposed mechanism is presented on Scheme 1.1.3 in which the acidic C2-hydrogen of the resulting 1,3-dimethylimidazolium cation is abstracted by the formed anion, leading to the

heterocarbene **2**, MeOH and CO_2.[27] Nucleophilic attack on CO_2 by the carbene leads to the observed zwitterion.



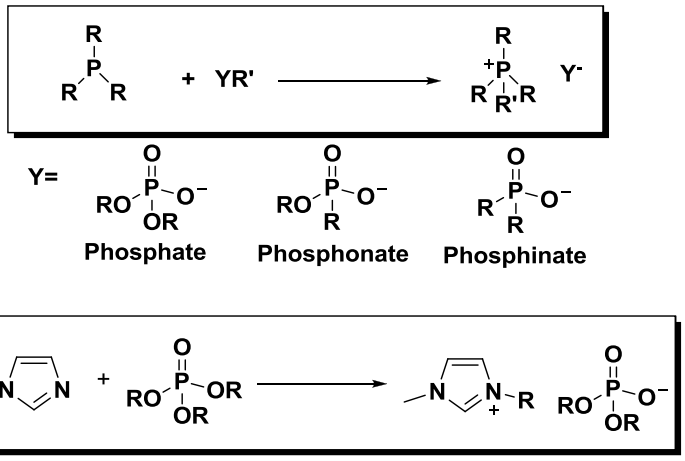
Scheme 1.1.3 – Proposed mechanism for the formation of the zwitterionic 1,3-dimethylimidazolium-2-carboxylate

Tommasi and Sorrentino[28] have also reported the halogen free synthesis of ILs using the zwitterionic 1,3-dimethylimidazolium-2-carboxylate **1**. Despite the thermal stability of this compounds towards decarboxylation in solution, the authors claimed that these compound readily react with dry methanol, benzoylacetone and benzaldehyde in the presence of a stoichiometric amount of $NaBF_4$, KPF_6 or $NaBPh_4$ quantitatively affording the corresponding 1,3-dialkylamidazolium salt (Scheme 1.1.4).[28]



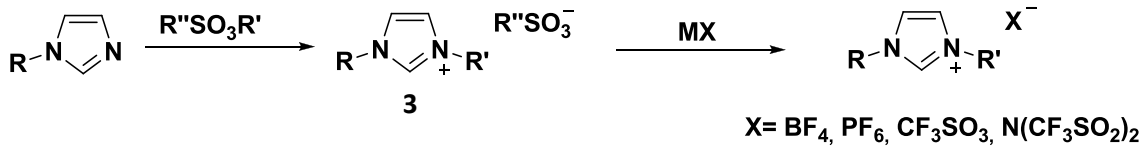
Scheme 1.1.4 – Halogen free synthesis of ILs using the zwitterionic 1,3-dimethylimidazolium-2-carboxylate.

Halogen-free phosphorus based ILs can be synthesized by direct reaction of tertiary phosphines or imidazoles with alkylating agents such as trialkylphosphates, dialkylphosphonates or monoalkylphosphinates (Scheme 1.1.5).[29]



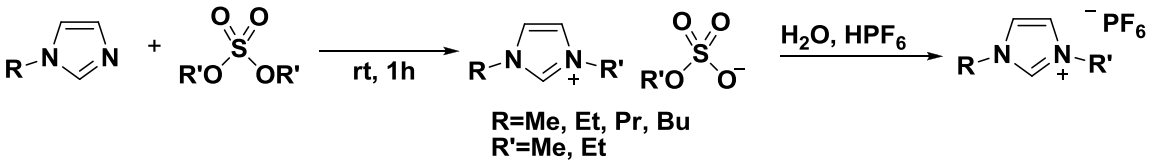
Scheme 1.1.5 – Halogen free synthesis of ILs based on phosphates, phosphonates or phosphinates.

A different approach to synthesize halide free ILs is by the direct addition of an alkylsulphonate into imidazoles. Dialkylimidazolium alkanesulphonate salts **3** can be precursors for different ILs, by anion metathesis. Dupont *et al.*[30]described the alkylation of *N*-alkylimidazoles with alkylsulphonate, performed under solventless conditions at room temperature affording, after 48–72h, the corresponding 1,3-dialkylimidazolium alkanesulphonate salt as crystalline solids in almost quantitative yields (Scheme 1.1.6).[30]



Scheme 1.1.6 – Synthesis of halogen free ILs by direct addition of alkylsulphonate into imidazoles.

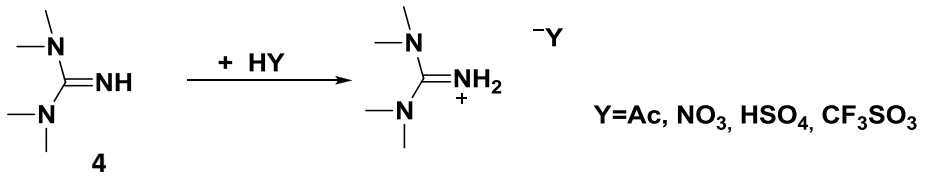
The hydrophilic IL [EMIM][$EtSO_4$] has received great attention, becoming one of the first ILs commercially available in bulk.[3] ILs containing methyl- and ethyl-sulphate anions can be easily and efficiently prepared under ambient conditions by the reaction of 1-alkylimidazoles with dimethylsulphate and diethylsulphate without the use of any solvent.[31] This synthesis is atom efficient and produces no waste. The resulting ILs can be used for subsequent metathesis, for example in the synthesis of [BMIM][PF_6] (Scheme 1.1.7).[31]



Scheme 1.1.7 – Halogen free synthesis of ILs containing methyl- and ethyl-sulphate anions, and for subsequent metathesis.

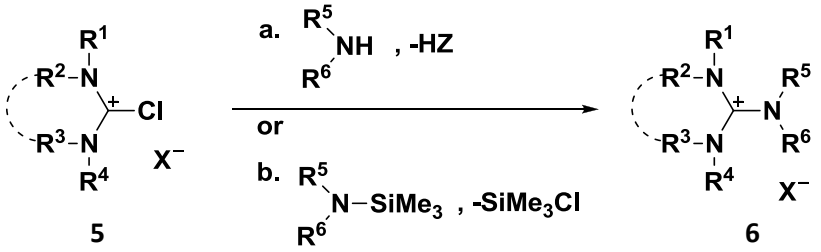
<u>Guanidinium based ILs</u>

Synthetic methods for ILs based on imidazolium, phosphonium or ammonium ILs are the most report on the literature. But recently, increasing interest in guanidinium-based ILs can be noticed, some of which are already commercially available.[32] Protic ILs based on the *N,N,N',N'*-tetramethylguanidine **4** (TMG) are synthesized through simple neutralizing of equimolar TMG with acids (Scheme 1.1.8).[33] Protic ILs based on guanidinium cations have been found to be useful in preparing an immobilized catalyst for hydrogenation of olefins[34], absorbing SO_2 from simulated flue gases[35], homogeneous and recoverable acidic catalysts for Henry reaction[36], one-pot synthesis of pyran[37], synthesis of 3,4-dihydropyridin-2-(1*H*)-ones[38], direct aldol reaction[39], *N*-formylation of amines[40], and catalyst for Boc protection of amines.[41]



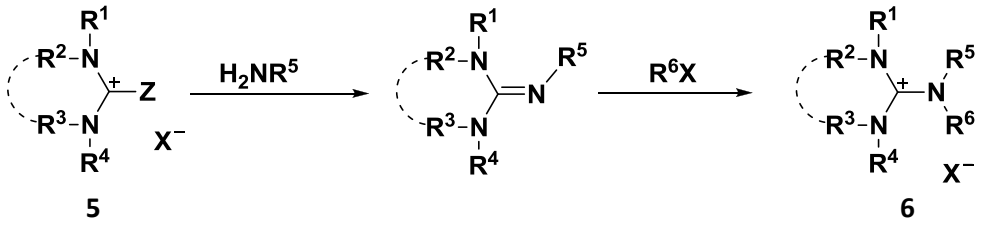
Scheme 1.1.8 – Synthesis of protic ILs based on guanidinium cation.

Hexaalkylguanidinium **6** salts possess better chemical stability than some of the other common classes of ILs due to the effective dissipation of the positive charge in the cation.[42] Different approaches to hexaalkylguanidinium salts **6** are reported on the literature. Probably the shortest pathway consists of the reaction of chloroformamidinium salts **5**, obtained by the chlorination of tetraalkylureas[43], with a *sec*-amine[44] or a dialkyl(trimethylsilyl)amine (Scheme 1.1.9).[45]



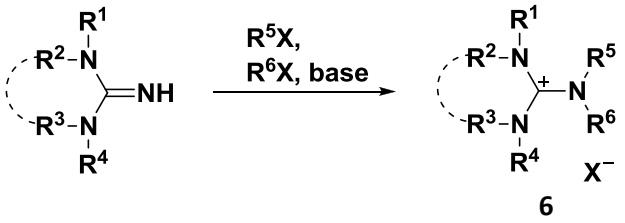
Scheme 1.1.9 – Direct formation of hexaalkylguanidinium salts from chloroformamidinium salts.

Instead of the direct reaction between chloroformamidinium salts **5** and *sec*-amines, a two-step procedure is often chosen, since allows a wider variation of alkyl substituents R^5 and R^6. Therefore, chloroformamidinium salt **5** is first combined with a primary amine to yield a pentaalkylguanidine (Scheme 1.1.10) which can be alkylated with a wide range of alkyl halides.[44a, 46]



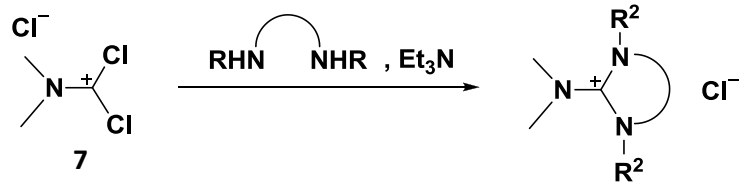
Scheme 1.1.10 – Two-step procedure for the synthesis of hexaalkylguanidinium salts

Alkylation of tetraalkylguanidines with haloalkanes is also used for the synthesis of hexaalkylguanidinium salts **6** (Scheme 1.1.11). This method has been known since 1979 where Santoro[47] have direct alkylated *N,N,N',N'*- tetramethylguanidine with different alkyl chloride. Recently several authors have used this method for the synthesis of several ILs based on guanidinium cation.[35b, 48]

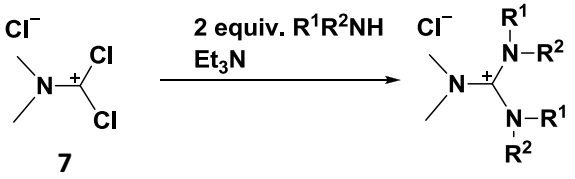


Scheme 1.1.11 – Synthesis of hexaalkylguanidinium salts by alkylation with haloalkanes.

Hexaalkylguanidinium salts **6** can also be obtained from *N*,*N*-dialkylphosgeniminium salts **7**, either by reaction with a bis(*sec*-amine)[49] (Scheme 1.1.12), or with 2 equiv. of a *sec*-amine[50] (Scheme 1.1.13).



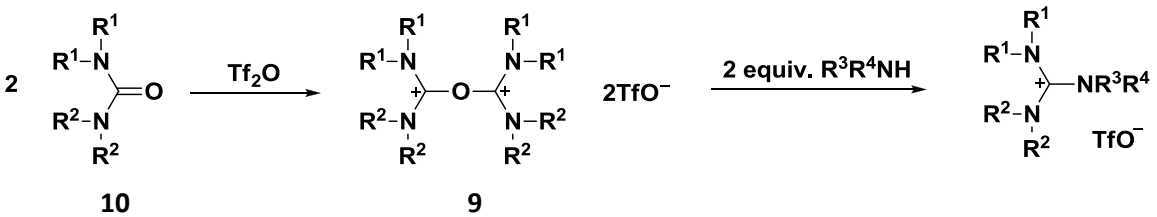
Scheme 1.1.12 – Synthesis of hexaalkylguanidinium salts starting from *N*,*N*-dialkylphosgeniminium salts.



Scheme 1.1.13 – Synthesis of hexaalkylguanidinium salts starting from *N*,*N*-dialkylphosgeniminium salts.

This last method (Scheme 1.1.13) has been developed in our laboratory [51] and several guanidinium based ILs were synthesized and characterized. Despite the high number of carbon atoms present hexaalkylguanidinium salts have a low tendency to crystallize even in the presence of anions which persistently become solid when combined with different cations.[50]

A general synthesis of hexaalkylguanidinium salts **6**, where no halide precursor is used, was described by Kunkel and Maas.[42] The starting material is tetraalkylurea **10** that react with triflic anhydride to give dication ether bis(triflate) **9** which can be cleaved with *sec*-amines (Scheme 1.1.14).



Scheme 1.1.14 – Synthesis of hexaalkylguanidium salts by starting from tetraalkylurea **10**.

Several applications for the hexaalkylguanidinium based ILs have been recently reported, for example as reaction media for oxidation of benzylic alcohols [46b], nucleophilic substitution reactions[52], CO_2 fixation[53], as stationary phases for capillary gas chromatography[54], as electrolytes in dye-sensitized solar cells[44b] and also as electrolytes for lithium battery.[55] Our laboratory has reported this type of ILs as solvents for Sharpless dihydroxylation.[56] The substitution of the *tert*-butanol/water solvent system by ILs generally resulted in better yields and enantioselectivities. Furthermore as a result of high affinity of the catalytic system for the IL phase, the presence of IL in the reaction mixture allows a simple, robust, efficient, and unique system for the reuse of the catalyst where remarkably low contamination of the product by osmium occurred.[56a] This reaction system in combination with the use of supercritical CO_2 in the separation process allowed a very simple, efficient, clean and robust system which does not need the use of organic solvents either for the reaction or for the separation of products and allows the isolation of the diol, in high yield and enantiomeric excess.[56b] This reaction was also performed using Chiral Ionic Liquids (CILs) as solvents, replacing the Sharpless chiral ligand, resulting in high yield and enantioselectivity (this reaction will be further discussed in section 1.1.4, page 26).[57] Another application of guanidinium based ILs developed in our laboratory was the absorption of dioxin compounds. The ILs used were stable at high-temperature and was possible to develop a selective and versatile separation process able to quantitatively capture dioxins from gaseous streams.[58] It was also possible to capture several others organic compounds from the vapour phase, such as 1,4-benzodioxane, biphenyl, xanthene, and menthol, using ILs developed in our laboratory.[59]

Task specific ILs

ILs with functionalized cation and/or anion have a wide range of potential applications.[60] Functionalized ILs or task-specific ILs as they are also known, are potentially useful as reaction media for chemical synthesis, as catalysts, lubrificants, etc (Figure 1.1.6) .[60c]

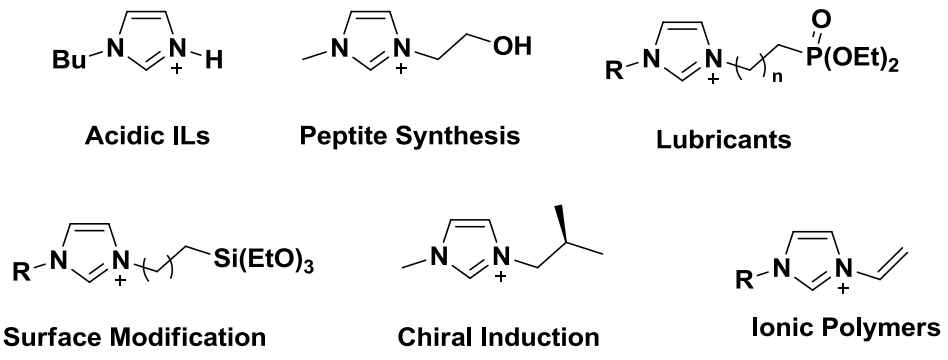
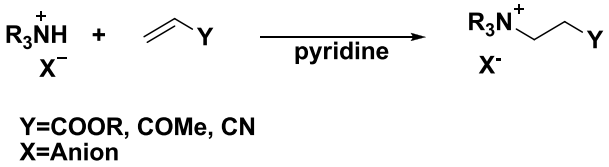


Figure 1.1.6 – Example for functionalised imidazolium cations and their potential applications [60c]

Various synthetic routes have been reported for the preparation of task-specific ILs. Cation functionalized ILs are generally prepared by quaternization of 1-alkylimidazole with a functionalized alkyl halide affording the desired functionalized imidazolium halide in usually good yield. Subsequent metathesis of the functionalized imidazolium halides with salts, such as $Na[BF_4]$ or $Li[Tf_2N]$, affords, in many cases, low-melting salts that can be classed as ILs. Halide free task-specific ILs are also reported in the literature, for example the synthesis of functionalized ILs by the protonation of a tertiary amine or phosphine, followed by a Michael-type addition to an α,β-unsaturated (Scheme 1.1.15).[61]



Scheme 1.1.15 – Synthesis of functionalized ILs.

Much less effort has been devoted to the synthesis of task-specific anions, although a selection is provided in Figure 1.1.7. Most examples are based on readily available materials, such as metal–carbonyl anions or amino acids.

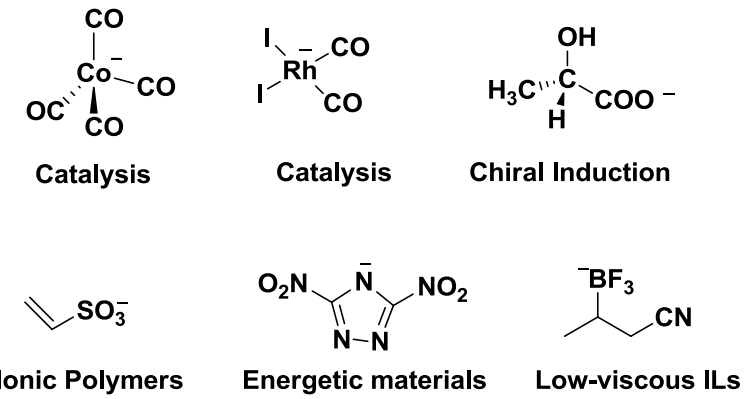


Figure 1.1.7 – Example for functionalised imidazolium anions and their potential applications [60c]

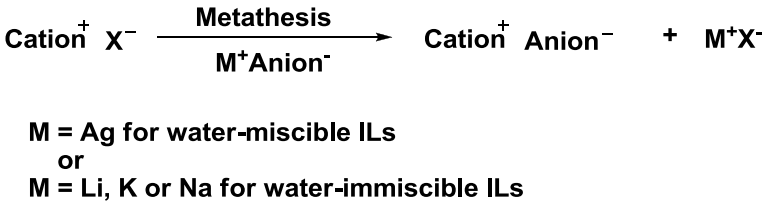
ILs with anions containing metal complexes are also called task specific ILs.[62] These novel functional ILs are regarded as promising new materials which can favourably combine the advantages of ILs with catalytic, [63] spectroscopic,[64] or magnetic[65] properties originated from the incorporated metal ion. Transition metal based ILs have been synthesized either by reaction of phosphonium or imidazolium halides with the corresponding metal halides, or by metathesis with alkali salts of the metal-based anions. For example Co and Ni based ILs[66] can be synthesized directly by mixing the corresponding metal chloride with [EMIM][Cl] under an inert atmosphere. Recently were reported magnetic ionic liquids (MILs), that are paramagnetic ILs, based on anions

comprising transition-metal coordination complexes,[65, 67] such as iron, cobalt, manganese or gadolinium.[68] MILs will be discuss in section 1.1.5 (please see page 41).

Chiral Ionic Liquids (CILs) are ILs with chirality on the anion and/or cation, although the major examples in the literature are based on chiral cations. This topic will be discuss in section 1.1.4, page 26.

1.1.3.2.2 Anion Synthesis

Once the desired cation is synthesized, several other ILs can be produced just by exchange the anion of the salt. The metathesis reaction can be divided into two categories: metathesis via a) free acids or group 1 metal salts (Li^+, K^+ or Na^+), or b) Ag salt metathesis (Scheme 1.1.16).[3] The water solubility of the ILs is very dependent on both the anion and cation present, and in general will decrease with increasing organic character of the cation. The most common approach for the preparation of water immiscible ILs is the metathesis reaction of the corresponding halide salt, either with the free acid of the anion, or its metal (Na, Li, or K) or ammonium salt. Firstly is prepared an aqueous solution of a halide salt of the desired cation.[21] The cation exchange is then carried out either with the free acid of the appropriate anion, or else with a metal or ammonium salt. These alternatives may be the favoured approach as the hydrogen, or the metal halide produced can easily be removed by washing with water.



Scheme 1.1.16 – Common approach for the synthesis of ILs by anion metathesis.

Alternatively, the metathesis reaction can be carried out completely in an organic solvent such as DCM or acetone. In both solvents the starting materials are not completely soluble; however the reaction can be carried out as a suspension. For example, in case of DCM, the metathesis reaction of 1-alkyl-3-methylimidazole with metal salt can be carried out at room temperature for about 24 h and then the suspension filtered. However, the halide by-products have a limited solubility in DCM and can dissolve slightly in the IL/ DCM mixture. Thus, when this method is employed it is important that the DCM extracts be washed with water to minimize the halide content of the final product.[69]

The preparation of water-miscible ILs is more difficult to achieve, as separation of the desired and undesired salts may be complex. In this case the anion metathesis can be achieved by

reaction of the corresponding chloride or bromide with the silver salt of the anion. This method remains the most efficient for the synthesis of water-miscible ILs, but is obviously limited by the relatively high cost of silver salts, and the large quantities of silver halide produced as by-product.[3, 69] On the other hand, complete precipitation of silver halides from organic solvents can also be quite slow, leading to silver-contaminated products. The nature of the precipitate can also be troublesome; in some cases the silver halide forms as submicron particles which are difficult to filter.[3] For these reasons metathesis reactions *via* free acids or alkali metal salts are preferred.

A different approach for the anion exchange of ILs is the use of ion exchange materials. These types of material are widely used in chemical industry and laboratory for separation, purification and as convenient heterogeneous reagents for synthetic cation or anion exchange.[70] Ion exchange materials are salts where one of the ions is fixed in a stationary (solid/gel) phase and the counter ion (in solution) is exchangeable (Figure 1.1.8).

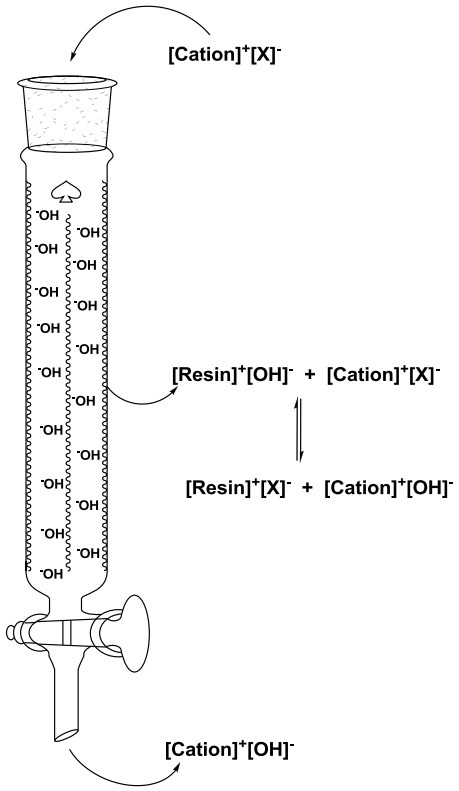


Figure 1.1.8 – Example of anion exchange of an IL using an ion exchange resin.

When a solution is passed through a column of ion exchange material, the counter ion of the material [X] will exchange with the corresponding ion of the solution [OH] and only species [Cation][OH] are eluted. Ion exchange resin has the advantage of performing both synthesis and purification in one step.

In ILs synthesis, the anion exchange resin Amberlite (OH form) is used. First is added to the column an aqueous or methanolic solution of the IL [Cation][X], where X is an halide anion. Passing through the column the halide anions are replaced by OH^- anions. The eluted solution contains the salt [Cation][OH] that is neutralized by the addition of an acid solution of the desired anion. This procedure is useful whenever the intermediate hydroxide salt is stable. Applying this protocol, Ohno and co-workers prepared ILs adding organic acids or natural aminoacids to the intermediate hydroxide solution.[71] They have synthesized twenty different ILs, based on aminoacids. The authors reported that these kinds of ILs are stable, and were miscible in organic solvents.[71b] Several others ILs composed wholly of biomaterials, that the authors named "Bio-ILs", where synthesized by the same group. On this work they have used the same Amberlite (OH form) protocol combining choline with several others bio-renewable carboxylic acids, such as hydrogen maleate, propionate, tiglate, and hydrogen succinate anions. A different protocol was reported by Dinares *et al.*[72] where the anion is incorporated in the resin before the anion exchange is carried out. In this way, a strong base anion exchange resin (OH form) is loaded with camphorate, acetate, mesylate, tosylate or lactate from the corresponding acid (Figure 1.1.9). The process involves the acid–base reaction with OH^-, resulting in the retention of the carboxylate anion in the resin and the displacement of the formed water together with the eluted solution. After that a solution of IL bearing anions such as [OTs], [SO_4], [I] or [Cl] was passed through the column, consequently the desired anion loaded on the resin were substituted by these anions to afford the expected ion pair.[72]

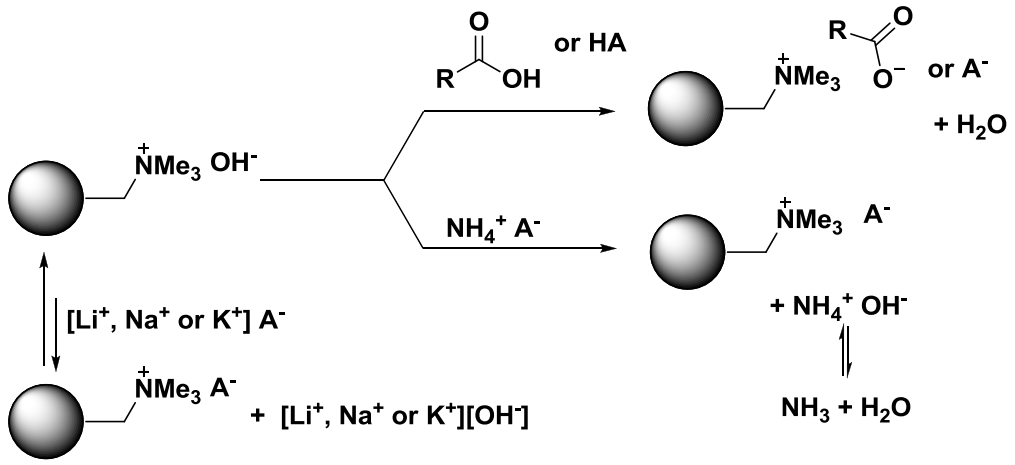
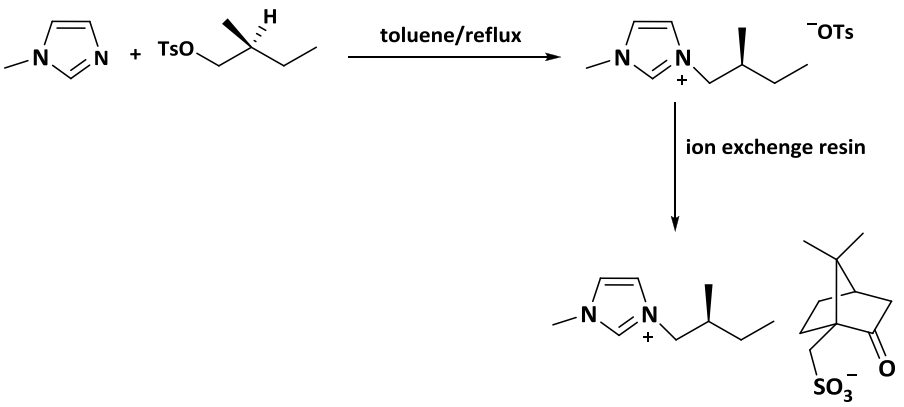


Figure 1.1.9 – Chemical processes involved when anion exchange resin OH form was treated with acids or ammonium salts. [72]

However, the treatment of the resin with strong acids can denaturalize the polymeric matrix by overheating during the loading, due to the high exothermic acid–base reaction.[72] To overcome

this problem the authors used ammonium salts to load the desired anions on the resin by the reaction of the acidic cation with the basic OH of the resin. In this way the OH on the resin is exchanged for the new anion, and ammonium hydroxide is formed and eluted from the resin. [72] A similar protocol was reported in 2005 by Machado[73], where the synthesis of a chiral IL was described using a anion exchange resin (Dowex). The first step of the synthesis is the alkylation of *N*-methylimidazole with (S)-2-methylbutyltosylate affording 1-methyl-3-((S)-2-methylbutyl-imidazium tosylate. The authors reported that the anion exchange of tosylate by other anion such BF_4 or camphorsulfonate, in the CH_2Cl_2/H_2O system is not possible, so they used an ion exchange resin charged with the desired anion. In this case they started with a strong anion exchanger (Dowex) charged with chloride anion, that change to HO^- passing an aqueous solution of sodium hydroxide through the column followed by an equimolar amount of (S)-camphorsulfonic acid (Scheme 1.1.17). After that a solution of 1-methyl-3-((S)-2-methylbutyl-imidazium tosylate is passed through the column, and the desired IL is obtained.



Scheme 1.1.17 – Synthesis of the chiral IL 1-methyl-3-((S)-2-methylbutyl-imidazium camphorsulfonate by ion exchange resin.

1.1.3.3 Purification of ILs

Depending on the type of IL the most common impurities are unreacted organic volatile compounds (e.g. unreacted amine, unreacted alkylating agent or trace amounts of residual solvent), halide impurities from incomplete anion exchange, other ionic impurities originating from contaminants in the reagents used, and water. These impurities can have a pronounced impact on the physical, spectroscopic and chemical characteristics of the IL, and therefore affect the performance of ILs in a give application. An obvious example is the melting point of 1,2-dimethyl-3-propylimidazolium chloride that varies from 58-66°C[74] to 138°C[19] in the literature. While several purification methods are known for conventional materials, the purification of ILs presents some difficulties. It is the otherwise advantageous properties of ILs (e.g. very low vapour pressure, low melting points and good miscibility with common solvents) that render

most of the traditional purification methods like distillation, recrystallization or extraction useless. In order to obtain pure ILs the use of rigorously purified starting materials and the employment of manufacturing procedures that meet the highest quality standards are essential.[21] But even then sometimes is not possible to achieve the highest purity due to the complexity of some synthetic pathways.

Residual water that may be present either because of the hygroscopic nature of many ILs or by introduction through the course of their preparation will preclude these liquids being used in water-sensitive reactions. In fact, the presence of water in haloaluminate ILs results in their decomposition through reaction with the aluminium halide species present.[75] High vacuum with heating is the most efficient way to obtain dry ILs. Although some ILs, like those based on formate or acetate anions can be unstable in these conditions. Therefore is important that the temperature is not very high. In this process is important the stirring of the IL due to some ILs high viscosity.

Halide and alkali metal salts originating as metathesis by-products can remain dissolved in ILs. For hydrophobic ILs simply washing with water until no salt is detected in the washings is very effective. With hydrophilic ILs removal of these salts can be more complex. The IL can be dissolved in a water immiscible solvent such as dichloromethane and washed as above. However, this usually leads to a significant loss in IL yield, although this loss can be reduced by using very cold water.[3] Passing the IL through silica gel have also been recommended as a method to reduce alkali metal halide salts.[76]

Although colourlessness is generally perceived as a prime quality criterion, a yellow, orange or somewhat brownish colouration of an IL does not indicates the purity of the IL, because colour is usually the result of unidentifiable trace amounts of impurities. [77] In most cases are possible to obtain colourless ILs, but with some anions (e.g. iodides, thiocyanates or chloride) it becomes very difficult, or even impossible to obtain colourless materials. For most applications of ILs colour is not a crucial parameter, although in the literature have been reported that ILs can be decolourised and hence purified using sorbents like carbon [77-78], alumina[78b] or silica.[77] Passerini and co-workers purified ILs by stirring over carbon at 70 °C, then stirring over alumina.[78b] Seddon and co-workers used a column filled with carbon and silica to remove coloured impurities from a range of ILs.[77] Davis *et al.* recommend stirring over carbon then passing down a short alumina column.[79] Indeed, sorbent treatment works well with many ILs and colourless or only slightly coloured materials can be obtained. However, it has been found that the use of sorbents to purify ILs can actually lead to further contamination.[80] In 2008 MacFarlene *et al.* showed that

sorbents like alumina, silica or charcoal can remain in the "purified" IL as nanoparticulate contamination. [80] Microfiltration (200 nm) can reduce the contamination to very low levels (<10 ppm) although even at this low level there is still an impact on the physicochemical properties of the IL. The authors claimed that for highest pure ILs advanced synthetic techniques are required, such as distillation.[81]

Closer studies reveal that ILs are neither completely non-volatile nor non-flammable.[81] Protic ILs (where is possible the proton transfer) may be "distilled" under reduced pressure by reversion to neutral acid and base and reconversion to the salt upon cooling and condensing. Rebelo *et al*. [82] reported on a method to predict the normal boiling points of ILs and the results of these predictions suggested that many *aprotic* ILs may be distillable without decomposition and recombination of decomposition products, and attempts were made to distill [C_{10} MIM][NTf_2] and [C_{12}MIM][NTf_2]. Small droplets of undecomposed IL formed on the upper walls of the distillation flask were subsequently characterized as pure IL. More recently[83] many ILs have been distilled without significant decomposition of the residue or distillate. The ILs were typically distilled at pressures of 0.001–5.0 mbar and temperatures of 200–300 °C. Reduced pressure was found to be essential since distillations performed close to ambient pressure led to IL decomposition. This studies show that distillation is a viable option for the ultrapurification of many ILs, but not all, for example some ILs decomposed under the distillation conditions used (e.g. salts of tetraalkylammonium, tetraalkylphosphonium, cholinium cations or halide, sulphate, carboxylate and triflate ions).[3] However, this technique can be very time consuming and is not yet practical for the large-scale purification of ILs.

1.1.3.4 Industrial applications of ILs

In the past few years ILs have achieved much interest as versatile compounds and are not any longer just a class of esoteric compounds. ILs are proving to be valuable and useful in a multitude of different applications. Table 1.1.1 describes possible applications of ILs in different scientific areas.

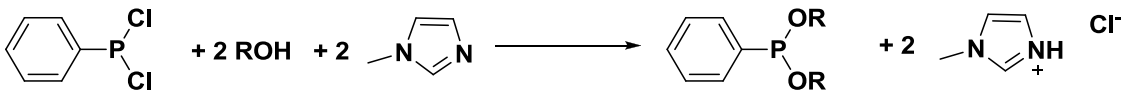
Table 1.1.1 – Application of ILs in different scientific areas.

ELECTROCHEMISTRY	Electrolyte in batteries; Metal plating; Solar Panels; Fuel cells; Electro-optics; Ion propulsion
BIOLOGICAL ISSUES	Biomass processing; Drug delivery; Biocides; Personal care; Embalming.
ANALYTICS	Matrices for spectrometry; Gas chromatography columns; Stationary phase for HPLC.
SOLVENTS AND CATALYSIS	Synthesis; Catalysis; Microwave chemistry; Nanochemistry; Multiphase reactions and extractions.

ENGINEERING	Coatings; Lubricants; Plasticisers; Dispersing agents; Compatibilisers.
PHYSICAL CHEMISTRY	Refractive Index; Thermodynamics; Binary and ternary systems.

The ILs supply should not be an issue for industrial users as there are now many manufacturers able to supply ILs on a multi-tonne scale.[10] However, the cost of some ILs will possibly inhibit their use on a large scale. Nevertheless, in some applications the investment is profitable due to the improved yield or purity of the final product, on the other hand there are less expensive options, such as choline based or alkylammonium derived salts. Despite the high prices of these compounds, ILs technology is growing at a rate that was unpredictable even five years ago, and several industrial applications have already being applied.

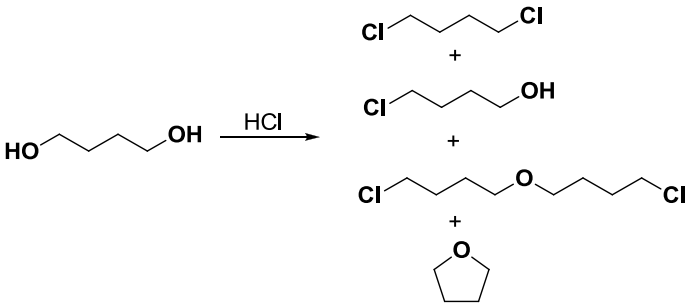
In 2002 was introduced to the BASF site in Germany the first publicly announced industrial process using ILs, the BASIL™ (*B*iphasic *A*cid *S*cavenging utilizing *I*onic *L*iquids) process. The basis of this process is very simple. In a chemical reaction, when an acidic by-product is formed the possibility of product degradation or to occur side reactions is enhanced. To avoid this problem is necessary to remove the acid from the reaction medium. Usually tertiary amines such as triethylamine are used to scavenge acids, but then a solid is formed, which difficult the industrial process due to the formation of suspensions. If acids have to be scavenged with base, formation of a salt is inevitable, but if the salt is liquid forming another phase from the product, the industrial process becomes easier and simple so, much cheaper. BASIL™ process used 1-alkylimidazole to scavenge the acid from an existing process which results in the formation of an IL based on 1-H-alkylimidazolium that can be easily removed from the reaction mixture (Scheme 1.1.18). This process increased the space/time yield of the reaction by a factor of 80,000. [84,85]



Scheme 1.1.18 – Formation of dialkoxyphenylphosphines with BASIL™ process.

BASF has serious invested on ILs applications, having at present several industrial applications using different ILs. For example, it is possible to break common azeotropes, such as water–ethanol and water–tetrahydrofuran using ILs.[86,87] BASF also demonstrated that hydrogen chloride dissolved in ILs can act as a phosgene substitute for the chlorodehydroxylation of alcohols. The transformation of alcohols into organic chlorides has been accepted as a general and basic transformation pathway in organic synthesis by using HCl gas, $SOCl_2$, PCl_3 and PCl_5. But all these reagents have drawbacks, for example the use of thionyl chloride has HCl and SO_2 as gaseous by-products, which can be a limitation in a large scale production. The reaction of

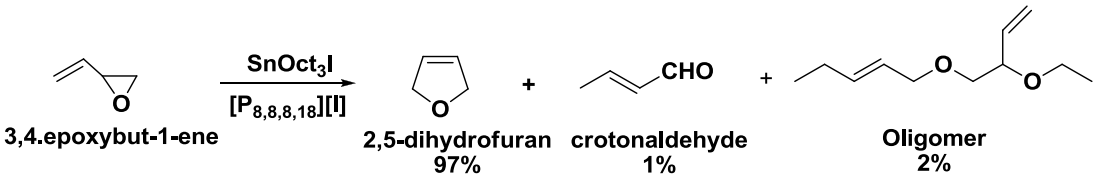
butan-1,4-diol with phosgene generates 1,4-dichlorobutane in essentially quantitative yield, but handling phosgene requires enormous safety efforts. Hydrogen chloride should be an ideal reagent for the chlorination of alcohols, due to inherent high atom economy, and avoidance of hazardous stoichiometric co-products, but this reaction is not selective, and several products can be formed (Scheme 1.1.19).



Scheme 1.1.19 – Reaction of butan-1,4-diol with HCl as chlorinating reagent.[88]

BASF have demonstrated that if the hydrogen chloride is dissolved in an IL first, only 1,4-dichlorobutane is formed, with almost 98% selectively.[89,90] Probably the IL enhances the nucleophilicity of the hydrogen chloride. A different application of ILs is now being developed by BASF, in collaboration with Prof. Robin D. Rogers, where the dissolution and processing of cellulose by means of ILs are being study.[91,92]

Although without the publicity of BASF, Eastman Chemical Company operated an IL-based plant for the synthesis of 2,5-dihydrofuran from 1996 to 2004. The process had been run as a commercial success but currently the plant is non-operational due to a decline in the market for the furan products.[93] This process was based on isomerisation of 3,4-epoxybut-1-ene to 2,5-dihydrofuran, which critically requires a Lewis acid catalyst, and a Lewis basic IL (Scheme 1.1.20). Phosphonium ILs were chosen over ammonium ILs due to their improved stability on the reaction medium.



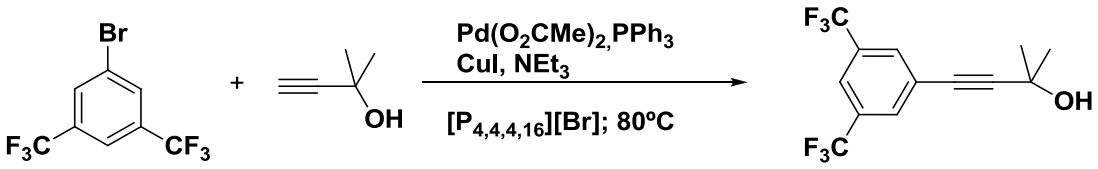
Scheme 1.1.20 – Isomerisation process of 3,4-epoxybut-1-ene to 2,5-dihydrofuran using tetraalkylphosphonium ILs.[93]

The Dimersol process is a traditional way to perform the dimerisation of alkenes into branched alkenes of higher molecular weight. This reaction is catalysed by a cationic nickel complex and is commonly operated without solvent.[93] The use of chloroaluminate(III) ILs as solvents for these

type of dimerisation was developed at IFP (Institut Français du Pétrole), especially by Nobel laureate Yves Chauvin and H. Olivier-Bourbigou[94] and the process was patent has Difasol. The IL introduction into the process generated a biphasic system where the products formed a second layer that could be easily separated and the catalysts remained in the IL phase. This novel process could be retro-fitted into existing Dimersol plants and the combined Dimersol-Difasol process has improved the catalyst activity and the product selectivity.

Degussa (presently part of Evonik Industries) also developed the application of ILs in different areas, such as hydrosilylation, paint additives, lithium-ion batteries and air products.[93] This company also developed the synthesis of organomodified siloxanes. These compounds are important in silicone industry, and are traditionally synthesized *via* the catalyzed hydrosilylation of Si-H functionalities with olefins. This reaction is catalyzed by small amounts of platinum, and is performed in a biphasic IL hydrosilylation process, where the catalyst is immobilized in the IL. When this biphasic process is compared to homogenous industrial hydrosilylation, several advantages are present, such as the possibility to recycle the catalyst/IL phase, and no product contamination is observed. [93, 95] Another application of ILs developed by Degussa is their use as secondary dispersant in universal pigment pastes (white base paint to be tinted) that can be used for all types of paints and coatings.[96] One of the advantages is the reduction of VOCs used in paints or coatings.

The Central Glass Company (Japan)[97] have studied in detail the Sonogashira coupling, a palladium–copper catalysed reaction of aryl halides and terminal alkynes(Scheme 1.1.21), allowing preparation of substituted alkynes, which can be used in optical, electronic and pharmaceutical applications.[93] The use of alkylimidazolium based ILs have decreased the reaction efficiency, although improved results were achieved with tetraalkylphosphonium based ILs. The product was easily extracted using hexane, and the IL/catalyst system could be recycled several times.



Scheme 1.1.21 – Sonogashira coupling using phosphonium based ILs.[93]

Io-Li-Tec in addition to commercialization of ILs, has also developed interesting applications of ILs in thermodynamic, biotechnology and electrochemical fields. For example the use of ILs as phase change materials[98], that are materials with the ability to store or release energy when

passing from solid to liquid phase, or *vice versa*. Some of the applications of these materials are cyclic storage and supply of thermal energy, latent heat storage devices, heat buffers and also cold buffers.

Several petrochemical companies such as Chevron, BP and ExxonMobil hold extensive patent portfolios relating to IL.[99] However, the only one to announce an industrial process based on ILs was PetroChina. This company have developed a process named Ionikylation, for the alkylation of isobutene with low-molecular-weight alkenes to produce gasoline using a composite-IL. Previous alkylation processes required the presence of a strong acid as catalyst, either sulfuric acid or hydrofluoric acid. Ionikylation process uses a composite-IL as homogeneous catalyst for alkylation reactions at room temperatures and moderate pressures.[100] The composite-IL is a kind of IL having anions in the form of ligands with two or more metallic centers, such as $[AlCuCl_5]^-$. The breakthrough of composite-IL on alkylation is the enhancement of the C_8 selectivity, especially for trimethylpentane, which octane number is more than 100.[41] This process have been tested at pilot plant, and retrofitted into an existing 65,000 tonnes per year sulfuric acid alkylation unit in China.[93, 100]

1.1.4 Chiral Ionic Liquids (CIL)

After the thalidomide tragedy (1957–1961), a strict control of the purity of enantiomers used in medicine was inducted. Worldwide, governmental agencies control all active drugs produced by the pharmaceutical industry with a special attention on the enantiomeric purity in case of chiral drugs. With time, less and less new drugs are introduced as racemates.[101] Therefore, the synthesis of enantiomeric pure compounds has been a challenge for chemists and different approached have been developed for enantiomeric pure synthesis. For example enantiomers can have a semi-synthetic origin this is, the staring material can be provide from a natural chiral source (chiral pool) and thereafter be modified maintaining the chiral centers from the original molecule. In this case is not necessary the use of chiral catalyst or solvent because the chiral center already exists. Another approach to synthesize chiral molecules is the use of prochiral substrates, where the starting material is not chiral. Chirality is induced by a chiral source in the reaction medium (asymmetric synthesis).[102] The chiral source can be chemical or enzymatic. In chemical asymmetric synthesis the most common strategy is the use of chiral catalysts, due to the difficulty, and high cost to synthesize chiral solvents. In 1975 an chiral amino ether was used as a solvent for the electrochemical reduction of ketones, and only 23% of ee was achieved on the final product.[103] So chiral induction is not a straightforward method, and the catalyst or the solvent used to induce chirality has to interact with the reactants or the reaction intermediates

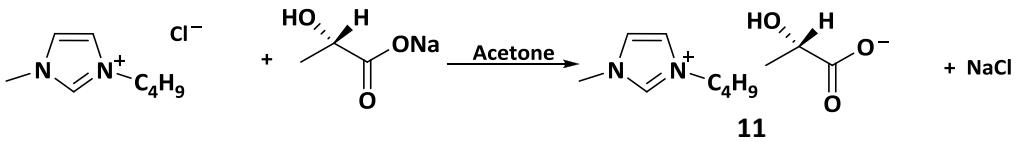
to be able to induce chirality on the final product. Recently ILs including chiral units, so called Chiral Ionic Liquids (CILs) have been used as solvents and/or catalysts in asymmetric reactions. In the last few years a growing number of CILs have been designed, synthesized, and utilized for potential applications in chiral discrimination, asymmetric synthesis, stereoselective polymerization, gas chromatography, and liquids crystals. [104] With the forthcoming of CIL, and due to their particular properties and the easiness of synthesis, these new chiral solvents should play a central role in enantioselective organic chemistry.

CILs can possess chirality either in the cation and/or the anion, although the major examples in the literature are based on chiral cations. The main reason is that most of chiral organic anions readily available in nature, such as lactate, tartrate or aminoacids, would exhibit higher melting points than the corresponding BF_4^-, PF_6^- and NTf_2^- salts, used as counter anions in the CILs having a chiral cation.

1.1.4.1 CILs based on chiral anion

Although CILs based on chiral anions have less attention in the literature, experimental results have proved that this class of CILs is extremely promising in asymmetric synthesis.[57] Regarding the work accomplished during these four years, main focus will be given to the synthesis of CILs based on chiral anions.

The first report of a CIL was made by Seddon *et al.* in 1999[105], where was performed the synthesis of [BMIM] in combination with a chiral anion, lactate. It was synthesised by anion metathesis of [BMIM][Cl] and the commercially available sodium (S)-2-hydroxypropionate in acetone (Scheme 1.1.22). This CIL was used as a solvent for the Diels Alder reaction of cyclopentadiene and ethyl acrylate. Although reasonable conversion rates and good diastereoselectivity (4.4:1 *endo/exo*) were achieved, there was no enantioselectivity observed on the final product (less than 5% ee).

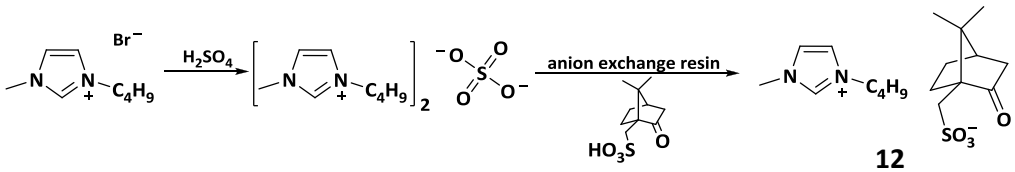


11

Scheme 1.1.22 – Synthesis of [BMIM][lactate]**11** by ion exchange with the IL [BMIM][Cl] in acetone.[105]

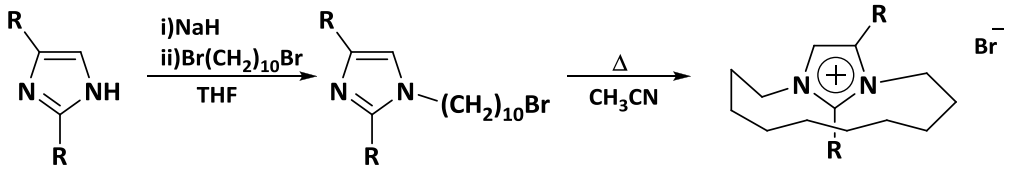
Ishikawa *et al.*[106] reported ILs based on camphorsulfonate anion (CSA) (Scheme 1.1.23). Despite the anion bulkiness and high molecular weight, [BMIM][CSA] was characterized has a viscous liquid. The authors have studied the cation–anion association in several sulfonate ILs, demonstrating that the bulky camphorsulfonate anion binds more loosely with the imidazolium

cation, than the smaller [CH_3SO_3] and [CF_3SO_3] anions,[106] resulting the lower melting point of CSA based ILs, while [BMIM][CH_3SO_3] is solid at room temperature. When CILs based on camphorsulfonate anion were tested as solvents for Diels–Alder reactions was observed a significant enhancement in the *endo/exo* stereoselectivity. These results were attributed to the increased number of free (naked) imidazolium cations, caused by the use of a camphorsulfonate anion. Indeed, the *endo/exo* selectivity of 10.3:1, determined in the presence of [BMIM][CSA] represents an excellent result when compared with [BMIM][lactate], above mentioned.



Scheme 1.1.23 – Synthesis of [BMIM][CSA] **12** [106].

In 2002, Saigo *et al*.[107] described the first CIL with a chiral unit in the cation and anion. The cation had a cyclophane-type planar chirality, and was prepared starting from imidazole derivate, as showed in the Scheme 1.1.24. The anion was the readily available camphorsulfonate [CSA]. Diastereomeric interaction between the cation and the chiral anion was demonstrated by ^{1}H-NMR spectrometry. Unfortunately, this new type IL (Figure 1.1.10) was produced only in its racemic form. Therefore, further separation techniques (such as chiral HPLC or crystallization) will be needed for the isolation of the two enantiomers in order to evaluate their potential usefulness as CILs.



Scheme 1.1.24 – Synthesis of cyclophane-type imidazolium salts

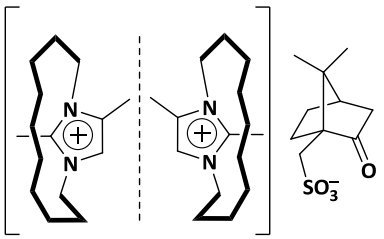
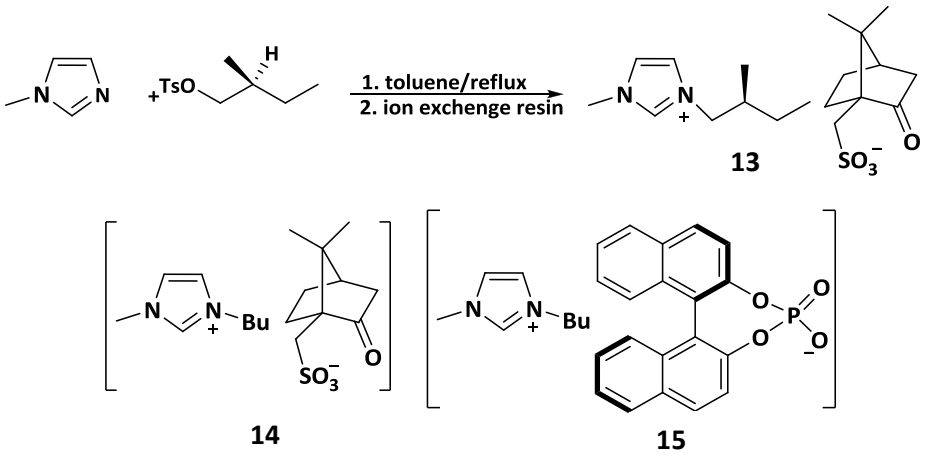


Figure 1.1.10 – CIL with chirality on the cation and anion[107]

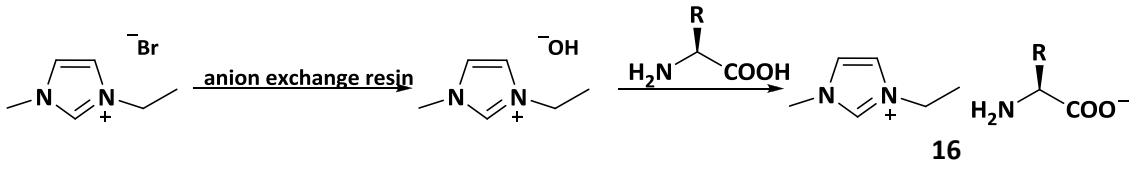
Machado *et al*[73] reported the synthesis of CILs based on chiral anions, and with chirality present on the cation and the cation. The synthetic method used for the preparation of the CILs was different. For example the synthesis of the CILs **14** and **15** was performed by simple anion

exchange of the commercially available [BMIM][Cl] with camphorsulfonate and (*R*)-1,10-binaphthylphosphate potassium salts in a CH_2Cl_2/H_2O solvent system. The CIL **14** is a very viscous golden oil and **15** a white solid (mp 78-80°C). [73] The IL with chirality on the cation and the anion was prepared starting from (S)-2-methylbutyltosylate in neat *N*-methylimidazole at 70°C affording a white hygroscopic solid in excellent yield. The authors reported that the anion exchange of tosylate by other anion such BF_4 or camphorsulfonate, in the usual CH_2Cl_2/H_2O system was not possible, so they used an ion exchange resin charged with the desired anion. In this case they started with a strong anion exchanger (Dowex) charged with chloride anion, that change to HO^- passing an aqueous solution of sodium hydroxide through the column followed by an equimolar amount of (S)-camphorsulfonic acid (Scheme 1.1.25), obtaining the desired CIL **13**. The authors did not report an application for this "double" CIL.



Scheme 1.1.25 – Synthesis of [BMM*IM][CSA] **13**, and structures of CILs [BMIM][CSA] **14**, [BMIM][BINAP] **15**[73].

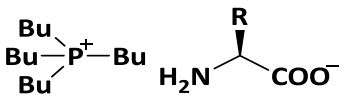
As described before (please see section 1.1.3.2.2, page 17), anion exchange resin can be an efficient and atom-economical method for the synthesis of ILs. In 2005, Ohno *et al*.[71b] reported a simple method for the synthesis of CILs containing amino acids as anions, using an anion exchange resin. [EMIM][OH] was prepared from [EMIM][Br] by anion exchange resin (Scheme 1.1.26), and then neutralized with twenty different aminoacids.



Scheme 1.1.26 – Synthesis of CIL possessing amino-acids anions **16** [71b].

All of the resulting amino acid ILs are nearly colourless liquids, showing a glass transition temperature ranging from –57 °C to 6 °C. However, viscosity and thermal stability require

improvement. In 2006, the same group[108] reported the design, synthesis, and properties of tetraalkylphosphonium-based amino acid ILs. Although ammonium- and pyrrolidinium-based amino acid CILs did not show improved properties compared to the corresponding imidazolium-based salts, positive results were obtained by introducing tetrabutylphosphonium [$P_{4,4,4,4}$] has CIL cations. Usually ILs based on phosphonium cations show good chemical and thermal stabilities, although the viscosity and melting points are usually higher than ammonium or imidazolium salts.[71b] The combination of the [P_{4444}] cation with twenty different amino-acid anions **17** (Figure 1.1.11) resulted in 15 liquid salts at room temperature, with lower viscosities and also higher decomposition temperatures.[108] These ILs with improved properties are expected to be used for various applications.



17

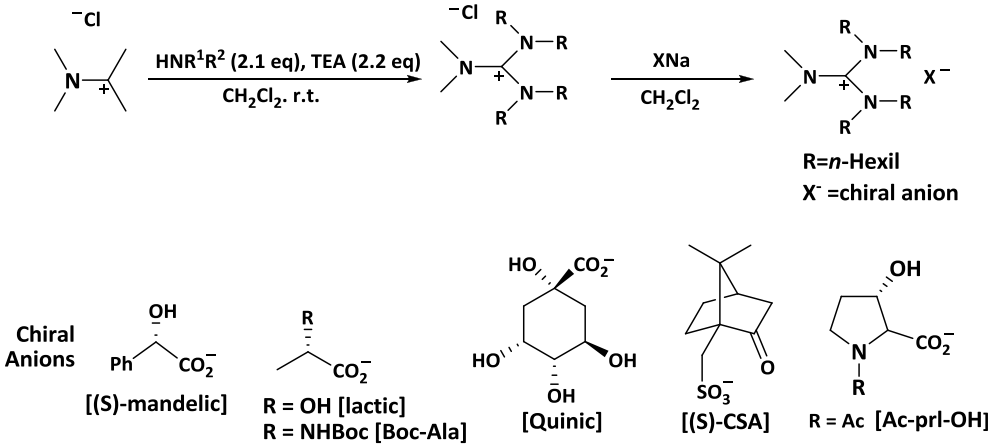
Figure 1.1.11 – Structure of CILs tetrabutylphosphonium-based amino acids CIL[108]([P_{4444}][AA]).

In 2006, Zhang *et al*.[109] also synthesised a series of [P_{4444}]-based CILs, with L-alanine, L-serine, and L-lysine as anions, synthesized by the same anion exchange method, starting from the [P_{4444}][Br], followed by neutralization. These CILs were characterized, and the CO_2 absorption behaviour was studied. The authors have showed that the CO_2 absorption capacity of these CILs can vary from 50 mol% till an equimolar amount when a small amount of water was present, indicating that water can assist on the absorption process of CO_2.

In 2006 Zhao *et al*.[110] reported the synthesis of CILs based on 1-ethyl-3-methylimidazolium [EMIM] in combination with several amino acids, using the same resin method as reported before.[71b] These CILs were used as media for the enzymatic resolution of phenylalanine, and was observed that at low IL concentrations the protease activity was stabilized and the enantioselectivity was increased. When CILs based on D-amino-acids were used, higher yields and enantioselectivity were generally obtained then with L-amino-acids. The authors explained this fact by the kosmotropic effect of the anion that strongly stabilizes the enzyme (D-amino-acids are usually more kosmotropic than the L- isomers). The best results were achieved with 0.5 M of the CIL [EMIM][D-Pro]: ee 92.9% and 97.2% yield. These are very good results, but comparable with those in pure water (ee 94.2% and 94.6 % yield).

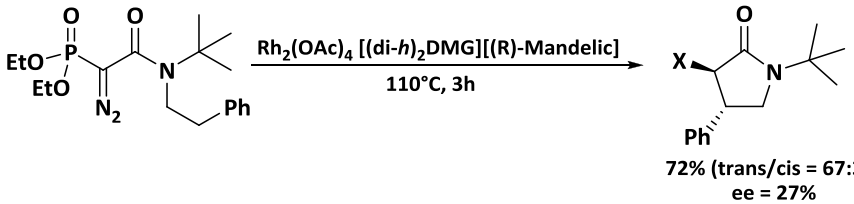
A different type of CIL was reported by this laboratory[57] based on tetra-*n*-hexyl-dimethylguanidinium cation [(di-*h*)$_2$DMG] and readily available natural chiral anions. The synthesis of the cation[50-51] started from the commercial available *N,N*-dimethylphosgeniminium

chloride with *N,N*-dihexylamine, as showed in the Scheme 1.1.27. These CILs presented moderate viscosity, high thermal stability and complementary stability to the ILs based on the imidazolium cation. More importantly, despite the high number of carbon atoms, *e.g.* 27 for [(di-*h*)$_2$dmg] cation, they are less prone to crystallize even in the presence of anions which persistently become solid when combined with different cations, such as imidazolium cation. The amino-acids used as anions were N-protected, so these CILs are not pH dependent as the others amino-acids reported before.[71b]

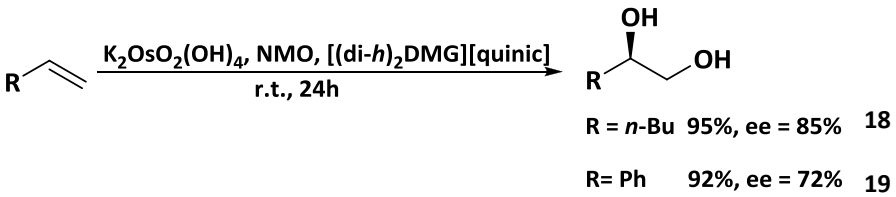


Scheme 1.1.27 – Synthesis of [(di-*h*)$_2$dmg] cation and combination of readily accessible chiral anions[57].

In order to test the effectiveness as chiral inductors, this new CILs were tested as solvents in asymmetric reactions. Afonso *et al.*[57] made an evaluation as a reaction medium in the following transformations: carbenoid intramolecular C–H insertion of α-phosphono-α-diazo-acetamides catalyzed by $Rh_2(OAc)_4$ (Scheme 1.1.28) and Sharpless asymmetric dihydroxylation (AD) (Scheme 1.1.29). Interestingly, for both transformations was possible to achieve yields and enantioselectivities similar or higher to the ones using traditional solvents.



Scheme 1.1.28 – Induction of chirality by CILs in C–H insertion of α-diazo-acetamides catalyzed by $Rh_2(OAc)_4$[57].

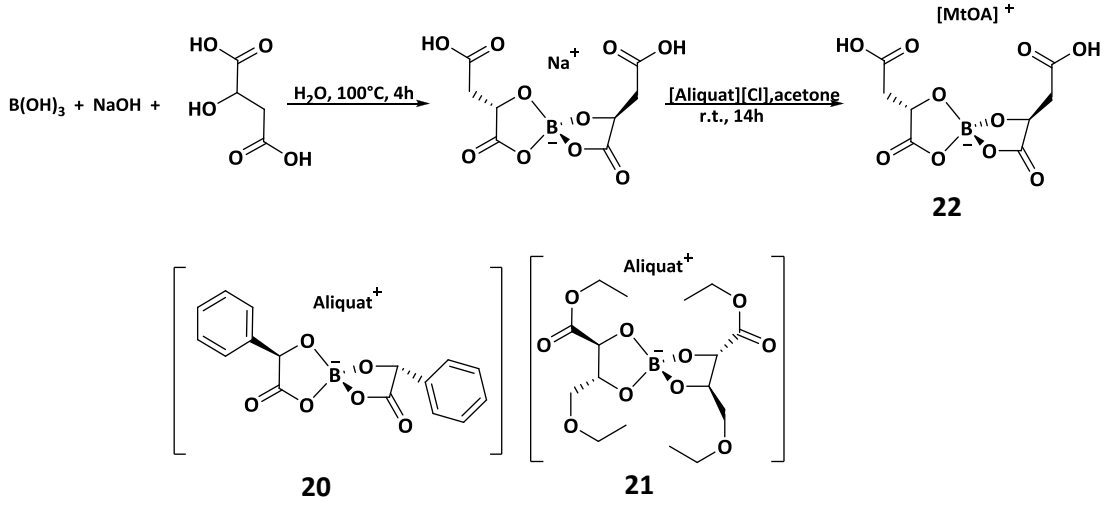


Scheme 1.1.29 – Induction of chirality by CILs in Sharpless AD[57].

Using the CIL [(di-*h*)$_2$dmg][(R)-mandelic] instead of the traditional organic solvent, 1,2-dichloroethane, in the presence of $Rh_2(OAc)_4$ catalyst, the *in situ* formation of Rh(II) carbenoid from α-phosphono-α-diazo-acetamide originates the γ-lactam in 72% yield (*trans/cis* 67/33) with a moderate enantioselectivity (ee 27%). Nevertheless, this constitutes an improvement when compared with the result obtained when the chiral Rh_2((R)-mandelate)$_4$ catalyst (ee 18%) was used.[111] The asymmetric induction probably occurs as a result of in situ ligand exchange and the chiral solvent environment.[57]

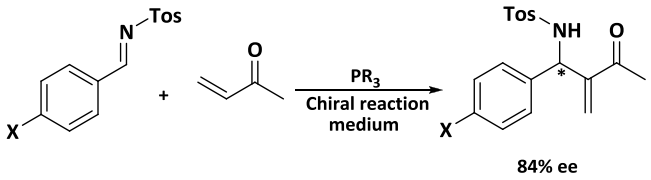
The Sharpless osmium-catalyzed asymmetric dihydroxylation (AD) of olefins was performed with CILs, and in the absence of bis(cinchona)alkaloid chiral ligands. The use of CILs as solvents induced better enantioselectivities (95% yield and ee 85%) than with the ones obtained using chiral ligand [DHQD]$_2$PHAL in *t*-BuOH/H_2O (1:1), (80% yield and ee 73% for **19**) .[56a] It should be mentioned that using a catalytic amount (5 mol%) of the CIL [(di-h)$_2$dmg][quinic] dissolved in *t*-BuOH/H_2O (1:1), lower yields (81%) and enantioselectivities (ee 40%) were obtained with compound **19**.[57]

All the CILs described were based on readily available chiral anions, such as aminoacids, or protected aminoacids. In 2006 Leitner et al.[112] reported a different type of chiral anions based on boronic acid. The cation was based on the commercially available IL Aliquat 336® (methyltrioctylammonium chloride, [Aliquat®][Cl]), and the chiral anion was prepared starting from boric acid, sodium hydroxide and chiral hydroxy acids (L-malic acid, mandelic acid and diethyl tartrate), as showed in the Scheme 1.1.30.



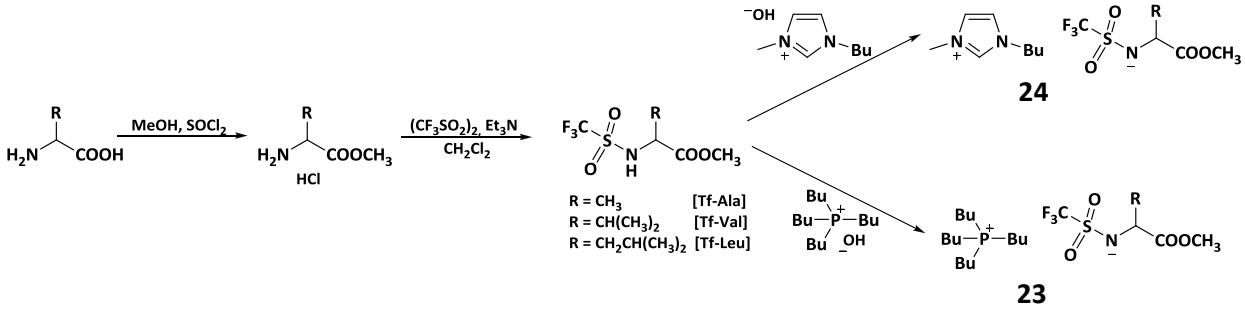
Scheme 1.1.30 – Synthesis of [MtOA][dimaleatoborate] **22** , starting from boric acid, sodium hydroxide and chiral L-malic acid. Another two CILs were synthesised by the same method starting from mandelic acid **20**, and diethyl tartrate **21** [112].

The CIL [Aliquiat®][dimaleatoborate] **20** was used as chirality source in the aza-Baylis–Hillman reaction (Scheme 1.1.31) and high enantioselectivity was achieved (84% ee). For this specific case an ionic transition state was postulated in which the chiral anion is incorporated as a kind of organocatalyst (Scheme 1.1.30).



Scheme 1.1.31 – Schematic aza-Baylis–Hillman reaction with PR_3 as catalyst, and the CIL as chiral reaction medium[112].

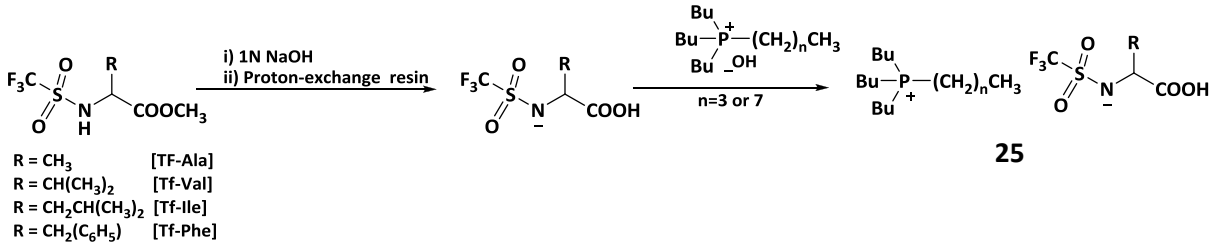
In the last few years Ohno *et al*. have been developing CILs based on chiral anions derived from amino-acids.[113] In 2006 this group first reported the synthesis of ILs composed of chiral and hydrophobic anions, which were derived from natural amino acids and modified with the trifluoromethane sulfonyl group and methyl ester group.[114] The synthesis of these CILs is represented in Scheme 1.1.32.



Scheme 1.1.32 – Synthesis of hydrophobic CIL based on [BMIM] **24** or [P_{4444}] **23** cations, and chiral anions derived from amino-acids[114].

Although properties such as melting point, viscosity, and hydrophobicity were not improved over typical hydrophobic ILs such as [BMIM][Tf_2N], these syntheses are the first simple preparation of hydrophobic ILs bearing a chiral anion. The use of different amino acids as starting materials allows choice of the physicochemical properties of the prepared CIL.

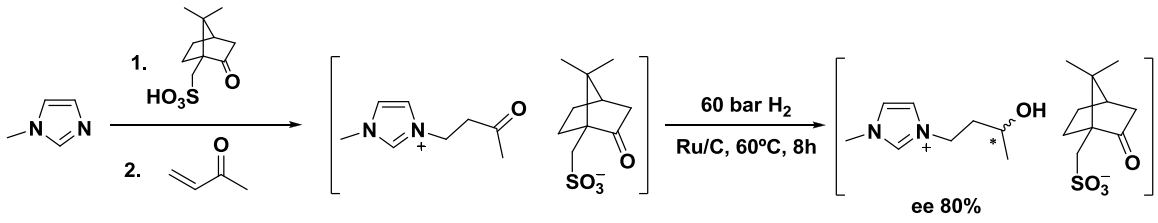
In 2007, Ohno *et al*.[115] also reported the synthesis of new CILs from natural amino acids, which exhibited lower critical solution temperature, (LCST)-type phase separation with water. The amino group on the amino acid was modified using a synthetic procedure similar to one above mentioned,[114] with an additional step of hydrolysis of the methyl ester groups (Scheme 1.1.33).



Scheme 1.1.33 – Synthesis of CILs that exhibit (LCST)-type phase separation with water[115].

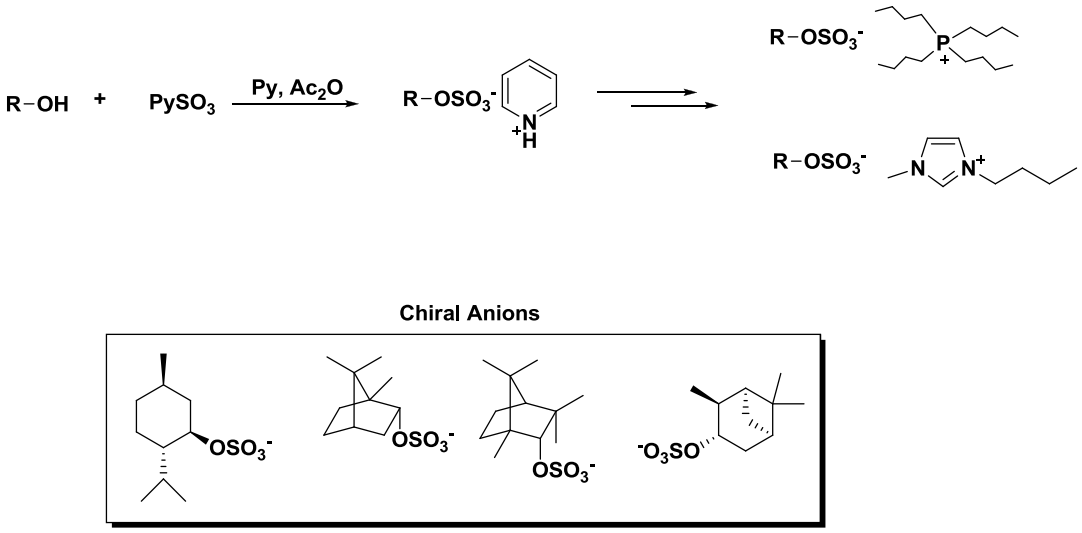
The phase-separation temperature of these mixtures depends reproducibly on the ion structure and water content. Increasing water content in the mixture and an increase in the hydrophobicity of the side chain can lower the phase-separation temperature. These results imply that the phase separation temperature of the mixture can be controlled by the side chain structure on the starting amino acid, by the alkyl chain length of the cation and by the water/IL ratio. Although the mechanism of the LCST-type phase behaviour of the ILs is not clear, the authors reported that these ILs could have a great impact on reaction and separation processes.

Wasserscheid and Schulz[101] have synthesized CILs with chirality on the anion and cation, starting from pro-chiral ILs (Scheme 1.1.34). The pro-chiral ILs was synthesized by protonation of *N*-methylimidazole with (R)-camphorsulfonic acid followed by a Michael-type addition of methyl vinyl ketone in an overall yield of over 95%.[61] After that hydrogenation of IL using achiral Ru/C catalyst in ethanol induced enantioselectivity up to 80% ee at the cationic part of the IL. The authors reported that the effective chirality transfer solely depends on the strength of ion pairing in an IL.[101, 116]



Scheme 1.1.34 – Synthesis of a pro-chiral IL followed by chiral hydrogenation, where the chirality is induced solely by the chiral anion.

In 2010 was reported the synthesis of CILs based on chiral sulphonates and sulphates.[117] The chiral sulphates were prepared starting from alcohols by the use of an excess of pyridine sulphur trioxide complex in the presence of acetic anhydride and an amine (Scheme 1.1.35). Whereas salts based on sulphonates anions had melting points below 100 °C, salts with sulphates anions were liquid at room temperature.



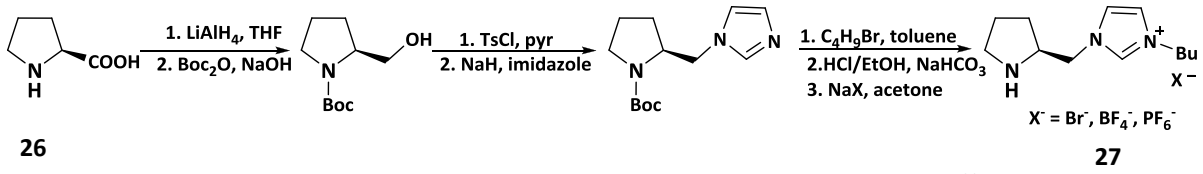
Scheme 1.1.35 – Synthesis of CILs based on chiral anions. [117]

In conclusion, the main chiral anions used to synthesise CILs are readily available natural chiral carboxylic- or amino-acids. Several groups used camphorsulfonate as an anion, despite its high molecular weight and bulky structure, and so far all are liquids at room temperature. When used as reaction medium CILs (bearing chirality on the anion) can induce chirality in asymmetric synthesis, being the best results obtained in the asymmetric dihydroxylation[57](95% yield and ee 85%) and in aza-Baylis–Hillman[112] (ee 84%), although the ee's are comparable to those obtained with the best traditional catalysts.

1.1.4.2 CILs based on chiral cations

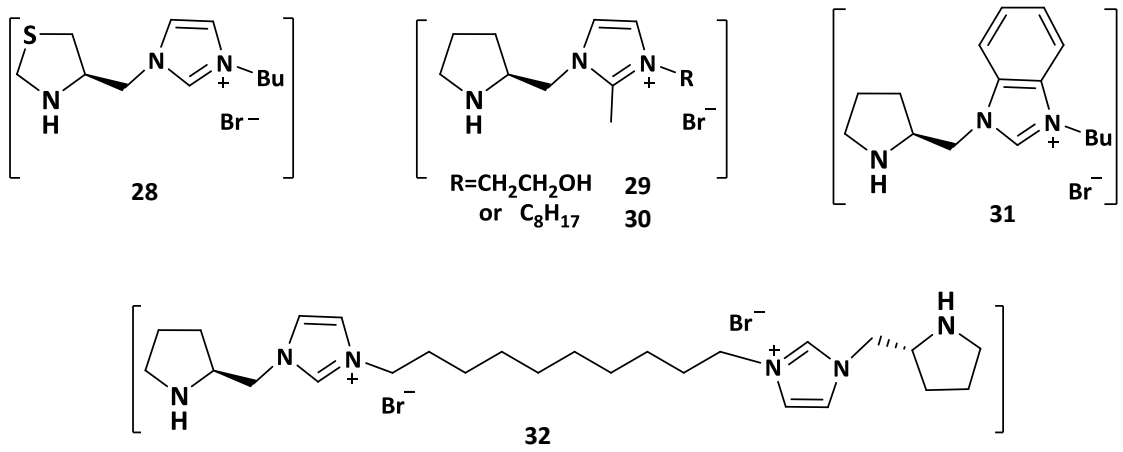
Has mentioned before the number of CILs reported in the last few years has increased exponentially, and the majority reported the synthesis of CIL containing the chiral unit on the cation.[104, 118] Taking into account the aim of this work, it's not possible to report all of CILs with a chiral unit on the cation. Only key examples of synthesis and applications in asymmetric synthesis of these CILs will be described.

Chiral pyrrolidines derived from L-proline **26** and its derivates were successfully used as highly enantioselective organocatalysts.[119] Based on this observation new pyrrolidine-based CILs were prepared and efficiently applied to the Michael addition. Luo *et al*.[120] designed and synthesized a series of chiral pyrrolidine-based CILs (Scheme 1.1.36) bonded to an imidazolium ring using L-proline as a starting material. Others pyrrolidine-type CILs **28**-**32** were also synthesized via a similar method. The synthetic procedure allows facile variations of the cations, anions, and side chains of the CILs. All the CILs obtained are viscous liquids at room temperature and soluble in moderately polar solvents, but insoluble in less polar solvents.



26 **27**

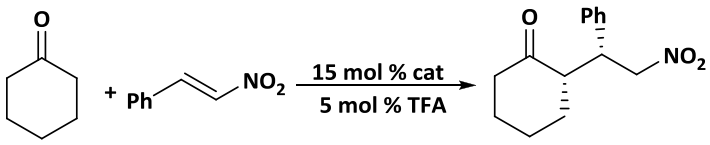
Scheme 1.1.36 – Synthesis of pyrrolidine-based CILs 20 from L-Proline 19[120a].



28 **29** **30** **31** **32**

Figure 1.1.12 – Pyrrolidine-based CILs derived from L-Proline synthesised by the same method as used to for **27**.[120]

These pyrrolidine-type CILs comprise a chiral pyrrolidine unit covalently tethered to an ionic-liquid moiety. The chiral pyrrolidine unit can serve as a catalytically active center: not only can the IL moiety act as a phase tag to facilitate the recycling and reuse of the catalyst, but it can also play an important role as an efficient chiral induction group to ensure high selectivity. These types of CILs thus combine both the advantages of organocatalysts and ILs.[120] Pyrrolidine-based CILs were applied as good catalysts in the asymmetric Michael addition reaction (Scheme 1.1.37).



Scheme 1.1.37 – Asymmetric Michael additions catalysed by Pyrrolidine-based CILs[120a]

The catalytic reactions were performed in the presence of trifluoroacetic acid (TFA) as co-catalyst, but no co-solvent was added, CILs act as both solvent and chiral catalyst. The pyrrolidine-imidazolium bromide and tetrafluoroborate, **27** demonstrated the best performance with almost quantitative yields and high diastereoselectivity (*syn/anti* = 99:1) and enantioselectivity (98% ee). Introduction of a methyl substituent on the imidazolium ring or of the OH group on the side chain of the cation led to a decrease in both catalytic activity and enantioselectivity. Recycling experiments evidenced that high selectivities were maintained but

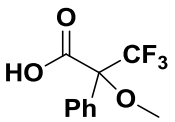
that a loss of activity appeared for the third and fourth runs, therefore, an increase of the reaction time from 8 to 48 h was required to achieve similar yields. The reaction was also efficiently extended to other Michael donors such as cyclopentanone, acetone or aldehydes but with moderate to good asymmetric inductions[120a].

The reported data show that ILs bearing chiral anions can also be used to induce asymmetry. If the key to effective chirality transfer lies in a strong interaction between the solvent molecules and the intermediates or transition states, as recently suggested,[101] functional ILs offer unique possibilities to create such arrangements for a wide range of transformations. Many CILs have been synthesised, but only a few have some chemical application. This might change in the future due to the increasing interest of chemist's in the field of chirality. Indeed, the concept of "tailor-made" chiral solvents is rather new, and could afford novel molecular structures and materials, as well as new insights for chiral recognition and chirality transfers.

1.1.4.3 Chiral discrimination using CILs in NMR spectroscopy

Enantiomeric purity of chiral compounds have been accessed by optical methods, where the optical rotation of the compound is determined by a polarimeter under defined conditions including temperature, solvent, and concentration, at a given wavelength of the incident plane-polarized light.[121] The optical purity of the sample can be obtained by comparing with the rotation of the known enantiopure sample of the same compound. This technique has been used as a general characterization of CILs in a number of organic solvents.[122] But other methods are also used for analysis of chiral compounds, e.g. chromatographic and spectroscopy techniques. Nuclear magnetic resonance (NMR), fluorescence[123], and near infrared[124] (NIR) are examples of techniques used for the analysis of chiral compounds, being NMR spectroscopy the most common. Although enantiomers cannot be distinguished in achiral medium, because the resonances of enantiotopic nuclei are isochronous (show the same chemical shift), diastereoisomers may be distinguished due to possessing anisochronous resonances (have different chemical shifts). [125] The integration of the diastereoisomers can give a direct measure of diastereoisomeric composition which is directly related to the enantiomeric composition of the original mixture. The determination of the enantiomeric purity using NMR therefore requires the use of a chiral auxiliary that converts the enantiomers mixture into a diastereoisomeric mixture.[126] For this purpose three traditional approaches can be used, i.e. chiral lanthanide shift reagents, chiral solvating agents and chiral derivatizing agents. Chiral solvating agents form diastereoisomeric complexes in situ with substrate enantiomers and may be used directly, without the need of derivatization.[126] Recently, CILs have been widely used as chiral solvating

agents in NMR studies. In these applications, CILs are dissolved in deuterated NMR solvents and used as the chiral solvating agent. Considering the solvent used, less polar solvents such as deuterated chloroform, benzene, and carbon tetrachloride tend to maximize the observed anisochrony between the diastereoisomeric complexes while more polar solvents such as deuterated acetonitrile, dimethyl sulfoxide may solvate the solute and decrease peak splitting.[103b, 126] As referred before, most CILs bear the chirality on the cation. Therefore a chiral anionic compound should be preferable to study the chiral discrimination mechanism between CILs and the chiral anionic compounds through a possible ion pairing interaction.[127] Mosher's acid (Figure 1.1.13) is widely used as chiral anionic probe for several reasons, for example the absence of α-hydrogen in the carboxylic group avoids racemisation problems during the formation of diastereoisomeric complexes. It is commercially available in enantiopure form, and since this compound have proton and also fluorine nuclei it is possible to investigate diastereomeric interactions by ^{1}H NMR or ^{19}F NMR.



33

Figure 1.1.13 – Structure of Mosher's acid ((R,S)-3,3,3-trifluoro-2- methoxy-2-phenylpropanoic acid).

The first example of spectroscopic chiral discrimination by CILs was reported in 2002 by Wasserscheid *et al.*.[128] It was described the synthesis of two different ILs with chiral cations derived from the 'chiral pool', in enantiopure form. The authors investigated the diastereomeric interactions between the sodium Mosher's salt and the CIL using ^{19}F NMR spectroscopy, and observed the split of the signal related to the CF_3-group of the racemic substrate, demonstrating that the substrate has been dissolved in a chiral environment (Figure 1.1.14). It is also noteworthy that the chemical shift difference for the two diastereomeric CF_3-groups largely depends on the concentration of the CILs in the deuterated solvent. Generally, the higher the CIL concentration is, the greater the splitting of ^{19}F NMR signal of the CF_3 becomes. Moreover, it was demonstrated that the addition of water to the chiral IL solution increases the extent of signal splitting.[128]

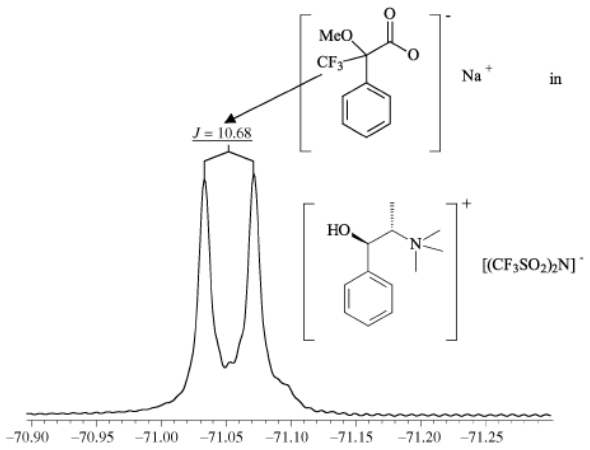


Figure 1.1.14 – Diastereomeric interactions between the sodium Mosher's salt and the CIL using ^{19}F NMR spectroscopy. Adapted from ref [128].

Several other groups have synthesized CILs possessing chiral cations, and have demonstrated their chiral recognition ability by investigating the diastereomeric interaction between the CILs and racemic Mosher's acid or sodium/silver salts.[129] Boulanger *et al*.[129b] reported in 2004 that polar groups present on the chiral cation increases the chemical shift difference, because it favours the hydrogen bonding between the cation and the anion substrate. They also reported that when water is added to the system, destroys the hydrogen bonding, leading to diminished chemical shift difference, that is on contradiction with the reported by Wasserscheid[128], that reported that when water is added to the system the chemical shift difference is increased.

Another study reported in 2006 have showed that the achiral anion of the IL can influence the diastereomeric interaction between the chiral cation and the respective anionic substrate (e.g. Mosher's salt).[129h] The authors explain this result by the availability of the cation to interact with the substrate, so if the cation strongly interact with their anion pair, is not available to interact with the substrate, and form diastereomeric complexes. This anion influence could result from either their steric size or hydrophobicity. The effect of anions on the diastereomeric interactions between CILs and Mosher's salt was further investigated by Malhotra and co-workers [129c], that observed that not only the chiral cation have effect on the on the chiral discrimination but also the achiral anion of the CIL can improve the chiral discrimination induced by the CIL. Furthermore the CIL concentration increase can also increase the chemical shift difference.

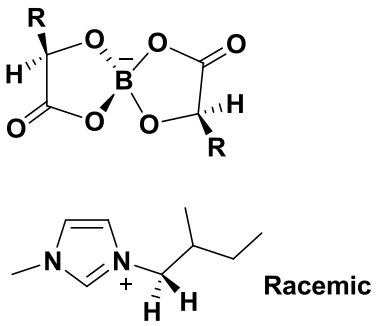
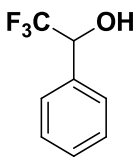


Figure 1.1.15 – Intramolecular chiral induction from a chiral anion to its cation.

Intramolecular chiral induction from a chiral anion to its cation through ion-pairing effect in a single CIL was observed in the asymmetric catalytic hydrogenation reaction (please see page 34).[101] Tran *et al.* have study the intramolecular and intermolecular chiral recognition of CILs containing chiral anions and racemic imidazolium based cations (Figure 1.1.15). [130] In this case enantiomeric recognition of the chiral anion toward both enantiomers of the cation lead to pronounced differences in the NMR peaks of the cation enantiomers. The authors postulated that a stronger ion pair formation will bring the anion closer to the cation and make their interaction stronger and, hence, produce larger splitting values. The chiral recognition was found to be dependent on solvent dielectric constant, concentration, and structure of the CILs. Interestingly, relatively strong enantiomeric recognition toward the racemic cation (1-methyl-3-(2-methyl-butyl) imidazolium) is induced by chiral anions; however the reverse is not true. In fact, chiral cation (*S*)-1-methyl-3-(2-methylbutyl) imidazolium did not show any appreciable chiral recognition toward racemic anions. [130]

Recently a series of CILs based on chiral sulphate anions was described (please see page 35) and their use as chiral shift reagents was showed, using 2,2,2-trifluoro-1-phenylethanol **34** (Figure 1.1.16) as racemic substrate. [117] The authors reported that with the majority of CILs tested no splitting was observed on the ^{19}F NMR doublet signal of the alcohol **34**, when $CDCl_3$ was used as deuterated solvent. But when the solvent was D_8-toluene the ^{19}F NMR doublet signal of the alcohol **34** was observed with all the CILs tested. The authors claimed that the solvent polarity (lower with toluene) determined these results, that is in agreement with Parker[126] that reports that less polar solvents increase the chemical shift difference.



34

Figure 1.1.16 – Structure of 2,2,2-trifluoro-1-phenylethanol.

Several CILs with chiral cation were studied as chiral solvating agents, but till now CILs with chiral anions have been neglected by the literature. Tran *et al.* [130] and Wasserscheid *et al.* [101]have study the intramolecular chiral recognition by the chiral anions of CILs. Tran *et al.* [130] have also demonstrated that an enantiomeric discrimination is possible using CILs with chiral anion and achiral cation toward another chiral cationic molecule such as a quinine derivative[130], although the anion effect on this chiral discrimination is not clear. Recently Winkel *et al.* [117] have demonstrated that CILs based on chiral anions can induce chirality on neutral molecules. The main interactions between the CILs and the racemic substrate were hydrogen bonds that lead to a split on the[19]F NMR signal of the racemic alcohol. In conclusion, the literature has showed that chiral induction using CILs with chiral anions are possible, but is not widely explored. More studies have to be done in this area.

1.1.5 Magnetic Ionic Liquids (MILs)

Among the various research areas in the field of novel functionalized ILs, the synthesis and application of Magnetic Ionic Liquids (MILs) has attracted considerable more recent interest. Paramagnetic ILs based on anions comprising transition-metal coordination complexes have been reported by several research groups (e.g. $[Fe^{III}X_4]^-$ (X: Cl, Br),[67, 131] $[Mn^{II}X_4]^{2-}$ (X: Cl, Br), [68] $[Co^{II}X_4]^{2-}$ (X: Cl, NCS, $N(CN)_2$),[68, 132] $[Gd^{III}Cl_6]^{3-}$,[68] and $[Dy^{III}(SCN)_{8-x}(H_2O)_x]^{-(5-x)}$ (x: 0–2)[133] anions pairing with conventional counter cations such as imidazolium or phosphonium based cations). Most of these MILs can be obtained simply by mixing the halide salts and the neutral metal complexes. For example dark brown IL [BMIM][$FeCl_4$] is formed by mixing crystalline [BMIM][Cl] and a slight excess of $FeCl_3$ under inert atmosphere.[65, 67] Among the first examples were those reported by Hayashi and Hamaguchi in 2004,[67] who described the IL [BMIM][$FeCl_4$] as a material with a large magnetic susceptibility. Several others IL based on different cations in combination with $FeCl_4$ as anion were reported,[65, 68, 134] although some of them have melting temperatures just above 100°C.[135] Freeman *et al.* [136]have studied [BMIM][$Fe^{III}Cl_4$] and $[BMIM]_2[Fe^{II}Cl_4]$, and showed that iron(III) chloride forms ILs from a mole ratio of 1 $FeCl_3$/1.9[BMIM][Cl] to 1.7 $FeCl_3$/1 [BMIM][Cl]. When [BMIM][Cl] is in excess, Raman scattering indicates the presence of $FeCl_4^-$, and when $FeCl_3$ is in excess, $Fe_2Cl_7^-$ begins to appear and the amount of $Fe_2Cl_7^-$ increases with increasing amounts of $FeCl_3$.

Yoshida *et al.* [131]prepared several MILs based on $[FeCl_4]^-$ and also $[FeBr_4]^-$, in combination with 1-alkyl-3-methylimidazolium cations and compared their macroscopic properties. They have concluded that the increasing of the cation alkyl chain leads to reduced fluidity and ionic conductivity mainly caused by the van der Walls attraction between the chains. Replacement of

chloride by bromide, which results in increased molecular weight, also has a significant impact on the physical properties of the liquids. Abbott et al.[134c] reported ILs with the $[FeCl_4]^-$ anion paired with both trimethyl ethanolammonium and dimethylphenylethanolammonium cations. Del Sesto *et al.*[68] have reported a series of paramagnetic ILs having tetraalkylphosphonium or alkylmethylimidazolium cations paired with tetrahedral or octahedral symmetry transition metal anions, for which the metal is iron, cobalt, manganese or gadolinium. ILs based on alkylmethylimidazolium cations possess an acidic proton in 2-position that makes the cation fairly strong hydrogen bond donor, particularly in the presence of metal halide anions,[68] resulting in a more organized structure of the IL leading to solid salt at room temperature. ILs based on bulky tetraalkylphosphonium cations leaded to liquids with all transition metal anions studied. The authors claimed that the tetraalkylphosphonium cation lack of acidic protons prevents the establishment of hydrogen bonded networks seen in the imidazolium salts. ILs based on these bulky cations are not conducive to crystallization. All the ILs showed simple paramagnetic behaviour over a temperature range of 300 K but still responded strongly to a magnetic field. Mudring and co-workers[133] focused on dysprosium-based ILs. ILs based on 1-hexyl-3-methylimidazolium in combination with $[Dy^{III}(SCN)_{8-x}(H_2O)_x]^{-(5-x)}$ (x: 0–2)[133] combine magnetic and luminescent properties. All the synthesized compounds showed strong response to the magnetic field, superior to the known transition metal ILs because of the magnetic moment of dysprosium(III) is twice the size of that of iron (III). [133] Interestingly, the dysprosium-containing IL also displayed luminescence, a behaviour already known for lanthanide based ILs.[64] Although the higher spin moments of certain f-block elements can produce ILs with stronger magnetism, the low cost and relative abundance of iron make Fe-based magnetic ILs attractive subjects for continued study.[60b] Okuno *et al.* [134a]demonstrated that nonmagnetic materials in a MIL that has a very large magnetic susceptibility, can be respond to a magnet. In this way can be transported and separated readily in the MIL with the help of magnetic field gradients (Figure 1.1.17).[134a]

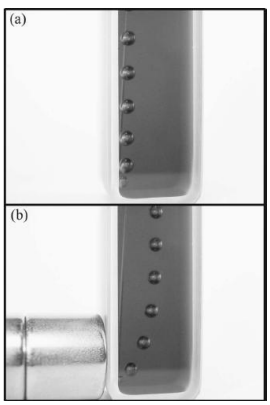
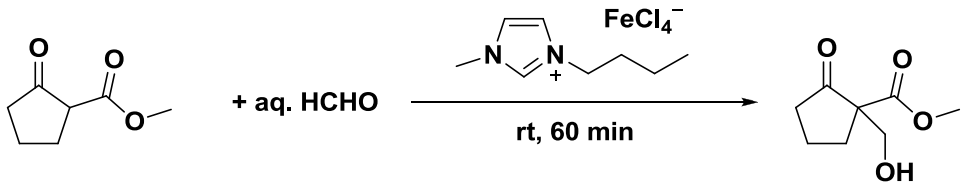


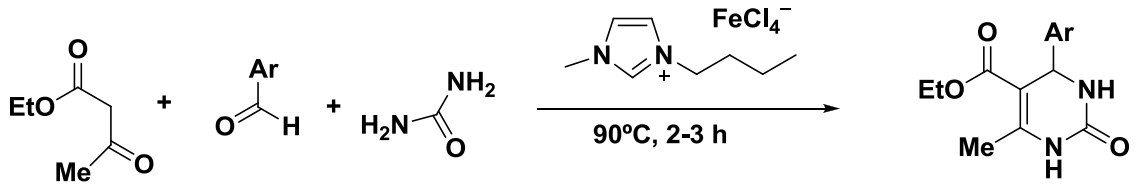
Figure 1.1.17 – Movement of N_2 bubbles in a magnetic IL in the absence a) and in the presence of a Nd magnet b). (Figure adapted from ref. [134a]).

Recently, imidazolium chloroferrates [BMIM][$FeCl_4$] has been introduced as a new series of Lewis acidic ILs in organic synthesis. In 2006 Bica and Gaertner[137] have demonstrated that aryl Grignard cross-coupling reactions can be catalyzed by [BMIM][$FeCl_4$]. Furthermore this MIL is air stable, and could be recycled for at least four times. The same authors[63] showed that [BMIM][$FeCl_4$] can catalyze the hydroxymethylation of β-keto esters using aqueous formaldehyde and a low catalyst loading of up to 0.1 mol% without co-solvents or additional surfactants (Scheme 1.1.38).



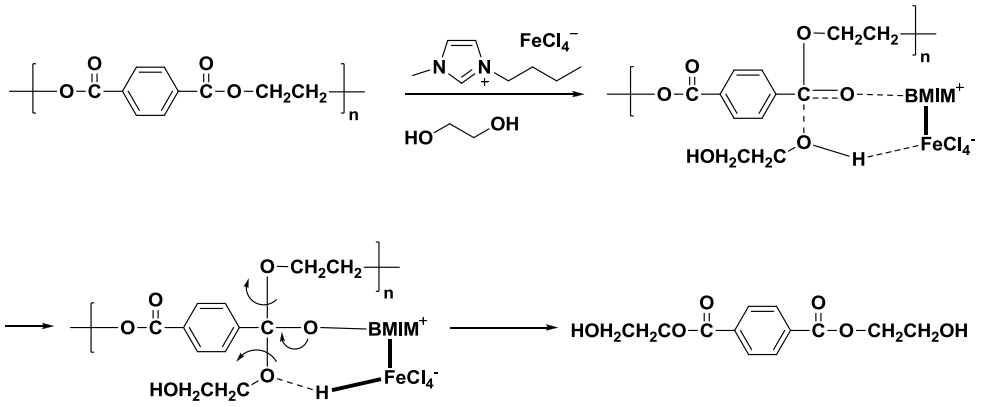
Scheme 1.1.38 – MIL-catalyzed hydroxymethylation using formaldehyde.

Chen and Peng[138] have showed that [BMIM][$FeCl_4$] is an efficient catalyst for the synthesis of 4-aryl-dihydropyrimidinones through Biginelli condensation (Scheme 1.1.39).



Scheme 1.1.39 – One-pot synthesis of 3,4-dihydropyrimidin- 2(1H)-ones under solvent-free conditions, by Biginelli condensation using [BMIM][$FeCl_4$] as catalyst.

The depolymerisation of poly(ethylene terephthalate) (PET) in ethylene glycol could be catalyzed by [BMIM][$FeCl_4$].[139] In fact this MIL exhibits higher catalytic activity compared with $FeCl_3$ or [BMIM][Cl]. The authors proposed a mechanism where the synergic effect of the cation and anion in [BMIM][$FeCl_4$] makes the attack of oxygen in ethylene glycol on the carbon cation of the ester group much easier (Scheme 1.1.40).



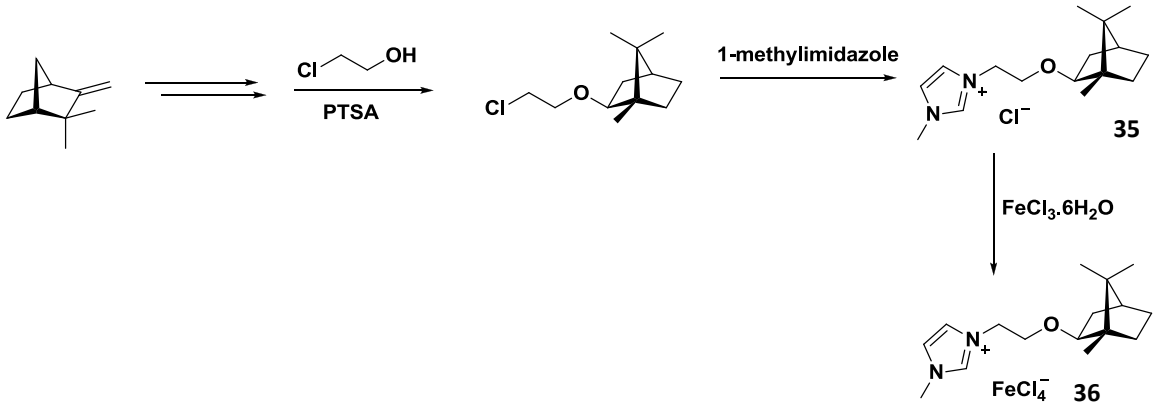
Scheme 1.1.40 – Proposed mechanism for the glycolysis of PET catalyzed by [BMIM][$FeCl_4$]. [139]

Kozlova *et al.* reported the use of paramagnetic ILs, [BMIM][$FeCl_4$][140] and [BMIM]$_2$[$CoBr_4$][141] as stationary phase for gas chromatography. No significant effects caused by the paramagnetic anion was observed, and the obtained results [BMIM][$FeCl_4$] are very close to those obtained for [BMIM][NTf_2]. Taking advantage of magnetic properties of MILs, Koo and co-workers[142] have showed that it is possible to recover the MIL from a reaction medium by application of a magnetic field.

MILs can have different applications, for example could be used as mechanical devices (e.g., magnetically operated switches) or as transport media that can be moved by magnetic fields in a controlled way inside closed network systems. Medical as well as engineering applications can be thought of in the future.

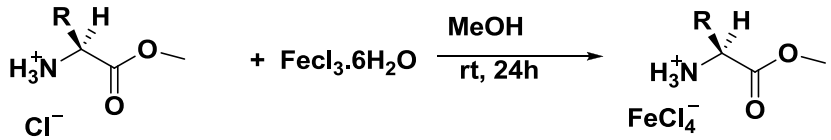
1.1.6 Chiral Magnetic Ionic Liquids (CMIL)

In 2007 was reported the synthesis of a chiral magnetic ionic liquid (CMIL) with a chiral cation derived from camphene.[143] The synthesis of the cation involves the reaction of (+)-camphene with chloroethanol under acid catalysis led, *via* a Wagner-Meerwein rearrangement to chloroethoxybomeol (Scheme 1.1.41). After quaternization of the 1-methyimidazole the IL **35** was obtained in 90% yield. The anion metathesis was achieved by addiction of $FeCl_3$ to the chloride salt, and compound **36** was obtained. In order to investigate the stereochemical induction of the synthesized CMIL the Diels-Alder reaction between acrylic acid and cyclopentadiene was performed. Some diastereoselectivity was obtained on the final product and was also possible to recycle the CMIL at least four times, but no enantioselectivity was observed. This means that although the CMIL can catalyze the Diels-Alder reaction, no chirality was induced by the chiral cation of the IL. Although the $[FeCl_4]^-$ anion could provide magnetic properties to the IL, this issue was not explored by the authors. [143]



Scheme 1.1.41 – Synthesis of camphor-based chiral IL, with $[FeCl_4]^-$ as anion.

In 2009 Warner and co-workers[144] have reported the synthesis of CMILs based on aminoacids, with $[FeCl_4]^-$ as anion, possessing simultaneous chiral and magnetic properties. L-amino acids methylester hydrochlorides were mixed with $FeCl_3.6H_2O$ in anhydrous methanol at room temperature, for 24 hours (Scheme 1.1.42), obtaining the desired CMILs. The authors report that the presence of the ammonium cation instead of the imidazolium cation could decrease the biological and environmental hazard potential, enhancing the biodegradability of the MCILs. The MCILs synthesized were characterized by ^1H and ^{13}C NMR although due to the paramagnetic properties of the MCILs, very dilute sample solutions in deuterated DMSO were used. Their paramagnetic properties were confirmed by use of SQUID (Quantum Design superconducting quantum interference device) measurements. In addition, their chiral discrimination toward chiral analytes was investigated by use of steady-state fluorescence spectroscopy. Using (R)- or (S)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) as substrate in the presence of $[L\text{-}AlaOMe][FeCl_4]$, two different emission spectra were obtained, confirming the chiral discrimination ability of the MCIL. The authors report that their strong response to a magnetic field could be particularly beneficial for providing an easier approach to recovering and recycling the MCILs used as asymmetric catalysts. [144]



Scheme 1.1.42 – Synthesis of chiral magnetic ionic liquids (CMILs), starting from L-amino acids methylester hydrochlorides and $FeCl_3.6H_2O$.

1.1.7 ILs and rheology

Since ILs are more viscous than conventional solvents, viscosity is an important property due to its strong effect on the rate of mass transport within solution. Identity of the anion has a large effect on the viscosity of an IL, in particular through their relative basicity and ability to

participate in hydrogen bonding.[145] For example, the perfluorinated BF_4^- and PF_6^- anions form much more viscous ILs (containing strong H-F interactions) than those formed by the weakly basic $N(Tf)_2^-$anion, in which the negative charge is extensively delocalized over the two sulfone groups.[146] Shift of the organic cation causes a more subtle change in viscosity, and this is attributed to the influence of van der Waals interactions; viscosity generally increases with increasing cationic size (for example, by in increasing alkyl chain length).[146]

The main impurities in an IL are the water and chloride contents, that can reduce the viscosity substantially.[147] The water content can vary in different samples of the same IL (especially in hygroscopic ILs). It is very important to measure the water and chloride contents of an IL before or after a rheological study.

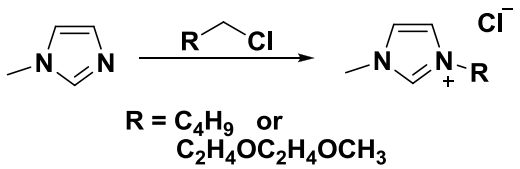
It is not possible to discuss this part of the work without a small and simple introduction about rheology, which is available in Appendix (section 6.1 page 223).

1.2 Results and discussion

1.2.1 Ionic Liquids Synthesis

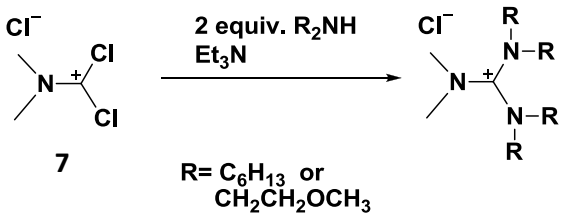
In this work several ILs were synthesized and depending on the cation, or the anion nature the synthesis can comprise different challenges. Were synthesized guanidinium, imidazolium and pyrrolidinium cations in combination with different anions.

ILs based on imidazolium cations were prepared by quaternization of *N*-methylimidazole with different haloalkanes (Scheme 1.2.1). This type of cation was synthesized without the use of an organic solvent, just by the addition of *N*-methylimidazole to the haloalkane in a small excess. The mixture was heated over night, and in the end of the reaction two different phases was formed, being the haloalkane excess (upper phase) removed by decantation. Depending on the reagents purity, the IL obtained was different. For example, [BMIM][Cl] was synthesized several times during this work, and could be obtained as a white solid (when the reagents were distilled before use), or as a yellow viscous liquid (when the reagents were not purified). [BMIM][Cl] is a very hygroscopic compound, so it was kept under an ether solution to avoid the water contamination.



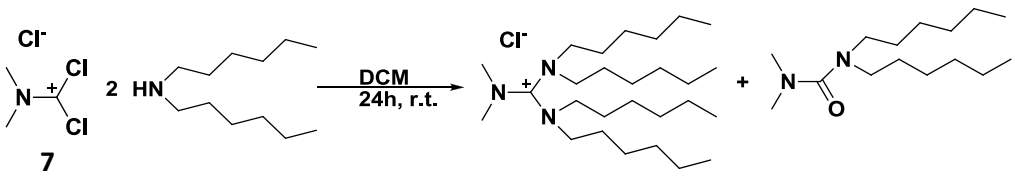
Scheme 1.2.1 – Quaternization of *N*-methylimidazole with chloroalkanes.

To obtain highly pure guanidinium based ILs, is not as straightforward as for imidazolium based ILs. This is because with imidazolium based ILs a simple distillation is enough to purify the starting reagents, although the synthesis of guanidinium based ILs have as starting material the *N*,*N*-dimethylphosgeniminium salt **7**, that is unstable and very difficult to purify. So the final IL is obtained with a brown colour.



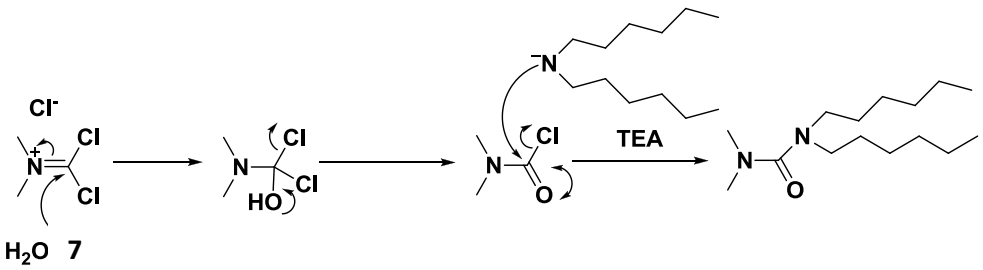
Scheme 1.2.2 – Synthesis of hexaalkylguanidinium salts starting from *N*,*N*-dialkylphosgeniminium salts.

Another difficult in this IL synthesis is that a secondary product can be formed, reducing the IL final yield (Scheme 1.2.3).



Scheme 1.2.3 – Synthesis of the IL *N,N,N'N'*-tetrahexyl-*N,N*-dimethylguanidinium chloride [(di-*h*)$_2$DMG][Cl], starting from the secondary amine, and *N*,*N*-dimethylphosgeniminium salt **7**.

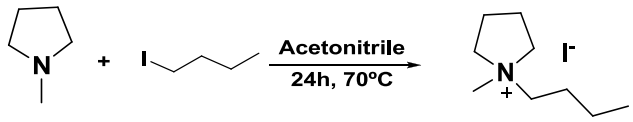
It was observed that the urea derivative formed had lower R_f value than the IL, so it was possible to separate this side product by column chromatography with silica gel, using AcOEt/Hx (1:1) as eluent. After total removal of the urea derivative, the eluent polarity was raised to dichloromethane, or even ethanol for the totally removal of the IL from the silica. A mechanism for the formation of the urea derivative is proposed (Scheme 1.2.4). This reaction is made in anhydrous conditions, but there a small amount of water from the compound **7** is always present, allowing the urea derivative formation. The amount of urea formed is dependent on the water quantity present.



Scheme 1.2.4 – Proposed mechanism for the urea derivate formation.

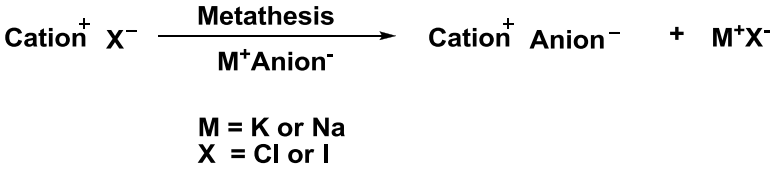
There are several aspects to consider during the guanidinium chloride synthesis. The system had to be completely anhydrous; the smaller amount of water present, smaller urea is formed. Given that a small amount of urea is always formed, the method to purify the IL is by column chromatography, using polar solvents.

It was also performed the synthesis of pyrrolidinium based ILs by quaternization of 1-methylpyrrolidine with 1-iodobutane. In this case the alkylating agent used was 1-iodobutane instead of the 1-chlorobutane. The reason is that 1-methylpyrrodine is less nucleophilic than others amines, such as *N*-methylimidazole, so is necessary the use of a more reactive reagent, for this nucleophilic substitution reaction. Iodine based ILs are more difficult to purified, and are more sensible to UV light. Therefore the [BMPyr][I] synthesized was kept protected from light.



Scheme 1.2.5 – Synthesis of [BMPyr][I] by quaternization of 1-methylpyrrolidine with 1-iodobutane.

Mostly of anion metathesis reactions were performed starting from the halide salt (chloride or iodide) combined with the sodium or potassium salt of the desired anion (Scheme 1.2.6).

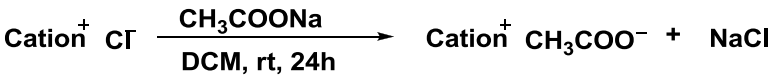


Scheme 1.2.6 –Synthesis of ILs by anion metathesis.

The method used was quite simple; the precursor salt was dissolved in dichloromethane (DCM) and was added 2 equivalents of the sodium or potassium salt of the desired anion. The alkali salt was not soluble on DCM, so was formed an heterogeneous solution, that was left stirring overnight. After that the remaining solid was filtered, and the organic phase passed through a silica/carbon column, to remove the remaining halide salt. The chloride content of the ILs obtained by this method were above 100 ppm, which is a very good result due to the fact that halide salts are very difficult to remove from the final IL. For some applications the presence of even 100 ppm of chloride can deactivate some catalysts, so other halide free synthetic method has to be performed.

As said before ILs colour is usually the result of unidentifiable trace amounts of impurities.[77] When a IL is purified in silica/carbon column not only the halide impurities are removed, but also the IL colour can became lighter or even colourless, depending on the initial colour of the IL. An important consideration is that the silica/carbon column has to be well packed in order to obtain better results.

With the objective of synthesize ILs based on acetate anion was performed the anion metathesis with sodium acetate salt in combination with the chloride salt of several cations, using DCM as solvent (Scheme 1.2.7). This method was successfully achieved with 1-butyl-3-methylimidazolium (BMIM) cation, but unfortunately no anion exchange was observed when [MOEOEMIM][Cl] was used.



Scheme 1.2.7 –Synthesis of ILs based on acetate anion.

So, a different approach was used; the anion metathesis was performed using an ion exchange resin (Amberlite OH form). The objective was to pass the IL chloride on the resin, to obtain [MOEOEMIM][OH], and neutralize with acetic acid (Figure 1.2.1). The NMR analysis of the obtained IL showed that the desired IL was not formed, and the acidic C2 proton of the imidazolium cation was not visible on the ^{1}H NMR spectrum, indicating that this cation was not stable on the resin.

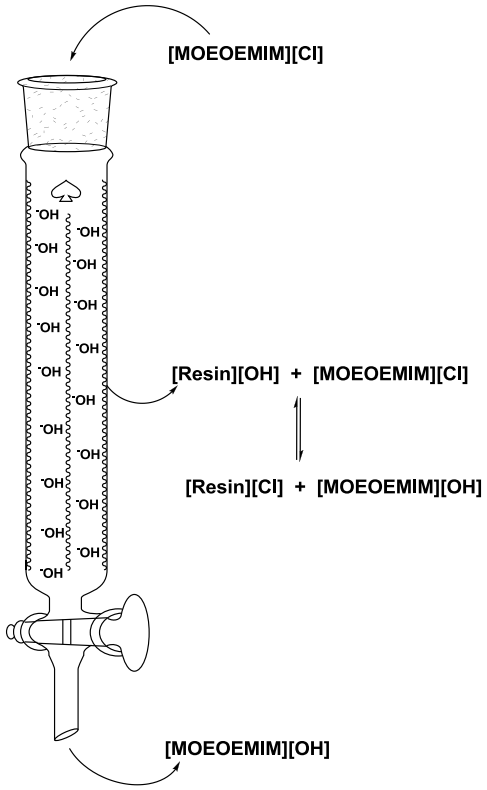


Figure 1.2.1 – Example of anion exchange of [MOEOEMIM][Cl]using an ion exchange resin.

At the time the [MOEOEMIM][OAc] was abandoned, but recently literature[72] shows a possible method to synthesize this IL. First the anion is incorporated in the resin before the anion exchange is carried out, by passing through the resin (Amberlite, OH form) a solution of ammonium acetate. The process involves the acid–base reaction with OH^-, resulting in the retention of the acetate anion in the resin. After that a solution of [MOEOEMIM][Cl] is passed through the column consequently the acetate anion loaded on the resin is substituted by the chloride anion, and the desired IL formed is eluted out of the resin.

Although the direct anion exchange of [Cation][Cl] to [Cation][OH] was not successful for [MOEOEMIM][Cl], due to cation instability, the same did not happen with the cations: Aliquat 336® [Aliquat®], trihexyl(tetradecyl)phosphonium [$P_{6,6,6,14}$], *N,N,N',N'*-Tetra-(2-methoxyethyl)-*N,N*-dimethylguanidinium, [$(C_3O)_4$DMG] and *N,N,N'N'*-tetrahexyl-*N,N*-dimethylguanidinium [(di-

h)$_2$DMG][Cl]. With all of these cations, the anion exchange from chloride to hydroxide where successfully achieved with the ion exchange resin Amberlite (OH form). After that the hydroxide salts were neutralized with acetic acid, and the desired IL was formed, with acetate as ion pair.

1-Ethyl-3-methylimidazolium [EMIM] cation is synthesized under ambient conditions by the reaction of *N*-methylimidazole with diethylsulphate without the use of any solvent.[31] Literature reported that this IL can be used for subsequent anion metathesis with for example HPF_6, but in case of acetate anion (sodium acetate salt) the anion exchange was not accomplished. The synthesis of [EMIM] cation do not involves the reaction of *N*-methylimidazole with ethylchoride because this reagent is a toxic gas. So another method for the synthesis of [EMIM][OAc] was performed. The synthesis of carbonate-based imidazolium salts was reported by Rogers *et al.* [148] starting from the zwitterionic 1,3-dimethylimidazolium-2-carboxylate **1** and H_2CO_3 in DMSO (Scheme 1.2.8).

1

Scheme 1.2.8 – Synthesis of [EMIM][HCO_3] starting from the zwitterionic 1,3-dimethylimidazolium-2-carboxylate 1 and H_2CO_3

The 1-ethyl-3-methylimidazolium hydrogen carbonate was purchase from Aldrich in a methanolic solution, and was added acetic acid, resulting on the formation of CO_2 and the desired IL. This process involves the acid–base reaction with of [EMIM][HCO_3] and a stronger acid (pKa<6.3), in this case acetic acid.

In Table 1.2.1 are described some properties of ILs synthesized.

Table 1.2.1 – Properties of some ILs synthesized.

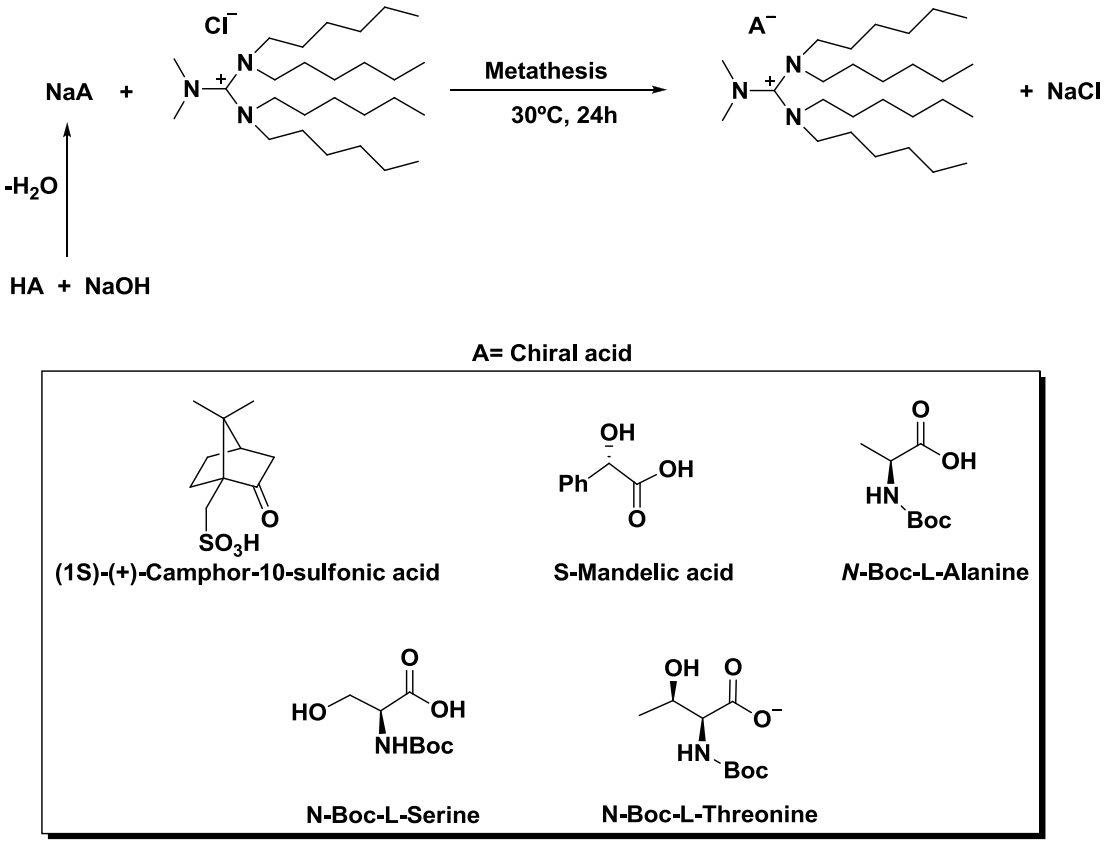
Ionic Liquids		Miscible [a]	Immiscible [a]	T_g(°C)[b]	T_{dec}(°C)[c]
[MOEOEMIM]	[Cl]	DCM,H_2O	Et_2O,Hex	-85.00	nd
	[DCA]	DCM,H_2O	Et_2O,Hex	-88.59	276.55
	[SAC]	DCM,H_2O	Et_2O,Hex	-63.59	242.66
	[ACES]	DCM,H_2O	Et_2O,Hex	-62.73	~180
	[SCN]	DCM,H_2O	Et_2O,Hex	-81.79	214.63
[$(C_3O)_4$DMG]	[Cl]	DCM,H_2O, Et_2O	Hex	-58.63	262.54
	[SAC]	DCM,H_2O, Et_2O	Hex	-49.34	>250
	[SCN]	DCM,H_2O, Et_2O	Hex	-67.73	>250

[BMIM]	[DCA]	DCM,H_2O	Et_2O,Hex	-6.00[d]	224.69
	[Cl]	DCM,H_2O	Et_2O,Hex	-63.00	nd
	[DCA]	DCM, Et_2O	H_2O, Hex	-77.18	250.00
[(di-h)$_2$DMG]	[SAC]	DCM, Et_2O	H_2O, Hex	-56.71	>300
	[ACES]	DCM, Et_2O	H_2O, Hex	-65.27	>225
	[SCN]	DCM, Et_2O	H_2O, Hex	-72.43	275

[a]miscible or immiscible in different organic solvents (DCM dichloromethane; Et_2O – diethyl ether; Hex – hexane); [b] Glass Temperature; [c] Decomposition Temperature; [d] melting point.

Studies on our laboratory in toxicity of ILs on human cell lines [149] (HT-29 and CaCo-2 cells) have concluded that imidazolium containing an ether moiety and choline cations, independently of the anion, were the less toxic among the ILs tested. On the other hand the combination of [(di-h)$_2$DMG] cation with different anions, resulted on toxic ILs (for this cell line). Although the cation [$(C_3O)_4$DMG], with the same guanidinium moiety is a non toxic IL (only was tested [$(C_3O)_4$DMG][Cl]). This was a quite surprising result, since it was expected that the toxicity derived from the guanidium moiety. Although, the alkylic chain appears to be is a dominant factor in the toxicity of ILs.

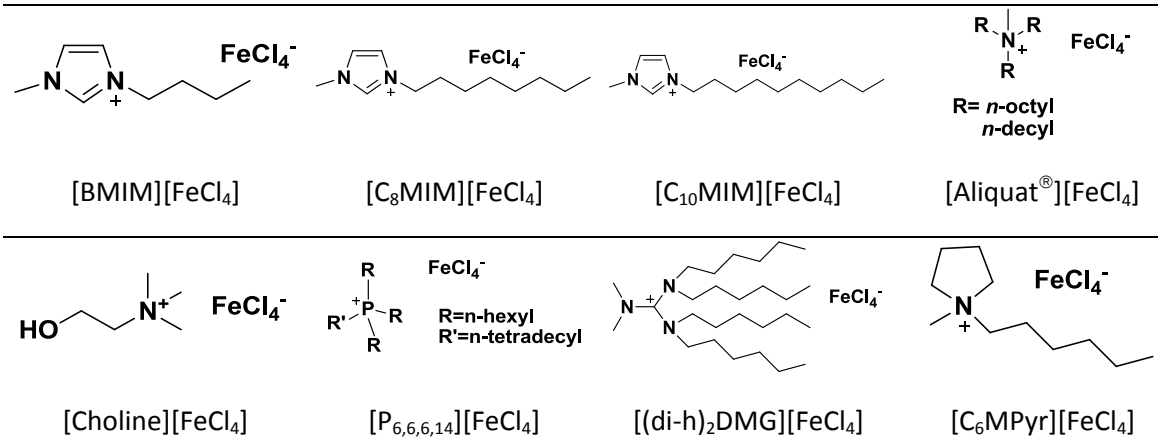
The synthesis of CILs was achieved by the anion exchange of chloride based ILs with readily available *N*-protected amino acids, or chiral carboxylic acids such as mandelic, camphorsulfonic, or quinic acid. All the amino acids used were *N*-protected, because it allowed a better stability of the final IL. The anion metathesis reactions with the cation [(di-*h*)$_2$DMG] were performed starting from the chloride salt combined with the sodium salt of the desired anion (Scheme 1.2.9).



Scheme 1.2.9 –Synthesis of ILs by anion metathesis.

The sodium salts of the respective chiral acid were made *in situ*, in a aqueous solution, that was added to a methanolic solution of [(di-*h*)$_2$DMG][Cl], and left stirring over night at 30°C. Then the solvents ethanol/water was removed by evaporation, and DCM was added to the solution. After filtration, to remove the excess salts, and passing through a silica/carbon column the desired CIL was obtained. The method used was not very effective because it was necessary at least 3 equivalents of the chiral acid relatively to the IL, for the exchange be complete. On the other hand, with some chiral acids, as quinic acid, the desired IL was not formed. Another method was used to synthesize CILs based on quinic acid. The [$P_{6,6,6,14}$][Quinic] was prepared starting from [$P_{6,6,6,14}$][Cl], using the resin Amberlite (OH form) as described before.

Magnetic ILs (MILs) were prepared just by the addition of $FeCl_3$ to chloride salts of several anions (Figure 1.2.2). A small excess of $FeCl_3$ was added to a solution of chloride salt and DCM, after stirring for one hour, the DCM was evaporated, and the MIL was passed through a silica column with DCM as eluent. The excess of $FeCl_3$ remained on the column, so the eluted IL was pure. Due to the magnetic nature of these MILs was not possible characterize them by NMR.



[BMIM][$FeCl_4$] [C_8MIM][$FeCl_4$] [C_{10}MIM][$FeCl_4$] [Aliquat®][$FeCl_4$]

[Choline][$FeCl_4$] [$P_{6,6,6,14}$][$FeCl_4$] [(di-h)$_2$DMG][$FeCl_4$] [C_6MPyr][$FeCl_4$]

Figure 1.2.2 – Magnetic ILs based synthesized.

All the synthesized MILs were liquid at room temperature, except for [Choline][$FeCl_4$] and [C_6MPyr][$FeCl_4$], that were solid, although with a low melting point (around 50°C).

1.2.2 Ionic Liquids Purification

For several reasons ILs purification is not an easy task. To avoid several purifications steps it is preferable to avoid the presence of some impurities, for example the use of purified reagents, and use of pure solvents in ILs synthesis every time possible. For guanidinium synthesis for example the starting material *N*,*N*-dimethylphosgeniminium chloride salt, is difficult to purify due to its instability, so the synthesis of this type of ILs cation will always involve the presence of some impurities. For example during the performance of this work it was purchase the reagent *N*,*N*-dimethylphosgeniminium chloride salt from different companies, and the purity of the compound was completely different. The cheapest and more yellow compound originated dark brown ILs, instead of yellow ILs that were synthesized with the most pure reagent.

Other inevitable impurity when chloroalkanes are used on the ILs synthesis is the chloride content of the IL. As said in the introduction this can be avoided by halide free ILs synthesis, but not always this type of synthesis is viable. So during this work some procedures were made to minimize this impurity. For example the uses of ion exchange resin to perform the anion metathesis. This method allows the decrease of chloride content, not detectable by potentiometric analysis of chloride ions used to measure the chloride content of ILs. When other metathesis methods are used, passing the IL through a silica/carbon column can decrease the quantity of chloride anions, and purification can be improved when silica/carbon column is very well packed. Another method used to remove not only the chloride content, but also the IL colour, is dissolve the IL in methanol, or ethanol, add activated carbon, heat and left stirring for at least one hour. This method remove several impurities present on the IL, but also decrease

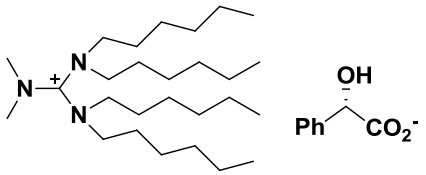
the IL final yield, because the impurities as well as the IL is adsorded by the activated carbon. Depending on the type of ILs application, the IL purity is not crucial, so several purifications steps can be avoided.

Water is other impurity present in ILs, and in some hydrophilic ILs can be very difficult to extract. For example, it is very difficult to remove all the water present in sample of the hygroscopic IL [BMIM][Cl]. This sample can be in high vacuum (10^{-3} mm Hg) with a magnet bar for one week, and still be water present on the IL. An efficient method to remove water from this IL is by freezing the IL with liquid nitrogen, and put at high vacuum, that is a "home-made" lyophilisation.

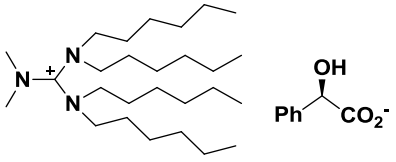
MacFarlene *et al.* showed that when sorbents like alumina, silica or charcoal can remain in the "purified" IL as nanoparticulate contamination.[80] Microfiltration (200 nm) can reduce the contamination to very low levels (<10 ppm) although even at this low level there is still an impact on the physicochemical properties of the IL. This observation is very important, because neither silica nor carbon is detected on NMR that is the main technique used to characterize ILs.

1.2.3 Asymmetric induction of CILs

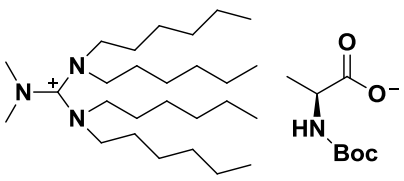
The enantiomeric recognition ability of the CILs synthesized was tested by investigating the diastereomeric interaction with different racemic probes by ^{19}F NMR. The method was very simple: it was mixed the CIL (Figure 1.2.3) with the NMR probe (Figure 1.2.4) (100:1, CIL/probe), and was introduced in a 3 mm NMR tube. This tube was introduced in a bigger NMR tube (5 mm), with $CDCl_3$ as deuterated solvent (Figure 1.2.5). Then ^{19}F NMR spectrum was recorded.



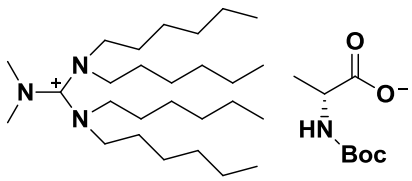
[(di-h)$_2$DMG][(S)-Mand]



[(di-h)$_2$DMG][(R)-Mand]



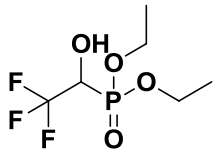
[(di-h)$_2$DMG][(L)-Boc-Ala]



[(di-h)$_2$DMG][(D)-Boc-Ala]

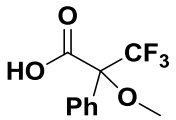
Figure 1.2.3 – CILs tested for asymmetric induction by ^{19}F NMR.

Three different NMR probes were chosen (Figure 1.2.4). It was important that CF_3 group was present not only to act as hydrogen bond acceptor, but also to be possible analyze the diastereomeric interactions by ^{19}F NMR. The compound 1-(9-anthryl)- 2,2,2-trifluoroethanol **39** is a hydrogen bond donor and can also interact with other compounds by π-stacking.[126]



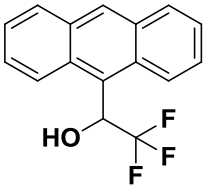
37

(R,S)-Diethyl (2,2,2-trifluoro-1-hydroxyethyl)-phosphonate



38

(R,S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (Mosher's acid)



39

(R,S)-2,2,2-Trifluoro-1-(9-anthryl)ethanol

Figure 1.2.4 – Probes used in ^{19}FNMR studies for the asymmetric induction studies.

Since all the CILs synthesized have chirality on the anion, our objective was to see if the chiral anion could form diastereomeric complexes with the target molecule (NMR probe described on Figure 1.2.4). It was expected that the racemic alcohol (**37** or **39**) would interact with the enantiopure anions of the CILs through hydrogen bonding. But unfortunately it was not observed a splitting on the CF_3 ^{19}F NMR signal. There are possible explanations for these unexpected results that not necessarily indicate lack of chiral induction by the CILs. The first point is that in our experiments, the CIL and the racemic probe were not dissolved in a deuterated solvent, so the anion-probe interactions could be effective; the NMR lock was possible due to the presence of a deuterated solvent outside of the NMR tube (Figure 1.2.5). If the CIL and the racemic probe were dissolved on a deuterated solvent, the solvent polarity should have an influence on the formation of a diastereomeric complex.

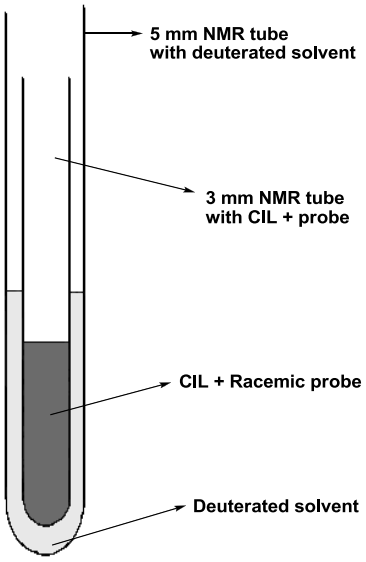


Figure 1.2.5 – NMR analysis of chiral induction by ILs.

On the other hand it is possible that the interaction of the NMR racemic probe and the chiral anion of the CIL were not strong enough to induce a considerable splitting on the NMR signal. A complementary functionality between the anion and the probe is preferable, for example if the probe is a hydrogen bond donor, the chiral solvating agents of choice should be a hydrogen bond acceptor.[103b] The main interactions observed with chiral solvating agents and NMR probes, such as Mosher's acid, reported on the literature, are ionic interactions, although some other interactions, such as hydrogen bonding may also contribute primary or secondarily toward association complexes.

Possible alternatives that were not explored at the time, is to dissolve the CIL and the probe in nonpolar solvents, such as deuterated chloroform. Another is to use a different probe, where ionic interactions with the chiral anion are possible, in a way to form diastereomeric complex. For example a salt with an organic racemic cation where is possible to see the split of the signal related to the CF_3 group of the racemic probe.

1.2.4 Rheological studies of CILs

Rheological studies of some synthesized ILs were performed. A simple introduction about rheology is available in Appendix (section 6.1 page 223), although it is possible to summarize some important characteristics of rheology. Rheology studies the response of a material when it is applied a strength (tension). Rheological properties report us how a material responds when is subject of a mechanic solicitation, this response is nothing more than the material structure expression due to their chemical composition.[150] There are basically three theoretical states of materials: linear elastic solid (Hooke solid), perfect fluid (Newtonian liquid) or viscoelastic

material.[151] Scientists have proposed several rheological models that describe the mechanical behaviour of these materials correlating some rheological properties. In this work all the fluids analysed were considered perfect fluids.

Perfect fluid has a plastic behaviour where any deformation ceases when the applied force is removed and the material don't reverse to the original form.[151] This type of material can be described by a model proposed by Newton where the force, or resistance (shear stress) is proportional to the velocity of movement (shear rate), ($\sigma = \eta \cdot \dot{y}$, where the proportional constant η is the viscosity, Pa.s). Several liquids follow the Newton law, so they are called Newtonian liquids. For these materials the viscosity does not vary with deformation rate or time (although varying with the temperature and pressure). In summary, a Newtonian behaviour follow some characteristics: the shear viscosity (η) does not vary with shear rate ($\dot{y}$), (Figure 1.2.6a) and the shear rate is proportional to the shear stress of the material (Figure 1.2.6b).[151]

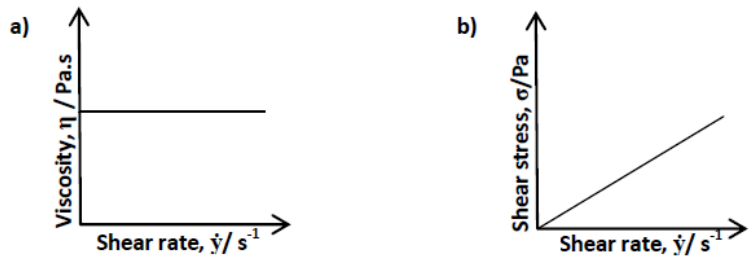
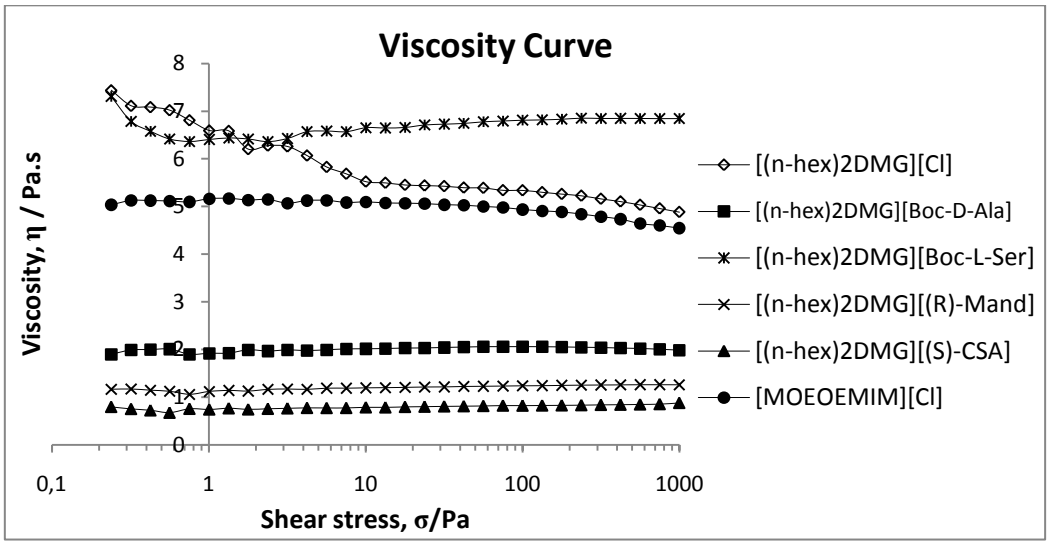


Figure 1.2.6 – Variation of: a) viscosity, η/Pa.s with shear rate ẏ/s-1, and b) shear stress, σ/Pa with shear rate ẏ/s-1.

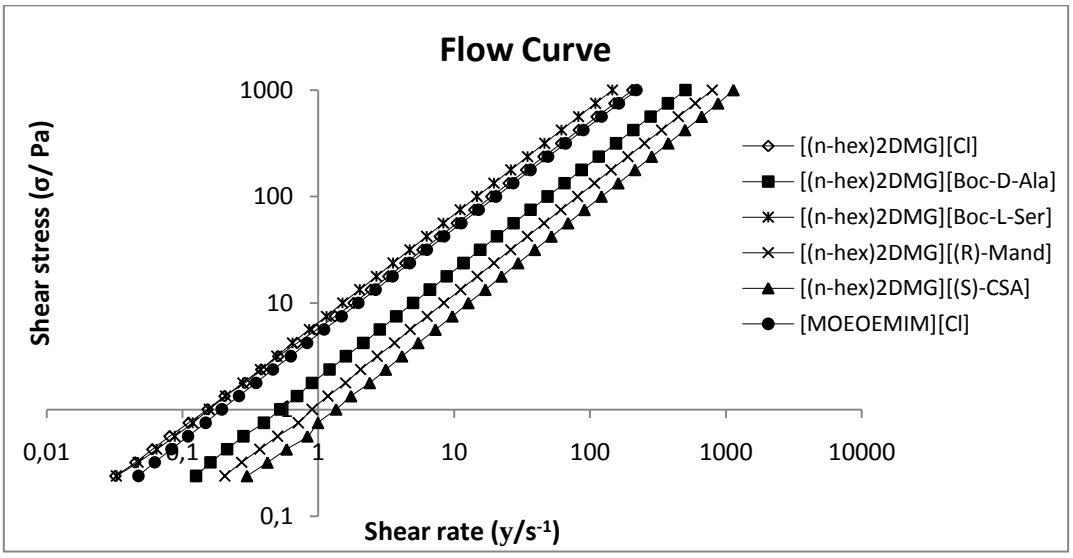
In this work were performed steady tests that consist in the application of a gradient of tension to the sample. These tests are used for the determination of apparent viscosity at several rates of deformation, allowing the determination of flow curves (representation of shear stress *vs.* shear rate) and viscosity curves (representation of viscosity *vs.* shear rate).[152] For Newtonian fluids the steady tests are sufficient to characterize the material, on the contrary, for the characterization of non-Newtonian materials is necessary several others, more complex tests.

In Graphic 1.2.1 are represented viscosity curves (shear rate *vs*. Viscosity) for all the ILs analysed. Viscosity do not vary with the shear stress applied, except for [(*n*-hex)$_2$DMG][Cl] that have a small fluctuation in the initials values of shear stress. This may be an artefact due to instrument initial inertia.



Graphic 1.2.1 – Viscosity *vs.* shear stress (logarithmic scale in xx axis) obtained at 20°C.

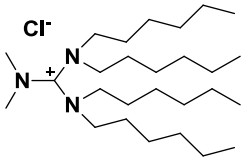
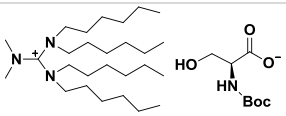
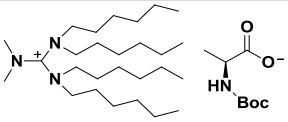
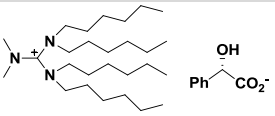
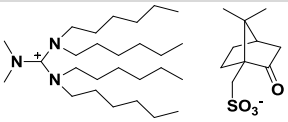
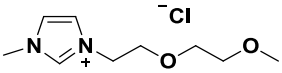
To confirm that [(*n*-hex)$_2$DMG][Cl] is a Newtonian fluid, it is possible to observe in Graphic 1.2.2 the flow curves. For all the ILs analysed shear stress is proportional to the velocity of movement (shear rate), so all ILs are Newtonian fluids, thus all have a constant viscosity.



Graphic 1.2.2 – Shear stress *vs.* shear rate obtained at 20°C.

Being the viscosity (η, Pa.s), the proportional constant of the Newton's equation ($\sigma = \eta \cdot \dot{y}$, shear stress is proportional to shear rate) it was possible to measure viscosities of several ILs (Table 1.2.2).

Table 1.2.2 – Structures of the measured ILs and respective values of viscosity, measured at 20°C.

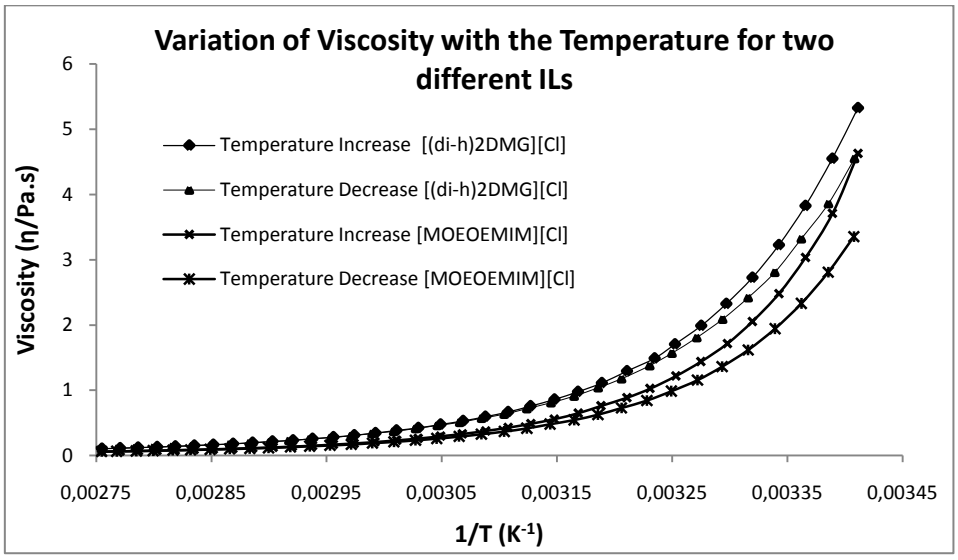
IL	Structure	Water content[a] (%)	Chloride content[b] (%)	Viscosity[c](η/Pa.s) 20°C
[(di-h)$_2$DMG][Cl]		6.08	-	4,97 ±0.01
[(di-h)$_2$DMG][Boc-Ser]		0.34	0.037	8,2±1.9
[(di-h)$_2$DMG][(L)-Boc-Ala]		1.26	0.472	1.97±0.04
[(di-h)$_2$DMG][(S)-Mand]		0.56	0.073	1.25±0.02
[(di-h)$_2$DMG][(S)-CSA]		0.78	0.006	0.88±0.02
[MOEOEMIM][Cl]		3.58	-	4.9±0.4

[a] The water content of each IL was determined by a volumetric Karl–Fischer Titration using HYDRANAL-Tritant 2 reagent. [b] The chloride contents were measured on a chloride electrode instrument. [c] All the measurements were performed three times; the viscosity values reported are the average of these measurements.

As predicted, the viscosity of ILs with the same cation and different anions can be quite different (for example the viscosity of [(*n*-hex)$_2$DMG][CSA] and [(*n*-hex)$_2$DMG][Boc-Ser], can differ 8 Pa.s, Table 1.2.2).

The viscosity of [(*n*-hex)$_2$DMG][Cl] and [MOEOEMIM][Cl] (same anion and different cations), are almost the same (Table 1.2.2). This is just one example, so it is not possible to generalize to all IL with the same anion. In fact, it is known that viscosity do not depend only on the anion of the IL, if the cation is different enough, even with the same anion, the viscosity can be very different.[146]

In Graphic 1.2.3 is described the variation of viscosity with the temperature, for [(*n*-hex)$_2$DMG][Cl] and [MOEOEMIM][Cl]. The IL was heated from 20° to 90°C (2°C min^{-1}) and cooled from 90°C to 20°, using a constant shear stress of 5 Pa. For the same sample, it was possible to study the viscosity variation with the temperature increase and subsequent decrease.



Graphic 1.2.3 – Variation of viscosity with temperature. Temperature is represented in inverse order to be possible to apply the Arrhenius equation.

The Arrhenius equation describes the viscosity dependence with the temperature: $\eta = \eta_\infty e^{\left(\frac{E_a}{RT}\right)}$, were η is the viscosity (units: Pa.s), η_∞ the viscosity at an infinite temperature, E_a the activation energy for viscous flow (units: J/mol), R the universal gas constant (8,314) and T the temperature (units: K). The activation energy is the measure of the energy barrier that must be overcome to allow the ions to move past each other and hence can be correlated with structural Information on ILs.[153]

The two ILs analysed follows the Arrhenius equation, so it was possible to measure the E_a for each one (Table 1.2.3).

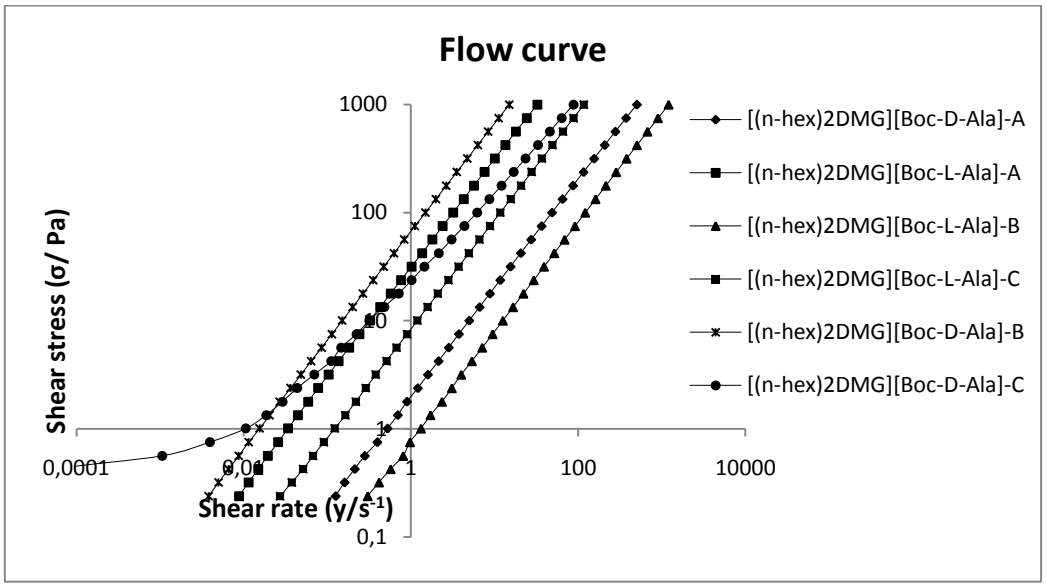
Table 1.2.3 – Activation energy values calculated based on Arrhenius equation

Ionic Liquid	Arrhenius equation		E_a (J/mol)*
[(di-*h*)$_2$DMG][Cl]	Temperature increase	$\eta = 8 \times 10^{-9} e^{\left(5912.8\frac{1}{T}\right)}$	51064±2603
	Temperature decrease	$\eta = 1 \times 10^{-8} e^{\left(5712.7\frac{1}{T}\right)}$	48097±14
[MOEOEMIM][Cl]	Temperature increase	$\eta = 1 \times 10^{-9} e^{\left(6449.3\frac{1}{T}\right)}$	54349±633
	Temperature decrease	$\eta = 3 \times 10^{-9} e^{\left(6036.5\frac{1}{T}\right)}$	51066±123

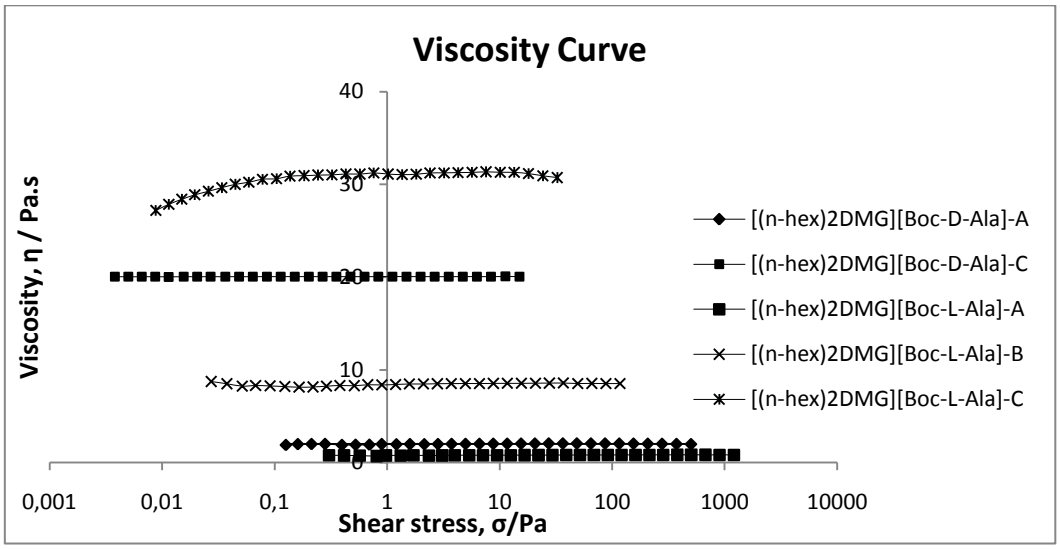
*All the measurements were performed three times; the E_a values are the average of these measurements.

The viscosity variation with temperature increase is slightly different from variation with temperature decrease, therefore the calculated E_a are also slightly different.

Rheology is a very sensitive technique, so a small difference on the sample purity the measurement can be quite different. Different CILs were synthesized during this work, including two enantiopure ILs of the same compound. For example were prepared the D and L enantiomers of Boc-alanine ([(di-h)$_2$DMG][Boc-D-Ala] and [(di-h)$_2$DMG][Boc-L-Ala]). During the rheological analysis of this two different enantiopure compounds, the viscosity values were completely different. This result was intriguing, because enantiomers have the same physical properties, and enantiomeric ILs should not also have the same physical properties? The analysis was repeated several times, and the results continued to be different for different enantiomers. The two enantiopure ILs were synthesized again, and the results were completely different from the initial ones (Graphic 1.2.4 and Graphic 1.2.5).



Graphic 1.2.4 – Shear stress vs. shear rate obtained at 20°C.



Graphic 1.2.5 – Viscosity *vs.* shear stress (logarithmic scale in xx axis) obtained at 20°C.

Either of the ILs viscosity agreed with the previous ones. This result is comprehensible because the water and chloride content can be different from the first synthesis. Two CILs D and L-Boc-Alanine were prepared in exactly the same conditions, and still their viscosity values were different. My explanation for these results relies on some procedures that could not be controlled during the enantiopure ILs synthesis. For example passing the two ILs trough different silica column, the silica content remained on the IL can be different, and it is not possible to control or quantify. This difference can reflected on the observed viscosity differences between the two enantiopure ILs.

It is important to measure the water and chloride contents of the IL before or after a rheological study. On this rheological study the rheology laboratory environment was not controlled, thus it was possible that the IL could absorb some air impurities during the measurement. To avoid this problem after the application of the sample in the rheometer was applied a thin layer of liquid paraffin, avoiding the direct contact of the sample with the air.

Every ILs measured in this work have a Newtonian behaviour, but some ILs can in fact have different behaviour, for example $[C_{10}MIM][SCN]$[154](1-decyl3-methylimidazolium thiocyanate) is a non-Newtonian fluid.

Rheology is a very useful technique to measure intrinsic properties of fluids. This technique has several applications in different areas, such as engineering (e.g. production of polymeric materials and others industrial substances), geophysics (e. g. the flow of lava), physiology, pharmaceutics and food analysis. As confirmed in this work, rheology is also used in organic chemistry to characterize small molecules.

1.3 Conclusions

ILs are very versatile compounds that have several application in different scientific areas. In chemistry these compounds can be used as solvents and/or catalysts enhancing the reaction rate, yields, and also selectivity. Synthesize a new IL can be an easy task (for example the anion metathesis of a known cation can originate a new IL with new properties), but the challenge is find an application where that IL can be useful. Although, for same others ILs the synthesis and purification can be quite difficult. For this reason is necessary to be careful to categorize ILs as general green solvents, since their synthesis and purification can use several organic solvents, and also a large amount of wastes.

The best method to achieve a high pure IL is by purifying the starting materials, although, in this work, were described different methods to achieve pure ILs. In this work was also demonstrated that ILs impurities, can in fact change some physical properties.

The syntheses of different ILs have been done, such as chiral and magnetic ILs. Although it was not possible to demonstrate by ^{19}F NMR that the CILs synthesized could induce chirality. This does not necessary indicate the lack of chiral induction by these CILs, it means that the approach used was not the most efficient.

2 Ionic Liquids & Carbohydrates

Carbohydrates solubility in some of the ILs described on the previous chapter is studied. It is also demonstrated the ability of some hydrophobic ILs to extract carbohydrates, or a mixture of carbohydrates from an aqueous solution.

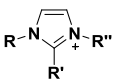
2.1 Introduction

2.1.1 Dissolution of carbohydrates

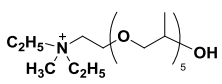
Carbohydrates are chiral organic molecules containing carbon, hydrogen, and oxygen in a typical ratio of 1:2:1. These molecules are readily available from natural and renewable resources and are relatively cheap. Usually, are very soluble in protic solvents, such as water, but not soluble in most common organic solvents due to the presence of a high number of hydroxyl groups, which limits their application. Pyridine, dimethylsulfoxide (DMSO) and dimethylformamide (DMF) are the few organic solvents able to dissolve carbohydrates. However, apart from considerable environmental concerns, in some enzymatic catalyzed transformations these solvents can deactivate enzymes, and therefore it is important to find new media that will improve carbohydrate dissolution and lead to better performance in carbohydrate chemistry.

In 2000, Sheldon and co-workers were the first to explore the use of ionic liquids (ILs) as reaction media for carbohydrate transformations.[155] Since then several works have been published, comprising carbohydrates solubility and/or carbohydrates transformations in ILs. This topic was firstly reviewed in 2005 by Linhardt *et al.* [156] where are described different applications of ILs in carbohydrate chemistry and biochemistry. Later on, an important review was published by Seoud [157] and several others reviews [158] that connect ILs and carbohydrates had been published. A wide range of ILs have been already tested for carbohydrate dissolution (Figure 2.1.1).

Cations



R=CH_3,R'=H, R''=	C_2H_5	**[EMIM]**
	C_4H_9	**[BMIM]**
	C_6H_{17}	**[C_6MIM]**
	C_8H_{17}	**[C_8MIM]**
	$C_{10}H_{21}$	**[C_{10}MIM]**
	CH_3OCH_2	**[MOMMIM]**
	$CH_3OCH_2CH_2$	**[MOEMIM]**
	$CH_3CH_2OCH_2CH_2$	**[EOEMIM]**
R=CH_3R'=CH_3,R''=C_4H_9		**[BM_2IM]**
R=CH_2CH_3,R'=H,R''=$CH_3(OCH_2CH_2)_3$		**[Me(OEt)$_3$EtIM]**
	$CH_3(OCH_2CH_2)_7$	**[Me(OEt)$_7$EtIM]**
	$CH_3(OCH_2CH_2CH_2)_3$	**[Me(OPr)$_3$EtIM]**

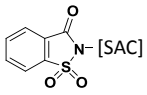


[Amm110]

R=C_4H_9		**[Bt_{14}]**
$CH_2C_6H_5$		**[Bt_{1Bn}]**

Anions

[ACES]



[SAC]

[BZ]

Cl^-	**[Cl]**
Br^-	**[Br]**
BF_4^-	**[BF_4]**
PF_6^-	**[PF_6]**
NCS^-	**[SCN]**
$(NC)_2N^-$	**[DCA]**
$CF_3SO_3^-$	**[TfO]**
$(CF_3SO_3)_2N^-$	**[NTf_2]**
$CH_3SO_4^-$	**[MS]**
CH_3COO^-	**[OAc]**

Figure 2.1.1 – Structures of the reported ILs for the dissolution of carbohydrates.

In 2000 Sheldon *et al.* first connected ILs and carbohydrates by exploring their potential as media for carbohydrate transformations.[155] In 2001 two different research groups[159] reported

glucose solubility on ILs based on the imidazolium unit. This type of cation have been the most studied so far to dissolve carbohydrates. MacFarlane *et al.* [160] described dicyanamide as an attractive anion to dissolve carbohydrates, due to the hydrogen bond acceptor properties, but only reported range values of solubility. Latter, Sheldon *et al.* [161] reported the solubility of carbohydrates in several ILs containing, among others, dicyanamide anion and oxygenated cation chains. The 1-alkyl-3-methyimidazolium in combination with several anions such as chloride- [Cl], tetrafluoroborate- [BF_4], hexafluorophosphate- [PF_6], dicyanamide- [DCA] were studied and surprisingly, [DCA] allowed a much higher dissolution of D-glucose than [BF_4] or [PF_6]: 145 ([DCA]), <0.5 ([BF_4]) and <0.5 ([PF_6]) g/L at 25°C (Table 2.1.1, entries 10, 16 and 14 respectively).[161] ILs containing an ether pendant substituent have been currently named by "sugar-philic" IL due to their capacity to establish hydrogen bonds with the hydroxyl groups of the carbohydrate.[159a, b] These oxygenated cations, such as 1-methoxymethyl-3-methylimidazolium- [MOMMIM], 1-methoxyethyl-3-methylimidazolium- [MOEMIM] and 1-ethoxyethyl-3-methylimidazolium- [EOEMIM] were also synthesized and tested for carbohydrates solubility. These ILs increased glucose solubility in the presence of the anions [BF_4] and [PF_6] but not in the presence of [DCA], for example [MOMMIM][BF_4] could dissolve 4.4 g/L of glucose, although [BMIM][BF_4] could only dissolve <0.5 g/L, and [MOMMIM][DCA] could dissolve 66 g/L of glucose, comparing with 140 g/L of [BMIM][DCA], values reported at 25°C[161] (other examples: Table 2.1.2, for [BF_4] entries 28, 34 and 40 *vs.*16, for [PF_6] entries 33 and 39 *vs.*14, for [DCA] entries 27, 32 and 38 *vs.* 10).[161] Sheldon *et al.*[161] concluded that the glucose solubility was more significantly influenced by the nature of the anion (being dicyanamide anion the best for carbohydrates dissolution) then the cation, where the [BMIM] was the best cation unit instead the ether pendant substituent cation as predicted.

With the objective of designing ILs that were able to dissolve carbohydrates but do not considerably inactivate enzymes, Zhao *et al.* [162] reported remarkable solubility results for glucose (Table 2.1.1, entries 46 to 51). This group tested the anion bis(trifluoromethane)sulfonimide – [NTf_2] with the cation [BMIM] and data demonstrated that D-glucose had a very poor solubility in this solvent (<0.5 wt.% at 60°C, Table 2.1.1,entry 23), but in the same conditions, [EMIM][OAc] was surprisingly a much better solvent allowing a dissolution of 60 wt.% of D-glucose at 60°C (Table 2.1.1, entry 9).[162] The authors have claimed that the hydrogen-bond forming anions, oxygen-containing cations, and low cation bulkiness promote the carbohydrate dissolution. Therefore, an optimization could be achieved through a fine design of IL structures. Thereby they have synthesised a series of imidazolium and tetraalkylammonium ILs carrying glycol-

substituent in the side chain, and acetate [OAc] as anion. They have successfully performed enzymatic transformations of glucose, and also cellulose in homogeneous ionic solutions.

With the objective of lipase-catalyzed synthesis of fatty acid sugar ester Koo *et al.*[163] reported the glucose solubility in ILs based mainly on inorganic anions (Table 2.1.1, entries 3-8, 17-22, 24 and 25). This group reported a new procedure that entails mixing an aqueous sugar solution into ILs followed by removal of the water from the solution, obtaining a supersaturated solution of carbohydrates in different ILs. The glucose concentrations in the supersaturated [EMIM][TfO] and [Bmim][TfO] were 19 and 10 times higher than in saturated ILs glucose solutions (when no water is added to the solution). In this way the lipase-catalyzed esterifications were successfully carried out in these supersaturated ILs solutions.

Table 2.1.1– Reported solubility's values of glucose on several ILs.

Entry (Ref.)	Ionic Liquid		Solubility (mg/mL)	Water content (wt. %)	Temp. (°C)
1[164]	[EMIM]	[DCA]	>100[b]	nd	75
2[164]		[MS]	~100[b]	nd	75
3[163]			89.6[a]	0.1	25
4[163]			133.2[a]	0.1	60
5[163]		[BF_4]	1.1[a]	0.1	25
6[163]			4.8[a]	0.1	60
7[163]		[TfO]	6.1[a]	0.1	25
8[163]			27.8[a]	0.1	60
9[162]		[OAc]	600[b]	nd	60
10[161]	[BMIM]	[DCA]	145[a]	<0.05	25
11[161]			211[a]	<0.05	40
12[161]			405[a]	<0.05	75
13[160b]			>100[a]	nd	RT
14[161]		[PF_6]	<0.5[a]	<0.05	25
15[159a]			<1.0[b]	nd	55
16[161]		[BF_4]	<0.5[a]	<0.05	25
17[163]			0.9[a]	0.1	25
18[163]			2.7[a]	0.1	50
19[163]			3.5[a]	0.1	60
20[163]		[TfO]	4.8[a]	0.1	25
21[163]			14.2[a]	0.1	50
22[163]			18.1[a]	0.1	60
23[162]		[NTf_2]	<0.5[b]	nd	60
24[163]	[C_8MIM]	[BF_4]	0.7[a]	0.1	25
25[163]			1.5[a]	0.1	60
26[159b]	[MOMMIM]	[Br]	450[b]	2.5	Heat
27[161]		[DCA]	66[a]	<0.05	25
28[161]		[BF_4]	4.4[a]	<0.05	25
29[161]		[TfO]	4.3[a]	<0.05	25
30[161]		[NTf_2]	0.5[a]	<0.05	25
31[159b]	[MOEMIM]	[Br]	450[b]	2.5	Heat

32[161]		[DCA]	91 [a]	<0.05	25
33[161]		[PF_6]	2.5 [a]	<0.05	25
34[161]		[BF_4]	2.8 [a]	<0.05	25
35[159a]			~5[b]	nd	55
36[161]		[TfO]	3.2 [a]	<0.05	25
37[161]		[NTf_2]	0.5 [a]	<0.05	25
38[161]	[EOEMIM]	[DCA]	70 [a]	<0.05	25
39[161]		[PF_6]	0.7 [a]	<0.05	25
40[161]		[BF_4]	2.8 [a]	<0.05	25
41[161]		[NTf_2]	0.5 [a]	<0.05	25
42[164]	[Bt_{14}]	[DCA]	>100[b]	nd	75
43[164]		[MS]	~60[b]	nd	75
44[164]	[Bt_{1Bn}]	[DCA]	~60[b]	nd	75
45[164]		[NTf_2]	~20[b]	nd	75
46[162]	[Amm110]	[DCA]	45[b]	nd	60
47[162]		[OAc]	300 [b]	nd	60
48[162]	[$Me(OEt)_3EtIM$]	[OAc]	800 [b]	nd	60
49[162]	[$Me(OEt)_7EtIM$]	[OAc]	260 [b]	nd	60
50[162]	[$Me(OPr)_3EtIM$]	[OAc]	450 [b]	nd	60
51[162]	[$Me(OEt)_3Et_3N$]	[OAc]	160 [b]	nd	60

a – solubility measured by UV; b – solubility measured by weight; c – solubility measured by HPLC analysis (mg of carbohydrate per g of IL). nd – not defined; rt – room temperature.

[MOMMIM] [DCA] and [MOEMIM] [DCA] could dissolve a much higher amount of sucrose than [BMIM] [DCA]: 249 g/L and 220 g/L, respectively, compared with 195 g/L for [BMIM] [DCA] (Table 2.1.2, entries 32161).[161] [BMIM] [DCA] could also dissolve a significant amount of lactose at 25°C (51 g/L), that increased considerable when the temperature was raised to 75°C (Table 2.1.2, entry 41 and 42). The same IL was not so efficient with amylose for the same experimental conditions (4 g/L).[161] [BMIM][Cl] was reported to dissolve fructose and sucrose up to 56 and 18 wt.%, respectively, at 110°C (Table 2.1.2, entries 5 and 18).[165]

Table 2.1.2 – Reported solubility's values of mono and di-saccharides on several ILs.

Entry (Ref.)	Carbohydrate	Ionic Liquid		Solubility (mg/mL)	Water content (wt. %)	T (°C)
1[163]	Fructose	[EMIM]	[BF_4]	7.7 [a]	0.1	25
2[163]				25.7 [a]	0.1	60
3[163]			[TfO]	32.8 [a]	0.1	25
4[163]				123.9 [a]	0.1	60
5[165]		[BMIM]	[Cl]	560[b]	nd	110
6[163]			[BF_4]	3.3 [a]	0.1	25
7[163]				15.9 [a]	0.1	60
8[163]			[TfO]	27 [a]	0.1	25
9[163]				87.5 [a]	0.1	60
10[165]		[BM_2IM]	[Cl]	400[b]	nd	120
11[164]	Sucrose	[EMIM]	[DCA]	~100[b]	nd	75

12[163]			[MS]	12.4 [a]	0.1	25
13[164]				~80[b]	nd	75
14[163]			[BF_4]	0.6 [a]	0.1	25
15[163]				0.6 [a]	0.1	60
16[163]			[TfO]	3.1 [a]	0.1	25
17[163]				7.1 [a]	0.1	60
18[165]		[BMIM]	[Cl]	180[b]	nd	110
19[161]			[DCA]	195 [a]	<0.05	25
20[161]				282 [a]	<0.05	60
21[163]			[BF_4]	0.5 [a]	0.1	25
22[163]				0.6 [a]	0.1	60
23[163]			[TfO]	2.0 [a]	0.1	25
24[163]				5.3 [a]	0.1	60
25[165]		[BM_2IM]	[Cl]	140[b]	nd	120
26[161]		[MOEMIM]	[DCA]	220 [a]	<0.05	25
27[164]			[MS]	~80[b]	nd	75
28[161]			[PF_6]	0.7 [a]	<0.05	25
29[161]			[BF_4]	0.4 [a]	<0.05	25
30[161]			[TfO]	2.1 [a]	<0.05	25
31[161]			[NTf_2]	0.13 [a]	<0.05	25
32[161]		[MOMMIM]	[DCA]	249 [a]	<0.05	25
33[161]				352 [a]	<0.05	60
34[161]		[EOEMIM]	[DCA]	50 [a]	<0.05	25
35[161]				240 [a]	<0.05	60
36[164]		[Bt_{14}]	[DCA]	~80[b]	nd	75
37[164]		[Bt_{1Bn}]	[DCA]	~20[b]	nd	75
38[164]			[MS]	~20[b]	nd	75
39[162]		[Amm110]	[DCA]	35[b]	nd	60
40[162]		[$Me(OEt)_3Et_3N$]	[OAc]	160	nd	60
41[161]	Lactose	[BMIM]	[DCA]	51 [a]	<0.05	25
42[161]				225 [a]	<0.05	75

a – solubility measured by UV; b – solubility measured by weight; c – solubility measured by HPLC analysis (mg of carbohydrate per g of IL). nd – not defined; rt – room temperature.

The dissolution mechanism of carbohydrates had been manly studied for cellulose. Rogers *et al.* [166] have reported that ILs based on anions with strong hydrogen bond acceptor ability increase the cellulose solubility due to the capacity of breaking the hydrogen bonding network present on the polymer. The cation can also influence cellulose solubility since the increase of the alkyl chain in the imidazolium unit reduces the effective anion concentration within the IL, although the anion effect is more pronounced.[166a] These results can be extrapolated to mono- and disaccharides. [167] In 2007 Young's *et al*. [167] performed a simulation study of glucose solvation by the IL 1,3-dimethylimidazolium chloride. They have concluded that the main solvation interactions present are through the chloride anion and the hydroxyl groups of the sugar. Although weak hydrogen bonding interactions trough the acidic hydrogen at the C-2 position of the imidazolium ring of the IL cation and the sugar are also present. The experimental data

reported in the last years on carbohydrates dissolution is quite impressive (Table 2.1.1 and Table 2.1.2), and can prove that the anion effect is indeed present, although the cation also affect the mono- and disaccharides solubility. Cations containing oxygen groups can be hydrogen bond acceptors thus increasing the sugar solubility in the IL. Although, this effect is not always present, for example [BMIM][DCA] can dissolve a larger amount of glucose than [MOEMIM][DCA] (Table 2.1.1, entries 10 *vs.* 32, respectively). The cation effect on carbohydrates solubility is not yet clear, and should be further explored, in a way to developed specific cations that could improve the carbohydrates solubility on ILs.

The main impurities present in ILs are water and chloride, and different studies have showed that these factors can influence the carbohydrates solubility on the IL. It was demonstrated that the solvation of carbohydrates involves stoichiometric hydrogen bonding of the hydroxyl protons and the chloride ions of the IL. [167-168] Consequently, the presence of chloride anions as impurity in the ILs is an important factor to consider, since it can influences the hydrogen bond basicity character of the IL, affecting the carbohydrate solubility.[169] Sheldon *et al.*[161] have demonstrated that chloride content on the IL can increase the carbohydrate solubility, although with a small effect, 282 g/L to 294 g/L of sucrose dissolved in [BMIM][DCA] in the presence of 1% of chloride. Nevertheless the majority of the studies presented in Table 2.1.1 and Table 2.1.2 do not report the chloride content of the ILs.

Water content of the IL can increase up to three times the solubility. We have[170] shown that for ILs based on chloride anion, a small fluctuation on the IL water content can significantly change the glucose solubility, although in dicyanamide based ILs this effect is not so pronounced (please see section 2.2.1, page 111).

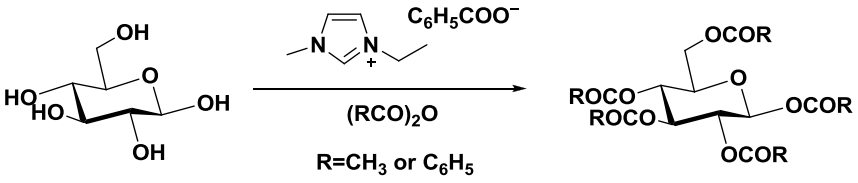
Several carbohydrate transformations have been reported using ILs has solvents. A few examples will be described here, taking special attention to the dehydration reaction of carbohydrates in ILs. This transformation is very important due to be possibility to obtain 5-hydroxymethylfurfural (HMF) that is very useful not only as intermediate for the production of the biofuel dimethylfuran (DMF) and also to create other important commodities molecules such as levulinic acid, 2,5-furandicarboxylic acid (FDA), 2,5-furandicarbaldehyde (DFF), dihydroxymethyl-furan and 5-hydroxy-4-keto-2-pentenoic acid.

2.1.2 Acetylation / Deacylation

Acetylation of carbohydrates is not only used as a protection strategy, but is also a useful methodology for the isolation and identification of sugars. Standard acetylation reaction is based

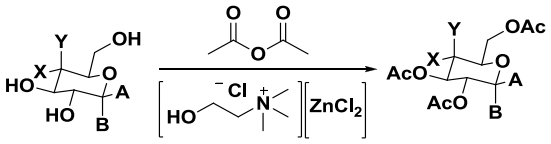
on the utilization of acetic anhydride as the primary reagent and counts with a large number of solvents and catalysts, where pyridine is the most common solvent/catalyst system. Although several others catalysts have been used, such as Lewis/Brønsted acids, heterogeneous or enzymatic catalysts. In recent years ILs have been showed to be not only useful solvents for this transformations, but also efficient catalysts, improving the reaction yield and the anomeric selectivity of the final products.

In 2002, MacFarlane *et al.* [160b] reported that [DCA]-based ILs were good solvents for saccharides and were also active base catalysts for their acetylation. In the absence of a catalyst, [BMIM] [DCA] was able to convert D-glucose into penta-*O*-acetyl-D-glucopyranose in 89% yield when 2 equivalents of the IL and 5 equivalents of acetic anhydride were used. The catalytic ability of [BMIM] [DCA] was confirmed when 0.5 equivalents of the IL was used, at 50°C, resulting 92% yield. The replacement of the [DCA] anion by [NTf_2] inhibited this reaction, and D-glucose was completely recovered. This result suggests that the basicity of [DCA] plays an important role in the process.[160b] Others saccharides were also tested with good conversion yields, such sucrose and raffinose, with 93 and 90% yield, respectively. Although good conversion yields were obtained in this work, no anomeric selectivity was obtained with ILs based on [DCA]. In 2003 Murugesan *et al.*[171] have reported that dialkylimidazolium benzoates ([BZ]) can also catalyze carbohydrates acetylation (Scheme 2.1.1). When α/β-D-glucose was used as substrate quantitative yields were obtained and the formation of the α-product was favoured. In the same conditions the acetylation of galactose or mannose resulted in lower yields (71 and 78% yield, respectively), and the β-product was favoured. The IL nature was showed to be important in the reaction efficiency, and also in the final product selectivity. As for [DCA] anions, the basicity of benzoate anions has showed to have an important role on the catalytic activity of the IL, since ILs with [BF_4] or [PF_6] as anions resulted in no product formation. The IL cation can also change the reactivity, since for higher alkyl chains on the imidazolium unit, the reaction yield decreased probably due to the higher viscosity of IL. On the other hand for [BMIM][BZ] and [EMIM][BZ] the β-product was favoured, although the α -product also was formed when [C_6MIM][BZ] was used as solvent/catalyst.[171]



Scheme 2.1.1 –Peracylation of glucose in [EMIM][BZ].

Since Lewis acids have been showed to be good catalysts for the acetylation of sugars, an IL based on choline and zinc chloride was tested for the acetylation of monosaccharides.[172] In a way to observe the anion effect, tin chloride based IL was also tested showing good conversion yields, although lower than the one obtained with zinc chloride. With the eutectic mixture choline chloride/urea no significant reaction was observed, showing that the presence of the Lewis acid is important in the reaction mechanism. Under optimized conditions, the reaction of acetic anhydride with β-1-*O*-methyl-glucose provided pure β-1-*O*-methyl-4-acetyl-glucose in a 96% yield (Scheme 2.1.2) [172]. It was possible to reuse the IL for four cycles with no efficiency lost. The impossibility to remove all the volatiles compounds in the different cycles, led to an appreciable decrease in the yields of subsequent reactions. On the other hand, the IL could also be reused for different reactions with very low levels of cross contamination.

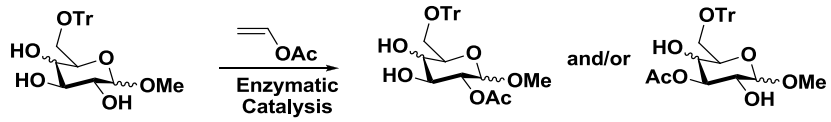


Scheme 2.1.2 – Acetylation of monosaccharides in ChCl-based ILs [172].

Enzymatic catalyzed acetylation of carbohydrates can be more selective than chemical methods, the main problem is that polar solvents that can efficiently solubilise carbohydrates, such as pyridine, dimethylsulfoxide (DMSO), dimethylformamide (DMF) and tetrahydrofuran (THF) decrease the enzyme activity and stability. ILs have been showed to be good solvents for biocatalysis [158a, 173], on the other hand, ILs can dissolve carbohydrates in high quantities, solving the solubility problem of this type of reactions. In 2001 Kazlauskas *et al.* [159c] reported the regioselective 6-*O*-acetylation of glucose, catalyzed by lipase B from *Candida antarctica* (CAL-B), with different ILs as solvent. They have tested seven ILs containing tetrafluoroborate as anion. Glucose acetylation formed the 6-*O*-acetyl glucose (>13:1 and up to >50:1, related to 3-*O*- acetyl glucose) with 88-99% selectivity. The difference in the obtained yields and selectivity's are explained by the IL ability to dissolve glucose. The best IL for this reaction was [MOEMIM][BF_4] that could dissolve the largest glucose quantity among the ILs tested, where the acetylated products were formed in 99% yield, of which 93% was the desired 6-*O*-acetyl product.

Kim et al. [174] have reported a study where is compared the reactivity and regioselectivity of the enzymatic acylation of monoprotected glycosides in ILs, based on hexafluorophosphate anion, and two organic solvents (THF and $CHCl_3$), Scheme 2.1.3. The reaction with methyl-6-*O*-trityl-D-glycoside in the presence of vinyl acetate *Candida rugosa* lipase (CRL) and the IL [BMIM] [PF_6] or

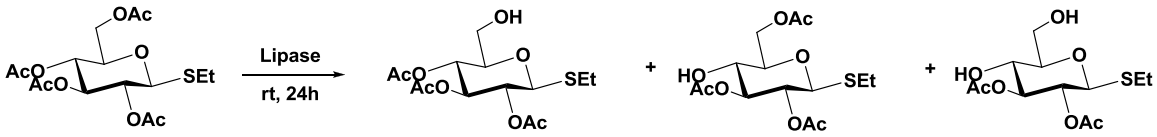
[MOEMIM] [PF_6] led to higher yields and a more regioselectivity (>98:1, acylated product in position 2: acylated product in position 3) than when conducted in THF or acetonitrile.[174]



Scheme 2.1.3 – *Candida rugosa* lipase -catalyzed acylation of glycosides. [174]

Acetylation of sucrose by Novozym 435 (*Candida antarctica* type-B lipase immobilized on acrylic resin) was also successfully performed in the presence of [BMIM] [DCA].[161]

[BMIM][PF_6] showed to be a good co-solvent for the deacylation of glucopyranosides in the presence of *Candida cylindracea* lipase (Scheme 2.1.4).[175] Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside was converted into ethyl 2,3,4-tri-*O*-acetyl-6-hydroxy-1-thio-β-D-glucopyranoside in a 100% yield, in the presence of [BMIM][PF_6] up to a concentration of 50%, in a solution of sodium phosphate buffer (50 mM, pH 7.0). When IL concentrations were higher than 50% the yield decreased, and at 100% IL, a different product was formed (ethyl 2,3,6-tri-*O*-acetyl-4-hydroxy-1-thio-β-D-glucopyranoside) in 54% yield. Lipases are well known to work efficiently in organic solvents, but the IL could improve the substrate solubility and the isolated yields, and was also able to modify completely the regioselectivity of the biocatalysed reaction.[175]



Scheme 2.1.4 – Lipase-catalyzed deprotection of the commercially available ethyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside in [BMIM][PF6] reaction mixtures.

2.1.3 Glycosylation

Alkyl glycosides and oligosaccharides play a key role in many biochemical reactions and in various stages of cell recognition and communication.[176] The formation of the glycosidic bond involves different charged intermediates whose reactivity strongly depends on the protecting group, the solvent and the catalyst. A wide range of reagents can be used as glycosyl donors in glycosylation reactions, such as glycosyl halides, thioglycosides, glycosyl phosphate, pentenyl glycosides and trichloroacetamidates, among others.[177]

In 2003 Pakulski [177] reported the glycosylation of glycosyl trichloroacetamidates with several alcohols and monosaccharides (Figure 2.1.2). For this reaction were used [BMIM][PF_6] as solvent, and TMSOTf (trimethylsilyl trifluoromethanesulfonate) as catalyst. The reaction of 2,3,4,6-tetra-

O-benzoyl-α-D-mannopyranosyl trichloroacetimidate as glycosyl donor and, allyl and benzyl alcohols, the only product formed were the α-mannopyranosides, due to a strong anomeric effect and the influence of the benzoyl group. The reaction of 2,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranosyl trichloroacetimidate and 2,3,4,6-tetra-*O*-acetyl-α,β-D-galactopyranosyl trichloroacetimidate with the respective alcohols originated the respective α or β-pyranosides, and, in some cases it was observed the formation of the deacetylated product in the O-2 position. Although α/β selectivities obtained with IL as solvent are generally similar to the selectivities found for classical conditions, the authors claim that the use of organic solvent is drastically lowered, and the IL can be recycled at least for one cycle.

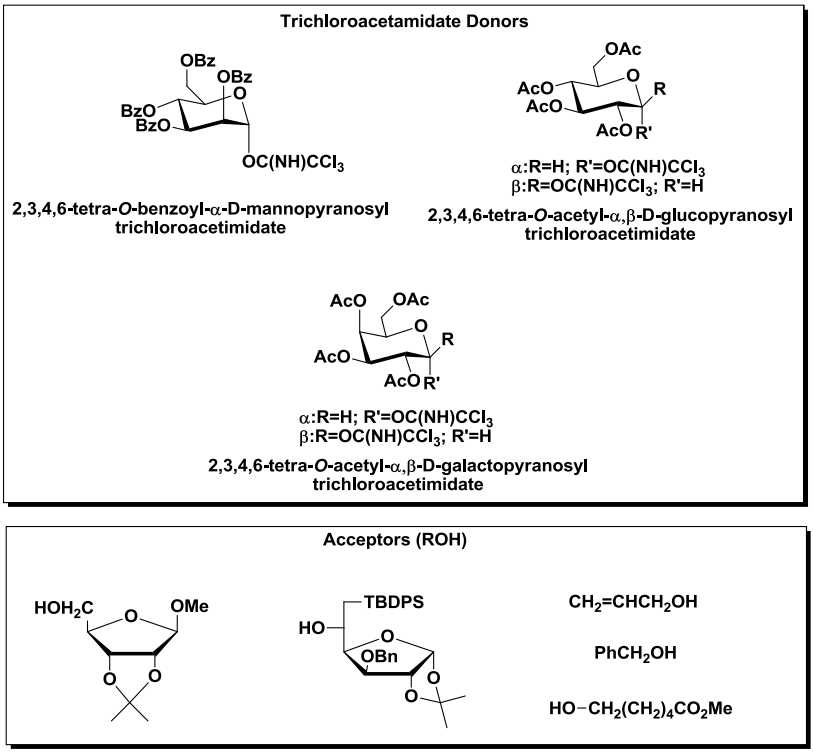
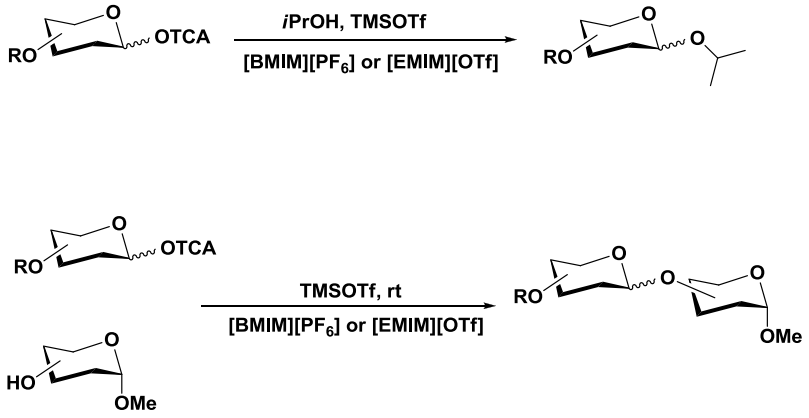


Figure 2.1.2 – Glycosylation of trichloroacetamidates glycosyl donors with alcohols using ILs as solvents.[177]

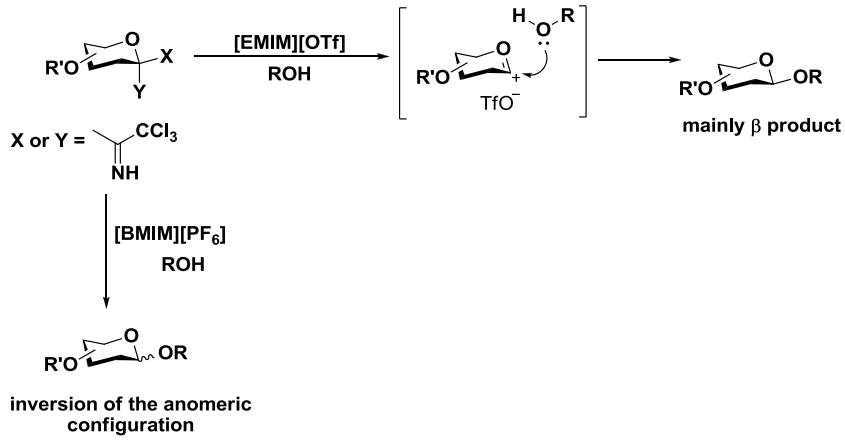
In the same year Poletti *et al.* [178] have reported the coupling of trichloroacetamidates glycosyl donors with 2-propanol or carbohydrates as glycosyl acceptors, in two different ILs: [BMIM][PF_6] and [EMIM][TfO], using trimethylsilyl triflate (TMSOTf) as reaction promoter (Scheme 2.1.5). They have observed that the anomeric selectivity strongly depends on the solvent and the presence or not of the catalyst. Having [BMIM][PF_6] as solvent and TMSOTf as catalyst the α-product was favoured, although with [EMIM][TfO] as solvent roughly no anomeric selectivity was observed. When the reaction was performed with [EMIM][TfO] and no catalyst was added the selectivity increased, favouring the formation of the β-product. It is important to mention that the β-glycoside was favoured when trichloroacetamidates bearing nonparticipating groups

at C-2 were used. These interesting results lead the authors to speculate on the possible assistance of the solvent in the reaction mechanism. The authors also reported that it was possible to recycle the IL, and in further cycles the product could be formed without the addiction of the acidic promoter, due to the capability of the IL to retain the catalytic properties of the Lewis acid.



Scheme 2.1.5 – Synthesis of isopropyl glycosides or disaccharides starting using trichloroacetamidates glycosyl donors, in ILs

The continuation of this study was reported in 2005 by the same group[179], where the reaction mechanism was further studied. The authors performed glycosylation with anomerically pure α- or β-trichloroacetimidate donors in coordinating and non-coordinating ILs (Scheme 2.1.6). When non-coordinating ILs were used, such as [BMIM][PF_6] or [EMIM][BF_4] the stereochemistry of the products was strongly dependent on the anomeric configuration of the donor, this is α-donors favour the formation of β-glycoside, and β-donors mainly afforded α-products, as happen with "classical" non coordinating organic solvents. When [EMIM][TfO] was used as solvent, with or without addition of the catalyst TMSOTf, the formation of β-glycoside was favoured regardless the stereochemistry of the starting material. This last result suggests a possible coordination of the triflate anion from the α-side of the oxonium ion, generated by trichloroacetimidate displacement (Scheme 2.1.6). To confirm this result the authors have performed an low-temperature ^{1}H NMR spectroscopic study, and have showed the formation of a transient α -glycosyl triflate, which shields the α-face of the oxonium ion and biases the attack of the acceptor from the β-face. On the other hand, the β-donors provide β-glycosides by preanomerization of the β-imidate to the α-imidate, and by formation of the α-glycosyl triflate transient. To explain the configuration inversion when non-coordinating ILs are used, further low-temperature ^{1}H NMR spectroscopic studies [180] have been done. A possible mechanism is the direct attack of the acceptor on trichloroacetimidate affording the glycoside product with the opposite anomeric configuration.



Scheme 2.1.6 – Glycosylation of trichloroacetamidates glycosyl donors with alcohols using ILs as solvents [179].

In agreement with previous reports[179-180] that triflate based ILs can be good glycosylation promoters, Galan *et al.*[181] have reported the use of [BMIM][OTf] as promoter for glycosylation of activated thioglycosides and trichloroacetimidates with several alcohols, including substrates bearing different protection groups (Figure 2.1.3). Thioglycosides donors can be activated by *N*-iodosuccinimide (NIS)/TMSOTf or trifluoromethanesulfonic acid (TfOH) combinations. Galan *et al.* have shown by ^{1}HNMR and ^{19}F NMR that the presence of a catalytic amount of acid is crucial for the formation of the iodonium ion from the NIS reagent and activate the thioglycoside donor, promoting the reaction. They have proven that the H-2 of the imidazolium moiety in the IL was not involved in the reaction by performing the reaction in the IL 1-butyl-2,3-dimethylimidazolium triflate. The reaction was not suppressed by the presence of the methyl group on C-2 position, so the acidic proton of the imidazolium is not participating directly in the activation of NIS. To identify the source of H^+ present in the reaction, they have quantify the water present in [BMIM][OTf], and proposed that the a catalytic amount of TfOH is released by the IL.

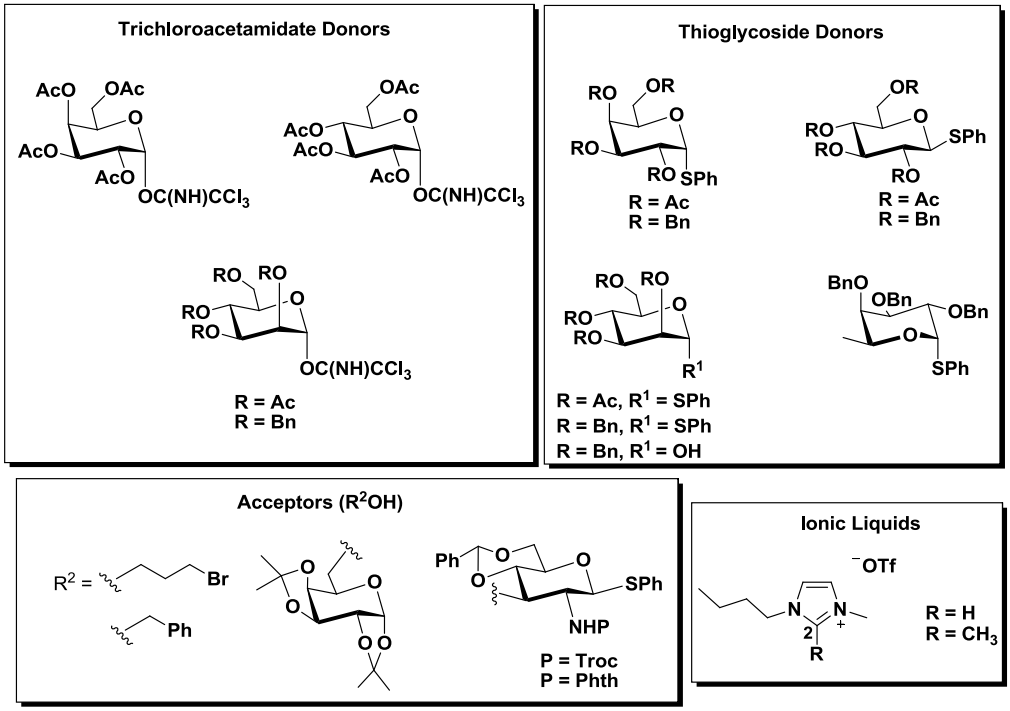


Figure 2.1.3 – Glycosylation of trichloroacetimidate and thioglycoside donors and glycoside acceptors.[181]

In a way to understand the effect of ILs structure in glycosylation reactions, Galan *et al.* [182] tested this reaction in several ILs based on imidazolium unit, in combination with different anions (Figure 2.1.4). Thioglycosides were chosen to be the glycoside donors, and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose was the model acceptor. Several hydrophilic ILs were tested, based on anions such as Cl, Br, $AlCl_4$, HSO_3 and PF_6 resulting in no reaction or degradation of the starting materials. From the ILs tested, only ILs based on anions with triflate, or triflimide could promote the glycosylation reaction, confirming that the anion effect on the IL is a crucial point in glycosylation reactions. The cation effect was also studied, and in a tentative to achieve better selectivity a chiral IL was synthesized, camphor-derived imidazolium triflate, and tested for the glycosylation reaction. Although the product was formed, the selectivity observed was similar to the ones observed with [BMIM][OTf], so the cation modification was not able to improve selectivity on the final product. The authors also synthesized ILs with hydrophobic groups in the C-2 position of the imidazolium unit in combination with OTf an NTf_2 anions, and tested on glycosylation reactions. The reactivity was increased, so good yields were obtained in less time, although the selectivity was similar to the one obtained with [BMIM][OTf]. These ILs were tested with peracetylated thioglycoside donors, which are electronically deactivated species, and no reaction was observed. The authors reported that further studies are being done to develop a more reactive IL that can promote the glycosylation reaction on electronically deactivated species.

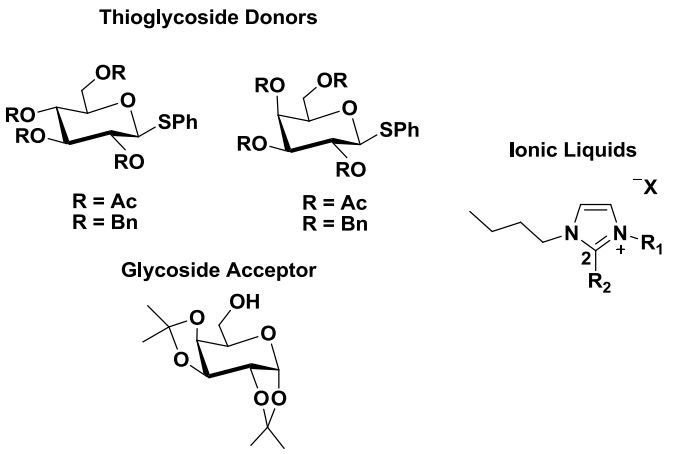
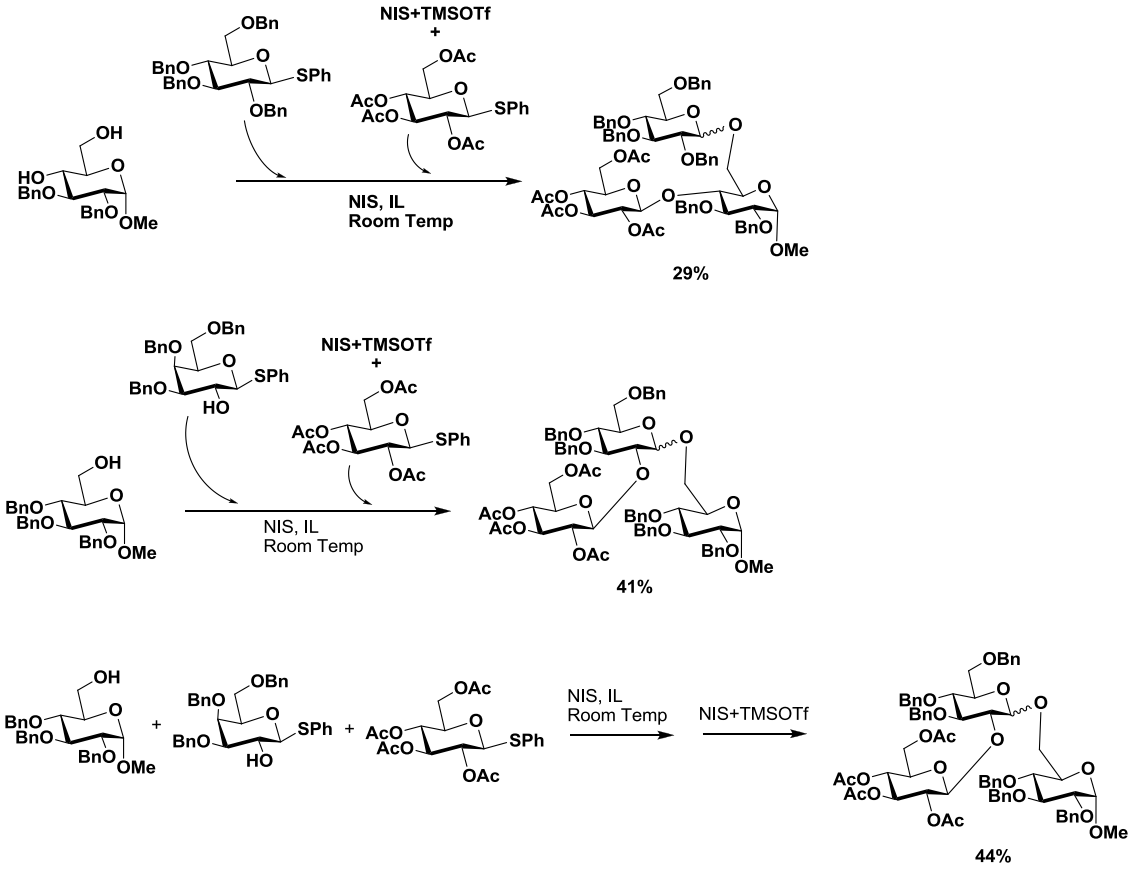


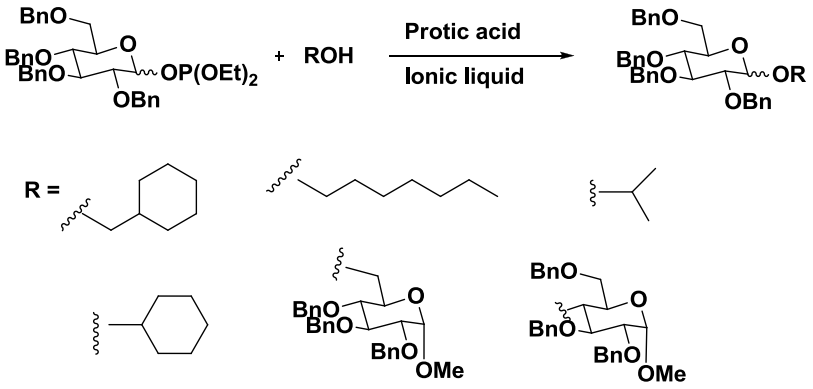
Figure 2.1.4 – ILs, thioglycoside donors and model acceptor for the glycosylation reaction.[182]

Regioselective glycosylation is an important methodology in oligosaccharides synthesis. Galan *et al.* [183] reported that [BMIM][OTf] in combination with NIS can selectively promote glycosylation reactions at room temperature. The reactivity of the glycosyl donor can be tuned by choosing the right combination of protecting groups, knowing that the glycosyl donors are less active ("disarmed") when the formation of oxycarbenium cation is disfavoured. On this basis regioselective coupling reactions can be achieved with activated glycosyl donors in presence of less active glycosides. In this work is presented a methodology to synthesize several trisaccharides by a one-pot glycosylation reaction where a partially protected 'armed' monosaccharide glycoside is used firstly as the glycosyl donor and the resulting product becomes the glycosyl acceptor in the following step (Scheme 2.1.7).



Scheme 2.1.7 – Synthesis of trisaccharides using NIS, [BMIM][OTf] and TMSOTf as reaction promoters[183].

Toshima *et al*. [184] reported the glycosylation reaction using glycosyl phosphite as glycosyl donors because this donors are effectively activated by both weak Lewis and protic acids. In this work the authors reported the use of the IL $[C_6MIM][NTf_2]$ as solvent for the coupling reaction between glucopyranosyl diethyl phosphate donors and different alcohols, having a catalytic amount of protic acid (1 mol%) as catalyst. With the same cation $[C_6MIM]$, different anions were tested, with the respective protic acids acting as reaction promoters, for example for $[C_6MIM][BF_4]$, the acid HBF_4 was used as catalyst and for $[C_6MIM]$ $[NTf_2]$, $HNTf_2$ was used as catalyst, and so on. The best yield was obtained with $[C_6MIM][NTf_2]$, and 1 mol% of $HNTf_2$, although with others IL the yield was also higher than 70%. In all cases the β-product was favoured. The authors tested the reaction in the same conditions, but using several organic solvents, concluding that a better yield was obtained with $[C_6MIM]$ $[NTf_2]$, although the selectivity obtained could be compared to the one obtained with DCM. The influence of the IL purity on the glycosylation reaction was studied, and was demonstrated that the halide content of the IL can decrease the efficiency of the reaction. In fact when 10 mol% of $[C_6MIM]$ [Cl] is added, no reaction product is formed (Scheme 2.1.8). It was possible to recycle the IL for at least 5 cycles without lost of efficiency.



Scheme 2.1.8 – Glycosylation reaction with glycosyl phosphate as glycosyl donor and several alcohols as glycosyl acceptors [184].

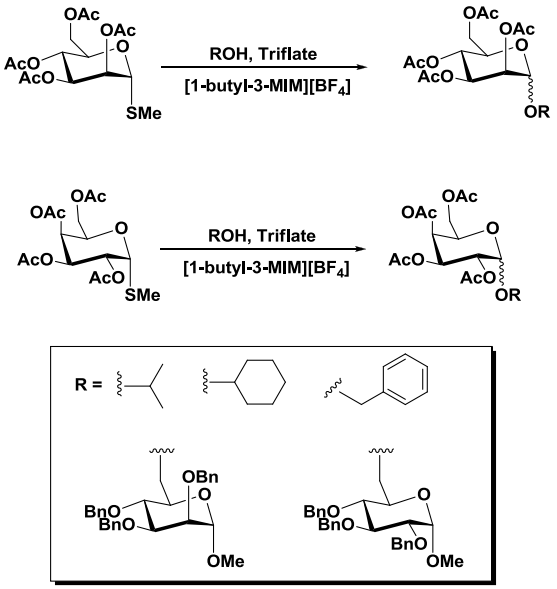
The same group Toshima *et al*. [185] reported in 2004 the glycosylation of glucopyranosyl fluoride and alcohols using an IL containing a protic acid. Depending on the IL used, the stereoselectivity could be different, for [C_6MIM] [NTf_2] containing $HNTf_2$ favoured the formation of the α-product. This is an interesting result, since as previous reported by the same group[184], the use of [C_6MIM] [NTf_2] containing $HNTf_2$ in the same reaction conditions, but using glycosyl phosphite as donor the formation of the β-product was favoured. The use of the system [C_6MIM] [OTf]/HOTf afforded the highest β-stereoselectivity. Similar results were obtained when the α- or the β-donors anomers were used, indicating that the stereoselectivity of the glycosylation is independent of the configuration at the anomeric center of the glycosyl donor. Thus this reaction proceeds via an S_N1 type pathway and involves an oxocarbenium ion intermediate. The authors reported that the α-stereoselectivity obtained with [C_6MIM] [NTf_2] containing $HNTf_2$, resulted from the anomeric effect, while the β-stereoselectivity shown using [C_6MIM] [OTf]/HOTf was due to the α-oriented coordination of the trifluoromethanesulfonate anion from the IL with the oxocarbenium ion intermediate. When 1-(3-cyanopropyl)-3-methylimidazolium trifluoromethane sulfonimidide ([1-(3-cyanopropyl)-3-MIM][NTf_2]) was used as solvent with $HNTf_2$ as catalyst a β-stereoselectivity was induced, indicating that the cyano group in the side chain of the imidazolium cation coordinates with the oxocarbenium intermediate and significantly affects the stereoselectivity of the glycosylation.

In 2007 Toshima *et al*. reported the aryl C-glycosylation with several glycosyl donors [186], including glycosyl fluorides, acetates and unprotected methyl glycosides. They also used a protic acid as catalyst in ILs. In this study, they took advantage of the non-vapour pressure of the ILs, so it was possible to perform the reaction at 2 mmHg with a yield increase from 40% to 60% at 60°C, in the same experimental conditions. One of the problems in glycosylation reactions is the presence of water, due to possible hydrolysis of the reactants. The protocol presented on this

work has the advantage to remove the water from the reaction medium. The best yield for the glycosylation of unprotected methyl glycosides was achieved when $[C_6MIM][NTf_2]$ containing $HNTf_2$ was used as solvent/catalyst, resulting in almost complete selectivity for the β-product. The same reaction was made in DCM, and not only was the yield improved in the IL, but this solvent could also be recovered and reused at least three times without the any loss of efficiency. Additionally, the reaction yield was still improved (98%) when the temperature was decreased to 25°C and the pressure remained at 2 mmHg [186] (Scheme 2.1.9).

Scheme 2.1.9 – Aryl C-glycosylation of several glycosyl donors in $[C_6MIM]$ $[BF_4]$ with HBF_4.[186]

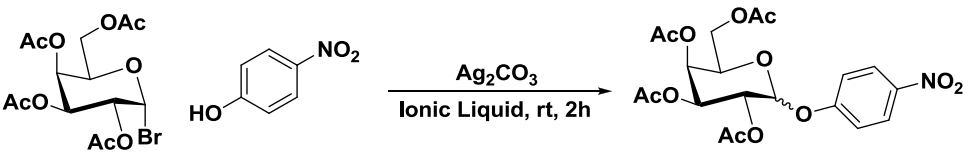
Ragaukas *et al.* reported [187] the synthesis of alkyl glycoside and disaccharides via the coupling of thioalkyl glycosyl donors with glycal acceptors (Scheme 2.1.10), employing $[BMIM][BF_4]$ as reaction medium, and methyl triflate as reaction promoter. With two equivalents of methyl triflate, at 25°C, and $[BMIM][BF_4]$ as solvent, moderate to good yields (39-81%) were obtained. The authors report that for methyl 2,3,4,6-tetra-*O*-acetyl-α-D-thiomannopyranoside, the α glycosides were the major products, while for substrate 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranoside, the major product were β-forms. Others ILs such as [BMIM] $[PF_6]$, [BMIM] [MS] and 1-butyl-1-pyrrolidinium bistriflimide, $[BMPyr][NTf_2]$ resulted in lower yields or no reaction. The water effect was also studied and it was observed that the reaction was not affected with small amounts of water (up to 4mM), but for higher water concentrations the reaction yield decrease until no reaction occurs. The stability of the methyl triflate was tested in the IL and several organic solvents with small quantities of water. It was observe that the relative hydrolysis rate of methyl triflate in DMSO was 100 times more reactive than in the IL. The authors explain this result by the ability of ILs act as liquid molecular sieves.[187]



Scheme 2.1.10 – Glycosylation reaction with various glycosyl donors.[187]

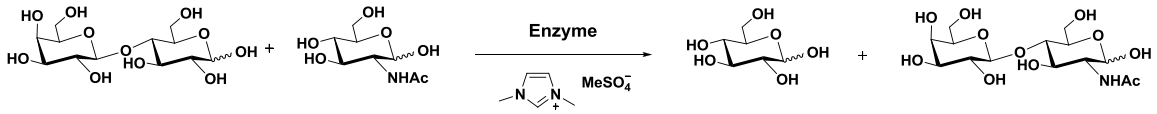
Glycosyl halides are also used to build glycosidic bonds, and glycosyl bromides and chlorides may be activated under traditional Koenigs–Knorr[188] conditions in the presence of a base such as silver carbonate.[189] In 2010 Malhotra *et al.* reported the evaluation of Koenigs-Knorr type couplings of glycosyl bromides in a series of molten salts and ILs.[189] The coupling of acetobromo-α-D-galactose with *p*-nitrophenol was chosen as reaction model and silver carbonate was used as glycosylation promoter at 25°C (Scheme 2.1.11). ILs based on [BMIM] in combination with different anions: [NTf_2], [PF_6], [OTf], or [BF_4]; or *N*-butylpyridinium [C_4Py][BF_4], *N*-hexylpyridinium [C_6Py][NTf_2] and *N*-butylpyrrolidinium [BMPyr][OTf] were used as reaction media, resulting in low to moderate yields. The only product formed was the β-anomer as a result of anchimeric assistance[190]. Among the imidazolium ILs, the combinations with the anions NTf_2 and PF_6 leaded to higher yields than the combinations with either OTf or BF_4. Decomposition of the starting glycosyl halide was observed in the presence of many bases with exception of silver carbonate and silver oxide. ILs based on imidazolium halides were tested as reaction solvent at 80°C, and the obtained yields were 54-70%, being the best one obtained with [BMIM][Cl]. According to reported data where Toshima *et al.*[184] showed that the addition of the chloride IL in the reaction medium resulted in reaction inhibition, and Galan *et al.*[182] tested several ILs based on halide anions with no product formation, the result presented on this work is quite surprising, and shows that depending on the glycosyl donor the IL influence on the reactivity can be reasonably different. So [BMIM][Cl] was chosen to further optimization studies, such as the stoichiometric effect of the base and phenol. [189] Increasing the amount of phenol (1 to 3 equivalents) the yield increased significantly (from 52% to 80%). The same effect was observed for the base (0.5 equivalents produced 30% yield whereas 2 equivalents resulted in 80% yield). Electron-rich and

electron-deficient aromatic alcohols were experimented with either acetobromo-α-D-galactose or acetobromo-α-D-glucose in the presence of silver carbonate at 80°C. Both the α and β product (α /β=0.08/0.37)were obtained in contrast with other works reported in the literature, which may be explain by the highest temperature used. Electron-deficient phenols that were substituted at the *ortho*- and *para*- positions gave higher yields than the corresponding *meta*-analog. Since electron-deficient phenols are more easily converted into the corresponding silver salts, it is possible that [BMIM][Cl] plays a role in facilitating this conversion by stabilizing the salt. The IL was recovered and reused twice for the same reaction without apparent efficiency loss.



Scheme 2.1.11 – Glycosylation of acetobromo-α-D-galactose and *p*-nitrophenol in ILs.

Kaftzik and co-workers [191] demonstrated that an optimal amount of IL was necessary to maximize the product yield and enzyme stability in the synthesis of *N*-acetyl lactosamine using β-galactosidase. *N*-acetyl-glucosamine and lactose react in the presence of β-galactosidase in a mixture of buffer solution and 1-methyl-3-methylimidalium methylsulfate [MMIM] [MS] (Scheme 2.1.12). The enzymatic activity dropped from 74% to 14% when the amount of IL varied from 25% to 50% (v/v). At 25% [MMIM] [MS] the overall yield was greatly improved and was almost twice the yield obtained for the reaction in conventional aqueous buffer. The selectivity increased and the enzyme stability was maintained in the presence of the IL. [191]



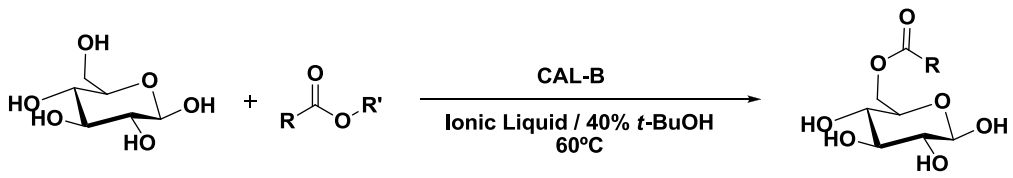
Scheme 2.1.12 – Enzyme-catalyzed synthesis of N-acetyllactosamine with the enzyme β-galactosidase.[191]

Enzymatic transglycosylation mechanism undergo with the formation of a covalent glycosylenzyme intermediate which normally reacts with water (hydrolysis) but can also be intercepted by an alternative, external nucleophile R-OH to yield glycosidic product. So the transglycosylation reaction will be optimized for a high concentration of nucleophile, and as low as possible water concentration.[192] Nidetzky *et al.* [192] have highlight the ability of ILs to suppress hydrolysis and reported the transgalactosylation reactions catalyzed by the β-glycosidase CelB from *Pyrococcus furiosus* at 80 °C and in the presence or absence of [MMIM] [MS] as co-solvent. The results showed that the interactions of the acceptor with the solvent molecules made a

major contribution to the observed transgalactosylation specificity of the enzyme, this is the presence of the IL as co-solvent leaded to a decrease in water activity and consequently suppressed secondary hydrolysis favouring nucleophilic attack of the glycosyl acceptor resulting in a higher enzymatic specificity and a higher glycosylation yield. Unfortunately, for lactose and D-xylose substrates, a significant yield increase was not observed by the addition of the IL.[192]

2.1.4 Synthesis of glucose fatty acid esters

Sugar fatty acid esters are non ionic surfactants used in cosmetic, pharmaceutical and food industries. A synthesis directly from sugar and fatty acid is difficult to perform due to the lack of solubility of the sugar in some organic solvent that is necessary for fatty acid dissolution. Additionally, denaturation of lipases is very likely to occur in the organic solvent, which is also not suitable for food industry. Consequently, ILs were tested as a new approach to catalyse the synthesis of sugar fatty acid esters. Bornscheuer *et al.* [193] have reported that glucose fatty acid ester synthesis with lipase B from *Candida antarctica* in the presence of [BMIM][BF_4] and *t*-butanol as co-solvent, could be observed, with 90% conversion, 75% yield and good purity (Scheme 2.1.13).[193] It was also tried the same reaction in pure IL, with immobilization of the enzyme in polyethyleneglycol (PEG), using lauric and myristic acid vinyl ester as substrate, but the conversions were not so good (30-35%).



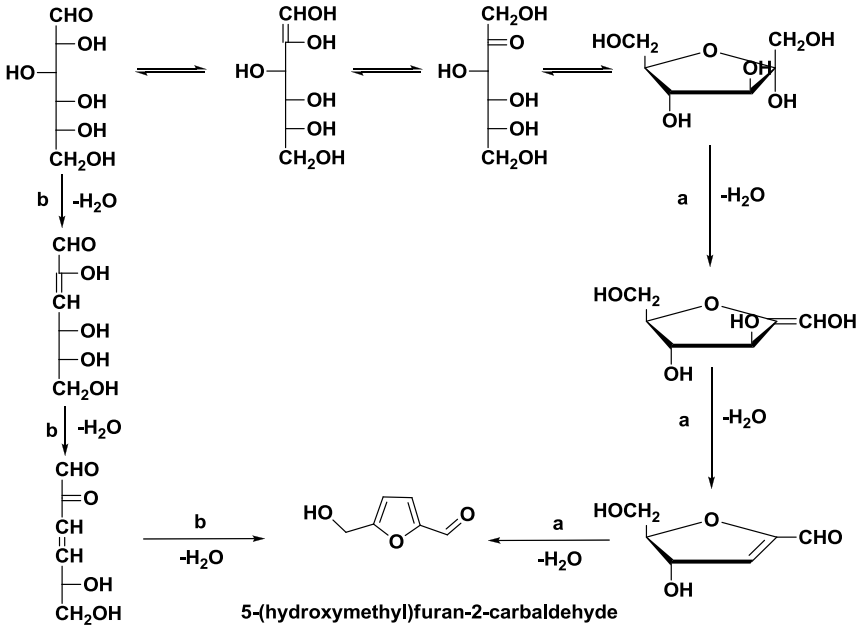
Scheme 2.1.13 – Glucose fatty acid ester synthesis in ILs. [193]

In 2008 Koo *et al.* [163, 194]reported the use of supersaturated sugar solutions in ILs for lipase-catalyzed esterifications in pure IL. The use of a supersaturated glucose solution in ILs drastically increased the reaction rate of Novozym 435 (*Candida antarctica* type B lipase immobilized on acrylic resin), compared with the method of using a saturated solution in the presence of glucose crystals[163]. The lipase-catalyzed direct esterification of glucose with lauric acid was efficiently carried out with the supersaturated glucose solution in pure IL [Bmim][TfO] with conversion level of 91%, at 100 h of reaction. In further studies[195] the Novozym 435 activity and stability were optimized in a mixture of two ILs [BMIM][TfO]/[C_8MIM][Tf_2N] in a ratio 1:1. Conversions yields reached approximately 80% after a reaction time of 80 hours at 50°C. In this system, 78% of the enzymatic activity remained after 5 cycles of reaction. The same authors have recently reported[196] the synthesis of fructose palmitate by lipase-catalyzed esterification in

ILs, where the application of ultrasound irradiation could improve the enzyme stability in a mixture of ILs ([BMIM][TfO]/[C_8MIM][Tf_2N] in a ratio 1:1.

2.1.5 Carbohydrates dehydration (HMF synthesis)

HMF (5-hydroxymethylfurfural) is synthesized manly by dehydration of monosaccharides by the loss of three water molecules. Disaccharides or polysaccharides, such as sucrose, cellobiose, inulin or cellulose, can be used as starting material, but a hydrolysis reaction is necessary to depolymerise into their monomers. For example, the main difficulty to transform sucrose into HMF is that the hydrolysis reaction is more efficiently catalyzed by a base, although the dehydration reaction of the fructose monomer is catalyzed by acids. The formation of HMF by dehydration is a very complex process due to the possibility side reactions. Antal *et al*. [197] reported the possible side products formed by decomposition of fructose in water at high temperatures: isomerisation, dehydration, fragmentation and condensation products. The mechanism for fructose dehydration reaction is not clear, and two different pathways are proposed to HMF formation (Scheme 2.1.14).[197-198]



Scheme 2.1.14 – Proposed pathways for HMF formation.[198]

2.1.5.1 Glucose vs. Fructose

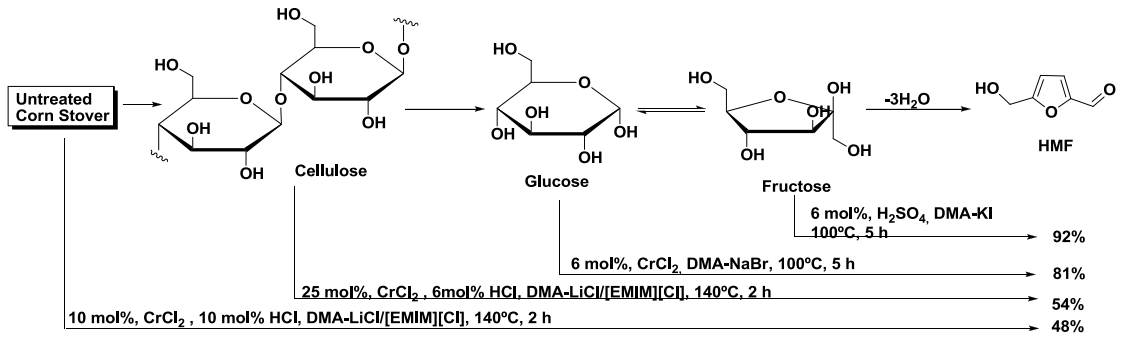
Glucose (aldose) reactivity to dehydration is lower than fructose (ketose), this fact have been explained by the lower relative abundance of acyclic glucose as compared to acyclic fructose in solution.[199] Glucose can form very stable ring structure, so the enolisation rate in solution is lower than fructose that form less stable ring structures.[199b] Since enolisation can be the determining step for HMF formation, fructose will reacts much faster than glucose.

2.1.5.2 HMF isolation methods

In most of HMF reported work the yield of HMF is obtained in solution and analysed by HPLC, or GC of both phases. It is important not only to optimize the synthesis of this compound, but also to develop an efficient isolation method. HMF is not easy to extract from aqueous phase, since the distribution coefficient between the organic and the aqueous phase is not favourable,[199b, 200] although this problem have been solved, and several organic solvents have been reported as efficient extraction solvents, such as MIBK (methyl isobutyl ketone)[201], DCM[201d], ethyl acetate[202], THF[203], ether diethylic[204], or acetone[205]. Organic solvents can improve the HMF synthesis, since it avoids the formation of by-products, such as soluble polymers, or humins, among others, [206] but the main problem is that polar organic solvents, such as DMSO or DMF[206a, 207], have a high boiling point, and due to reactive nature of HMF at high temperatures[201d, 208], a distillation separation process becomes undesirable. ILs have been a promising solvent for carbohydrates transformations.[156] ILs have been reported not only as solvents, but also as reaction promoters for carbohydrate dehydration reactions[209], and with some ILs is possible to isolate the HMF final product by extraction with a low boiling point solvent.[202c, 209b] Although, efficient separation techniques need to be developed in order to make the efficient methods of synthesis, economically viable for higher scale production.

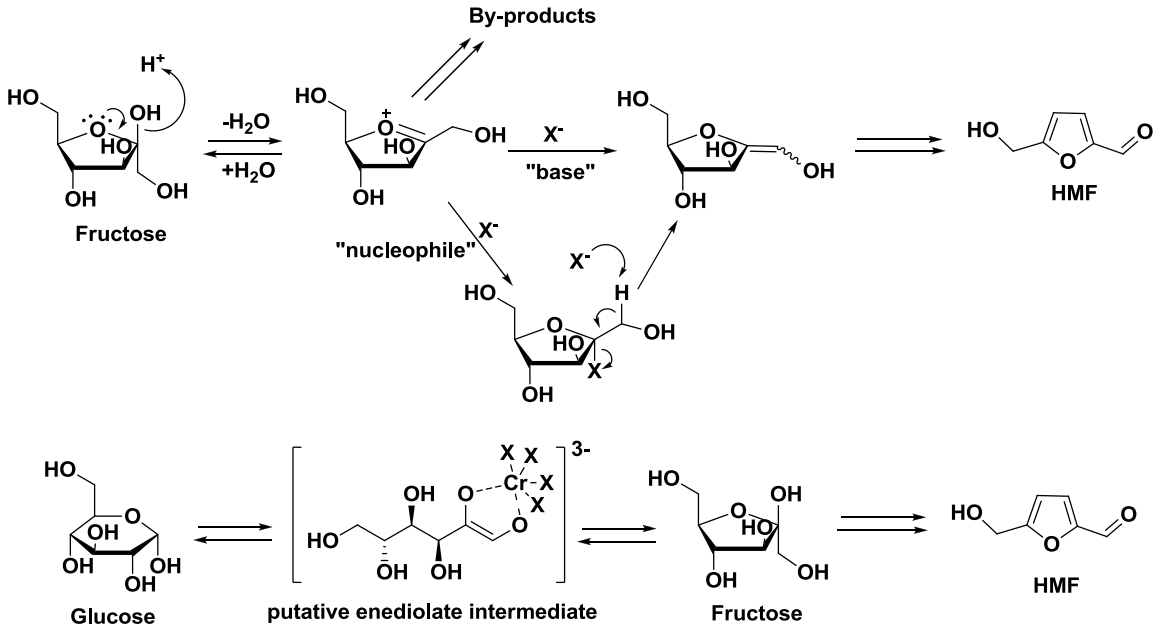
2.1.5.3 HMF Synthesis

Binder and Raines reported[210] the use of authentic lignocellulosic biomass as starting material for HMF production, using DMA-LiCl (N,N-dimethylacetamide- Lithium chloride) as solvent (Scheme 2.1.15). They initiated the study with fructose as starting material, with H_2SO_4 as catalyst and DMA-Lithium salt as solvent, and tested several additives, such as [EMIM][Cl] and other ILs. When different lithium salts were tested, it was observed that fluoride ions are completely ineffective for HMF synthesis (Table 2.1.3, entry 4), although bromide and iodide ions, which tend to be less ion-paired than fluoride and chloride[210], achieved HMF yields up to 92% (Table 2.1.3, entry 5). Based on these and others experimental results the authors proposed a reaction mechanism, involving an oxocarbenium ion that is attacked by the halide ion (Scheme 2.1.16).



Scheme 2.1.15 – Production of HMF using biomass as starting material, with different catalysts and with or without the use of ILs. [210]

HMF production starting from glucose was also tested with $CrCl_2$, $CrCl_3$ or $CrBr_3$ as catalyst with DMA-LiCl (or other salts such as LiBr, LiI) as solvent (Table 2.1.3, entries 6-9). The halide effect also was very pronounced with this substrate. With chloride anions present in the reaction mixture ($CrCl_2$ as catalyst and DMA-LiCl as solvent, Table 2.1.3, entry 6) were obtained HMF yields up to 60%, that were enhanced to 62% with the addition of [EMIM][Cl] as additive (Table 2.1.3, entry 7). Although the addition of iodide ions in the reaction mixture with $CrCl_2$ as catalyst did not improved the HMF yields the same did not happen with bromide ions that improved HMF yields up to 80% (Table 2.1.3, entry 9). Cellulose was also tested as HMF source with $CrCl_2$ and HCl as catalysts. Dissolution of purified cellulose in a mixture of DMA-LiCl and [EMIM][Cl] and addition of $CrCl_2$ or $CrCl_3$ produced HMF from cellulose in up to 54% yield within 2 h at 140 °C (Table 2.1.3, entries 10, 11). Due to cellulose insolubility neither lithium iodide nor lithium bromide produced high yields of HMF (Table 2.1.3, entry 12). Finally the synthesis of HMF from lignocellulosic biomass was also studied. A 48% HMF yield (based on cellulose content of the biomass) was achieved with this substrate in near conditions as for cellulose (Table 2.1.3, entry 13). The authors propose that the formation of HMF from cellulose in DMA-LiCl occurs via saccharification followed by isomerisation of the glucose monomers into fructose and dehydration of fructose to form HMF. It was possible to separate the HMF formed by an ion-exclusion chromatographic separation, where over 75% of HMF was recovered. Binder and Raines are the authors of a patent that describes this technology with the aim of 2,5-dimethylfuran manufacture.[211]

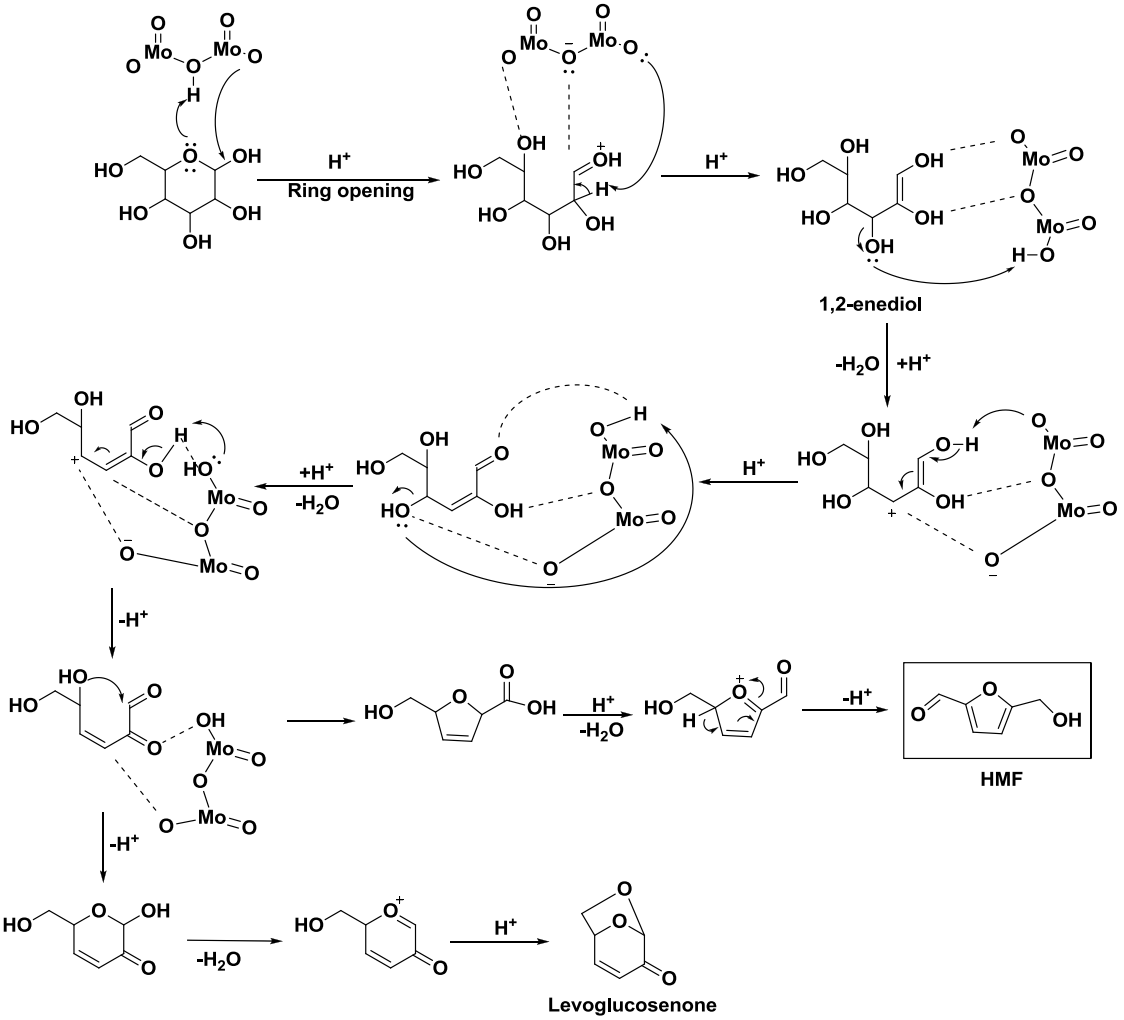


Scheme 2.1.16 – Proposed mechanism for formation of HMF using chromium based catalysts, and ILs.[210]

Almost complete conversion of the monosaccharides, fructose, glucose and mannose were observed in the presence of a Brønsted acid, H_2SO_4 at 120°C within 4 hours, in a IL [BMIM][Cl].[212] With fructose the main product observed was HMF (Table 2.1.3, entry 1), with 85% yield. The authors reported that a similar result was obtained when the reaction was performed without the presence of H_2SO_4. For glucose and mannose, although the conversion was almost complete, the main product formed was not HMF, confirming that dehydration of ketoses is quicker than aldoses.[198] HMF stability in [BMIM][Cl]/H_2SO_4 was also studied, resulting in almost complete recovery of HMF added (7% conversion and 1% solid residues formation). Other stabilities studies of HMF in [BMIM][Cl] with different reaction conditions were done[213], also leading to almost complete HMF recovery, thereby HMF is stable in [BMIM][Cl]. The stability of HMF in the reaction conditions ([BMIM][Cl]/H_2SO_4 at 120°C after 4 hours), but in the presence of glucose was tested, and was observed an increase of HMF conversion (48%), and almost complete glucose conversion (96%). It was also observed an increase of the solid residues, compared with the solid formed with only glucose. This indicates that HMF in these conditions can react with monosaccharides or monosaccharides degradation products.

Several liquid (H_2SO_4, CF_3SO_3H, CH_3SO_3H, CF_3COOH, HNO_3, HCl and H_3PO_4) and solid acids, [12-tungstophosphoric acid (12-TPA ($H_3PW_{12}O_{40}$)), 12-molybdophosphoric acid (12-MPA ($H_3PMo_{12}O_{40}$)), 12-tungstosilicic acid (12-TSA ($H_3SiW_{12}O_{40}$)), and 12-molybdosilicic acid (12-MSA ($H_3SiMo_{12}O_{40}$))] were tested as catalysts for glucose dehydration to HMF, with [EMIM][Cl] as solvent (Table 2.1.3, entries 18-32).[202d] With all of these catalysts were formed 4 to 20% of

humins, and others by-products. 12-MPA was chosen to further studies due to the best performance and selectivity (Table 2.1.3, entry 26, 71% glucose conversion with 89% HMF selectivity). With this catalyst several others ILs, such as [EMIM][Cl], [BDMIM][Cl] (1-butyl-2,3-dimethylimidazolium chloride) and [BMPy][Cl] (*N*-butyl-*N*-methylpyridinium chloride) were tested (Table 2.1.3, entries 28-30). There was a lower activity of 12-MPA in the ILs [BDMIM][Cl] and [BMPy][Cl] when compared with the other two. With [BDMIM][Cl] the lower activity is maybe due the acidic proton lost from the imidazolium cation. So the lost of the acidity in the solvent, in this case the IL, reduces the glucose conversion, and HMF selectivity. With [BMIM][Cl] or [EMIM][Cl] as solvent, and acetonitrile as co-solvent the glucose conversion was enhanced up to 99%, with a 98% HMF selectivity, and no formation of humins was observed (Table 2.1.3, entries 31 and 32). A glucose dehydration mechanism by 12-MPA is proposed (Scheme 2.1.17), and the authors claim that 1,2-enediol is the key intermediate in the reaction pathway to HMF. The high selectivity of heteropoly acids is attributable to stabilization of the reaction intermediates involved in formation of HMF.



Scheme 2.1.17 – Proposed mechanism for HMF formation using 12-molybdophosphoric acid as catalyst. The authors key intermediate 1,2-enediol. [202d]

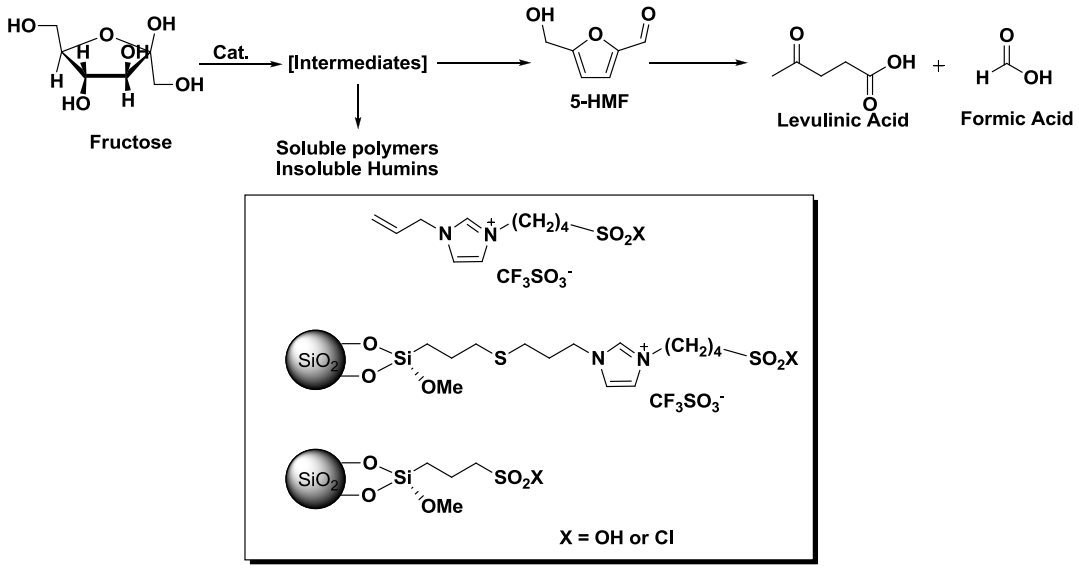
Table 2.1.3 – Conversion of carbohydrates to HMF catalyzed by mineral or organic acids.

		Reaction conditions				Post-reaction details				
Entry (Ref.)	Biomass source	Solvent	Catalyst	Temp (°C)	Time	Conversion (%)	HMF Selectivity (%)	Isolation/ determination method	Isolated yield (%)	Catalyst reuse
1[212]	Fructose	[BMIM][Cl]	H_2SO_4	120	4 hours	100	85	HPLC	-	-
2[210]	Fructose (10 wt.%)	DMA-LiCl	H_2SO_4	100	5hours	-	63	HPLC	-	-
3[210]	Fructose (10 wt.%)	DMA/ [EMIM][Cl]	H_2SO_4	100	2hours	-	84	HPLC	-	-
4[210]	Fructose (10 wt.%)	DMA/LiF	H_2SO_4	80	2hours	-	0	HPLC	-	-
5[210]	Fructose (10 wt.%)	DMA/ LiBr NaBr LiI NaI	H_2SO_4	100	4hours 2hours 6hours 5hours	-	92 93 89 91	HPLC	-	-
6[210]	Glucose (10 wt.%)	DMA-LiCl	$CrCl_2$	100	5 hours	-	60	HPLC	-	-
7[210]	Glucose (10 wt.%)	DMA-LiCl/ [EMIM][Cl]	$CrCl_2$	100	6 hours	-	62	HPLC	-	-
8[210]	Glucose (10 wt.%)	DMA/LiI	$CrCl_2$	100	4 hours	-	54	HPLC	-	-
9[210]	Glucose (10 wt.%)	DMA/LiBr	$CrBr_2$	100	6 hours	-	80	HPLC	-	-
10[210]	Cellulose	DMA-LiCl/ [EMIM][Cl]	$CrCl_2$/ HCl	140	2 hours	-	54	HPLC	-	-
11[210]	Cellulose	[EMIM][Cl]	$CrCl_2$/ HCl	140	1 hours	-	53	HPLC	-	-
12[210]	Cellulose	DMA/ LiI LiBr	$CrCl_2$/ HCl	140	3 hours	-	<1 <1	HPLC	-	-
13[210]	Corn stover	DMA-LiCl/ [EMIM][Cl]	$CrCl_2$/ HCl	140	2 hours	-	48	HPLC	-	-
14[214]	Fructose	Fructose/ [Chol][Cl] (4:6)	PTSA	100	30 min	-	67	Ethyl acetate extraction/ HPLC	-	-
15[214]	Inulin	Fructose/ [Chol][Cl] (5:5)	PTSA	90	1 hour	-	57	Ethyl acetate extraction/ HPLC	-	-
16[214]	Glucose	Fructose/ [Chol][Cl] (4:6)	$CrCl_2$	110	30 min	-	45	Ethyl acetate extraction/ HPLC	-	-
17[214]	Sucrose	Fructose/ [Chol][Cl] (5:5)	$CrCl_2$	100	1 hour	-	62	Ethyl acetate extraction/ HPLC	-	-
18[202]d	Glucose	[EMIM][Cl]	H_2SO_4	120	3 hours	93	66	Ethyl acetate extraction	-	-
19[202]d	Glucose	[EMIM][Cl]	CF_3SO_3H	120	3 hours	87	46	Ethyl acetate extraction	-	-
20[202]d	Glucose	[EMIM][Cl]	HNO_3	120	3 hours	56	77	Ethyl acetate extraction	-	-
21[202]	Glucose	[EMIM][Cl]	CF_3COOH	120	3 hours	58	75	Ethyl acetate extraction	-	-

[d]										
22[202d]	Glucose	[EMIM][Cl]	HCl	120	3 hours	53	62	Ethyl acetate extraction	-	-
23[202d]	Glucose	[EMIM][Cl]	CH_3SO_3H	120	3 hours	73	58	Ethyl acetate extraction	-	-
24[202d]	Glucose	[EMIM][Cl]	H_3PO_4	120	3 hours	17	95	Ethyl acetate extraction	-	-
25[202d]	Glucose	[EMIM][Cl]	12-TPA	120	3 hours	82	81	Ethyl acetate extraction	-	-
26[202d]	Glucose	[EMIM][Cl]	12-MPA	120	3 hours	71	89	Ethyl acetate extraction	-	-
27[202d]	Glucose	[EMIM][Cl]	12-TSA	120	3 hours	69	82	Ethyl acetate extraction	-	-
28[202d]	Glucose	[BMIM][Cl]	12-MPA	120	3 hours	71	89	Ethyl acetate extraction	-	-
29[202d]	Glucose	[BDMIM][Cl]	12-MPA	120	3 hours	57	88	Ethyl acetate extraction	-	-
30[202d]	Glucose	[BMPy][Cl]	12-MPA	120	3 hours	52	87	Ethyl acetate extraction	-	-
31[202d]	Glucose	[EMIM][Cl]/ acetonitrile	12-MPA	120	3 hours	99	98	Ethyl acetate extraction	-	-
32[202d]	Glucose	[BMIM][Cl]/ acetonitrile	12-MPA	120	3 hours	99	98	Ethyl acetate extraction	-	-

PTSA – p-toluenesulfonic acid; **TPA** - 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$); **MPA** – 12-molybdophosphoric acid ($H_3PMo_{12}O_{40}$); **TSA** – 12-tungstosilicic acid ($H_3SiW_{12}O_{40}$); **MSA** – 12-molybdosilicic acid ($H_3SiMo_{12}O_{40}$); **[EMIM][Cl]** – 1-ethyl-3-methylimidazolium chloride; **[BMIM][Cl]** – 1-butyl-3-methylimidazolium chloride; **[BDMIM][Cl]** – 1-butyl-2,3-dimethylimidazolium chloride; **[BMPy][Cl]** – 1-butyl-3-methylpyridinium chloride; **PVP** – poly(1-vinyl-2-pyrrolidinone); **MIBK** – methyl isobutyl ketone; **DMSO** – dimethylsulfoxide; **THF** – Tetrahydrofuran; **DMA** – N,N-dimethylacetamide; **[Chol][Cl]** – Choline chloride.

The use of ILs as solvents and reaction promoter was reported by Yokoyama *et al.*.[215] In this work was used microwave irradiation as heating source, in a Lewis acidic IL [ASCBI][OTf] (3-allyl-1-(4-sulfurylchloridebutyl) imidazolium trifluoromethanesulfonate), and a Brønsted acidic IL [ASBI][OTf] (3-allyl-1-(4-sulfobutyl) imidazolium trifluoromethanesulfonate) and their silica gel immobilized counterparts were tested for the fructose dehydration reaction (Scheme 2.1.18).[215] The two ILs with DMSO as co-solvent, converted fructose with very good yields, and good selectivity for HMF (Table 2.1.4, entries 2 and 3). The Lewis acidic IL was a better reaction medium than the Brønsted acidic IL. These ILs when immobilized in silica converted fructose with 100% yield, but with medium selectivity for HMF (Table 2.1.4, entries 4 and 5).



Scheme 2.1.18 – Dehydration of fructose to HMF in the presence of acidic catalysts.[215]

Several ILs were tested for the conversion of fructose to HMF, including Brønsted and Lewis acids (ChoCl/metal chlorides), and bases (ChoCl/urea, 1,1,3,3-tetramethylguanidinium trifluoroacetate and lactate) and ChoCl-based deep eutectic mixtures, at 80°C for 1 h, without adding any catalyst.[202a] The Lewis acids $ZnCl_2$ and $CrCl_3$ in ChoCl/metal chloride produce less than 20% of HMF (Table 2.1.4, entries 7 and 8). The most efficient solvent/catalyst tested was choline chloride/citric acid that lead to 91.1% conversion with 83.8% HMF selectivity (Table 2.1.4, entry 6). Ethyl acetate was reported as extraction solvent and showed a good efficiency. Due to the immiscibility with the IL reactive phase the product formed was extracted without any cross-contamination (Figure 2.1.5). This IL system has the advantage being biodegradable and non-toxic. [202a]

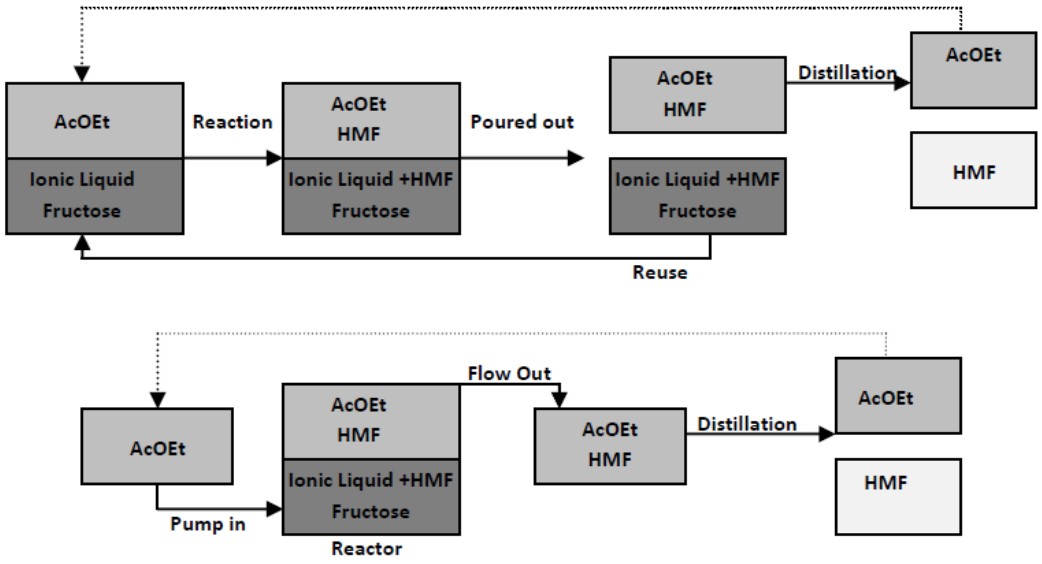


Figure 2.1.5 – Process of the biphasic system, IL and ethyl acetate.

Recently Han and co-workers[202c] reported the one pot inulin hydrolysis and fructose dehydration with moderate HMF selectivity (Table 2.1.4, entries 9-11) in choline based ILs at 80°C. The acidic CholCl/oxalic acid and CholCl/citric acid IL act as solvent and catalyst, and was possible to recycle CholCl/oxalic acid system for at least six cycles, just by extracting the product with ethyl acetate. A biphasic reaction system with ethyl acetate as extracting solvent provided an improved HMF selectivity (Table 2.1.4, entry 10).

Fayet *et al.* reported in 1983[216] the HMF synthesis from fructose, glucose, sucrose, inulin, and levan (fructose polymer). Different pyridinium salts were tested as promoters for HMF synthesis. With fructose, inulin and levan a moderated HMF yield was achieved with pyridinium chloride, at 120°C for 30 minutes (Table 2.1.4, entries 12, 13 and 14). The same didn't happen with glucose or sucrose, where the HMF yield was very low (Table 2.1.4, entry 15 and 16).

Table 2.1.4 Conversion of carbohydrates to HMF using acid solvents promoters

		Reaction conditions				**Post-reaction details**				
Entry (Ref.)	**Biomass source**	**Reaction medium**	**Catalyst**	**Temp. (°C)**	**Time**	**Conversion (%)**	**HMF Selectivity (%)**	**Isolation/ determination method**	**Isolated yield (%)**	**Catalyst/reaction medium reuse**
1[209b]	Fructose	1-H-3-methyl imidazolium chloride	-	90	45 min	100	92	Diethylether extraction	86	IL reused for 5 cycles
2[215]	Fructose	[ASBI][Tf]/ DMSO	-	100 (MW)	6 min	98	80	HPLC		
3[215]	Fructose	[ASCBI][Tf]/ DMSO	-	100 (MW)	6 min	100	84	HPLC		
4[215]	Fructose	ILIS-SO_3H/ DMSO	-	100 (MW)	4 min	100	70.1	HPLC		
5[215]	Fructose	ILIS-SO_2Cl/ DMSO	-	100 (MW)	4 min	100	67.2	HPLC		
6[202a]	Fructose	Choline chloride/citric acid	-	80	1 hour	91.1	83.8	Ethyl acetate extraction	72.2	IL reused for 8 cycles
7[202a]	Fructose	Choline chloride/ $CrCl_3$	-	80	1 hour	92	<20	Ethyl acetate extraction		
8[202a]	Fructose	Choline chloride/ $ZnCl_2$	-	80	1 hour	25	<7	Ethyl acetate extraction		
9[202c]	Inulin	Choline chloride/ oxalic acid	-	80	2 hours	100	56	Ethyl acetate extraction		IL reused for 6 cycles
10[202c]	Inulin	Choline chloride-oxalic acid/ ethyl acetate	-	80	2 hours	100	64	Ethyl acetate extraction/ HPLC		
11[202c]	Inulin	Choline chloride/	-	50+80	2+2 hours	88	65	Ethyl acetate extraction/	-	-

		citric acid						HPLC	
12[216]	Fructose	Pyridinium chloride	-	120	30 min	-	70	Silica gel chromatography (ethyl acetate/ petroleum ether)	70
13[216]	Inulin	Pyridinium chloride	-	120	30 min	-	60		
14[216]	Levan	Pyridinium chloride	-	120	30 min	-	60	-	
15[216]	Glucose	Pyridinium chloride	-	120	30 min	-	5		
16[216]	Sucrose	Pyridinium chloride	-	120	30 min	-	30	Silica gel chromatography (ethyl acetate/ petroleum ether)	30
17[209a]	Fructose (10 wt.%)	[EMIM][Cl]	-	120	3	100	70	HPLC	
18[209a]	Glucose (10 wt.%)	[EMIM][Cl]	-	180	3	40	<5	HPLC	

[ASBI][Tf] - 3-allyl-1-(4-sulfobutyl) imidazolium trifluoromethanesulfonate; **[ASCBI][Tf]** - 3-allyl-1-(4-sulfurylchloridebutyl) imidazolium trifluoromethanesulfonate; **DMSO** - Dimethylsulfoxide; **[EMIM][Cl]** - 1-ethyl-3-methylimidazolium chloride; **DCM** – dichloromethane; **ILIS** – ionic liquids immobilized on silica gel.

The dehydration of fructose using [BMIM][Cl] with the sulfonic ion-exchange resin, Amberlist® 15 as catalyst was developed by Qi *et al*..[213b] Were tested several mineral and Lewis acids, and solid acid anion-exchange resins, being the best catalyst Amberlyst® 15. This catalytic system resulted in a 98.6% fructose conversion with a selectivity of 83.3% for HMF, at 80°C and with a reaction time of 10 min (Table 2.1.5, entries 1 and 2). The water content of the IL was also taking in account, and for water contents above 5 wt.% the conversion yield and HMF selectivity decreased. Although there was no HMF self polymerization products, other by-products could be analyzed with HPLC, such as glucose, levulinic acid and formic acid, but with very low yields. The authors tested the HMF stability in this catalytic system by adding an HMF sample in the same reaction conditions, recovering 99.8% after reaction time. The HMF was extracted with ethyl acetate, so the IL and the catalyst could be recycled for at least 7 cycles.[213b]

The same authors[213a] reported the conversion of fructose into HMF with same Amberlyst® 15 as catalyst in the same solvent [BMIM][Cl], but in this work the reaction conditions were milder and the reaction underwent at room temperature (Table 2.1.5, entry 3). [BMIM][Cl] viscosity at room temperature is high, so it was not possible to stir the reaction solution without the addition of a co-solvent. Small amounts of different co-solvents were added to the reaction mixture, such as DMSO, methanol, ethanol, ethyl acetate, supercritic carbon dioxide, being acetone the most efficient although with all the others organic solvents the conversion and HMF yields were also

above 80%. To improve the reaction efficiency the substrate fructose has to be pre-dissolved in the IL in a water bath at 80°C for 20 minutes. The time reaction was higher than in the last work[213b] (6 hours *vs.* 10 minutes) but this method has the advantage of being performed at room temperature. By-products were also formed but in lower yields than 2%.[213a]

Hydrophobic and hydrophilic ILs ([BMIM][PF_6] and [BMIM][BF_4]), were tested as solvents for the fructose dehydration with Amberlyst® 15 or PTSA as catalysts. [217] The addition of DMSO as co-solvent increased the HMF selectivity, mainly due to an increase on fructose solubility. The fructose dehydration reaction in [BMIM][Cl] reported by Watanabe *et al.* [213a], in the same temperature conditions, was much faster, and selective than when performed with [BMIM][BF_4][217] reported in this work (Table 2.1.5, entries 1 *vs.* 8). This observation is maybe due to fructose solubility differences between [BMIM][BF_4] and [BMIM][Cl]. The addition of DMSO to [BMIM][BF_4], increase the HMF yield to a higher value than obtained with [BMIM][Cl] (Table 2.1.5, entries 4 *vs.* 1).

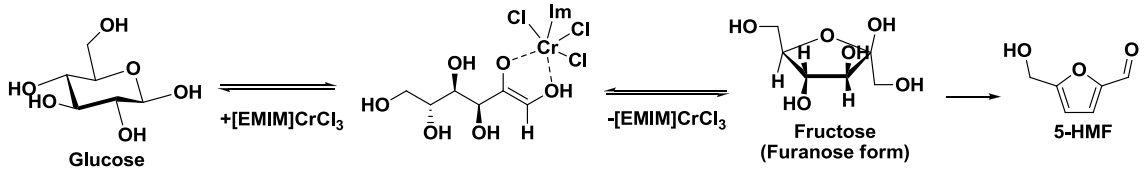
Table 2.1.5 – Conversion of carbohydrates to HMF under heterogeneous conditions.

		Reaction conditions				**Post-reaction details**			
Entry (Ref.)	**Biomass source**	**Solvent**	**Catalyst**	**Temp. (°C)**	**Time**	**Conversion (%)**	**HMF Selectivity (%)**	**Isolation/ determination method**	**Catalyst, reaction medium reuse**
1[213b]	Fructose (20 wt.%)	[BMIM][Cl]	Amberlyst-15	80	10 min	98.6	83.3	HPLC	Catalyst/solvent recycling for at least 7 cycles
2[213b]	Fructose (20 wt.%)	[BMIM][Cl]	Amberlyst-15	120	1 min	99.3	82.2	HPLC	-
3[213a]	Fructose (20 wt.%)	[BMIM][Cl]/ Acetone	Amberlyst-15	25 (rt)	6 hours	90.3	86.5	HPLC	-
4[217]	Fructose	[BMIM][BF_4]: DMSO (5:3)	Amberlyst-15	80	32 hours	-	87	HPLC/UV	-
5[217]	Fructose	[BMIM][BF_4]: DMSO (5:3)	PTSA	80	32 hours	-	68	HPLC/UV	-
6[217]	Fructose	[BMIM][PF_6]: DMSO (5:3)	Amberlyst-15	80	24 hours	-	80	HPLC/UV	-
7[217]	Fructose	[BMIM][PF_6]: DMSO (5:3)	PTSA	80	20 hours	-	75	HPLC/UV	-
8[217]	Fructose	[BMIM][BF_4]	Amberlyst-15	80	3 hours	-	52	HPLC/UV	-

[a] HMF selectivity is based on fructose content; **[BMIM][Cl]** – 1-ethyl-3-methylimidazolium chloride; **[BMIM][BF_4]** – 1-butyl 3-methyl imidazolium tetrafluoroborate ; **[BMIM][PF_6]** – 1-butyl 3-methyl imidazolium hexafluorophosphate ; **DMSO** – Dimethylsulfoxide; **DMF** – dimethylformamide, **NMP** - 1-methyl-2-pyrrolidinone; **MIBK** – methyl isobutyl ketone; **DCM** – dichloromethane; **HT** – Mg–Al hydrotalcite.

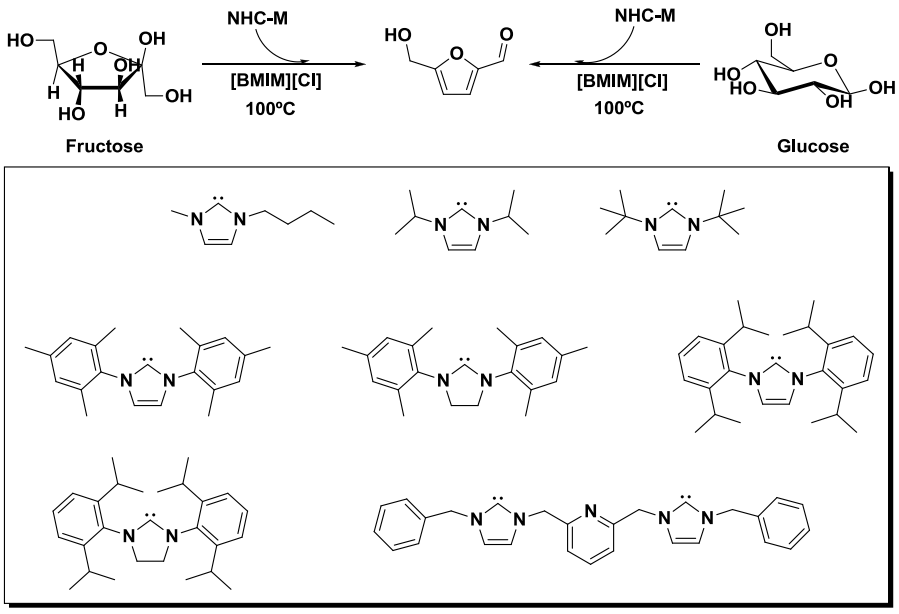
Zhang *et al.* reported[209a] the synthesis of HMF starting from fructose or glucose with very good selectivity. They have studied the effect of different ILs in the fructose dehydration. After chosen [EMIM][Cl] as solvent, they tested different catalysts, such as several metal chlorides, mineral and Lewis acids. Using [EMIM][Cl] as solvent, and no catalyst added was obtained a fructose

conversion of almost 100%, with approximately 70% selectivity, the only requirement was an increase of temperature to 120°C (Table 2.1.6, entry 1). For glucose this system was not so efficient, even at 180°C only 40% conversion was obtained, with less than 5% selectivity (Table 2.1.6, entry 2). When a catalytic amount of chromium (II) chloride was added, glucose conversion increased to near 70%, with more than 90% conversion (Table 2.1.6, entry 3). The authors propose that the catalyst [EMIM][Cl]/$CrCl_2$ was responsible for the isomerisation of glucose to fructose and then, fructose was rapidly converted to HMF (Scheme 2.1.19) .[209a] The HMF stability was studied, where pure HMF was heated at 100°C for 3 hours in [EMIM][Cl] in the presence of a catalytic amount of $CrCl_2$, a 98% of the HMF was recovered. When no $CrCl_2$ was added to the system, only 28% of the initial HMF was recovered. Similar studies were done with other metal halides with high HMF recovery, $CuCl_2$, VCl_4, and H_2SO_4 with 85, 86 and 98% recovery, respectively. So a catalytic amount of some metal chlorides can, not only catalyze the dehydration reaction, but also stabilize the final product. This maybe one of the main reasons for no polymeric by-products is observed, only a negligible amount of levulinic acid was formed.



Scheme 2.1.19 – Proposed metal halide interaction with glucose in [EMIM][Cl]. [209a]

Using [BMIM][Cl] as solvent (100°C, 6 hours), several NHC/metal (N-heterocyclic carbene ligand) complexes were tested as catalysts for the dehydration of fructose and glucose (Scheme 2.1.20).[218] The authors conclude that bulky NHC ligands protect the Cr center from reacting with [BMIM][Cl] and form a sterically crowded metal center, therefore providing a highest catalytic efficiency. A good HMF selectivity was achieved, using these NHC/Cr complexes as catalysts, 96% and 81% for fructose and glucose respectively (Table 2.1.6, entries 7 and 5). The HMF yield was confirmed by GC, but it was also possible to separate the HMF product from the reaction medium by a simple ether ethylic extraction. After that, the catalyst and the IL could be recycled for at least three cycles, where there was observed some selectivity lost when glucose was used as substrate. A higher fructose and glucose concentration was tested (20 wt.%) and was obtained no selectivity decreased (Table 2.1.6, entries 6 and 8).

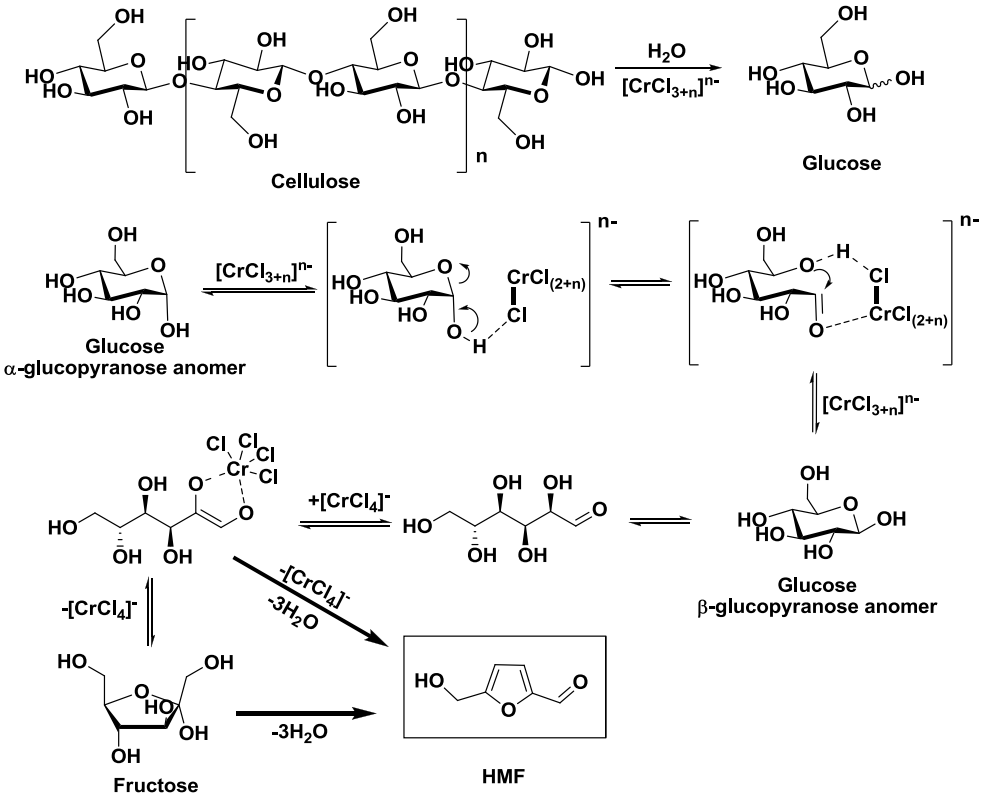


Scheme 2.1.20 – Conversion of sugars into HMF over NHC/metal catalysts.[218]

The HMF conversion using [EMIM][HSO_4] and [BMIM][Cl] with different substrates, with or without extracting solvents (toluene or MIBK) was studied.[201b] [EMIM][HSO_4] with toluene or MIBK as extracting solvents, completely converted fructose in 79 and 88% HMF yield, respectively (Table 2.1.6, entry 9 and 10). This system was not so efficient with glucose, so the authors change the IL to [BMIM][Cl] with $CrCl_3$ as catalyst. This catalyst was chosen instead of $CrCl_2$ since it is more stable and easily handled under air, much cheaper and, on the other hand, it is very likely that Cr^{2+} is oxidized to Cr^{3+} in the IL system containing dissolved air and water.[201b] The system with [BMIM][Cl]/$CrCl_3$ without a extracting solvent result on a 81% HMF yield, that was improved when toluene was added to the reaction system as an extracting solvent (Table 2.1.6, entry 11 *vs.* 13). This result is comparable with the reported[219] glucose dehydration in [BMIM][Cl]/$CrCl_3$ with microwave irradiation as a heating source, for only one minute, where the isolated HMF yield was 91% (Table 2.1.6, entry 18). Others substrates were tested, such as inulin, sucrose, cellobiose, and cellulose (Table 2.1.6, entry 14, 15, 16 and 17 respectively). Although high HMF selectivity was achieved for inulin, and sucrose, the same didn't happen with cellobiose or cellulose, even adding H_2SO_4 into the reaction system for cellulose.

In 2009, Li *et al.*[219] reported the transformation of glucose and cellulose in [BMIM][Cl] with $CrCl_3$ as catalyst affording HMF yields of 91 and 61% when subjected to a microwave irradiation of 400W for only one and two minutes, respectively (Table 2.1.6, entries 18 and 19). Different cellulose samples were tested reaching 53-62% HMF yields, indicating that this method is not affected by cellulose type nor polymerization degree. The high yields obtained from cellulose are explained by the complete cellulose dissolution on the ILs, leaving cellulose chains accessible to

chemical transformations, and also because [BMIM][Cl] has excellent dielectric properties for the transformation of microwave into heat. Although Zhang *et al.* [209a] reported smaller HMF yields for glucose transformation with $CrCl_3$ (Table 2.1.6, entries 4 *vs.* 18) in [EMIM][Cl], the authors believe that the microwave irradiation can improve the catalyst behaviour. A mechanism for this transformation was proposed (Scheme 2.1.21).



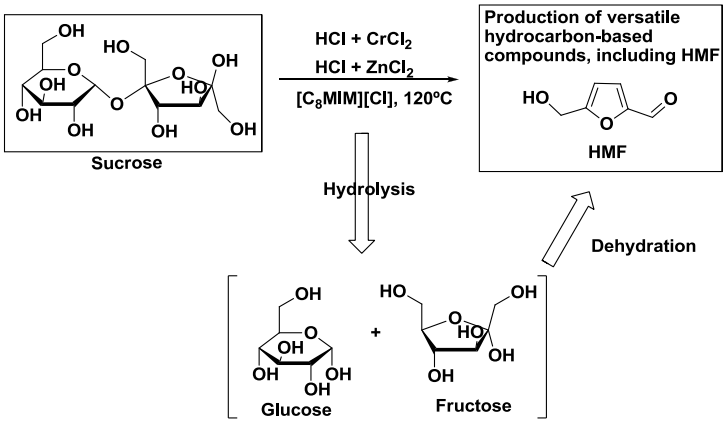
Scheme 2.1.21 – Proposed mechanism for the conversion of cellulose to HMF catalyzed with $CrCl_3$ in [BMIM][Cl].[219]

An extension of this work was made recently by the same authors, were they have tested this microwave assisted transformation with other biomass resources, such as corn stalk, rice straw and pine wood.[220] In this work $CrCl_3 \bullet 6H_2O$ was used as catalyst in [BMIM][Cl], for 2-3 minutes at 400W microwave irradiation. Different biomass sources were tested for dehydration to HMF, such as cellulose, corn stalk, rice straw and pine wood. Once again the HMF yield improvement when using microwave heating was confirmed (Table 2.1.6, entries 23 *vs.* 24). This reaction was also tested with [BMIM][Br] with similar results as with [BMIM][Cl] (Table 2.1.6, entries 24 *vs.* 25). [BMIM][Br] also can dissolve lignocellulosic biomass, thereby the authors reported that the reaction medium has little effect on the dehydration efficiency as long as the solvent dissolves lignocellulosic biomass.

Chen *et al.* [205] studied the cellulose conversion into HMF using a IL/water mixture with $CrCl_2$ as catalyst. At 120°C, with 10 mol% of $CrCl_2$ in [EMIM][Cl] (no water added) was observed an 89% HMF conversion (Table 2.1.6, entry 26). This high HMF yield implies that not only glucose was converted to HMF, but also others reducing sugars present after cellulose hydrolysis. To enhance the cellulose hydrolysis and dehydration, water was added to this catalytic system, resulting in a HMF yield decreasing, even at higher temperatures (Table 2.1.6, entries 24 *vs.* 28).

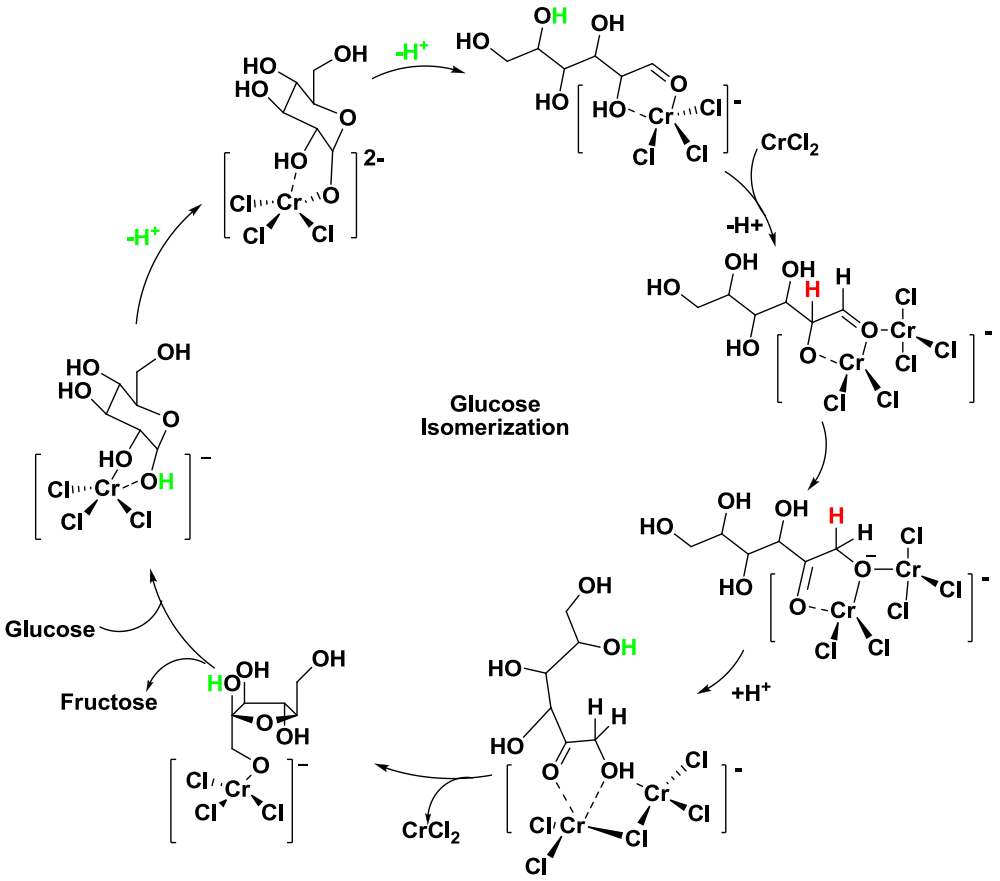
Recently Zhang *et al.* [221] studied cellulose transformation to HMF in the IL [EMIM][Cl] using a pair of two metal catalysts, $CrCl_2$ and $CuCl_2$ with a HMF yield of 55.4% (Table 2.1.6, entry 29). In this work a study was done to achieve the best molar ratio for the two catalysts $CrCl_2$ and $CuCl_2$, and was observed that as little as 3 mol% of $CrCl_2$ in the paired metal chlorides was sufficient to activate the $CuCl_2$ – dominant catalyst in the [EMIM][Cl] solvent. The catalyst and the solvent could be recycled for three times using MIBK as extracting solvent. A mechanism for this transformation is being studied by the authors.

Studies on sucrose hydrolysis and further dehydration to HMF were than by Chung *et al.*[222], using a different IL, 1-octil-3-methylimidazolim chloride ($[C_8MIM][Cl]$) as solvent and two metal chloride as catalysts ($CrCl_2$ or $ZnCl_2$) in a acidic medium, HCl (Scheme 2.1.22). According to the authors, the acidic medium will improve the sucrose hydrolysis, and the catalysts $CrCl_2$ or $ZnCl_2$ will catalyze further glucose dehydration. Firstly sucrose hydrolysis to glucose and fructose monomers was studied in $[C_8MIM][Cl]$ solutions at 120°C. Even without acid addition the sucrose hydrolysis occurs in $[C_8MIM][Cl]$, although with longer reaction times . With the acid addition the hydrolysis happen faster, but it was also possible to see a fast fructose disappearance, probably due to the strong chemical reactivity for isomerisation, dehydration, fragmentation or condensation reactions. The authors didn't report the by-products formed. When the catalyst $CrCl_2$ is added to the system an HMF yield improvement is observed. Depending on HCl and sucrose concentrations the time reaction was adjusted (Table 2.1.6, entries 30-32). The best HMF achieved was 82% for a sucrose concentration of 20% with 0.5M HCl and $CrCl_2$ as catalyst (Table 2.1.6, entry 30). A 50% wt/v sucrose concentration was also tested, resulting on a decrease of the HMF yield to 53.2% (Table 2.1.6, entry 32).



Scheme 2.1.22 – Sucrose hydrolysis followed by glucose and fructose dehydration to HMF, using $[C_8MIM][Cl]$ as solvent.[222]

In 2009 combing kinetic experiments, in situ X-ray absorption spectroscopy (XAS), and density functional theory (DFT) calculations the reactivity of chromium (II) chloride towards selective glucose dehydration in an IL medium was further studied by Pidko *et al.*. [223] The key reaction of the catalytic system [EMIM][Cl]/$CrCl_2$, as reported before[209a], is the isomerisation of glucose to fructose. In this work the authors propose a mechanism based on that proposed for the enzymes. In this chemical system the high concentrated and mobile chloride anions from the IL promote various (de)protonation reactions important for the glucose isomerisation (Scheme 2.1.23). In enzymes, such transformations are catalyzed by basic amino acid residues at the active site. The unique transient self-organization of Cr^{2+} dimers to facilitate the rate-controlling H shift in glucose isomerisation is possible as a result of the dynamic nature of the Cr complexes and the presence of moderately basic sites in the IL.



Scheme 2.1.23 – Proposed mechanism for the glucose transformation to HMF.[223]

Table 2.1.6 Conversion of carbohydrates to HMF under heterogeneous chromium based catalysts.

		Reaction conditions				Post-reaction details				
Entry (Ref.)	Biomass source	Solvent	Catalyst	Temp. (°C)	Time	Conv. (%)	HMF Selectivity (%)	Isolation/ determination method	Isolated yield (%)	Catalyst, reaction medium reuse
1[209a]	Fructose (10 wt.%)	[EMIM][Cl]	-	120	3 hours	100	70	HPLC	-	-
2[209a]	Glucose (10 wt.%)	[EMIM][Cl]	-	180	3 hours	40	<5	HPLC	-	-
3[209a]	Glucose (10 wt.%)	[EMIM][Cl]	$CrCl_2$	100	3 hours	70	90	HPLC	-	-
4[209a]	Glucose (10 wt.%)	[EMIM][Cl]	$CrCl_2$	100	3 hours	43	70	HPLC	-	-
5[218]	Glucose (10 wt.%)	[BMIM][Cl]	NHC/ $CrCl_2$	100	6 hours	-	81	Diethyl ether extraction/ GC	-	3 cycles
6[218]	Glucose (20 wt.%)	[BMIM][Cl]	NHC/ $CrCl_2$	100	6 hours	-	80	GC	-	-
7[218]	Fructose (10 wt.%)	[BMIM][Cl]	NHC/ $CrCl_2$	100	6 hours	-	96	Diethyl ether extraction/ GC	-	3 cycles
8[218]	Fructose (20 wt.%)	[BMIM][Cl]	NHC/ $CrCl_2$	100	6 hours	-	96	GC	-	-
9[201b]	Fructose	[EMIM][HSO4]/ Toluene	-	100	30 min	100	79	Toluene extraction/ HPLC	-	-
10[201b]	Fructose	[EMIM][HSO_4]/ MIBK	-	100	30 min	100	88	MIBK extraction/ HPLC	-	-
11[201b]	Glucose	[BMIM][Cl]/ toluene	$CrCl_3$	100	4 hours	91	91	HPLC	-	

12[201]b	Glucose	[BMIM][Cl]/ MIBK	$CrCl_3$	100	4 hours	79	79	MIBK extraction/ HPLC	-	
13[201]b	Glucose	[BMIM][Cl]	$CrCl_3$	100	4 hours	83	81	HPLC	-	
14[201]b	Inulin	[EMIM][HSO_4]/ MIBK	-	100	30 min	-	73	MIBK extraction/ HPLC	-	
15[201]b	Sucrose	[BMIM][Cl]/ MIBK	$CrCl_3$	100	4 hours	-	73	MIBK extraction/ HPLC	-	
16[201]b	Cellobiose	[BMIM][Cl]/ MIBK	$CrCl_3$	100	4 hours	-	37	MIBK extraction/ HPLC	-	
17[201]b	Cellulose	[BMIM][Cl]/ MIBK	$CrCl_3$/ H_2SO_4	100	4 hours	-	9	MIBK extraction/ HPLC	-	
18[219]	Glucose	[BMIM][Cl]	$CrCl_3$	≈200 (MW 400W)	1 min	-	91	Silica gel chromatography (ethyl acetate/petroleum ether)	91	-
19[219]	Cellulose	[BMIM][Cl]	$CrCl_3$	≈200 (MW 400W)	1 min	-	61	Silica gel chromatography (ethyl acetate/petroleum ether)	61	-
20[220]	Cellulose	[BMIM][Cl]	$CrCl_3$	≈200 (MW 400W)	2.5 min	-	62	HPLC	-	-
21[220]	Corn stalk	[BMIM][Cl]	$CrCl_3$	≈200 (MW 400W)	3 min	-	45	HPLC	-	-
22[220]	Rice straw	[BMIM][Cl]	$CrCl_3$	≈200 (MW 400W)	3 min	-	47	HPLC	-	-
23[220]	Pine wood	[BMIM][Cl]	$CrCl_3$	≈200 (MW 400W)	3 min	-	52	HPLC	-	-
24[220]	Pine wood	[BMIM][Cl]	$CrCl_3$	100 (oil bath)	60 min	-	6.4	HPLC	-	-
25[220]	Pine wood	[BMIM][Br]	$CrCl_3$	≈200 (MI 400W)	3 min	-	44	HPLC	-	-
26[205]	Cellulose	[EMIM][Cl]	$CrCl_2$	120	6 hours	-	89	Acetone extraction/ HPLC	-	-
27[205]	Cellulose	[EMIM][Cl]/ H_2O	$CrCl_2$	120	12 hours	-	13	Acetone extraction/ HPLC	-	-
28[205]	Cellulose	[EMIM][Cl]/ H_2O	$CrCl_2$	140	2 hours	-	40	Acetone extraction/ HPLC	-	-
29[221]	Cellulose (10wt.%)	[EMIM][Cl]	$CrCl_2$/ $CuCl_2$	120	8 hours	-	57.5	HPLC	-	-
30[222]	Sucrose (20% w/v)	[C_8MIM][Cl]	HCl/ $CrCl_2$	120	30 min	-	82.0	HPLC	-	-
31[222]	Sucrose (30% w/v)	[C_8MIM][Cl]	HCl/ $CrCl_2$	120	60 min	-	67.7	HPLC	-	-
32[222]	Sucrose (50% w/v)	[C_8MIM][Cl]	HCl/ $CrCl_2$	120	60 min	-	53.2	HPLC	-	-

MIBK – methyl isobutyl ketone; **MW** – Microwave irradiation; **[BMIM][Cl]** – 1-ethyl-3-methylimidazolium chloride; ; **[EMIM][Cl]** – 1-ethyl-3-methylimidazolium chloride; **[C_8MIM][Cl]** – 1-octyl-3-methylimidazolium chloride; **NHC** – *N*-heterocyclic carbene ligand.

Several metal chloride were screened in a IL, [BMIM][Cl], with the objective of finding the best catalyst for fructose dehydration at room temperature.[203] Tungsten salt catalyst provided the

best HMF yield (Table 2.1.7, entries 1 and 2). Several organic solvents, IL immiscible and with low boiling point where tested as extracting solvent (Table 2.1.7, entries 2-4). THF provided a biphasic reaction with higher HMF yields than the IL system without co-solvent (Table 2.1.7, entries 1 *vs.* 2). It was possible to isolate the HMF product with THF as the extraction solvent, and the IL/catalyst could be recycled. Also a continuous batch process for the conversion of fructose to HMF in a THF–[BMIM][Cl] biphasic system was developed (Figure 2.1.6), and tested with a bigger amount of fructose (10 g) as starting material.[203]

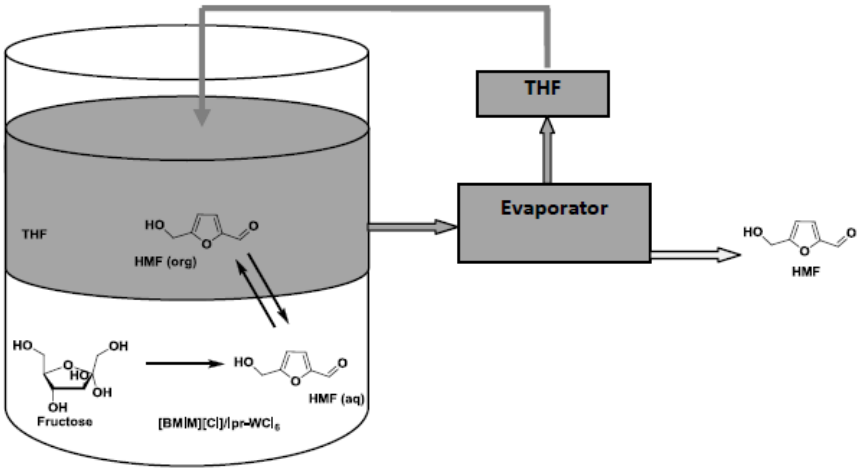
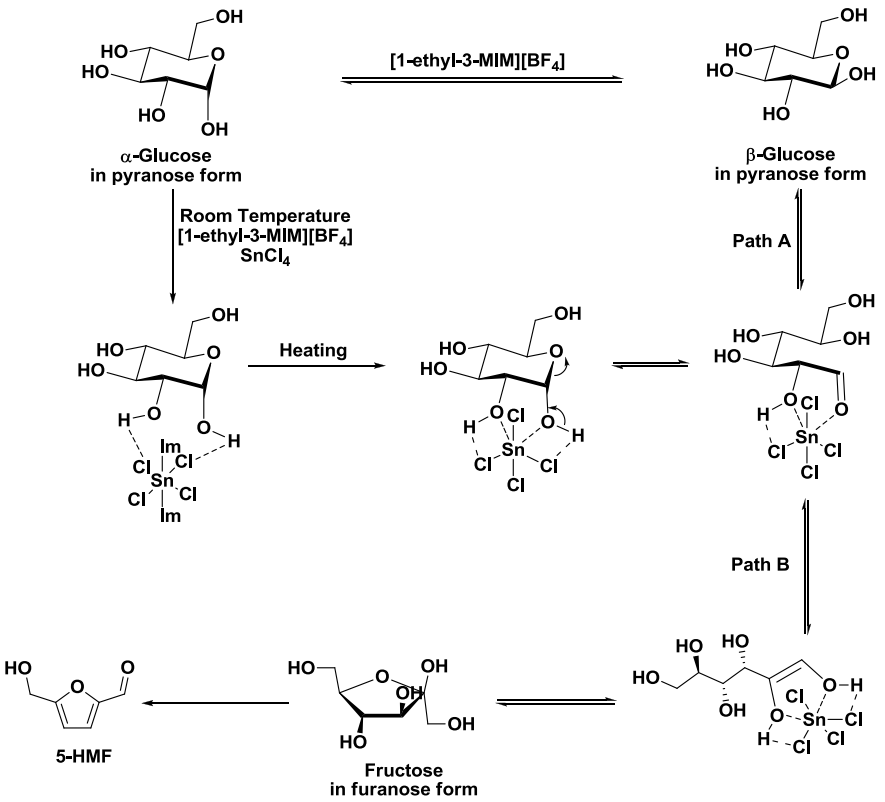


Figure 2.1.6 – Continuous batch process for the conversion of fructose to HMF in a THF–[BMIM][Cl] biphasic system.[203]

A screening was done in DMSO with different metal catalysts (100 °C, 3 hours) for glucose dehydration.[202b] The best where chromium, aluminium and tin chlorides. The last one was chosen for being the most efficient. With this catalyst several ILs where tested, and was observed that for ILs based on anions having coordination abilities, such as chloride (Cl), bis(trifluoromethane)sulfonimide (NTf_2), trifluoroacetate (TFA), trifluoromethylsulfonate (OTf) or saccharin (SAC), the HMF yields were lower than with other type of anions (BF_4, tetrafluoroborate). The authors suggested that these anions could compete with the interaction of glucose and the Sn atom inhibiting the HMF formation. The IL with best selectivity was the [EMIM][BF_4] (Table 2.1.7, entry 5). Based on these and others experimental evidences, the authors proposed a mechanism involving a five or six member ring quelate complex of the Sn atom and glucose (Scheme 2.1.24). Others saccharides were also tested, such as sucrose, cellobiose, inulin and starch, providing reasonable HMF selectivity (Table 2.1.7, entries 6-9).[202b] After a product extraction with acetate, was possible to recycle the $SnCl_4$/[EMIM][BF_4] catalytic system.



Scheme 2.1.24 – Proposed mechanism for glucose transformation into HMF, using $SnCl_4$/[EMIM][BF_4] catalytic system.[202b]

Table 2.1.7 – Conversion of carbohydrates to HMF promoted by miscellaneous catalysts.

		Reaction conditions				Post-reaction details				
Entry (Ref.)	Biomass source	Solvent	Catalyst	Temp. (°C)	Time	Conversion (%)	HMF Selectivity (%)	Isolation/ determination method	Isolated yield (%)	Catalyst, reaction medium reuse
1[203]	Fructose (20 wt.%)	[BMIM][Cl]	WCl_6	50	4 hours	-	63	THF extraction	-	Catalyst/solvent recycling
2[203]	Fructose (20 wt.%)	[BMIM][Cl]/ THF	WCl_6	50	4 hours	-	72	THF extraction	-	Catalyst/solvent recycling
3[203]	Fructose (20 wt.%)	[BMIM][Cl]/ MIBK	WCl_6	50	4 hours	-	61	MIBK extraction	-	Catalyst/solvent recycling
4[203]	Fructose (20 wt.%)	[BMIM][Cl]/ EtOAc	WCl_6	50	4 hours	-	59	EtOAc extraction	-	Catalyst/solvent recycling
5[202b]	Glucose 17wt.% 20 wt.% 23 wt.% 26 wt.%	[EMIM][BF_4]	$SnCl_4$	100	3 hours	98 99 100 99	62 61 61 58	Ethyl acetate extraction	-	Catalyst/solvent recycling for at least 4 cycles
6[202b]	Fructose	[EMIM][BF_4]	$SnCl_4$	100	3 hours	100	62	Ethyl acetate extraction	-	-
7[202b]	Sucrose (17 wt%)	[EMIM][BF_4]	$SnCl_4$	100	3 hours	100	65	Ethyl acetate extraction	-	-
8[202b]	Cellobiose	[EMIM][BF_4]	$SnCl_4$	100	3 hours	100	57	Ethyl acetate extraction	-	-
9[202b]	Starch	[EMIM][BF_4]	$SnCl_4$	100	3 hours	100	47	Ethyl acetate extraction	-	-

FeVOP – Iron Vanadyl phosphate **[BMIM][Cl]** – 1-ethyl-3-methylimidazolium chloride; ; **[EMIM][Cl]** – 1-ethyl-3-methylimidazolium chloride; **DMSO** – Dimethylsulfoxide; **MIBK** – methyl isobutyl ketone; **Co-gel -** Cobalt acetylacetonate encapsulated in sol–gel silica

Recently[224], lanthanides (III) chlorides were tested as catalysts for glucose dehydration to HMF, using ILs as solvents. First was tested the HMF stability in different ILs at 100°C, although all the ILs tested showed some HMF degradation, imidazolium based ILs with halides as anion showed the lowest degradation degree. Next, several lanthanides chloride were tested as catalyst for glucose dehydration in two different ILs, [BMIM][Cl] and [EMIM][Cl], an improvement was observed when lanthanide chlorides were present as catalysts. The strongest Lewis acid $YbCl_3$, gave the highest yield, although still moderated HMF yields (Table 2.1.8, entries 1-4). The authors suggest that this reaction undergoes with a different mechanism from the chromium chloride catalytic system, once the yield is favoured in hydrophobic ILs, and the Cr catalysis yield decreases with the hydrophobicity of the ILs.

Table 2.1.8 – Conversion of glucose to HMF catalyzed by YbCl3.

		Reaction conditions				**Post-reaction details**				
Entry (Ref.)	**Biomass source**	**Solvent**	**Catalyst**	**Temp .(°C)**	**Time**	**Conversion (%)**	**HMF Selectivity (%)**	**Isolation/ determination method**	**Isolated yield (%)**	**Catalyst, reaction medium reuse**
1[224]	Glucose	[EMIM][Cl]	$YbCl_3$	160	1 hour	-	8	HPLC	-	-
2[224]	Glucose	[BMIM][Cl]	$YbCl_3$	160	1 hour	-	20	HPLC	-	-
3[224]	Glucose	[C_6MIM][Cl]	$YbCl_3$	160	1 hour	-	19	HPLC	-	-
4[224]	Glucose	[C_8MIM][Cl]	$YbCl_3$	160	1 hour	-	22.5	HPLC	-	-

[BMIM][Cl] – 1-ethyl-3-methylimidazolium chloride; **[EMIM][Cl]** – 1-ethyl-3-methylimidazolium chloride; **[C_8MIM][Cl]** – 1-octyl-3-methylimidazolium chloride; **[C_6MIM][Cl]** – 1-hexyl-3-methylimidazolium chloride.

In the recent years was observed considerable efforts in order to achieve more efficient integrated process for the transformation of carbohydrates to HMF in which ILs provides considerable advantages. While a considerable achievement has been reported for the conversion of fructose to HMF, the transformation of glucose, sucrose and cellulose is still an open issue. The main difficult for glucose based carbohydrates transformation to HMF is the isomerisation step to fructose, which requires different conditions from the fructose dehydration step. So the overall process based on two independent steps may be more desirable as has been already explored by combination of basic/acid[207] or enzymatic/acid[225] catalytic systems.

More efficient reaction conditions (lower temperature, and higher carbohydrate initial concentration), higher conversions and HMF selectivity are desirable. On the other hand these improvements had to be compatible with more environmentally integrated processes of reaction and final product isolation and also with reaction media reuse.

2.2 Results and discussion

2.2.1 Carbohydrates Solubility in ILs

ILs based on dicyanamide anion can dissolve a large quantity of carbohydrates[160a, 161], but remarkable results can also be achieved with ILs based on different anions such as acetate [OAc].[13] As an alternative of ILs based on dicyanamide anion, in this work were synthesized ILs based on saccharine, acesulfame and thiocyanate anions and described for the first time as media for carbohydrates dissolution.[170] Beyond these novel anions, ILs based on chloride, dicyanamide and acetate were combined with novel cations, and tested not only for carbohydrates dissolution, but also tested as extractors of carbohydrates in aqueous solution. ILs based on imidazolium, guanidinium, phosphonium and ammonium cations were used for the carbohydrates dissolution and extraction studies (Figure 2.2.1). The synthesis of these ILs was described in the previous chapter.

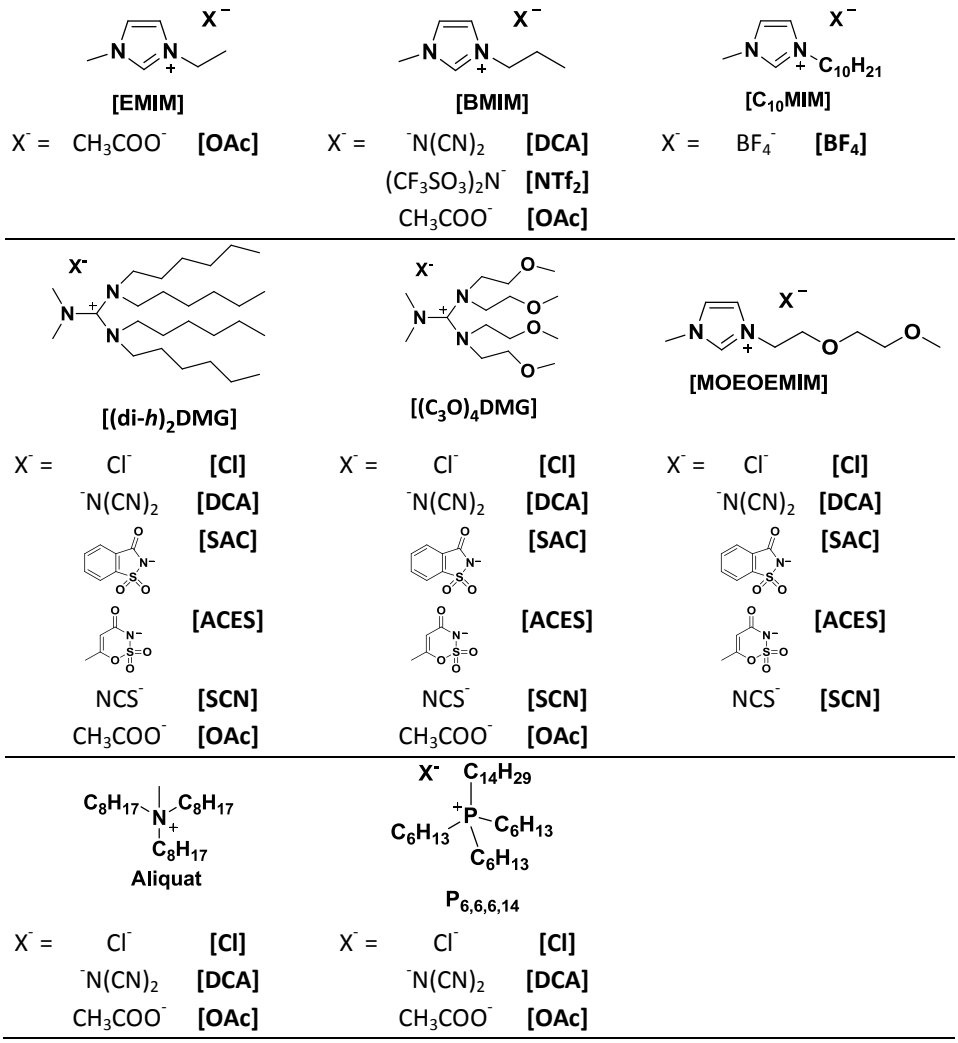


Figure 2.2.1 – Structure of ILs synthesized and tested on carbohydrates dissolution and extraction experiments.

Solubility experiments were made by addition of small amounts of the carbohydrate into the IL, at a controlled temperature of 35°C. When the IL solution was saturated the sample was centrifuged and the supernatant analyzed by a HPLC system with a reverse phase C_{18} column and a refractive index detector, with mobile phase 100% water. For ILs insoluble in water, the mixture IL plus carbohydrate were dissolved in DCM, precipitating the carbohydrate. After an extraction with water, the IL remained on the DCM, and the carbohydrate was extracted to the aqueous phase. The aqueous phase was then evaporated till dryness and was added a known amount of water. The final concentration was determined by HPLC analysis. All the solubility results (Table 2.2.1 and Table 2.2.2) were obtained by HPLC analyses which were in agreement with the expected range considering the overall amount of carbohydrate added to the IL. The water content in the IL was measured after the dissolution experiments.

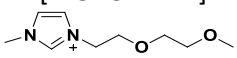
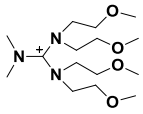
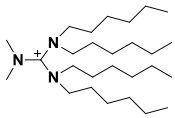
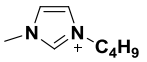
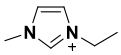
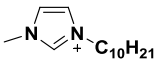
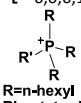
To ensure that no sample dispersion of sugar crystals in the IL was occurring, a sample of glucose dissolved in [MOEOEMIM][Cl] was analyzed in a microscope (200x magnification), and complete dissolution of glucose crystals was observed in the IL (please see Appendix, section 6.2, page 230).

ILs based on dimethylguanidinium cation have a high number of carbon atoms (27 for [(di-*h*)$_2$DMG] cation) nevertheless possess a low tendency to crystallize even in the presence of anions which persistently become solid when combined with different cations.[50] In this context it was synthesized dimethylguanidinium cations with two different side chains, with an ether pendant substituent, [$(C_3O)_4$DMG] and with an alkyl chain ([(di-*h*)$_2$DMG]). Table 2.2.1, show that the introduction of oxygen in the alkyl chain from guanidinium cation significantly improve the solubility of glucose when compared with the alkyl guanidinium cation, [(di-*h*)$_2$DMG]. In fact, at 35°C, [$(C_3O)_4$DMG][Cl] and [$(C_3O)_4$DMG][OAc] can dissolve the impressive amount of 38 and 31% (Table 2.2.1, entries 7 and 11), respectively. This solubility improvement by the introduction of ether groups in the alkyl chain can be explained by the capacity to establish hydrogen bonds with the hydroxyl groups of the carbohydrate.[159a, b] Although ILs with imidazolium unit cations indicates the absence of this effect, [MOEOEMIM][DCA] and [BMIM][DCA], at 35°C, can dissolve approximately the same amount of glucose (19 and 18% respectively, Table 2.2.1, entries 2 and 19). This difference can be explained by the increased effective concentration of the oxygen groups in ILs based on guanidinium cations when compared with imidazolium based ILs.

From Table 2.2.1 it is possible to observe that the solubility is mainly determined by the cation nature, being the solubility lower for more hydrophobic ILs such based on phosphonium [$P_{6,6,6,14}$] and ammonium [Aliquat] cations. On the other hand it is possible to observe an anion effect

although less significant, being the acetate based ILs the best solvents for glucose dissolution. Despite the higher viscosity of saccharine based ILs, Table 2.2.1 shows a comparable solubility behaviour for glucose in these novel ILs and ILs based on dicyanamide anion (e.g. 19.01% in [MOEOEMIM][DCA] *vs.* 18.97% in [MOEOEMIM][SAC], Table 2.2.1, entries 2, 3 and 5).

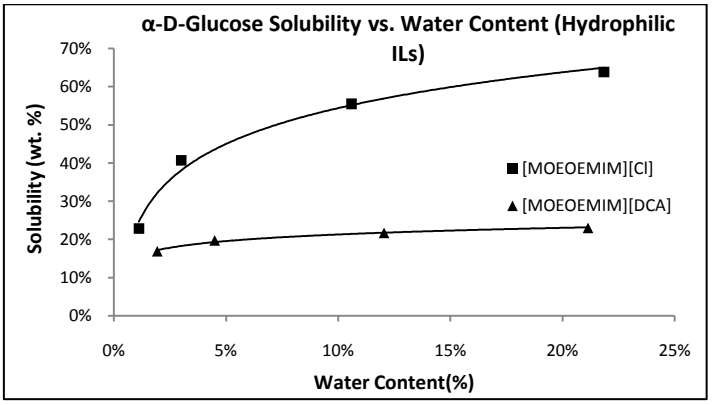
Table 2.2.1– Observed glucose solubility in several novel ILs at 35°C

Entry	Ionic Liquid		Solubility (wt.%)[a]	Water content (wt. %)[b]
1	[MOEOEMIM] 	[Cl]	29.28	3.26
2		[DCA]	19.01	0.80
3		[SAC]	18.97	0.66
4		[ACES]	14.39	0.62
5		[SCN]	18.38	0.81
6	[$(C_3O)_4$DMG] 	[Cl]	38.58	1.29
7		[DCA]	6.19[c]	6.48
8		[SAC]	20.59	1.75
9		[ACES]	8.44[c]	6.75
10		[SCN]	11.34	0.94
11		[OAc]	31.73[c]	3.18
12	[(di-*h*)$_2$DMG] 	[Cl]	6.61	2.95
13		[DCA]	2.88	0.25
14		[SAC]	3.66	0.41
15		[ACES]	2.27	0.30
16		[SCN]	1.95	0.29
17		[OAc]	14.40[c]	5.66
18	[BMIM] 	[NTf_2]	0.59	0.12
19		[DCA]	18.56	1.06
20		[OAc]	39.41[c]	24.00
21	[EMIM] 	[OAc]	43.89[c]	14.58
22	[C_{10}MIM] 	[BF_4]	0.44	0.46
23	[$P_{6,6,6,14}$]  R=n-hexyl R'=n-tetradecyl	[Cl]	4.69	6.43
24		[DCA]	0.50	0.03
25		[OAC]	4.90[c]	6.41
26	[Aliquat®]  R= *n*-octyl *n*-decyl	[Cl]	2.26	0.18
27		[DCA]	1.25	0.05
28		[OAc]	4.05[c]	4.10

[a] g of carbohydrate per 100 g of IL determined by HPLC analysis. [b] Observed water content after glucose dissolution. [c] g of carbohydrate per 100 g of IL determined by weight.

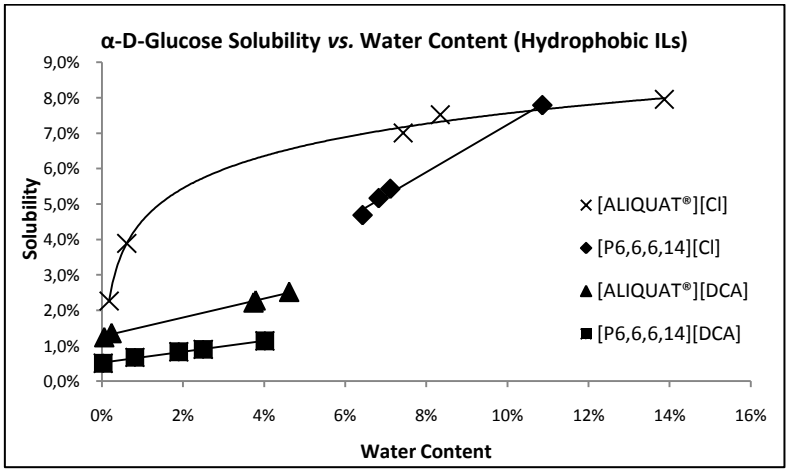
ILs based on acetate anions can dissolve a large quantity of glucose ([$(C_3O)_4$DMG][ACET] 31.73%; [BMIM][OAc] 39.41%; [EMIM][OAc] 43.89%, Table 2.2.1, entries 11, 20 and 21) notwithstanding these ILs are more hygroscopic than the others ILs analyzed, water content can be over 20%. In

order to observe how the IL water content influences the carbohydrate solubility behaviour, it was performed a study using different water content percentages for two hydrophilic ILs (Graphic 2.2.1) and four hydrophobic ILs (Graphic 2.2.2). The results for the two hydrophilic ILs are quite different, whereas a small amount of water (variation of 2% in the water content) increased the glucose solubility over 10.0% in the case of [MOEOEMIM][Cl], in contrast for [MOEOEMIM][DCA] the water effect is not so considerable (Graphic 2.2.1).



Graphic 2.2.1 – Variation of glucose solubility with the water content in hydrophilic ILs at 35°C; [a]Solubility of glucose wt. %.

For hydrophobic ILs (Graphic 2.2.2) the type of anion also influences the water effect on glucose solubility. ILs based on chloride anion have a higher water content, when saturated than those that are based on dicyanamide anions, and a small fluctuation on the water content of the IL can change significantly the solubilities values. Dicyanamide based ILs can dissolve less amount of glucose, but are not so dependent of the water content of the IL than those based on chloride anion. Additionally, a slightly increase of glucose solubility requires more water addition than for chloride based ILs. There is also a cation effect, indeed ammonium based ILs can dissolve a larger quantity of glucose than phosphonium based ILs.



Graphic 2.2.2 – Variation of glucose solubility with the water content in hydrophobic ILs at 35°C.

ILs with ether pendant groups can dissolve several other carbohydrates including mono and disaccharides (Table 2.2.2). Fructose can be two times more soluble in the IL [MOEOEMIM][DCA] than glucose. This result (48.99%, Table 2.2.2, entry 4) is the best result known for fructose, only comparable with the [BMIM][Cl], 56.0% at 110°C (Table 2.1.2, entry 5).[165]

Table 2.2.2 – Solubility of mono- and di-saccharides in ILs.

Entry	Carbohydrate	Ionic Liquid		Solubility [a] (wt.%)	Water content [b] (wt.%)
1	Glucose	[MOEOEMIM]	[Cl]	29.28	3.26
2			[DCA]	19.01	0.80
3	Fructose	[MOEOEMIM]	[Cl]	14.10	2.69
4			[DCA]	48.99	0.58
5	Sucrose	[MOEOEMIM]	[Cl]	17.11	0.7
6			[DCA]	11.06	0.48
7	Lactose	[MOEOEMIM]	[Cl]	10.69	0.8
8			[DCA]	16.55	1.0

[a]g of carbohydrate per 100 g of IL determined by HPLC analysis. [b]Observed water content after carbohydrate dissolution.

2.2.2 Extraction of carbohydrates from an aqueous phase with ILs

The complete dissolution of carbohydrates using an adequate media is an important factor in the carbohydrate chemistry, but for specific cases is also relevant the possibility to remove or recover these compounds from aqueous solutions.[226] Carbohydrate extractions from aqueous solutions have been reported using quaternary ammonium salts and lipophilic boronic acids, which can form reversible covalent complexes with diol groups from carbohydrates moieties.[226-227] Hydrophobic ILs have been recently reported as potential extractors of metals[228], or polar organic compounds[75] such as alcohols[229] from aqueous phase. Additionally to the dissolution of carbohydrates studies it was also possible to describe a simple method for the extraction of carbohydrates, where hydrophobic ILs can extract directly carbohydrates from an aqueous solution without the need of a surfactant, or a buffer solution in the aqueous phase.

[(di-*h*)$_2$DMG][DCA] is a hydrophobic IL, not soluble in water, but still solubilises a large quantity of glucose, when compared with the hydrophobic IL, [BMIM][PF_6][161] (2.88 % *vs.* <0.05 %, Table 2.2.1, entry 13 vs. Table 2.1.1, entry 14, respectively). To take advantage of this property, it were performed extraction studies for glucose (Table 2.2.3), and glucose-fructose, lactose-sucrose, fructose-lactose mixtures (1:1 wt.) from an aqueous solution to the IL (Table 2.2.4). This study was complemented with different hydrophobic ILs.

The extraction method is simple: the sugar is dissolved in the aqueous solution, and mixed with the hydrophobic IL for one week. Then the two phases are separated and was added dichloromethane to the organic layer in which sugar dissolved in the IL. The carbohydrate

precipitates immediately. Following filtration and washing with dichloromethane the sugar recovered shows no trace of IL. On the other hand, after evaporation of dichloromethane, the IL is recovered without any traces of carbohydrates, and can be recycled for, at least, three times (recycling experiments were made with [(di-*h*)$_2$DMG][DCA], Table 2.2.3, entries 1 to 3).

Table 2.2.3 shows the extraction values for glucose from aqueous phase to several hydrophobic ILs. For [BMIM][NTf$_2$], [C$_{10}$MIM][BF$_4$] and [Aliquat®][DCA] the quantity extracted from the aqueous phase is similar to the solubility of glucose in the IL saturated with water (Table 2.2.3, entries 8, 9 and 5). For ammonium and phosphonium chloride ([Aliquiat®][Cl] and [P$_{6,6,6,14}$][Cl]) the glucose extracted from the aqueous phase is much smaller than the IL can dissolve (Table 2.2.3, entries 4 and 6), maybe due to the extraction equilibrium has not been achieved in the experiment running. Interestingly [P$_{6,6,6,14}$][DCA] can extract a much larger quantity than those the IL can dissolve (4.23 5 *vs.* 1.14 %, Table 2.2.3, entry 7). This result can be due to the formation of water microenvironments consisted of glucose solubilised in water inside the IL.[230]

Table 2.2.3 – Extraction of glucose from a aqueous phase (500 mg/mL) by hydrophobic IL.

Entry	Ionic Liquid		Quantity extracted (wt. %)	Solubility [a] (wt. %)	Water content[b] (wt. %)
1	[(di-*h*)$_2$DMG]	[DCA]	2.70(cycle1)	3.68	6.0
2			2.63(cycle2)		
3			2.69(cycle3)		
4	[Aliquat®]	[Cl]	3.46	7.95	13.9
5		[DCA]	2.25	2.52	4.6
6	[P$_{6,6,6,14}$]	[Cl]	3.64	7.79	10.8
7		[DCA]	4.23	1.14	4.0
8	[BMIM]	[NTf$_2$]	1.19	1.10	1.6
9	[C$_{10}$MIM]	[BF$_4$]	3.29	3.20	10.8

[a] solubility of glucose in the IL previously saturated with water (g of glucose per 100 g of IL). b – maximum water contents in the IL (saturated IL).

Extraction results of a mixture of carbohydrates from an aqueous phase (500 mg/mL) to several hydrophobic ILs are shown in Table 2.2.4. The method of extraction used was the same for extraction of single carbohydrates. The selectivity was calculated based on ^{1}H NMR spectra presented in Appendix (Figure 6.2.2-4, page 228). The ratio between two known peaks from each carbohydrate was measured defining the extraction selectivity.

For two monosaccharides mixture (glucose/fructose), ILs based on dicyanamide anions can extract a larger quantity than ILs with chloride as anion (Table 2.2.4, entries 1, 3 and 5). All the five hydrophobic ILs tested can extract this mixture with relative selectivity, extracting a higher amount of glucose than fructose. When a mixture of two disaccharides (sucrose and lactose) is

extracted from an aqueous phase the cation influence the quantity extracted. With the IL based on [(di-*h*)$_2$DMG] cation a small amount of the mixture is extracted (Table 2.2.4, entry 6), increasing with ILs based on [$P_{6,6,6,14}$] cation (either with dicyanamide or chloride as anion, Table 2.2.4, entries 9 or 10). ILs based on [Aliquat®] cation can dissolve the biggest amount of the mixture of disaccharides (sucrose/lactose), although with almost no selectivity (Table 2.2.4, entries 7 and 8).

Table 2.2.4– Extraction of a mixture of carbohydrates from an aqueous phase (500 mg/mL) to a hydrophobic IL.

Entry	Mixture of carbohydrates extracted	Ionic Liquid		Quantity extracted (wt. %)	Selectivity [a] (wt. %)
1	Glucose/Fructose (G/F – 50:50 wt.%)	[(di-*h*)$_2$DMG]	[DCA]	5.78	71.6G/28.4F
2		[Aliquat®]	[Cl]	2.31	80.2G/19.2F
3			[DCA]	7.22	69.2G/30.8F
4		[$P_{6,6,6,14}$]	[Cl]	1.68	82.5G/17.5F
5			[DCA]	5.22	77.8G/22.2F
6	Sucrose/Lactose (S/L – 50:50 wt.%)	[(di-*h*)$_2$DMG]	[DCA]	1.52	53.8S/46.2L
7		[Aliquat®]	[Cl]	3.76	-S/-L
8			[DCA]	3.73	48.8S/51.2L
9		[$P_{6,6,6,14}$]	[Cl]	2.83	-S/-L
10			[DCA]	2.42	55.1S/44.9L
11	Fructose/Lactose (F/L – 50:50 wt.%)	[(di-*h*)$_2$DMG]	[DCA]	6.84	51.9F/48.1L
12		[Aliquat®]	[Cl]	2.02	-F/-L
13			[DCA]	1.08	54.6F/45.4L
14		[$P_{6,6,6,14}$]	[Cl]	1.37	-F/-L
15			[DCA]	2.68	47.3F/52.7L

a – ratios determined by ^{1}HNMR (for detailed information please see Appendix, Figure 6.2.2-4, page 228).

When a monosaccharide and a disaccharide (fructose and lactose respectively) are mixed in an aqueous phase and extracted with five different hydrophobic ILs the results can be quite different (Table 2.2.4, entries 11 to 15). [(di-*h*)$_2$DMG][DCA] can extract a surprising amount of 6.84 % (Table 2.2.4, entry 11) of the mixture, while the others four ILs only extract 1.0 to 2.6% with no selectivity. In summary, [(di-*h*)$_2$DMG][DCA] is an efficient IL to extract monosaccharides (G/F), but not so appropriated to extract disaccharide mixtures (S/L); [Aliquat®][Cl] and [$P_{6,6,6,14}$][Cl] can extract a large quantity of disaccharide mixture (S/L), but are not so efficient extracting monosaccharide mixture (G/F).

2.3 Conclusions

Carbohydrates are important molecules, since are readily available chiral molecules and can play key roles in biological recognition processes and in many important areas of food and chemical industry.[231] The derivatization of carbohydrates is still a challenging task, because of their low solubilities in almost any solvent but water. ILs are able to dissolve highly polar compounds, including carbohydrates, and thus pose a promising alternative that opens up a broad variety of new opportunities in carbohydrates chemistry. ILs have applications as solvents, catalysts, catalyst/solvents in chemical reactions and as solvents for enzymatic reactions. Since carbohydrates and ILs were first connected in 2002[155], a limited number of studies have been carried out to investigate the solubility of carbohydrates in ILs.

In this work were carry out solubility studies of mono- and di-saccharides on ILs, and have been demonstrated that the introduction of ether functionality in the alkyl chain of ILs based on dimethylguanidinium cation IL, can improve the dissolution of carbohydrates. It was also showed that saccharine, thiocyanate and acetate anions can be an alternative to ILs based on dicyanamide or halide anions, which can deactivate some enzymes.

The extraction of carbohydrates from aqueous solutions by ILs was also studied, and was showed that hydrophobic ILs can extract a large quantity of glucose or mono- and di-saccharides mixtures using a simple extraction method. It was observed that depending on the IL used the quantity of glucose extracted can be superior to those the IL can dissolve, resulting from the formation of water microenvironments consisted of glucose solubilised in water inside the IL. When a mixture of carbohydrates was extracted it was observed some selectivity on the partition studies, for example [Aliquat®][Cl] and [$P_{6,6,6,14}$][Cl] can extract a large quantity of disaccharide mixture, but are not so efficient extracting a monosaccharide mixture.

3 *Trans*-Dihydroxylation of olefins

In this chapter is described the study of *trans*-dihydroxylation of olefins. Different catalyst and oxidants were screened. In the optimized conditions several substrates were tested, and also the compatibility with other functional groups was studied.

3.1 Introduction

Has referred on chapter 1 (please see section 1.1.3, page 5) organic solvents are widely used in chemical processes mainly due to their easiness to be removed by evaporation. The disadvantage is that these volatile compounds can be released from many sources in the chemical process resulting in VOC emissions to the atmosphere. Ideally a chemical reaction should be solvent-free,[232] but if it is not possible, the solvent used should be more environmentally friendly, such as being low toxic, non-flammable, easy to recycle and inert.[10] Water is an inexpensive solvent, nevertheless is non-toxic and non-flammable and a range of organic transformations can be done in water.[233] From a green chemistry viewpoint the use of water as a solvent has many advantages but also some disadvantages, for example distillation can be energy intensive, and contaminated waste streams may be difficult to treat. It is worth emphasizing that it is important to study the whole manufacturing process, not just the reaction stage. In spite of the fact that water have many interesting properties which are now being exploited in synthetic chemistry.

For some reactions selectivity improvements and/or significant rate enhancements can be obtained by conducting the reaction in water. An important example of the latter was the finding by Breslow[234] that Diels-Alder reaction between cyclopentadiene and butenone was over 700 times faster in water than in many organic solvents. This increased rate has been attributed to the hydrophobic effect. Owing to the difference in polarity between water and the reactants, water molecules tend to associate amongst themselves, excluding the organic reagents and forcing them to associate together forming small drops, surrounded by water. Interestingly, several other organic transformations were found to be accelerated substantially in water, including the aldol condensation,[235] benzoin condensation[236] and Claisen rearrangement.[237] The scope of possible reactions using water as a solvent is quite remarkable and water is much under-utilized as a solvent in many academic and industrial research institutions.

1,2-Diols are important building blocks, not only for the syntheses of pharmaceuticals, agrochemicals, pheromones, or liquid crystals[238], but also as chiral auxiliaries or ligands for asymmetric synthesis.[239] There are several synthetic methodologies to synthesize 1,2-diols,[239-240] for example, by reduction,[241] epoxide ring-opening,[242] dihydroxylation,[243] and pinacol coupling reactions, [244] being the olefin dihydroxylation a straightforward method for the synthesis of this type of compounds.

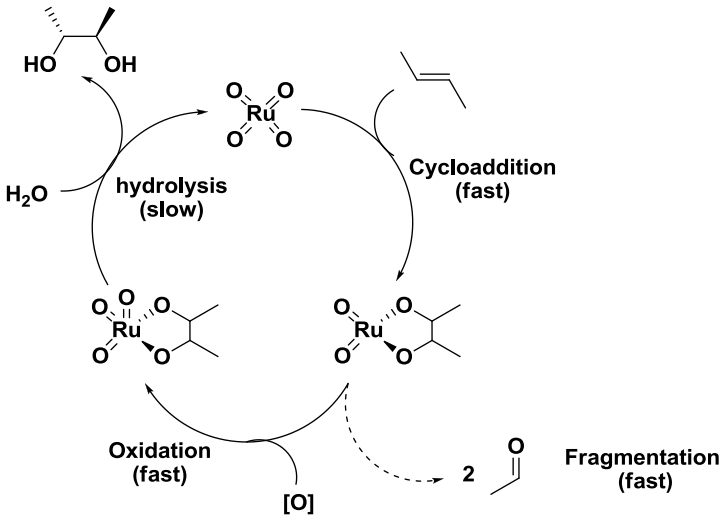
Various established chemical methods are available in the literature for the *cis*- or *trans*-dihydroxylation of olefins. These two approaches will be discussed separately.

3.1.1 *Cis*-dihydroxylation

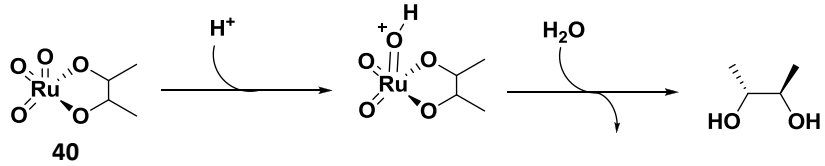
Within the past twenty years the osmium-catalyzed dihydroxylation became a benchmark reaction when it comes to generality and selectivity.[243, 245] Osmium tetroxide is the only efficient catalyst known today for asymmetric dihydroxylation for enantiomerically pure product.[246] However, some problems are connected with osmium-catalyzed reactions; the catalyst is very expensive, volatile and toxic, preventing a successful application on an industrial scale. To overcome these drawbacks, complexation of osmium with ligands, which are heterogenized on soluble and insoluble polymers,[247] silica gel,[248] ion exchange[249] or dendrimer[250] support has been attempted by several groups.[251] In order to overcome the problem of toxicity, cost and also to have environmentally benign process for dihydroxylation of olefins, there is a need to search for an alternative metal catalyst system for the production of vicinal diols. Catalytic systems such Os/Re,[252] Os/Pd and Os/W[253] have been reported for *cis*-dihydroxylation, however addition of co-oxidant and/or addition of various carboxylic acids for maintaining acidic medium is essential for this reaction. Different alternative oxidants have been tried in order to circumvent the use of osmium, transition metal catalysts such as ruthenium,[254] manganese,[255] molybdenum[246] and bio-inspired nonheme Fe-complex[256] have been used to convert olefins into *cis*-1,2-diols.

Ruthenium (VIII) oxide, prepared *in situ* from ruthenium (III) chloride with sodium periodate, has been reported as catalyst for dihydroxylation reactions.[257] This type of oxidation reaction is in general very fast (longer reaction times results in lower the yields of diols). Due to the high redox potential of the catalyst the reactions are often not very selective and difficult to control.[257a] Recently an intensive study was made by Plietker[254a] in a way to understand the RuO_4^- catalyzed reaction. Several factors influencing the selectivity and reactivity, such as the solvent used, temperature and pH were studied. The authors have reported that the addition of carboxylic acids could influence on the selectivity, although not significantly. Stronger Brønsted acids showed a significant influence on the selectivity and, increasing the amount of acid resulted in a fast conversion paired with a good selectivity within 5 minutes. The effect of the acid can be rationalized in analogy to the acid catalyzed cleavage of carboxylic acid esters by activation of the intermediate ruthenate **40** *via* coordination of a proton to one of the Ru–O-bonds (Scheme 3.1.1). The resulting electro deficient ruthenate should react fast with the

incoming water to give the desired diol and catalyst. In this way the formation of the 1,2-diol as final product is favourable to the over oxidized aldehyde product.



Activation of ruthenate by protonation



40

Scheme 3.1.1 – Postulated activation of ruthenate by protonation.

Feringa *et al.* [258] have used manganese complexes as catalysts for dihydroxylation using hydrogen peroxide as oxidant. However they have shown that the use of various carboxylic acids as co-catalysts is essential in this case, and depending on the carboxylic acid used, the epoxide was obtained as a major product along with *cis*-diol.

Oldenburg and Que[259] have used bio-inspired nonheme iron complexes for *cis*-dihydroxylation of olefins. A tridentate ligand that mimics the facial *N*,*N*,*O* site of the mononuclear iron center in the deoxygenases was used, and its iron(II) complex has been found to catalyze olefin *cis*-dihydroxylation almost exclusively. However this reaction needs ten equivalents of hydrogen peroxide with respect to catalyst, and the turnover numbers reported are extremely low.

It was also reported the *cis*-dihydroxylation catalyzed by molybdenum complexes using hydrogen peroxide or TBHP as oxidant.[246] Several olefins were tested successfully, and it was possible to recycle the catalyst efficiently. The authors report that this catalyst has potential to be used for asymmetric dihydroxylation with use of chiral cyclopentadiene as ligand instead of simple cyclopentadiene, although no further results were published.

Recently[260] the *cis*-dihydroxylation of olefins was reported with palladium as catalyst ($Pd(OAc)_2$), in the presence of a base, and O_2 as oxidant. This result was achieved when the authors were studying the palladium-catalyzed oxidative cleavage of olefins with oxygen in the presence of an acid. They have tested several aromatic olefins and achieved good conversion yields when the reaction was performed at 100°C.

3.1.2 *Trans*-dihydroxylation

Several methods for the *anti* dihydroxylation of alkenes have been reported, [261]occurring mainly by epoxidation and hydrolysis by metal catalysis [262] or biocatalysis.[263] In this section will be discussed different methods available in the literature to prepare *trans*-diols starting from olefins. Special attention will be given to synthetic methods without the use of organic solvents or with a non-metal catalyst.

3.1.2.1 Metal catalysis

Cobalt-containing mesoporous silica showed catalytic activity for the dihydroxylation of cyclohexene.[264] The authors tested this reaction with cyclohexene as substrate, and observed that not only the *trans*-diol is formed, but also the *cis*-diol and the epoxide (conversion, and selectivity detected by GC analysis). The authors propose that the reaction proceeds via epoxidation followed by its hydrolysis, the reaction possibly proceeds via C=C bond breaking and simultaneous C-OH bond formation through a radical pathway. Different oxidants were tested, hydrogen peroxide, *tert*-butyl hydroperoxide (TBHP) and molecular O_2 with acetonitrile as solvent. A mixture of cis/trans isomers was achieved for these oxidants, being the higher *trans*-diol selectivity obtained with TBHP as oxidant, 91%, with 85% conversion.

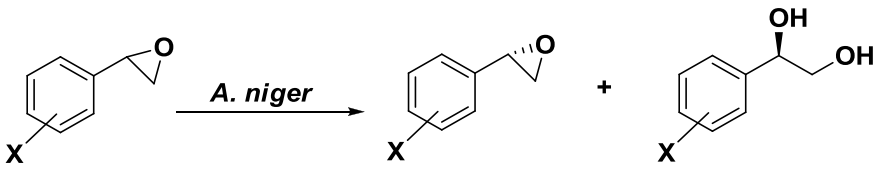
In 2009[262a] was reported a method to prepare 1,2-diols from the oxidation of olefins by *t*-butyl hydrogen peroxide (TBHP). Several metal oxides were tested, such as catalysts MoO_3, VO_5, Nb_2O_5, Cr_2O_3, and WO_3. MoO_3 was found to be the most active catalyst for the dihydroxylation of cycle-olefins. Although the obtained conversion was quite good, the 1,2-diol selectivity was only moderated. This catalyst is not efficient with alkyl olefins, such as 1-hexene. The reactions were made in toluene, and the optimized conditions were obtained between 60-100°C, for 12 hours reaction. The authors claimed that 1,2-diol formed had the *trans* configuration, although no evidences of this fact were reported.

Warwel *et al.* [265] have reported oxidation of olefins with hydrogen peroxide in dioxane solvent forming vicinal diols, using Re_2O_7 as catalyst. The authors reported that the reaction is believed to proceed *via* epoxidation, followed by an acid-catalysed opening of the oxirane-ring. Several olefins were tested with moderated yields. The selectivity for the *trans*-diol is only reported for

the transformation of cyclohexene that was completely transformed into *trans*-1,2-cyclohexanediol.

3.1.2.2 Biocatalysis

Different works[263b, c] have shown the enantioselective hydrolysis of racemic epoxides by epoxide hydrolases. Dong *et al.*[33c] have described the enantioselective biohydrolysis of various substituted styrene oxides using whole fungus cells of *Aspergillus niger* (Scheme 3.1.2). The authors showed that the substitution on the aromatic ring strongly influences the resolution rate and also the enantioselectivity. More reaction time is needed when the benzene ring is not substituted. Better enantioselectivity results were obtained in most cases when hydrolyzing *para*- and *ortho*-substituted styrene oxides. Although good to excellent enantioselectivity were obtained, the selectivity for the enantiopure 1,2-diol was very low.



Scheme 3.1.2 – Enantioselective hydrolysis of racemic epoxides by *Aspergillus niger.*

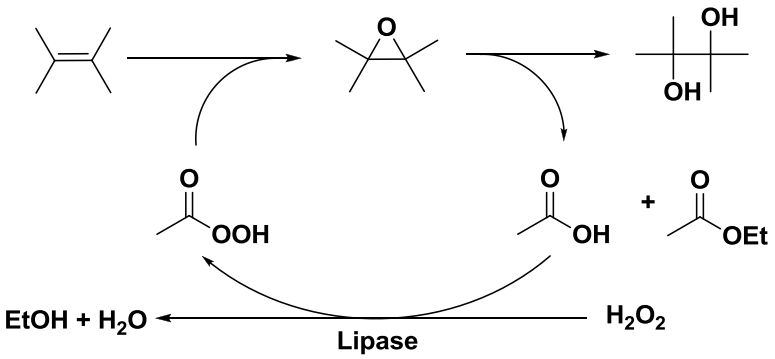
In 2006 Wu and co-workers [33b] reported also the biohydrolysis of various substituted styrene oxides using two different epoxide hydrolases. In this work good enantioselectivity was obtained for the majority of substrates testes, with high selectivity for the enantiopure 1,2-diol.

Chang and co-workers[266] also used epoxide hydrolases for the synthesis of enantiopure vicinal *trans*-diols. Two different substrates were tested, and the hydrolysis of *N*-benzyloxycarbonyl-3,4-epoxy-pyrrolidine and cyclohexene oxide with the epoxide hydrolase of *Sphingomonas* sp., gave the corresponding vicinal *trans*-diols in high ee and yield.

The same group reported the bacterial strain *Sphingomonas* sp. as biocatalyst for the *trans*-dihydroxylation of *N*-substituted 1,2,5,6-tetrahydropyridines and 3-pyrrolines giving the corresponding 3,4- dihydroxypiperidines and 3,4-dihydroxypyrrolidines, respectively, with high enantioselectivity and high activity.[267]

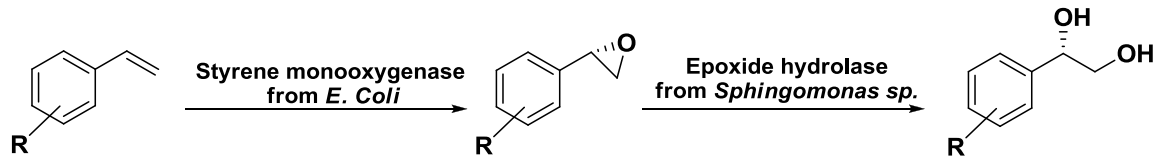
Recently was reported the lipase-catalyzed dihydroxylation directly from olefins using immobilized lipase from *Pseudomonas*.[263a] In this work was used microwave irradiation and hydrogen peroxide (50% aq. sol.) as oxidant. In only 5-10 minutes of microwave irradiation (150W, 60°C) several olefins can be converted in the respective 1,2-diols with 70-90% yields. The enzyme could be recycled for three cycles without denaturation. The author report that an

intermediate epoxide is formed (Scheme 3.1.3), although for the majority of the substrates no epoxide intermediate was isolated. In the same reaction conditions, no formation of 1,2- diol was observed for cholesterol and stigmasterol, the respective epoxides were stable and did not undergo ring opening to the diols.



Scheme 3.1.3 –Dihydroxylation of olefins using microwave irradiation by lipase-catalyzed system. [263a, 268]

Xu *et al.*[268]developed a tandem biocatalysts system for the asymmetric dihydroxylation of olefins, with this method the synthesis of vicinal diols with high ee was obtained by selecting the appropriate biocatalysts for each reaction step from different microorganisms and combining them in the desired form and at the desired ratio (Scheme 3.1.4). In this work was used a two liquid phase system, so the olefin is on the organic phase and the biocatalysts are on the aqueous phase. The isolation of the epoxide intermediate is not necessary, and when is formed on the aqueous phase the epoxide goes again to the organic phase. Once again on the aqueous phase the epoxide hydrolysis is accomplished by the epoxide hydrolase of *Sphingomonas* sp.. The authors claimed that the diol product was easily separated, but no isolation method was reported, the results where quantified by HPLC. The yields and enantioselectivies reported were very good to excellent.

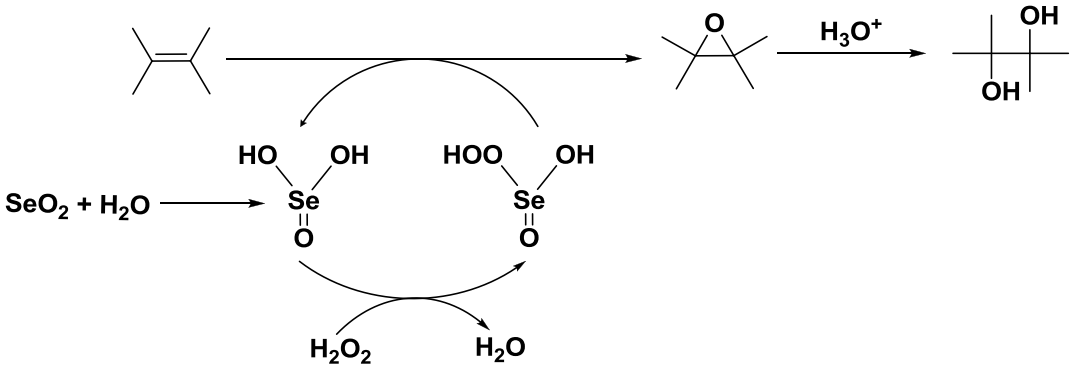


Scheme 3.1.4 – Biocatalytic asymmetric dihydroxylation of aryl olefins.

3.1.2.3 Others catalysts

Recently[269] was reported a catalytic system for *trans*-dihydroxylation of olefins with selenium dioxide and hydrogen peroxide. In a typical reaction, perseleninic acid, formed from selenium dioxide (20 mol%) and hydrogen peroxide (2 equiv.), oxidizes the olefins in good yields (50–88%). The olefin is epoxidized by the perseleninic acid and the epoxide is opened by an S_N2-

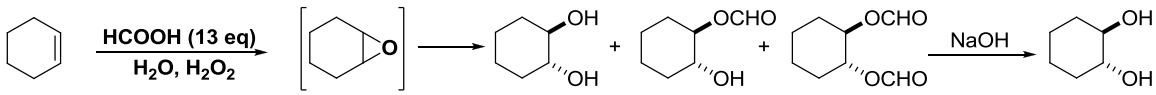
type reaction. Aliphatic olefins exhibited better results in comparison to aromatic olefins and sterically hindered double bonds showed poor yields compared to less hindered ones. The drawback of this reaction is the need of 1,4-dioxane/water (1:1) solvent system (1,4-dioxane is classified as carcinogen compound).



Scheme 3.1.5 – Trans-dihydroxylation of olefins with selenium dioxide as catalyst.[269-270]

3.1.2.4 Organocatalysis

Adkins and Roebuck[271] established in 1948 the use of formic acid as solvent for the *trans*-dihydroxylation of cyclohexene, with hydrogen peroxide aqueous solution as oxidant. This method uses a large excess of formic acid (13 equiv.), and because the reaction is extremely exothermic, the olefin need to be added slowly. Recently the same reaction was reported in a microreactor.[272] The authors claimed that the *trans*-1,2-cyclohexanediol obtained by microreactor technology is much more pure, since the solid obtained is white. In this work is no longer necessary the slow addition of the olefin, although is still necessary a second step to neutralize the acidic solvent and hydrolyze the formed formate and isolate the product.



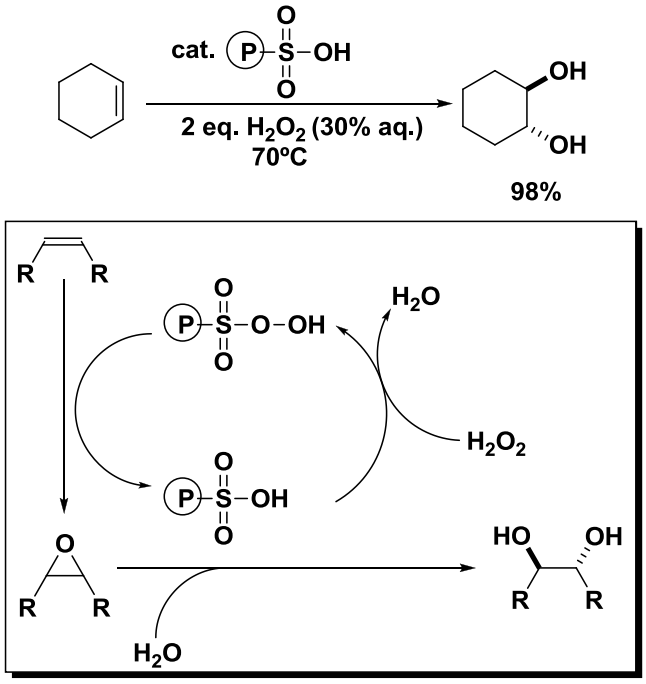
Scheme 3.1.6 – Synthesis of *trans*-1,2-cyclohexanediol using formic acid as catalyst/solvent.

Sato *et al.*[273]reported the dihydroxylation of olefins in an aqueous medium with H_2O_2 as oxidant and Nafion® (sulfonic resin in the acidic form) as catalyst. First the reaction was optimized for the model substrate cyclohexene, and others sulfonic resins were tested, such Amberlite, although resulting in lower yields. The optimized conditions were achieved with Nafion® as catalyst, at 70°C, for 21 hours. In these conditions was possible to recycle the catalyst for at least five times without lost of efficiency. Several other substrates were tested, and moderate to good yields were obtained. However Nafion® is a quite expensive sulfonic resin and the reaction works only above room temperature (70°C).

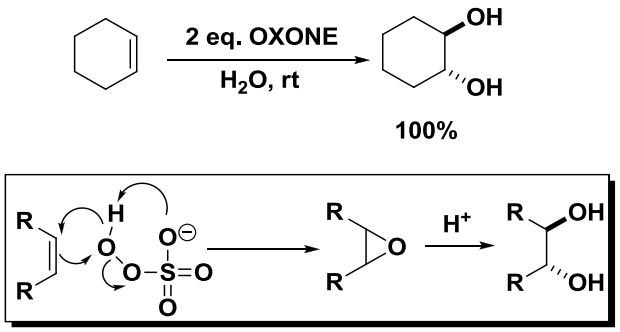
A different method for the olefin dihydroxylation uses Oxone® as catalyst/oxidant,[274] which is a commercial available triple salt, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, synthesised from H_2O_2 and H_2SO_4 followed by neutralization with K_2SO_3.[274,275] The authors reported that in acidic (pH<1.7) aqueous solutions of Oxone® the epoxide was produced from cyclooctene, although for all the others olefins tested the formation of 1,2-diols was observed. Adjustment of initial pH to > 6.7 with $NaHCO_3$ the epoxide of the respective olefin was formed. In this way the authors obtained different selectivity by adjusting the initial pH of the reaction mixture. The dihydroxylation of the olefin can be made in water at room temperature, but for some substrates an increase of temperature is needed, conducting to a faster decomposition of Oxone®.[274]

3.1.2.5 Mechanism

The mechanism of the dihydroxylation reaction catalyzed by Nafion® or Oxone® is proposed by the authors (Scheme 3.1.7 and Scheme 3.1.8, respectively). [273-274] Both proposed mechanisms undergo by epoxidation, followed by ring opening, in acidic conditions.



Scheme 3.1.7 – Postulated mechanism for the dihydroxylation of olefins catalyzed by Nafion®.



Scheme 3.1.8 – Postulated mechanism for the dihydroxylation of olefins catalyzed by Oxone®.

3.2 Results and discussion

As said before, in 2005[273] was published a work were a sulfonic resin (Nafion®) was reported as catalyst for the dihydroxylation of olefins, using hydrogen peroxide as oxidant. Although this is an efficient method, only works for temperatures over 70°C, which can became a problem for some substrates, such as styrene that have a low boiling point (bp.). Therefore, an efficient method for the *trans*-dihydroxylation of olefins, with lower temperatures, and more accessible catalysts was developed.

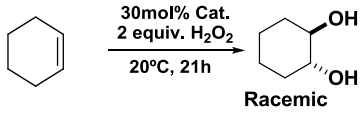
3.2.1 Scope and Limitations

Using cyclohexene as model substrate different promoters, oxidants and experimental conditions were tested. Initially were tested several sulfonic acids as catalysts for the cyclohexene transformation to *trans*-1,2-cylohexanediol, at room temperature (20°C), Table 3.2.1. In a way to find a quicker and easy way to screen several sulfonic acids the reaction crude (aqueous phase) was analysed by ^{1}H NMR. To quantify the product formed, after the time reaction a known quantity of an internal standard was added to the crude reaction. The choice of the internal standard was made based on 1) should be inert on the dihydroxylation reaction (so could also be an acid), and 2) the internal standard ^{1}H NMR spectrum could not overlap the product or reactants ^{1}H NMR spectra. *p*-Bromobenzoic acid was tested, but was not soluble in D_2O, that is the deuterated solvent used to follow the reaction. The internal standard selected was the chloroacetic acid, because is inert in the reaction, and was soluble in the deuterated solvent chosen. In addition the NMR spectrum is simple and do not overlap the reagents or products NMR spectra. In this way it was possible to determine the product yield by NMR, as follows (Internal standard (**IS**) is chloroacetic acid, please see Appendix, section 6.6, page 249):

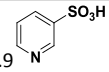
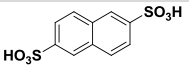
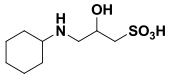
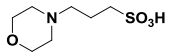
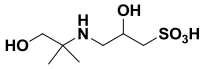
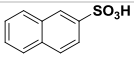
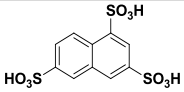
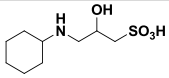
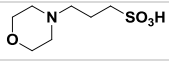
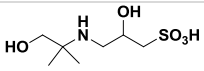
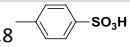
$$mol(diol) = \frac{Integration\ of\ diol\ NMR\ peack\ (2.9\ ppm)}{Integration\ of\ IS\ NMR\ peack\ (3.8\ ppm)} * \frac{IS\ mass\ added}{IS\ Molecular\ Weight}$$

In the absence of catalyst, there was no reaction between cyclohexene and H_2O_2. Using 30 mol% of catalyst, the majority of the acids tested resulted in a very low yield (Table 3.2.1, entries 1-11). Even for very strong acids, such as CF_3SO_3H, or not so strong acids such as PSA (Table 3.2.1, entries 4 and 6, respectively) the obtained yield was less than 3%. This indicates that the acid pKa is not decisive to its catalytic efficiency. CAPSO, MOPS and AMPSO in conjugation with the respective sodium salt, are usually used as buffers.[276] These three compounds when tested resulted in no catalyst activity (Table 3.2.1, entries 9-11).

Table 3.2.1 – Screening of *trans*-dihydroxylation of cyclohexene, with hydrogen peroxide as oxidant and by different sulfonic acids as reaction promoter [a].



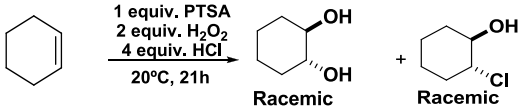
41 **42**

Entry	Scale of 41 (mmol)	Catalyst[b] (30 mol%)		Yield of 42(%)
1	1	pKa -3.5	H_2SO_4	4
2	1	pKa -2.6	$MeSO_3H$	0[c]
3	2.5	pKa +0.7	$PhSO_3H$	6
4	1	pKa -14	CF_3SO_3H	3
5	2.5	pKa -6.0	HCl	2[d]
6	2.5	pKa +2.9 	PSA	0[c]
7	2.5		PESA	2
8	2.5		NDSA	2
9	1	pKa 9.6 	CAPSO	0[c]
10	1	pKa 7.2 	MOPS	0[c]
11	1	pKa 9.0 	AMPSO	0[c]
12	2.5		NSA	15[d]
13	2.5		NTSA	35[d]
14	2.5		CAPSO	15[d]
15	2.5		MOPS	5[d]
16	2.5		AMPSO	6[d]
17	2.5	pKa -2.8 	PTSA	28

[a] Method H (described in page 196): Catalyst (30 mol%), H_2O_2 (30% aq., 2 equiv.) and cyclohexene (1 or 2.5 mmol) were stirred for 21h at 20°C; [b]pKa data from http://www.sigmaaldrich.com/portugal.html, http://users.hartwick.edu/ericksonm/pKa_tables.pdf or http://pt.wikipedia.org (6 August 2010); [c] Product was not detected in the aqueous phase, by ^{1}H NMR; [d] Method S (described in page 206): The acid was generated *in situ* from the respective sodium salt by adding HCl in the beginning of the reaction. In these cases the main product was *trans*-2-chloro-cyclohexanol **43**.

The objective in this stage of the work was to screen several sulfonic acids that could have a catalytic activity on this reaction. Being only available the sodium salts of naphthalene-2-

sulfonic acid (NSA) and naftalene-1,3,7-trisulfonic acid (NTSA), these compounds were also tested. In these cases the acid was generated *in situ* from the respective sodium salt, adding HCl (one equivalent respecting to the sodium salt) before the addition of others reactants. Although the catalytic performance was improved (Table 3.2.1, entries 12 and 13), the product formed was not only the expected diol **42**, but also the *trans*-2-chloro-cyclohexanol **43**. This result can be explained by the competition between water and chloride anions to open the epoxide ring, formed in this reaction. With this result in hands, HCl was also tested as catalyst resulting in no catalytic activity (Table 3.2.1, entry 5). The acids CAPSO, MOPS and AMPSO were also generated *in situ* from the respective sodium salts and although the catalyst performance was slightly improved (Table 3.2.1, entries 14-16 *vs.* 9-11) the obtained result was not clean, and a mixture of diol **42** and chlorohydrin **43** was obtained. In a way to obtain the chlorohydrin as major product a large excess of HCl was added to the cyclohexene reaction catalysed by PTSA Scheme 3.2.1. But the same 1:1 mixture of diol **42** and chlorohydrin **43** was obtained.

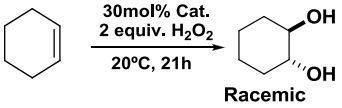


41 **42** **43**

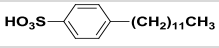
Scheme 3.2.1 – Cyclohexene reaction with HCl for the formation of **43**.

Another source of chloride anion was tested, NaCl was added to the system in 1 to 2 equivalents, but the competition between water and the chloride anion attack to the epoxide ring was still very high. For this reason the approach to obtain the chlorohydrin was abandoned, and the reaction study of the cyclohexene dihydroxylation continued with the study of more possible catalysts for this reaction (Table 3.2.2).

Table 3.2.2 – Screening of *trans*-dihydroxylation of cyclohexene, with hydrogen peroxide as oxidant and by different sulfonic acids as reaction catalyst [a].



41 **42**

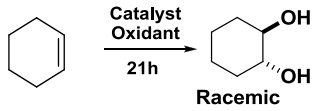
Entry	Scale of 41 (mmol)	Catalyst[b] (30 mol%)	Yield of 42 (%)
1	2.5	 (S)-CSA	34
2	2.5	pKa -2.8 PTSA	28
3	2.5	 DBSA	23
4	2.5	pKa +3.5 HCOOH	34
5	2.5	Nafion®	0[c]
6	2.5	Amberlyst 15®	17

[a] Method H (described in page 196): Catalyst (30 mol%), H_2O_2 (30% aq., 2 equiv.) and cyclohexene (2.5 mmol) were stirred for 21h at 20°C; [b]pKa data from http://www.sigmaaldrich.com/portugal.html,http://users.hartwick.edu/ericksonm/pKa_tables.pdf or http://pt.wikipedia.org (6 August 2010); [c] Product was not detected in the aqueous phase, by ^{1}H NMR.

The best catalyst performance was obtained with the acids CSA, PTSA and DBSA (Table 3.2.2, entries 1 to 3), although with moderated yield values. In a way to compare these results with the catalysts reported on the literature, was performed the cyclohexene dihydroxylation with formic acid, Nafion® and Amberlyst® 15 as catalysts, in 30 mol% at room temperature (Table 3.2.2, entries 4 to 6). The reported catalysts in these mild conditions were not so efficient, in fact Nafion® showed no activity at room temperature, and the formic acid reaction needed a second step for the diol **42** to be formed (neutralization and hydrolysis step). So the results obtained with the catalysts CSA, PTSA and DBSA were promising, because in the same conditions, had the same or better performance than the literature reported catalysts (Table 3.2.2, entries 1-3 *vs.* 4-6). But still the reaction conditions had to be optimized to improve the yield values. DBSA was not used in further studies, due to its price being much higher when compared with the other two acids that had bigger efficiency (CSA and PTSA, Table 3.2.2, entries 1 and 2). Next was studied the oxidant influence on the cyclohexene dihydroxylation.

Hydrogen peroxide used as oxidant till now was replaced by 2 equivalents of Oxone®, with CSA as catalyst, leading to 92% yield (Table 3.2.3, entry 1). The result was promising, so the same reaction was tested without the presence of CSA as catalyst, and 87% yield was achieved (Table 3.2.3, entry 3). Unluckily this last result was already been published by Ford[274] in 1991 although this article was completely ignored by others authors that have worked in the same field. Since Oxone® is a salt derived from sulfuric acid and hydrogen peroxide, was tested the possibility to regenerate Oxone® with hydrogen peroxide as co-oxidant. So Oxone® was added in 30 mol%, with hydrogen peroxide in excess (2 equiv.), without catalyst (Table 3.2.3, entry 4). Only 38% yield was achieved, therefore Oxone® is not regenerated *in situ* by hydrogen peroxide. Oxone® is a powerful oxidant for the dihydroxylation of cyclohexene, but cannot be regenerated thus recycled, producing high amounts of waste. In a green chemistry context, others oxidants are preferred, for example hydrogen peroxide where the only by-product formed is water.

Table 3.2.3 – *Trans*-dihydroxylation of cyclohexene with different oxidants[a].



41 **42**

Entry	Oxidant	Catalyst (mol%)	Scale of 41 (mmol)	Temp.(°C)	Method [b]	Yield (%)
1	Oxone® (2equiv.)	CSA (30 mol%)[c]	1	20	A	92.0[e]
2	Oxone® (2 equiv.)	CSA (30 mol%)[d]	2.5	20	A	nr
3	Oxone® (2 equiv.)	-	1	20	A	87.0
4	Oxone® (30 mol%) + H_2O_2 (2 equiv.)	-	1	20	A	28
5	Urea peroxide (2 equiv.)	CSA (30 mol%)[c]	2.5	20	A	2
6	Urea peroxide (2 equiv.)	CSA (30 mol%)[d]	2.5	20	A	nr
7	H_2O_2 (1.2 equiv.)	PTSA (100 mol%)	25	20	B	70.0[f]
8	H_2O_2 (1.2 equiv.)	PTSA (20 mol%)	25	50	B	80.9[f]
9	H_2O_2 (2 equiv.)	PTSA (100 mol%)	25	50	B	95.5

[a]Promoter (20-100 mol%), oxidant (1.2-2 equiv.) and cyclohexene (1-25 mmol) were stirred for 21h; [b]Method I (describe in page 198): yield was calculated by ^{1}H NMR with chloroacetic acid as internal standard. Method J (described in page 198): the product was isolated by extraction of crude reaction with diethyl ether; [c]Solvent: H_2O; [d]Solvent: [C_{10}MIM][BF_4]. [e]Reaction time: 48 h; [f]In the end of the reaction the color was black; nr - no reaction.

Urea peroxide was also tested as oxidant for this reaction in the presence of CSA as catalyst (Table 3.2.3, entries 5 and 6). The reaction was tested in the presence of water or ionic liquid ([C_{10}MIM][BF_4]) as solvents, resulting in no cyclohexene conversion. This means that the urea peroxide is not a strong enough oxidant for this reaction.

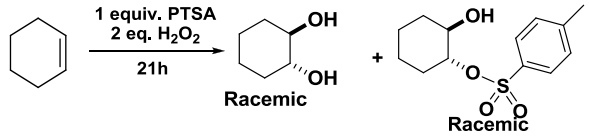
Hydrogen peroxide was chosen as the oxidant for the cyclohexene dihydroxylation reaction. In attempt to optimize the amount of hydrogen peroxide used, were tested different quantities of this oxidant (Table 3.2.3, entries 7 to 9). With one equivalent or 30 mol% of PTSA as catalyst, using 1.2 equivalents of H_2O_2, resulted in a black final reaction colour, although obtained yield was very good (Table 3.2.3, entries 7 and 8). The best result obtained with this oxidant was using 2 equivalents with PTSA as catalyst (the catalyst amount and the temperature optimizations will be discuss next).

The stability of the two chosen catalysts, CSA and PTSA was followed by ^{1}H NMR in the presence of hydrogen peroxide, at room temperature for 21 hours. CSA suffers a slowly degradation over time. It is suspected that the ketone moiety present in CSA can undergo a Bayer-Villiger oxidation. For this reason PTSA was chosen to be the catalyst for further studies on this reaction.

The cyclohexene dihydroxylation starts as a biphasic reaction, where the organic phase is the olefin, and the aqueous phase is the 30% aqueous solution of hydrogen peroxide and the acid catalyst. After complete conversion of the olefin, the reaction mixture is homogeneous, due to the diol **42** solubility in the aqueous phase. In the laboratory is easy to see the reaction evolution, by seeing the olefin disappearance. Since it is a biphasic reaction an efficient stirring is very important.

Another important factor in this reaction is the concentration of the aqueous phase of the reaction. When no water is added to the reaction system the diol **42** is formed in 88.2% yield, although trace amounts of 2-hydroxycyclohexyl-4-methylbenzenesulfonate **44** is also formed (detected by ^{1}H NMR), Table 3.2.4, entry 42. The formation of this compound is due to the competition of water and PTSA to the epoxide ring opening (further discussion is made in the reaction mechanism section 3.2.3, page 142). When water was added to the reaction (before the substrate addition) was observed a decrease in the diol **42** yield and an increase of **44** yield, (Table 3.2.4, entries 1 to 5). The addition of water to the hydrogen peroxide solution implies a temperature increase indicating a peroxide destruction, consequently a smaller amount of PTSA is oxidized to the respective peroxysulfonic acid, leaving available a larger amount of PTSA to act as nucleophile, and open the epoxide ring.

Table 3.2.4 – Concentration effect on the *trans*-dihydroxylation of cyclohexene, with PTSA as catalyst[a].



41 **42** **44**

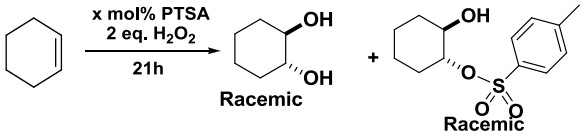
Entry	Scale of 41 (mmol)	Temp.(°C)	Added water (mL)	PTSA	Yield of 42 (%)[b]	Yield of 44(%)[c]
1	25	20	10	1 equiv.	55.7	40.2
2	25	20	8	1 equiv.	41.0	38.0
3	25	20	7	1 equiv.	47.6	30.3
4	25	20	6	1 equiv.	58.0	25.7
5	25	20	5	1 equiv.	63.0	15.9
6	25	20	-	1 equiv.	88.2	-[d]

[a]PTSA (1 equiv.), H_2O_2 (30% aq., 2 equiv.), water (x mL) and cyclohexene (25 mmol) were stirred for 21h at room temperature; [b]Method I (described in page 198): yield of diol **42** determined by ^{1}HNMR using chloroacetic acid as internal standard; [c] Isolated yield of **44** was obtained by precipitation adding water to the crude reaction before filtration; [d] Trace amounts of compound **44** was detected by ^{1}H or ^{13}CNMR of the crude reaction.

The study of the optimum amount of catalyst started with a relative small scale of 2.5 mmol of substrate (250 µL), Table 3.2.5, entries 1 to 4. At room temperature, the increase of the

catalyst percentage was proportional to the yield obtained, this is for 30 mol% of PTSA the obtained yield was 27%, for 50 mol% was obtained 50% yield, and so on (Table 3.2.5, entries 1 to 4). These results lead to the conclusion that the reaction could be stoichiometric. When the reaction scale was increased to 25 mmol of substrate, the yield fall in to 50%, even with 1 equivalent of PTSA (Table 3.2.5, entries 4 *vs.* 5). This result may be explained by the low stirring efficiency, since now the scale is ten times bigger than before.

Table 3.2.5 – *Trans*-dihydroxylation of cyclohexene with PTSA as catalyst[a].



41 **42** **44**

Entry	Scale of 41 (mmol)	Temp.(°C)	PTSA (mol%)	Method [b]	Yield of 42 (%)	Yield of 44 (%)
1	2.5	20	30	K	27.1	[c]
2	2.5	20	50	K	50.1	[c]
3	2.5	20	70	K	59.0	[c]
4	2.5	20	100	K	88.2	-[c]
5	25	20	100	L	50.3	49.0 [d]
6	25	0	100	L	50.0[f]	50.0[d]
7	25	35	100	L	67.8	20.0[d]
8	25	50	100	L	97.7	-[e]
9	25	50	30	L	96.9	-[e]
10	25	50	20	L	95.5	-[e]
11	25	50	15	L	86.0	-[e]
12	250	50	20	L	93.5[f]	-[e]

[a]PTSA (20-100 mol%), H_2O_2 (30% aq., 2 equiv.) and cyclohexene (2.5-25 mmol) were stirred for 21h; [b]Method K (described in page 199): yield determined by ^{1}HNMR using chloroacetic acid as internal standard; Method L (described in page 199): product isolated by extraction of crude reaction with diethyl ether; [c] It was not possible to quantify the yield of *trans*-2-hydroxycyclohexyl-*p*-toluenesulfonate **44** by ^{1}H NMR due to the insolubility in D_2O, that was the solvent used to calculate the yield of diol **42**, although it was possible to observe traces of **44** in the ^{1}H NMR spectra. [d]Isolated yield of **44** was obtained by precipitation after adding water to the crude reaction before filtration; [e]Compound **44** was not detected by ^{1}H or ^{13}CNMR of the crude reaction; [f]Reaction time: 72h.

As said before, due to the low boiling point of some olefins, the reaction temperature had to be as low as possible, but so far the reaction efficiency was not optimized. Different temperatures lower than 50°C were tested for higher reaction efficiency (Table 3.2.5, entries 5 to 8). In fact the reaction temperature was crucial, and for 50°C almost complete conversion was observed, without the formation of the side product **44** (Table 3.2.5, entry 8). At this temperature the amount of catalyst used could be decreased up to 20 mol% without lost of efficiency (Table

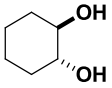
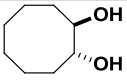
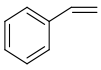
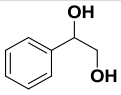
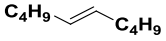
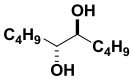
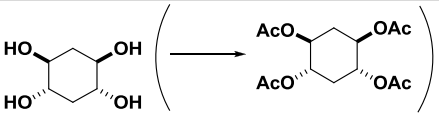
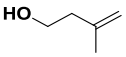
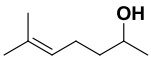
3.2.5, entries 8 to 11). A ten times larger reaction scale, 250 mmol of substrate, was performed with an excellent yield, although a higher reaction time was needed (Table 3.2.5, entry 12).

Exploring a way to obtain **44** as major product, the reaction temperature was decrease up to 0°C. Although the time reaction was increased to obtain a complete conversion of the cyclohexene, the compounds **42** and **44** were formed in the same proportion as at room temperature (Table 3.2.5, entries 6 vs. 5). So was concluded that the competition of water and the PTSA to open the epoxide ring is always present, even at low temperatures.

The optimization of the reaction conditions allowed the identification of efficient catalysis (20 mol% of PTSA) at 50°C using 2 equivalents of H_2O_2, providing the diol **42** in 95.5% yield. In these conditions several others substrates were tested. Due to the low boiling point of cyclohexene (82°C) and others olefins, the reactions were performed at 50°C in a closed glass vessel that tolerates high pressures (so called reactor), in a way to assure that no cyclohexene was lost by evaporation, lowering the obtained yield.

The formation of **45** was achieved in 82.9% (Table 3.2.6, entry 2). The transformation of cyclopentene into the respective diol **46** was tested with 1 equivalent of PTSA, at room temperature, and moderate yield was obtained (Table 3.2.6, entry 3). This result was improved by increasing the temperature to 50°C, and decreasing the PTSA amount to 20 mol%, resulting in 95% yield. For this substrate a smaller quantity of the catalyst resulted in a better performance, but for example with cyclooctene as substrate the product is not formed with 20 mol% of PTSA, in fact is needed 1 equivalent of the catalyst to achieve a yield of 75% (Table 3.2.6, entry 4). For styrene the reaction is also more efficient with 1 equivalent of catalyst, although the yield improvement is only 5% when compared to the result obtained with 20 mol% of catalyst PTSA (Table 3.2.6, entry 5). For 1-hexene, a yield improvement was observed when the PTSA quantity was increased from 20 mol% to 1 equivalent (Table 3.2.6, entry 6). But when the reaction temperature was increased to 70°C, even with 20 mol% of PTSA, the yield obtained was only 86% (Table 3.2.6, entry 6). *Trans*-5-decene was transformed in the respective diol **50** in only 65% yield, although the olefin conversion was almost complete (Table 3.2.6, entry 7). For 1,4-cyclohexadiene transformation was very interesting to observe that only one product was formed with 76% yield (Table 3.2.6, entry 8). The spectral data comparison of this compound with the reported in the literature didn't assure the *trans-trans* stereochemistry, so this product was acetylated, and the *trans,trans*-cyclohexane-1,2,4,5-tetrayltetraacetate (**52**) was achieved in 100% yield, confirming the *trans, trans*-cyclohexane-1,2,4,5-tetraol **51** stereochemistry.

Table 3.2.6 – *Trans*-dihydroxylation of several olefins with PTSA as catalyst, at 50°C[a].

Entry	Substrate	Product	PTSA (mol%)	Yield (%)[b]
1		 **42**	20	95.5
			100	97.7
2		 **45**	20	82.9
3		 **46**	20	95.7
			100	55.7[c,d]
4		 **47**	20	nr
			100	75.5
5		 **48**	20	86.4
			100	91.6
6		 **49**	20	62.4
			20	86.8[e]
			100	80.0
7		 **50**	20	65.0[i]
8		 **51** **52**	20	76.7[d,f]
9		-	20[g]	nr
			100[g]	nr
10		-	20[h]	-
11		-	20[h]	-
12		-	20[h]	-
13		-	20[h]	-

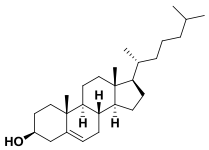
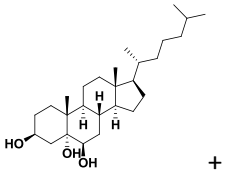
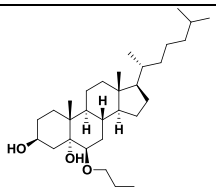
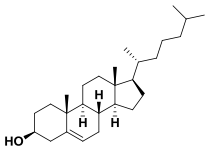
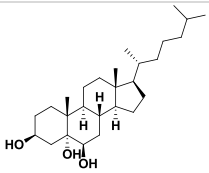
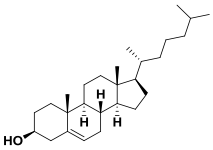
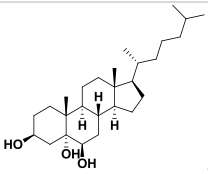
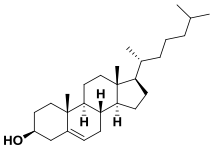
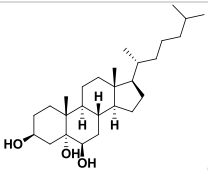
[a]PTSA (20 mol%), H_2O_2 (30% aq., 2 equiv.) and substrate (25 mmol) were stirred for 21h at 50°C, unless stated; [b]Method M (described in page 199): product isolated by extraction of crude reaction with diethyl ether; [c]Temperature of 20°C; [d]Method K (describe in page 199): yield determined by ^{1}HNMR using chloroacetic acid as internal standard; [e]Temperature 70°C; [f]To confirm the *trans-trans*-cyclohexane-1,2,4,5-tetraol **51** geometry, this product was acetylated to *trans, trans*-cyclohexane-1,2,4,5-tetrayl tetra acetate **52**; [g]Reaction performed at 50 and 70°C without product formation; [h]Reaction performed at 20

and 50°C, but in the end of the reaction the colour was black, and a complex mixture of several products was formed; [i]Reaction time: 72h nr – no reaction;

Although several reaction conditions were tested for the stilbene transformation, no product was ever observed (Table 3.2.6, entry 9). Stilbene is a hydrophobic compound that is not soluble on the reactive aqueous phase of the reaction. For this reason the substrate was dissolved in propan-1-ol, which is a more polar solvent, and then added to the reaction. Even so there was no reaction, with 20 mol%, or 1 equivalent of PTSA, at room temperature, 50 or 70°C. As previous used for cyclohexene transformation (please see Table 3.2.2, page 130), DBSA acting as a surfactant could be a good catalyst for this substrate. With 20 or 50 mol% of DBSA at 50°C no reaction was again observed. A reason proposed for the non reactivity of stilbene is that the performance of this reaction is not so good for *trans*-olefins substrates, as observed for *trans*-5-decene (Table 3.2.6, entry 7), and the high hydrophobicity of stilbene do not allow the catalyst access to the olefin. Other olefins containing the hydroxyl moiety were tested (Table 3.2.6, entries **10** and **11**), resulting in complex mixture of several products, indicating over oxidation of the substrate. The 2-methyl-1,3-butadiene and cyclopentadiene, conjugated dienes were also tested and a complex mixture of several products was obtained, indicating over oxidation of this type of compounds.

Cholesterol was tested as substrate for this reaction. The results obtained are summarized in Table 3.2.7. Cholesterol is not soluble in water, so once again was needed a co-solvent to increase the solubility of the substrate in the reactive aqueous solution. First was tested with propan-1-ol as co-solvent. The result was quite unexpected, the respective diol **53** was formed in moderated yield, but also other product was formed, that was assumed to be compound **54**. Unfortunately NMR data was not enough to conclude about the structure of this product, and different analysis has to be performed. If the product formed is compound **54**, it was formed by the competition between water and propan-1-ol to open the epoxide ring. Several others co-solvents were tested with the objective of obtaining the respective ether as major product. The alcohols tested had a larger hydrophobic moiety to create a shell over the substrate, favouring the alcohol introduction. With hexan-1-ol, octan-1-ol or dodecan-1-ol the only product formed, with moderated yields, was diol **53**.

Table 3.2.7 – Cholesterol dihydroxylation with 20 mol% of PTSA, at 75°C, for 48 hours with different co-solvents[a].

Entry	Substrate	Co-solvent	Product	Yield (%)[b]
14		Propan-1-ol	 **53** +  **54**	**53**- 55.8 **54**- 34.5
15		Hexan-1-ol	 **53**	55.8
16		Octan-1-ol	 **53**	59.3
17		Dodecan-1-ol	 **53**	53.0

[a]PTSA (20 mol%), H_2O_2 (30% aq., 2 equiv.) and cholesterol (25 mmol) dissolved in the co-solvent were stirred at 75°C, for 48h; [b] stereochemistry is based in the literature. [277]

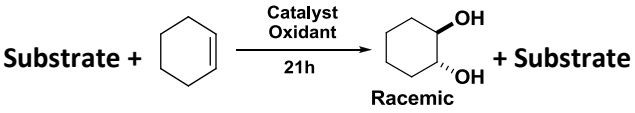
3.2.2 Substrates stability in reaction conditions

The dihydroxylation reaction showed to be a simple, robust mild organocatalyzed method in aqueous media. In order to extend the advantage and limitations of this methodology, the compatibility with other functional groups was studied. The substrate tolerance in the optimized conditions was explored by performing the dihydroxylation of cyclohexene in the presence of an equimolar amount of other substrates containing different functional groups (Table 3.2.8). To facilitate the substrate stability examination, is available in Appendix the ^{1}H and ^{13}C NMR comparison of the reaction crude with the individuals NMR spectra of the substrate and the diol **42** (please see Appendix section 6.3, page 232-246).

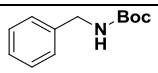
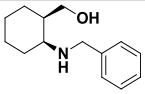
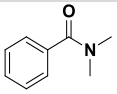
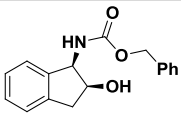
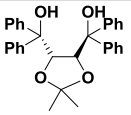
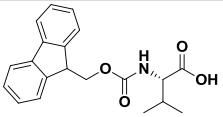
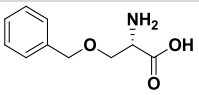
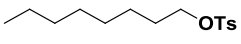
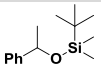
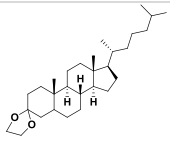
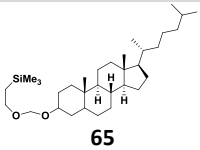
Amine protection groups such as Boc (*tert*-butyloxycarbonyl, **55**) and Cbz (carbobenzyloxyl,**58**), Table 3.2.8, entries 1 and 4, respectively, are stable under the reaction conditions (20 mol% PTSA, 2 equiv. H_2O_2, 50°C, 21 hours). On the contrary, benzyl protecting group **56** was not stable, and no formation of the diol **42** was observed (Table 3.2.8, entry 2). Fmoc ((9H-fluoren-9-yl)methyl carbamate,**60**) was not totally stable in the reaction conditions, but was still

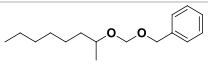
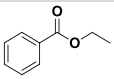
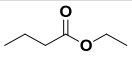
possible to recover 40% of the added amount and diol **42** was formed and isolated in 89% (Table 3.2.8, entry 6). N,N-dimethylbenzamide **57** stability, and diol **42** formation were confirmed by ^{1}H and ^{13}C NMR, but was not possible to isolate them by silica gel chromatography, so the recovered yield could not be quantify (Table 3.2.8, entry 3). Ethynylbenzene **66** was not stable, and probably ocorred polymerization under the reaction conditions, due to the formation of a black solid mass, that was not possible to perform ^{1}H or ^{13}C NMR (Table 3.2.8, entry 12). Two different ketals stability were tested (Table 3.2.8, entries 5 and 10), the ketal **64** that is a ketone protection group was not stable in the reaction conditions, although was observed the diol **42** formation in 87% yield. A hindered ketal **59** was also tested and was possible to recover 94% of this substrate, and diol **42** was obtained in 87% isolated yield. Several functionalized alcohols groups were tested. *para*-Toluenesulfonyl group in compound **58** was stable under the reaction conditions with 83% recovery, and 98% diol **42** yield (Table 3.2.8, entry 8). This result is discussed further in reaction mechanism section (please see section 3.2.3, page 142). The SEM (**65**) protection group was also stable, with 84% recovery, although only 66% of diol **42** was formed (Table 3.2.8, entry **11**). The O-protected amino acid O-benzyl-serine **61** was stable in the reaction conditions (Table 3.2.8, entry 7). Since the amino group was not protected, apparently a neutralization of the acidic catalyst PTSA occurs and no reaction of the cyclohexene is observed. When the amount of PTSA is raised to 70 mol%, and **61** is decreased to 50 mol%, cyclohexene is transformed into diol **42** (Table 3.2.8, entry 7). It was not possible to perform a chromatographic separation of these products due to the amino acid moiety be unprotected, so the compound is retained in silica gel. The TBDMS (*tert*- butyldimethylsilyl, **63**) protection group was not stable in the reaction conditions, although the diol **42** was formed in 61% yield (Table 3.2.8, entry 9). SEM ([2-(trimethylsilyl)ethoxy]methyl, **65**) was recovered in 84%, and the diol **42** yield was 66% (Table 3.2.8, entry 11). Ethyl esters of the benzoic acid **68** and the propanoic acid **69** were also tested (Table 3.2.8, entries 14 and 15). These two compounds did not have the same behaviour, the protected benzoic acid was stable in the reaction conditions, although the less stable protected propanoic acid **69** was hydrolyzed into ethanol and propanoic acid.

Table 3.2.8 – Trans-dihydroxylation of cyclohexene with PTSA as catalyst (20 mol%), at 50°C in the presence of substrates with different functional groups [a].



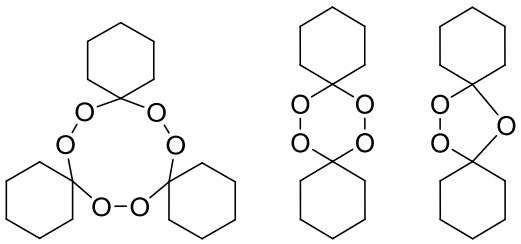
41 **42**

Entry	Substrate	Stability (% recovered)[b]	Yield of 42 (%)[b]
1	 **55**	Yes (96%)	86
2	 **56**	No	nr
3	 **57**	Yes[c]	nd
4	 **58**	Yes (85%)	87
5	 **59**	Yes (94%)	87
6	 **60**	Yes/No (40%)	89
7	 **61**	Yes[c] Yes[c,d]	nr nd
8	 **62**	Yes (80%)	98.1
9	 **63**	No [e]	61.0
10	 **64**	No	87.0
11	 **65**	Yes (84.5%)	66.7
12	 **66**	No	-

13	 **67**	No	72.3
14	 **68**	Yes (76%)	98
15	 **69**	No	75

[a]Method N (described in page 204): PTSA (20 mol%) and H_2O_2 (30% aq. sol., 2 equiv.) were stirred for 5 minutes, then was added the cyclohexene (1-2.5 mmol) and the substrate (50 or 100 mol%). After 21 hours stirring at 50°C, the reaction mixture was extracted with diethyl ether, and the mixture was separated by column chromatography on silica gel; [b]Substrate stability based on TLC, crude ^{1}H and ^{13}C-NMR analysis and recover of substrate by preparative TLC/column chromatography. [c]Stability confirmed by ^{1}H and ^{13}C NMR, but the added substrate was not isolated; [d]70 mol% of PTSA; [e] – 1-Phenylethanol was isolated; nr – no reaction; nd – not determined.

Cyclohexanone was also tested under the reaction conditions, this time without the addition of cyclohexene. At room temperature, to a solution of 20 mol% of PTSA and 2 equivalents of H_2O_2, was added 1 equivalent of cyclohexanone. A complete different product was formed, that structure is not clear so far. Several attempts to induce crystallization in order to achieve a X-ray diffraction pattern were unsuccessful, despite the several solvent systems tested. From the NMR spectra, is possible to expect that the structure is similar to **70, 71** or **72,** but the NMR data do not mach with the one reported in the literature for this type of compounds.[278] These types of compounds are well established in the literature, and some are known for anti-malaria or explosives properties.[279]



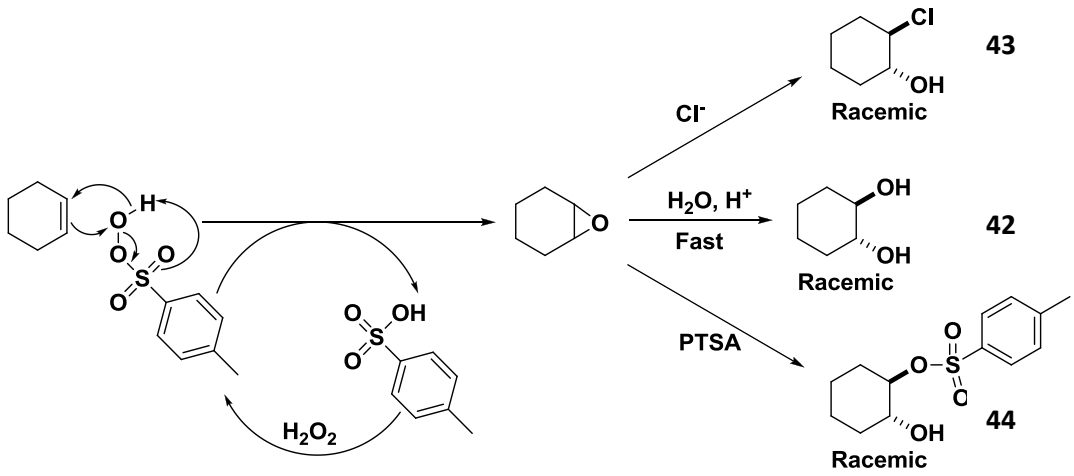
70 **71** **72**

Figure 3.2.1 – Possible products for the reaction of cyclohexanone with hydrogen peroxide at room temperature.

In general overview there is a high compatibility for a considerable range of functional groups, demonstrating the milder conditions of this organocatalyzed methodology in aqueous medium.

3.2.3 Proposed mechanism

The observation of exclusive formation of *trans*-1,2-cyclohexandiol **42** (Table 3.2.5, entry 8) and in some conditions the formation of the corresponding of *trans*-2-hydroxycyclohexyl-4-methylbenzenesulfonate **44** (Table 3.2.5, entry 6), or the *trans*-2-chloro-cyclohexanol **43** (Scheme 3.2.1) support a mechanism via epoxidation by the corresponding peroxysulfonic acid following by acid catalyzed ring opening (Scheme 3.2.2). Several experiments have been performed in order to confirm this reaction mechanism.



Scheme 3.2.2 – Proposed reaction mechanism, with several products formed.

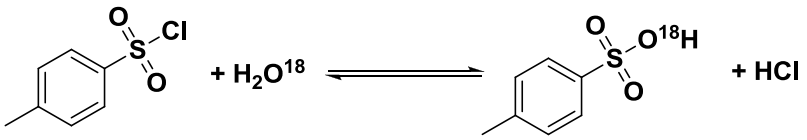
The reaction with *p*-toluenesulfonate sodium salt in replacement of PTSA in the presence of H_2O_2 resulted in no cyclohexene reaction, even with one equivalent of the salt. This mean that the acid is needed to be oxidized by H_2O_2 as reactive intermediate for epoxide ring formation.

The commercial cyclohexene oxide originated quantitatively the corresponding diol **42** in only 5 minutes, at room temperature with 20 mol% of PTSA in H_2O. Although in an aqueous solution without PTSA cyclohexene oxide didn't react. This result can explain why cyclohexene oxide was never detected by following the reaction by ^{1}H and ^{13}C NMR under different experimental conditions, the opening of the epoxide ring happens very fast in acidic conditions.

Another experimental observation is that once the product **44** is formed was not hydrolysed to the respective diol **42**, even in the presence of 3 equivalents of PTSA at 50°C. This means that the exclusive formation of diol **42** at 50°C resulted from a faster hydrolysis of the epoxide ring, thus product **44** was not an intermediate of the reaction. This result can also explain why the compound **62** was not hydrolysed in the reaction conditions (20 mol% PTSA, 2 equiv. H_2O_2, 50°C, 21 hours, Table 3.2.8, entry 8). In the presence of PTSA, H_2O_2 and cyclohexene were tested different compounds that could act as nucleophile for the epoxide ring opening, such as

pentane-2,4-dione (acetylacetone), *p*-toluenesulfonamide, acetamide and methoxybenzene. For all of these cases, the exclusive product formed was diol **42**, confirming that at 50°C faster hydrolysis of the epoxide ring occurs.

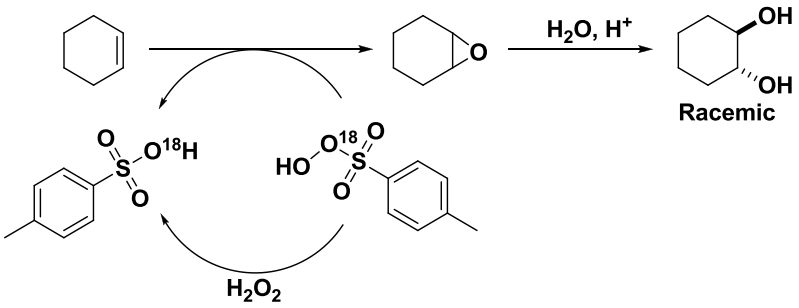
The synthesis of PTSA enriched in ^{18}O, from 4-toluenesulfonyl chloride and enriched ^{18}O water was performed. This reaction should be an easy hydrolysis reaction of the 4-toluenesulfonyl chloride to PTSA, although experimentally it was not so easy.



Scheme 3.2.3 – Enriched ^{18}O p-toluenesulfonic acid by the hydrolysis of 4-toluenesulfonyl chloride.

With the addition of water (4 equivalents) to 4-toluenesulfonyl chloride with stirring at room temperature, or at 70°C (temperature of melting point of 4-toluenesulfonyl chloride) no product was formed.This may be explained by the fact that 4-toluenesulfonyl chloride is a hydrophobic compound, and did not mixture with water. Dissolving 4-toluenesulfonyl chloride in acetone, and by adding 4 equiv. of water no hydrolysis product was also formed, even under reflux for 6 hours! The hydrolysis reaction was only accomplished when 4 equiv. of H_2O were added to 1 equivalent of 4-toluenesulfonyl chloride dissolved in toluene, in reflux overnight. When the reaction was cooled to room temperature, PTSA precipitated almost immediately. This experiment was done several times with distillated water, and the obtained yield was always 50%. When the exact same experiment (on the same scale) was done with enriched water ($^{18}OH_2$) the yield obtained was 1.6%. When PTSA was formed, the released HCl was still in solution, so was believed that an equilibrium was present, and the PTSA formation can be reversible. This may be the reason for 4-toluenesulfonyl chloride hydrolysis product was so difficult to obtain.

By using the catalyst PTSA enriched in ^{18}O under optimized dihydroxylation conditions, was observed by MS that ^{18}O retained exclusively in the recovered catalyst and not in the formed diol (Scheme 3.2.4, please see Appendix, section 6.5, page 248). The collected information supported an expected mechanism resulted of epoxidation followed by fast ring opening by water in which both steps are catalysed by PTSA.

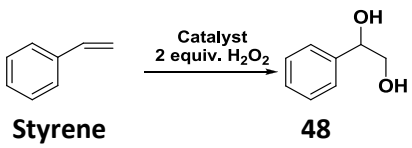


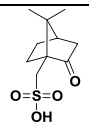
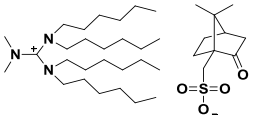
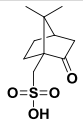
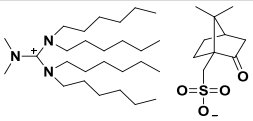
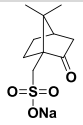
Scheme 3.2.4 – Proposed mechanism for the dihydroxylation reaction with PTSA as catalyst.

3.2.4 Asymmetric version attempts

Since (S)-CSA, that is a chiral sulfonic acid, can catalyze the cyclohexene dihydroxylation, it was tested if could induce some chirality into the product. It was used styrene as substrate because the HPLC analysis to detect enantioselectivity was easier for this substrate, since is UV visible, and diol **42** is not and also the epoxidation gives a meso precursor. With styrene as substrate, the reaction with 30 mol% of (S)-CSA and 2 equivalents of H_2O_2, at 50°C was tested (Table 3.2.9, entry 1). The product formed **48** was analyzed by HPLC with a chiral column, and no enantioselectivity was observed. So it was tested another approach. Was used the chiral ionic liquid (CIL) with (S)-camphorsulfonate as anion, ([(di-*h*)$_2$DMG][(S)-CSA] described in Chapter 1), as reaction solvent with no catalyst added, (Table 3.2.9, entries 2 to 4). No product was observed, at room temperature, 50 or 70°C. To understand the reason why no reaction was observed, it was performed an experiment with the sodium salt of the CSA, a similar procedure as before prepared for PTSA catalyst (described in section 3.2.3) and once again no reaction was observed (Table 3.2.9, entry 7). This result confirms that the acid was needed to be oxidized by H_2O_2 and form the epoxide ring. So it was added 30 mol% of (S)-CSA with [(di-*h*)$_2$DMG][(S)-CSA]as solvent, and H_2O_2 as oxidant, with styrene as substrate, at room temperature (Table 3.2.9, entries 5 and 6). The reaction mixture after 48 hours reaction transformed into a hard mass, maybe due to styrene polymerization. So the reaction temperature was raised to 50°C for a shorter period, 21 hours, product **48** was formed with 52% yield but once again no enantioselectivity was observed.

Table 3.2.9 – (S)-CSA and/or [(di-*h*)$_2$DMG][(S)-CSA] as chiral inductors for the *trans*-dihydroxylation of styrene [a].



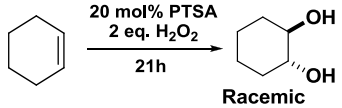
Entry	Catalyst	Solvent	Temp. (°C)	Time reaction (hours)	Yield of 48 (%)	Enantiomeric excess (ee)[b]
1	 (S)-CSA (30 mol%)	H_2O	50	21	69	0
2	-	 [(di-*h*)$_2$DMG][(S)-CSA]	20	21 or 48	-	-
3			50	21 or 48	-	-
4			70	21 or 48	-	-
5	 (S)-CSA (30 mol%)	 [(di-*h*)$_2$DMG][(S)-CSA]	20	48	-	-
6			50	21	52%	0
7	 Sodium (S)-camphorsulfonate	H_2O	50	48	-	-

[a] Method O (described in page 204): (S)-CSA and/or [(di-*h*)$_2$DMG][(S)-CSA], H_2O_2 (30% aq., 2 equiv.) and styrene (2.5 mmol) were stirred for 21 or 48 hours. [b]Determined by chiral HPLC analysis.

3.2.5 Catalyst reuse

The possibility to achieve catalyst reuse was explored by using again cyclohexene as model substrate (Table 3.2.10). Just by extraction of the reaction mixture with diethylether, followed by new addition of H_2O_2 and the substrate, was possible to recycle the catalyst at least seven times. In all cycles the reaction was complete and the diol **42** was obtained pure, after solvent evaporation without need of further purification by chromatography (please see Appendix, section 6.4, page 247). The high efficiency of the reuse process was due to the preferential partition of the PTSA catalyst to the aqueous phase. The need of higher reaction time to achieve completion of the reaction was probably due to some observed lost of the catalyst in the organic solvent extraction.

Table 3.2.10 – Reuse of the catalyst [a].



41 **42**

Cycle	Yield of 42 (%)	Reaction time (hours)
1	95.5	24
2	105.6	48
3	97.3	60

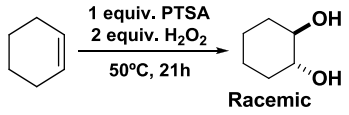
4	97.5	72
5	96.3	72
6	99.1	96
7	97.3	96
8	65.3	120

[a]Method P (described in page 205): PTSA (20 mol%, 951.1 mg), 2 equiv. H_2O_2 (2 equiv., 30% aq. sol., 5.66 g) were stirred for five minutes, and then the cyclohexene was added (25 mmol, 2.5 mL), at 50°C. After time reaction the crude aqueous phase was extracted with diethylether (3x100 mL). The aqueous phase was concentrated by water evaporation, and the next cycle started by adding H_2O_2 (30% aq. sol., 2 equiv., 5.66 g) and the substrate (25 mmol, 2.5 mL). Diethylether was removed from the organic layer, and the diol **42** was obtained in very high purity.

3.2.6 Synthesis and isolation of *trans*-1,2-cylohexanediol using an organic solvent free protocol

Considerable efforts have been devoted for finding more environmental-friendly chemical processes such as reduction of emissions of volatile organic compounds (VOCs). Reduction or elimination of the traditional solvents, usually toxic and inflammable, provides an approach to prevent pollution. Besides the reaction conditions the work up process can also contribute to the environmental pollution of the total process. For this reason was tried to developed a isolation method for diol **42**, where no organic solvents were used.

During the study of the reaction model (Scheme 3.2.5) it was assumed that the best conversion yields were achieved with one equivalent of PTSA at 50°C, for 21hours (although the reaction was further optimized, as early described, decreasing the catalyst quantity to 20 mol%). So, in these conditions was developed a greener protocol where diol **42** could be isolated without the use of organic solvents.



41 **42**

Scheme 3.2.5 – Model reaction of cyclohexene transformation to *trans*-1,2-cyclohexanediol with 1 equivalent of PTSA, 2 equivalents of H_2O_2, at 50°C for 21 hours.

It was observed that diol **42** forms an azeotropic mixture with water, so it was not possible to remove diol **42** from the reaction mixture just by water evaporation without losing some compound percentage. It is known that azeotropic mixtures can be separated into their pure components by addition of a solvent or a new component, which interacts with the different components altering their volatilities.[280]

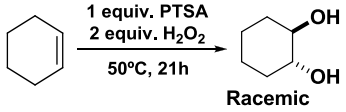
The developed process of diol **42** synthesis was very easy, it was done just by mixing hydrogen peroxide with PTSA, and the substrate, and after 21h at 50°C diol **42** was obtained in very good

yields, even in bigger scale synthesis (25 mL of substrate). The main problem observed was the isolation of diol **42** from water, and the PTSA reagent. After complete conversion of the substrate, the acid was neutralized with sodium bicarbonate, forming the salt *p*-TsONa and the excess of H_2O_2 was reduced with Na_2SO_3. It was observed that the presence of *p*-TsONa can destroy the azeotropic mixture of water and diol **42**. Consequently, separation of the water can be achieved by simple evaporation, without the loss of the diol.

In the end of the water evaporation was obtained a hard solid as a mixture of *p*-TsONa and the final product. These two compounds can be isolated by sublimation, where the diol **42** can be obtained in high purity. Sublimation here was used not only as ultimate purification technique, but is used also to separate two different compounds. In addition the overall process does not require any organic solvent, which will provide some green chemistry credits.[5a] The yield of this reaction was 79%, at 75°C in 4h, but can be improved up to 97%, at 50°C in 21h. The yield can be determined by ^{1}HNMR, in the presence of an internal standard (chloroacetic acid).

To show the reaction reproducibility, was performed several times on a 0.10-0.25 mol scale (Table 3.2.11) that were also reproducible by undergraduate students, allowing the isolation of *trans*-1,2-cyclohexanediol in 62.3%. Due to simplicity of the protocol, and the didactic techniques used, this work was accepted in the *Journal of Chemical Education.*

Table 3.2.11 – Results for several experiments accomplished in a round-bottomed flask with a water condenser, with *trans*-1,2-cyclohexanediol as substrate, *p*-toluenesulfonic acid (1 eq.) as the reaction promoter, and H_2O_2 (2 eq.) as oxidant reagent.



41 **42**

Entry	Scale of 41 (mmol)	Temp. (°C)	Time Reaction (h)	Yield of 42 (%)	Isolated product (%)[b]	Melting point of 42 (°C)[d]
1	10	65	4h	62.1	93.4	99-100
2	10	75	4h	65.0	86.1	97-100
3[e]	10	75	4h	64.4	94.7	88-98
4	25	50	21	89.2	73.3	100-101
5	25	50	21	91.3	73.6	99-102
6	25	50	21	89.0	67.6	99-100
7	25	50	21	73.5	88.8	98-100
8	25	50	21	97.9[a]	66.8	94-97
9	50	50	21	89.2	70.7	89-94
10	25	25	21	50.0[c]	50.0	-
11[e]	25	50	21	100[a]	55.7	97-100

[a] Methods Q and R (described in page 205): Reaction made in a glass reactor (closed flask) in the same conditions as the others experiments. The observed conversion was higher due to the occurrence of some evaporation of volatile cyclohexene on an open vessel (entries 4-7, 9, 10). [b] Yield of the product isolated by sublimation. Not all the converted product was recovered by sublimation, possibly due to the ineffective separation of the trans-1,2-cyclohexanediol from the sodium p-toluenesulfonate salt. However it was possible to recover 100% of the converted product by extraction of the aqueous solution (after neutralization and H2O2 reduction) with ethyl acetate (3×100 mL). [c] Trans-2-hydroxycyclohexyl-p-toluenesulfonate was formed in 50 % yield, and isolated (Isolation: After 24h of reaction at room temperature add 10 mL of water to the reaction mixture precipitating *trans*-2-hydroxycyclohexyl-p-toluenesulfonate. Filter and wash with water. The solid can be characterized by NMR (Appendix, Figure 6.6.8 and 6.6.9, please see page 253). In the aqueous phase, trans-1,2-cyclohexanediol can be isolated as mentioned above). [d] Observed melting point of the sublimed trans-1,2-cyclohexanediol (reported Aldrich mp 100-103°C). [e] Results of a experiment accomplished by a 1st year master student.

In Table 3.2.11 it was possible to see that not all the product was recovered by sublimation. In fact, ^{13}C NMR spectrum of the remaining solid after sublimation shows that there are still *trans*-1,2-cyclohexanediol present (Appendix, please see Figure 6.6.8 and 6.6.9, please see page 253). Thus, this separation was not complete, but this experiment shows to the student that was possible to separate two different compounds by sublimation.

3.3 Conclusions

In this work was developed a straightforward and efficient method for the *trans*-dihydroxylation of olefins. First different catalysts were tested, and the best one was PTSA, that is cheap acid present in common organic chemistry laboratories. The best oxidant and also solvent were screened, being hydrogen peroxide in aqueous solution the most efficient one. In this way was described a very simple method for the *trans*-dihydroxylation of different olefins.

To test the stability of different functional groups in the reaction conditions, substrates processing several protection groups, or different functional groups were tested, and interestingly several groups were stable. This means that this reaction is compatible with a vast number of substrates.

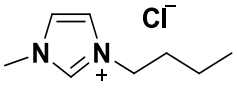
On the other hand, due to the simplicity of the developed method for the *trans*-dihydroxylation, it was developed a organic free protocol where the *trans*-1,2-cyclohexanediol was synthesized and separated from the reaction medium without the use of organic solvents. This method is based on the fact that *trans*-1,2-cyclohexanedion/water azeotropic mixture can be broken in the presence of the *p*-toluenesulfonate sodium salt. In this way it was possible remove the water by distillation, and isolate and purify the diol in only one step, by sublimation.

4 Experimental

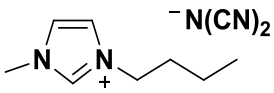
On this chapter is described all the experimental procedures performed in this work.

4.1 Reactions Index

4.2 Compounds Index



[BMIM][Cl]
Section 4.4.1.1.1, page 165



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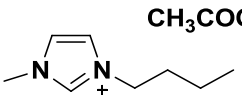
Section4.4.1.1.2 page 165



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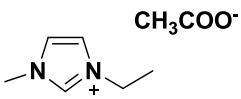
Section4.4.1.1.3 page 165



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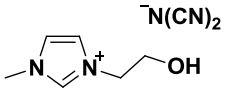
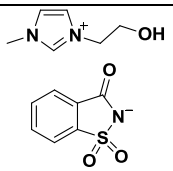
Section 4.4.1.1.4 page 166



[C_2OHMIM][DCA]
Section 4.4.1.1.5 page 166



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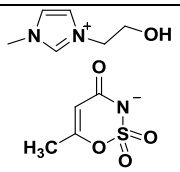
Section 4.4.1.1.6 page 167



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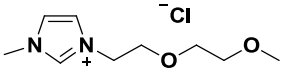
Section 4.4.1.1.7 page 167



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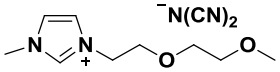

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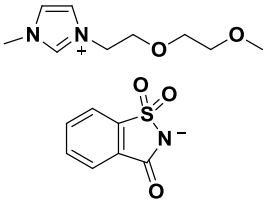
Section 4.4.1.2.1 page 169



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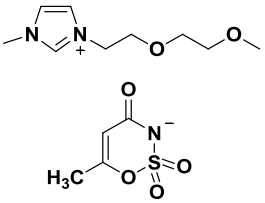

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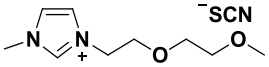
Section 4.4.1.2.3 page 170



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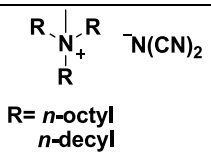
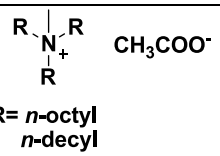
Section 4.4.1.2.4 page 170



[Aliquat®][DCA]
Section 4.4.1.2.5 page 171



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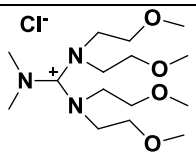
Section 4.4.1.2.6 page 171



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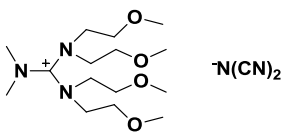
Section 4.4.1.2.7 page 172



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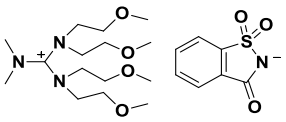

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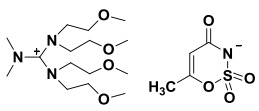
Section 4.4.1.2.9 page 173



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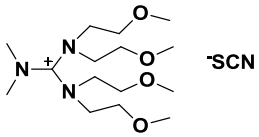

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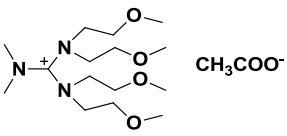
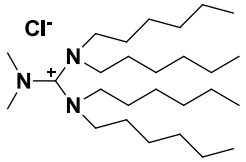
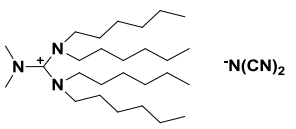
Section 4.4.1.2.11 page 174



[$(C_3O)_4$DMG][OAc]
Section 4.4.1.2.12 page 175



[(di-h)$_2$DMG][Cl]
Section 4.4.1.2.13 page 176



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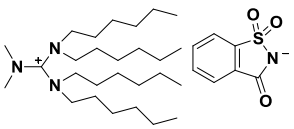
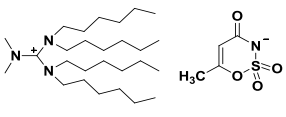
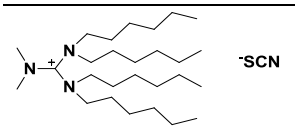
Section 4.4.1.3.1 page 177



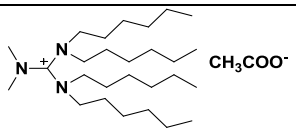
[(di-h)$_2$DMG][SAC]
Section 4.4.1.3.2 page 178



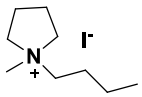
[(di-h)$_2$DMG][ACES]
Section 4.4.1.3.3 page 178



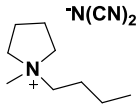
[(di-h)$_2$DMG][SCN]
Section 4.4.1.3.4 page 179



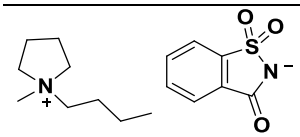
[(di-h)$_2$DMG][OAc]
Section 4.4.1.3.5 page 179



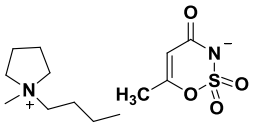
[BMPyr][I]
Section 4.4.1.3.6 page 180



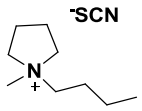
[BMPyr][DCA]
Section 4.4.1.4.1 page 180



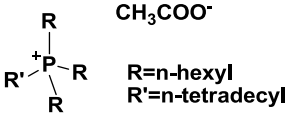
[BMPyr][SAC]
Section 4.4.1.4.2 page 181



[BMPyr][ACE]
Section 4.4.1.4.3 page 181

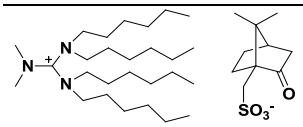


[BMPyr][SCN]
Section 4.4.1.4.4 page 182

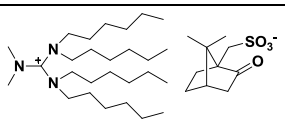


[$P_{6,6,6,14}$][OAc]
Section 4.4.1.4.5 page 182

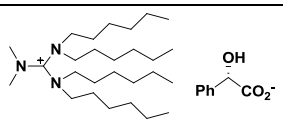
Chiral Ionic Liquids (CILs)



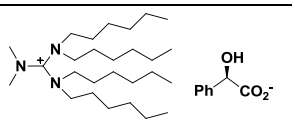
[(di-h)$_2$DMG][(S)-CSA]
Section4.4.2.1.1 page 183



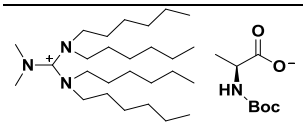
[(di-h)$_2$DMG][(R)-CSA]
Section 4.4.2.1.2 page 184



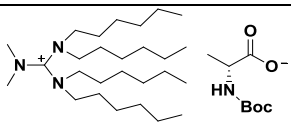
[(di-h)$_2$DMG][(S)-Mand]
Section 4.4.2.1.3 page 185



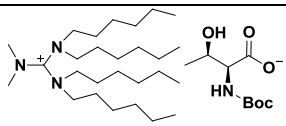
[(di-h)$_2$DMG][(R)-Mand]
Section 4.4.2.1.4 page 185



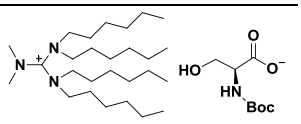
[(di-h)$_2$DMG][Boc-L-Ala]
Section 4.4.2.1.5 page 186



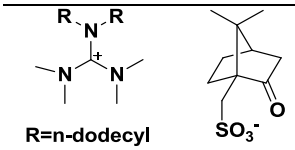
[(di-h)$_2$DMG][Boc-D-Ala]
Section 4.4.2.1.6 page 186



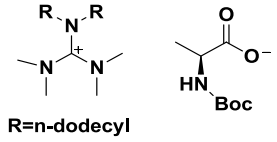
[(di-h)$_2$DMG][Boc-L-Thr]
Section 4.4.2.1.7 page 187



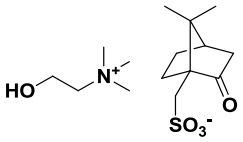
[(di-h)$_2$DMG][Boc-L-Ser]
Section 4.4.2.1.8 page 187



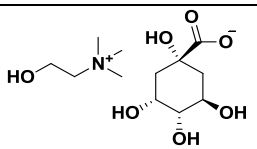
[C_{12}TMG][(S)-CSA]
Section 4.4.2.1.9 page 188



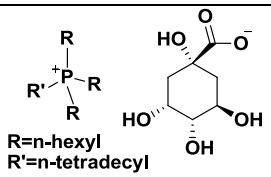
[C_{12}TMG][Boc-L-Ala]
Section 4.4.2.1.10 page 188



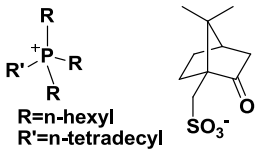
[Choline][(S)-CSA]
Section 4.4.2.1.11 page 189



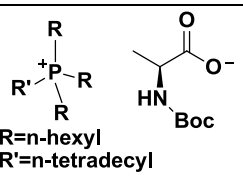
[Choline][Quinic]
Section 4.4.2.1.12,page 189



[$P_{6,6,6,14}$][Quinic]
Section 4.4.2.1.13 page 190

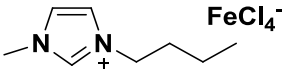


[$P_{6,6,6,14}$] [(S)-CSA]
Section 4.4.2.1.14 page 190



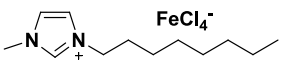
[$P_{6,6,6,14}$][Boc-L-Ala]
Section 4.4.2.1.15 page 191

Magnetic Ionic Liquids



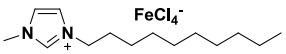
[BMIM][$FeCl_4$]

Section 4.4.3.1.1 page 192



[C_8MIM][$FeCl_4$]

Section 4.4.3.1.2 page 192



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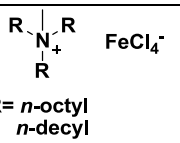
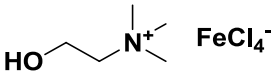
Section 4.4.3.1.3 page 192



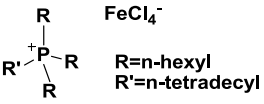
[Aliquat][$FeCl_4$]

Section 4.4.3.1.4 page 192



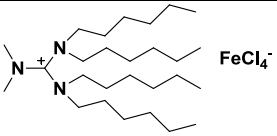
[Choline][$FeCl_4$]

Section 4.4.3.1.5 page 193



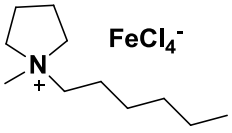
[$P_{6,6,6,14}$][$FeCl_4$]

Section 4.4.3.1.6 page 193



[(di-h)$_2$DMG][$FeCl_4$]

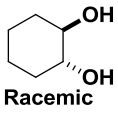
Section 4.4.3.1.7 page 193



[C_6MPyr][$FeCl_4$]

Section 4.4.3.1.8 page 194

Dihydroxylation Products

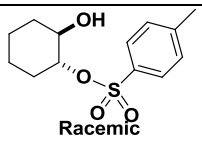


42

Section 4.6.1.4.1 page 199

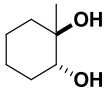
43

Section 4.6.2 page 206



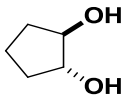
44

Section 4.6.1.4.11 page203



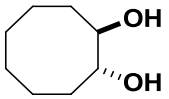
45

Section 4.6.1.4.2 page 200



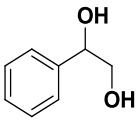
46

Section 4.6.1.4.3 page 200



47

Section 4.6.1.4.4 page 200



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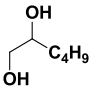
Section 4.6.1.4.5 page 201



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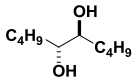
Section 4.6.1.4.6 page 201



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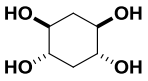
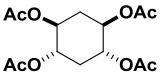
Section 4.6.1.4.7 page 201



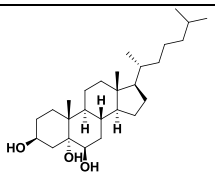
51

Section 4.6.1.4.9 page 202



52

Section 4.6.1.4.10 page 203



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Section 4.6.1.4.8 page 202

4.3 General remarks

4.3.1 General methods

All glassware was oven-dried prior to use. In anhydrous transformations the glassware was over dried by flame drying under argon. In these transformations solvents used were distilled and dried under argon atmosphere according to standard procedures:[281] dichloromethane and triethylamine were distilled over CaH_2.

All aqueous solutions were prepared with distilled water. All the chemicals used in this work that are not herein described, were commercially obtained in reagent grade (> 97 % purity), except some compounds mentioned in the respective section that were obtained from our laboratory collection.

4.3.2 Detection, isolation and purification of reaction products

Reaction mixtures were analyzed by TLC using ALUGRAM® SIL G/UV_{254} from Macherey-Nagel (Ref. 818133, silica gel 60), F_{254} from Merck (Ref. 105554, silica gel 60), and visualisation of TLC spots was effected using UV and phosphomolybdic acid solution. Flash chromatography was carried out on silica gel 60 M from Macherey-Nagel (Ref.815381). The eluents used are described in each experimental procedure. High Pressure Liquid Chromatography for the enantiomeric excess determination was carried out using a Dionex P680 pump equipped with a diode array detector and Chiral LUX column.

4.3.3 Reaction products characterization

NMR spectra were recorded in a Bruker AMX 400 or Ultrashield Bruker Avance II 300 or Bruker Avance II 400 using $CDCl_3$ or D_2O as solvent. All ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to $(CH_3)_4Si$ (external standard). All coupling constants are expressed in Hz. All isolated new products were identified using bidimensional NMR experiments when needed. The most frequently used experiments were COSY, DEPT and HMQC. For the cases where previously described products were obtained, ^1H and ^{13}C NMR spectra were recorded and compared with the chemical shifts described in the literature.

Melting points were determined in a Electrothermal Mod IA6304 capillary apparatus.

The water content was determined by a volumetric Karl–Fischer Titration using HYDRANAL-Tritant 2 reagent.

Chloride contents were measured on a chloride electrode instrument.

Microanalysis (C, H, N analyzer) of each synthesized ionic liquid was performed by the Laboratório de Análises at REQUIMTE, Portugal.

Ionic liquids viscosity was analyzed by using a controlled-stress rheometer (RS-300, Haake, Germany), in Instituto Piaget, Pragal.

4.4 Ionic Liquids Synthesis

[Aliquat®][Cl] was purchased from Aldrich. $[P_{6,6,6,14}][Cl]$ and $[P_{6,6,6,14}]$ [DCA] were kindly donated by CYTEC. $[C_{10}MIM][BF_4]$, $[C_{10}MIM][Cl]$, $[C_8MIM][Cl]$, $[BMIM][NTf_2]$, [Choline][OH] and $[C_2OHMIM][Cl]$ were kindly donated by Solchemar. $[C_{12}TMG][I]$ was kindly given by Carolina Marques.

Rheological studies

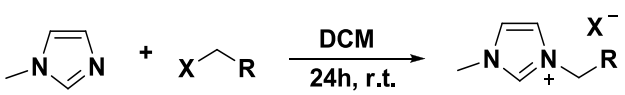
The viscosity of the ionic liquids was analyzed by using a controlled-stress rheometer (RS-300, Haake, Germany), (please see Attachments, section 6.1, page 223). Steady-state flow measurements were carried out using a cone-plate sensor C20/2ºTi. The torque amplitude was imposed by using a logarithmic ramp of shear stress, which was increased in 30 min intervals from 0.01 to 1000 Pa, to decrease the initial acceleration and the effects due to instrument inertia. The temperature of the samples were maintained at 20±0.5 ^{o}C by means of a circulating water bath (DC30, Haake, Germany), and they were measured with a thermocouple attached to the stationary element. The temperature dependence of the viscosity was also studied. The ionic liquids were heated from 20^{o} to 90^{o}C (2^{o}C min^{-1}) followed by cooling from 90^{o}C to 20^{o}, using a constant shear stress of 5 Pa. All the measurements were performed at least twice.

Potentiometric analysis

Chloride content was determined in a potentiometer Radiometer PHM 250, with a standard electrode Radiometer REF 251, and a chloride ion selective electrode Radiométer ISE 25 Cl. The analysis were made in ethanol solutions, and the chloride precursor was used as standard (example, for $[(di\text{-}h)_2DMG]$ [CSA] chloride analysis, $[(di\text{-}h)_2DMG][Cl]$ in methanol was used as standard solution).

4.4.1 Ionic Liquids

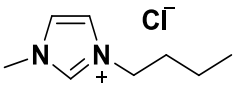
4.4.1.1 General procedure for the synthesis of alkyl imidazolium chloride ILs (Method A)[19]



Method A: Under argon atmosphere was added *N*-methylimidazole (1 equiv.) and the alkyl halide (1.2 equiv.) that was heated to 80°C overnight. In the end of the reaction two phases were obtained, being the upper layer the unreacted starting material. The two phases were separated, and the ionic liquid phase was washed with diethyl ether two times. The obtained

product was purified in a flash chromatography column with silica and activated carbon, with DCM as eluent. The product was left under vacuum (<1 mm Hg) at 80°C overnight.

4.4.1.1.1 Preparation of 1-Butyl-3-methyl imidazolium Chloride [BMIM][Cl]



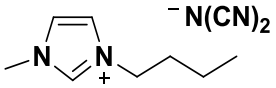
Following Method A (page 164): *N*-methylimidazole (50 mL, 0.63 mol) and 1-chlorobutane (92.8 mL, 0.89 mol) were stirred overnight at 65°C. The obtained product when washed with diethyl ether started to crystallize and 1-butyl-3-methyl imidazolium chloride was obtained as a hygroscopic white solid (100.4g, 95%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 10,39 (s, 1H), 7,59 (s, 1H), 7,43 (s, 1H), 4,22 (t, 2H, *J(H, H)*- 7,2 Hz), 4,01 (s, 3H), 1,79 (quint, 2H, *J(H, H)*- 7,5 Hz), 1,26 (sex, 2H, *J(H, H)*- 7,4 Hz), 0,84 (t, 3H, *J(H, H)*- 7,4 Hz).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 137.6; 123.6; 121.9; 49.6; 36.4; 32.0; 19.3; 13.2.

Product spectral data identical to previously reported.[282]

4.4.1.1.2 Preparation of 1-Butyl-3-methyl imidazolium dicyanamide [BMIM][DCA]



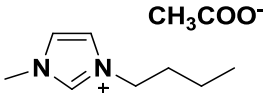
To a solution of [BMIM][Cl] (19.9 g, 0.11 mol) in dichloromethane (50 mL) was added $NaN(CN)_2$ (12.3 g, 0.14 mol) and the mixture was stirred at room temperature for 24 hours. The sodium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residual oil was then purified by passing through a column with silica and activated carbon, and the solvent removed under vacuum. The residue was stirred under vacuum (<1 mmHg) at 60°C overnight. 1-Butyl-3-methyl imidazolium dicyanamide was obtained as a yellow liquid (17.4g, 75%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 8.52 (s, 1H), 7.50 (s, 1H), 7.40 (s, 1H), 4.10 (t, 2H, *J(H,H)*= 6.8Hz), 3.80 (s, 3H), 1.70 (q, 2H, *J(H,H)*= 7.3Hz), 1.33 (sex, 2H, *J(H,H)*=7.3Hz), 0.90 (t, 3H, *J(H,H)*= 7.3Hz).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 135.9, 123.6, 122.3, 119.7, 49.4, 35.8, 31.5, 19.0, 12.9.

Product spectral data comparable to previously reported.[161]

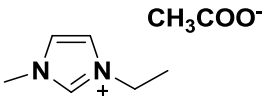
4.4.1.1.3 Preparation of 1-Butyl-3-methyl imidazolium acetate [BMIM][OAc]



To a solution of [BMIM][Cl] (1.0 g, 5.72 mmol) in a mixture EtOH/H_2O (1:1, 10 mL) was added CH_3COONa (0.930 g, 11,4 mmol) and the mixture stirred at room temperature for 24 hours. The solvents were removed by evaporation, and then was added dichloromethane to precipitate the sodium acetate in excess and the sodium chloride formed. The salts were removed by filtration and the organic phase evaporated under vacuum. The residual oil was then purified by passing through a column with silica and activated carbon, and the solvent removed under vacuum with dichloromethane as eluent. The residue was stirred under vacuum (<1 mmHg) at 60°C overnight. 1-Butyl-3-methyl imidazolium acetate was obtained as a yellow liquid (0.631 g, 60%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 9.03 (s, 1H), 7.30 (s, 1H), 7.16 (s, 1H), 4.85 (s, 3H), 3.80 (t, 2H, *J(H,H)=* 8.0 Hz), 3.57 (s, 3H), 1.35, (m, 2H), 0.81 (sex, *J(H,H)*=8.0 Hz), 0.39 (t, 3H, *J(H,H)=* 10Hz).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 176.4; 137.19; 123.44; 121.87; 49.13; 35.96; 31.70; 18.93; 12.99
Product spectral data identical to previously reported.[72, 283]

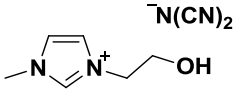
4.4.1.1.4 Preparation of 1-Ethyl-3-methyl imidazolium acetate [EMIM][OAc]



To a solution of [EMIM][HCOO] (1.0 g, 5.80 mmol) in a mixture EtOH/H_2O (1:1, 10 mL) was slowly added CH_3COOH (0.348 g, 11,6 mmol) and the mixture stirred at room temperature for 24 hours. The solvent mixture and CH_3COOH in excess were removed by evaporation. The residual oil was then purified by passing through a column with silica and activated carbon with dichloromethane as eluent, and the solvent removed under vacuum. The residue was stirred under vacuum (<1 mmHg) at 60°C overnight. 1-ethyl-3-methyl imidazolium acetate was obtained as a yellow liquid (0.80 g, 81%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 8.54 (s, 1H, NC*H*N), 7.32 (s, 1H, NC*H*CHN), 7.26 (s, 1H, NCHC*H*N), 4.68 (s, 3H, CH_3CO), 4.079 (q, 2H, *J(H,H)=* 10 Hz, CH_3CH_2N), 3.73 (s, 3H, NCH_3), 1.34 (t, 3H, *J(H,H)=* 10Hz, CH_3CH_2N).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 179.81; 135.48; 123.38; 121.80; 57.33; 44.69; 35.50; 16.78.
Product spectral data similar to previously reported.[284]

4.4.1.1.5 Preparation of 1-(2-hydroxyethyl)-3-methylimidazolium Dicyanamide [C_2OHMIM][DCA]

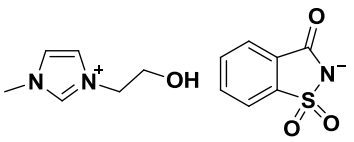


To a solution of [C_2OHMIM][Cl] (2.00 g, 12.3 mmol) in a mixture MeOH/acetone (0.5:2; 5 mL) was slowly added $NaN(CN)_2$ (1.53 g, 1.4 equiv.). The mixture stirred at room temperature for 24 hours. The sodium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residual oil was then purified by passing through a column with silica and activated carbon with DCM, and the solvent removed under vacuum. The residue was stirred under vacuum (<1 mmHg) at 60°C overnight. 1-(2-hydroxyethyl)-3-methylimidazolium dicyanamide was obtained as a yellow liquid (1.93 g, 82%).

1H-NMR δ (400 MHz, $CDCl_3$): 8.6 (s, 1H), 7.45 (s, 1H), 7.40 (s, 1H), 4.26 (t, *J(H, H)*- 4,76 Hz, 2H), 3.87 (m, 5H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 136.23; 124.04; 122.89; 120.49; 60.23; 51.98; 36.15.

4.4.1.1.6 Preparation of 1-(2-hydroxyethyl)-3-methylimidazolium Saccharine [C_2OHMIM][SAC]

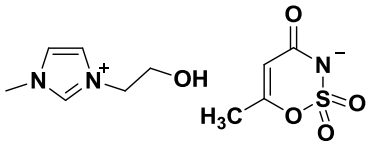


To a solution of [C_2OHMIM][Cl] (2.00 g, 12.3 mmol) in a mixture of MeOH/acetone (0.5:2; 5 mL) was slowly added sodium saccharin (3.47 g, 1.4 equiv.). The mixture was stirred at room temperature for 24 hours. The sodium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residual oil was then purified by passing through a column with silica and activated carbon with DCM, and the solvent removed under vacuum. The residue was stirred under vacuum (<1 mmHg) at 60°C overnight. 1-(2-hydroxyethyl)-3-methylimidazolium saccharin was obtained as a yellow liquid (2.55 g, 65%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 8.58 (s, 1H), 7.69, (m, 2H), 7.61 (s, 2H), 7.32 (s, 1H), 7.26 (s, 1H), 4.15 (t, *J(H, H)*- 4.7 Hz, 2H), 3.78 (t, *J(H, H)*- 4.8 Hz, 2H), 3.74 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 172.71; 142.31; 136.66; 134.20; 133.70; 132.77; 123.97; 122.80; 120.63; 60.14; 51.91; 36.08.

4.4.1.1.7 Preparation of 1-(2-hydroxyethyl)-3-methylimidazolium Acesulfame [C_2OHMIM][ACE]



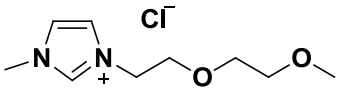
To a solution of [C_2OHMIM][Cl] (1.06 g, 6.5 mmol) in a mixture MeOH/acetone (0.5:2, 5 mL) was slowly added potassium acesulfame (1.81 g, 1.4 equiv.). The mixture stirred at room

temperature for 24 hours. The sodium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residual oil was then purified by passing through a column with silica and activated carbon with DCM, and the solvent removed under vacuum. The residue was stirred under vacuum (<1 mmHg) at 60°C overnight. 1-(2-hydroxyethyl)-3-methylimidazolium acesulfame was obtained as a yellow liquid (1.10 g, 58%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 8.67 (s, 1H), 7.43 (s, 1H), 7.38 (s, 1H), 5.58 (s, 1H), 4.24 (t, *J(H, H)*- 4.8 Hz, 2H), 3.85 (m, 5H), 2.03 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 172.54; 164.52; 136.79; 124.07; 122.91; 101.36; 60.22; 51.98; 36.16; 19.39.

4.4.1.1.8 Preparation of 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium Chloride [MOEOEMIM][Cl]



Following Method A (page 164): *N*-methylimidazole (50 mL, 0.63 mol) and 1-chloro-(2-(2-methoxyethoxy)ethane (98 mL, 0.95 mol) were stirred overnight at 90°C. The obtained product when washed with diethyl ether and 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium chloride was obtained as a yellow viscous liquid (104.0g, 75%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 10.03 (s, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 4.53 (m, 2H), 3.98 (s, 3H), 3.78 (t, *J(H, H)*- 4.5 Hz, 2H), 3.54 (m, 2H), 3.42 (m, 2H), 3.25 (s, 3H).

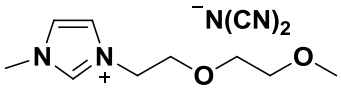
^{13}C-NMR δ (400 MHz, $CDCl_3$): 137.71; 123.19; 122.93; 71.46; 70.92; 70.15; 58.19; 49.52; 36.43.

Product spectral data identical to previously reported.[285]

4.4.1.2 General procedure for the synthesis of 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium with different anions [MOEOEMIM][Anion] (Method B)

To a solution of [MOEOEMIM][Cl] (1 equiv.) in dichloromethane was added NaX (1.4 equiv.) and the mixture was stirred at room temperature overnight. The sodium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residue was then purified by passing through a column with silica and activated carbon, and the solvent removed under vacuum. The IL was stirred under vacuum (<1 mmHg) at 60°C overnight.

4.4.1.2.1 Preparation of 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium Dicyanamide [MOEOEMIM][DCA]



Following Method B (page 168): [MOEOEMIM][Cl] (1g, 4.5 mmol) and $NaN(CN)_2$ (0.56g, 1.4 equiv.) were stirred overnight in dichloromethane and 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium dicyanamide was obtained as a yellow oil (1.05g, 92.4%).

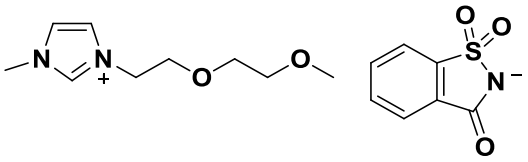
^{1}H-NMR δ (400 MHz, $CDCl_3$): 9.02 (s, 1H); 7.49 (s, 1H); 7.36 (s, 1H); 4.35 (t, 2H, *J(H,H)*=3.4 Hz); 3.93 (s, 3H); 3.79 (t, 2H, *J(H,H)*=3.4 Hz); 3.57 (t, 2H, *J(H,H)*=1.7 Hz); 3.46 (t, 2H, *J(H,H)*=1.7 Hz); 3.28 (3H, s).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 136.50; 123.23; 122.99; 119.60; 71.28; 70.03; 68.24; 58.65; 49.66; 36.28.

Elemental analysis calc. (%) for $C_{11}H_{17}N_5O_2 \cdot 0.5\ H_2O$: C 50.76; H 6.97; N 26.91. Found: C 50.74, H 7.04; N 28.13.

Product spectral data identical to previously reported.[170]

4.4.1.2.2 Preparation of 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium Saccharine [MOEOEMIM][SAC]



Following Method B (page 168): [MOEOEMIM][Cl] (1g, 4.5 mmol) and sodium saccharin (1.30 g, 1.4 equiv.) were stirred overnight in dichloromethane and 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium saccharine was obtained as a yellow oil (1.52g, 91.2%).

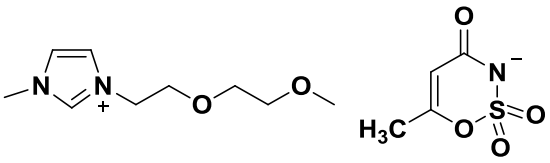
^{1}H-NMR δ (400 MHz, $CDCl_3$): 9.57 (s, 1H); 7.75(m, 1H); 7.69 (m, 1H); 7.54 (m, 2H); 7.46 (s, 1H); 7.26 (s, 1H); 4.44 (t, 2H, *J(H,H)*=4.5 Hz); 3.95 (s, 3H); 3.78 (t, 2H, *J(H,H)*=4.5 Hz); 3.55 (t, 2H, *J(H,H)*=3.3 Hz); 3.42 (t, 2H, *J(H,H)*=3.3 Hz); 3.26 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 169.47; 144.02; 137.62; 133.84; 132.13; 131.67; 123.29; 123.11; 122.74; 119.68; 71.74; 70.41; 68.80; 58.72; 49.53; 36.31.

Elemental analysis calc. (%) for $C_{16}H_{21}N_3O_5S \cdot 1.5\ H_2O$: C 48.72; H 6.13; N 10.65; S 8.13. Found: C 48.67, H 6.21; N 10.62; S 8.02.

Product spectral data identical to previously reported.[170]

4.4.1.2.3 Preparation of 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium Acesulfame [MOEOEMIM][ACES]



Following Method B (page 168): was obtained from [MOEOEMIM][Cl] (1 g, 4.5 mmol) and potassium acesulfame (1.28 g, 1.4 equiv.) were stirred overnight dichloromethane and 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium acesulfame was obtained as a yellow oil (1.453 g, 92.5%).

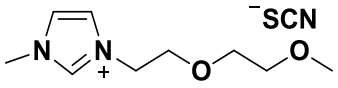
^{1}H-NMR δ (400 MHz, $CDCl_3$): 9.39 (s, 1H); 7.47 (s, 1H); 7.29 (s, 1H); 5.46 (s, 1H); 4.41 (t, 2H, *J(H,H)*=4.5 Hz); 3.93 (s, 3H); 3.79 (t, 2H, *J(H,H)*=4.5 Hz); 3.58 (m, 2H); 3.46 (m, 2H); 3.30 (s, 3H); 1.99 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 170.42; 161.98; 137.42; 123.16; 122.85; 101.39; 71.84; 70.43; 68.78; 58.77; 49.55; 36.29; 19.86.

Elemental analysis calc. (%) for $C_{13}H_{21}N_3O_6S{\cdot}0.1\ H_2O$: C 44.71; H 6.12; N 12.03; S 9.18. Found: C 44.19, H 6.31; N 12.29; S 9.31.

Product spectral data identical to previously reported.[170]

4.4.1.2.4 Preparation of 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium Thiocyanate [MOEOEMIM][SCN]



Following Method B (page 168): [MOEOEMIM][Cl] (1 g, 4.5 mmol) and KSCN (0.68 g, 1.4 equiv.) were stirred overnight in dichloromethane and 1-(2-(2-methoxyethoxy)-ethyl)-3-methylimidazolium thiocyanate was obtained as a yellow oil (0.99 g, 90.12%).

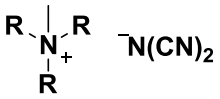
^{1}H-NMR δ (400 MHz, $CDCl_3$): 9.14 (s, 1H); 7.53 (s, 1H); 7.43 (s, 1H); 4.41 (t, 2H, *J(H,H)*=3.3 Hz); 3.97 (s, 3H); 3.80 (t, 2H, *J(H,H)*=3.3 Hz); 3.56 (t, 2H, *J(H,H)*=3.1 Hz); 3.43 (t, 2H, *J(H,H)*=3.1 Hz); 3.25 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 136.65; 131.24; 123.13; 123.02; 71.27; 69.97; 68.45; 58.62; 49.64; 36.36.

Elemental analysis calc. (%) for $C_{10}H_{17}N_3O_2S{\cdot}0.4\ H_2O$: C 47.94; H 7.16; N 16.77; S 12.80. Found: C 47.47, H 6.98; N 17.16; S 12.74

Product spectral data identical to previously reported.[170]

4.4.1.2.5 Preparation of Aliquat® dicyanamide [Aliquat®][DCA]



R= *n*-octyl
***n*-decyl**

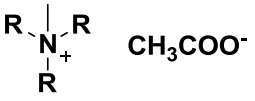
To a solution of [Aliquat®][Cl] (2:1 mixture of methyl trioctyl- and methyl tridecylammonium chloride, MW 432g/mol) (2 g, 4.6 mmol) in dichloromethane was added $NaN(CN)_2$ (0.57 g, 6.4 mmol) and the mixture stirred at room temperature overnight. The sodium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residue was then purified by passing through a column with silica and activated carbon with dichloromethane as eluent, and the solvent removed under vacuum. The IL was stirred under vacuum (<1 mmHg) at 60°C overnight. Aliquat® dicyanamide was obtained as colourless oil (1.78 g, 77%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 0.86 (t, 9H, *J(H,H)*=5.2Hz, C*H*3), 1.25-1.35 (m, 42H, (C*H*2)7-CH3), 1.68 (br s, 6H, C*H*2), 3.12 (s, 3H), 3.27 (m, 6H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 14.10; 22.20; 22.77; 26.31; 26.45; 29.10; 29.19; 29.51; 29.58; 29.70; 29.80; 29.96; 31.90; 32.08; 47.79; 61.57; 119.73.

Product spectral data identical to previously reported.[154]

4.4.1.2.6 Preparation of Aliquat® acetate [Aliquat®][OAc]



R= *n*-octyl
***n*-decyl**

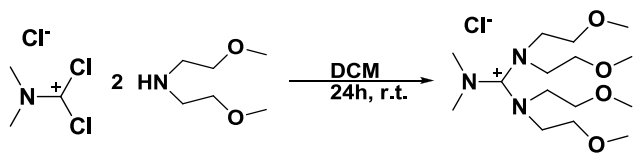
A solution of [Aliquat®][Cl] (2:1 mixture of methyl trioctyl- and methyl tridecylammonium chloride, MW 432g/mol) (2 g, 4.6 mmol) in methanol (10 mL) was passed through a column with Amberlite IRA-400 (OH) resin. A solution of acetic acid (0.331 g, 5.52 mmol) in methanol was slowly added to [Aliquat®][OH] obtained from the column and the mixture stirred at room temperature for 30 minutes. The solvent and the residual acetic acid were removed under vacuum. The IL was stirred under vacuum (<1 mmHg) at 60°C overnight. Aliquat® acetate was obtained as colourless oil (2.2 g, 97%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.62 (m, 2H), 3.12 (s, 3H), 2.01 (s, 3H), 1.63 (br s, 1.63), 1.32 (m, nCH_2), 0.86 (m, 9H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 175.83; 61.57; 48.91; 31.82; 31.62; 29.40; 29.35; 29.09; 29.00; 26.27; 25.75; 22.63; 22.56; 22.23; 22.11; 14.07; 14.03.

Product spectral data identical to previously reported.[286]

4.4.1.2.7 Preparation of N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium Chloride [$(C_3O)_4$DMG][Cl]



To a suspension of *N*,*N*-dimethylphosgeniminium chloride (2.0 g; 12 mmol) in anhydrous dichloromethane (20 mL) at 0 °C (ice bath) and argon atmosphere, was added drop wise a mixture of *bis*-(2-methoxyethyl)amine (3.81 mL, 2.1 equiv.) and triethylamine (8.8 mL, 2.2 equiv.) in anhydrous dichloromethane (30 mL). After 30 min at 0 °C the reaction was stirred at room temperature for 24 h. The solvent was removed under vacuum and an aqueous solution of NaOH (2 M; 20 mL) was added. The mixture was washed with diethyl ether (3x25 mL). The water was removed under vacuum, the residue extracted with dichloromethane (50 mL), dried ($MgSO_4$), the solvent evaporated and the product left under vacuum (<1 mm Hg) at 80°C overnight. N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium chloride was obtained as a brown liquid with 92.5 % yield.

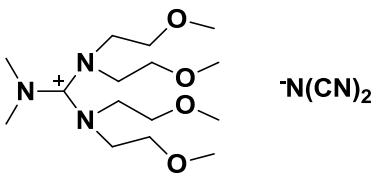
^{1}H-NMR δ ($CDCl_3$, 400 MHz): 3.43-3.1 (m, 16 H); 3.03 (s, 6H); 3.00 (s, 6 H); 2.77 (s, 6H).

^{13}C-NMR δ (100 MHz, $CDCl_3$): 165.04; 68.59; 58.53; 58.41; 49.16; 48.44; 40.11.

Elemental analysis calc. (%) for $C_{15}H_{34}ClN_3O_4 \cdot 1.4\ H_2O$: C 47.27, H 9.73, N 11.03. Found: C 47.27, H 10.07, N 11.16.

Product spectral data identical to previously reported.[170]

4.4.1.2.8 Preparation of N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium dicyanamide [$(C_3O)_4$DMG][DCA]

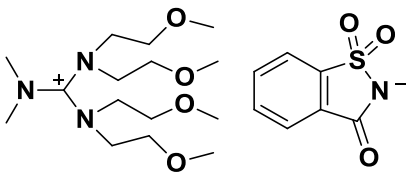


To a solution of $[(C_3O)_4DMG][Cl]$ (1g, 2.8 mmol) in dichloromethane (10 mL) was added $NaN(CN)_2$ (0.348 g, 1.4 equiv.) and the mixture stirred at room temperature for 24 hours. The sodium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residual oil was then purified by passing through a column with silica and activated carbon, and the solvent removed under vacuum. The residue was stirred under vacuum (<1 mmHg) at 60ºC overnight. N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium dicyanamide was obtained as brown oil (1.02 g, 92.5%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.60-3.33 (m, 16H); 3.29 (s, 6H); 3.27 (s, 6 H); 2.98 (s, 6H).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 165.27; 119.89; 68.64; 68.60; 58.75; 58.62; 49.39; 48.61; 40.10
Elemental analysis calc. (%) for $C_{17}H_{34}N_6O_4$: C 52.83, H 8.87, N 21.74. Found: C 52.89, H 8.96, N 21.99.

Product spectral data identical to previously reported.[170]

4.4.1.2.9 Preparation of N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium saccharine [$(C_3O)_4$DMG][SAC]

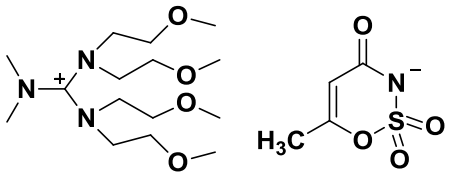


To a solution of $[(C_3O)_4DMG][Cl]$ (1g, 2.8 mmol) in dichloromethane (10 mL) was added sodium saccharin (0.80 g, 1.4 equiv.) and the mixture stirred at room temperature for 24 hours. The sodium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residual oil was then purified by passing through a column with silica and activated carbon, and the solvent removed under vacuum. The residue was stirred under vacuum (<1 mmHg) at 60°C overnight. N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium saccharine was obtained as a brown oil (0.85 g, 60.5%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 7.80 (m, 1H); 7.74 (m, 1H); 7.51 (m, 2H); 3.66-3.45 (m, 16H); 3.34 (s, 6H); 3.28 (s, 6 H); 3.07 (s, 6H).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 165.33; 145.25; 135.44; 131.41; 130.69; 123.09; 119.46; 69.05; 58.75; 58.58; 49.55; 48.75; 40.28.
Elemental analysis calc. (%) for $C_{22}H_{38}N_4O_7S{\cdot}0.7\ H_2O$: C 51.28, H 7.71, N 10.87, S 6.22. Found: C 51.76, H 7.79, N 10.95, S 5.57.

Product spectral data identical to previously reported.[170]

4.4.1.2.10 Preparation of N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium Acesulfamate [$(C_3O)_4$DMG][ACES]



To a solution of [$(C_3O)_4$DMG][Cl] (1g, 2.8 mmol) in dichloromethane (10 mL) was added potassium acesulfame (0.788g, 1.4 equiv.) and the mixture stirred at room temperature for 24 hours. The potassium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residual oil was then purified by passing through a column with silica and activated carbon, and the solvent removed under vacuum. The residue was stirred under vacuum (<1 mmHg) at 60°C overnight. N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium acesulfamate was obtained as brown oil (1.298 g, 96.1%).

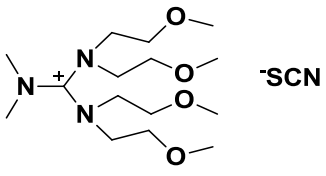
^{1}NMR δ (400 MHz, $CDCl_3$): 5.4 (s, 1H); 3.62-3.32 (m, 16H); 3.29 (s, 6H); 3.27 (s, 6 H); 3.00 (s, 6H); 1.96 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 169.54; 165.30; 160.19; 102.40; 68.84; 58.71; 58.56; 49.43; 48.63; 40.16; 19.90.

Elemental analysis calc. (%) for $C_{19}H_{38}N_4O_8S$: C 47.29, H 7.94, N 11.61, S 6.64. Found: C 47.37, H 8.37, N 11.52, S 6.12.

Product spectral data identical to previously reported.[170]

4.4.1.2.11 Preparation of N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium Thiocyanate [$(C_3O)_4$DMG][SCN]



To a solution of [$(C_3O)_4$DMG][Cl] (1g, 2.8 mmol) in dichloromethane (10 mL) was added KSCN (0.38 g, 1.4 equiv.) and the mixture stirred at room temperature for 24 hours. The potassium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residual oil was then purified by passing through a column with silica and activated carbon, and the solvent removed under vacuum. The residue was stirred under vacuum (<1 mmHg) at 60ºC

overnight. N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium thiocyanate was obtained as a brown oil (0.46 g, 43.7%).

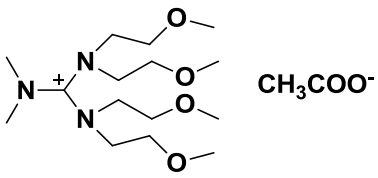
^{1}NMR δ (400 MHz, $CDCl_3$): 3.60-3.37 (m, 16H); 3.25 (s, 6H); 3.22 (s, 6 H); 3.02 (s, 6H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 165.27; 130.67; 68.77; 58.69; 58.56; 49.42; 48.63; 40.18.

Elemental analysis calc. (%) for $C_{16}H_{34}N_4O_4S \cdot 0.7\ H_2O$: C 49.13, H 9.12, N 14.32, S 8.20. Found: C 49.47, H 9.23, N 14.56, S 7.73.

Product spectral data identical to previously reported.[170]

4.4.1.2.12 Preparation of N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium Acetate [$(C_3O)_4$DMG][OAc]



A solution of [$(C_3O)_4$DMG][Cl] (1g, 2.8 mmol) in methanol (10 mL) was passed through a column with Amberlite IRA-400 (OH) resin. Acetic acid (1.1 equiv.) in methanol was slowly added to [$(C_3O)_4$DMG][OH] obtained from the column and the mixture stirred at room temperature for 30 minutes. The solvent was removed under vacuum. The residual acetic acid was removed by stirring under vacuum (<1 mmHg) at 60°C overnight. N,N,N',N'-Tetra-(2-methoxyethyl)-N,N-dimethylguanidinium acetate was obtained as yellow oil (0.988 g, 93.0%).

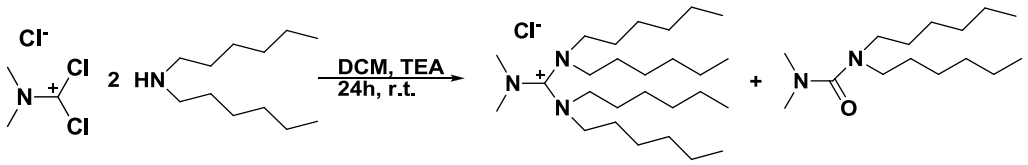
^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.57-3.35 (m, 16H); 3.24 (s, 6H); 3.21 (s, 6 H); 2.99 (s, 6H); 1.96 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 175.25; 165.21; 68.78; 58.68; 58.54; 49.40; 48.63; 40.24; 23.00.

Elemental analysis calc. (%) for $C_{17}H_{37}N_3O_6 \cdot 2.5\ H_2O$: C 48.10, H 9.97, N 9.90. Found: C 48.44, H 10.24, N 10.24.

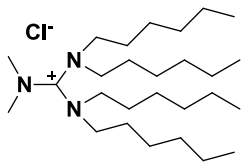
Product spectral data identical to previously reported.[170]

4.4.1.2.13 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium chloride [(di-h)$_2$DMG][Cl]



To a suspension of *N*,*N*-dimethylphosgeniminium chloride (14.4 g; 87 mmol) in anhydrous dichloromethane (20 mL) at 0 °C (ice bath) and argon atmosphere, was added drop wise a mixture of di-*n*-hexylamine (44.1 mL, 186 mmol) and triethylamine (28.2 mL, 195 mmol) in anhydrous dichloromethane (50 mL). After 30 min at 0 °C the reaction was stirred at room temperature for 24 h. The organic phase was washed with aqueous solution of 10% HCl, and then the solvent was evaporated, and the residue was dissolved in diethyl ether and washed with water. The organic phase was dried ($MgSO_4$), the solvent evaporated. The residual oil was then purified by passing through a column with silica and activated carbon with hexane/ethyl acetate (1:1), to separate the product from the urea derivate formed. The solvent was removed under vacuum. The product was left under vacuum (<1 mm Hg) at 80°C overnight. *N,N,N'N'*-tetrahexyl-*N,N*-dimethylguanidinium chloride was obtained as a brown liquid with 80 % yield.

Characterization of **N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium chloride [(di-*h*)$_2$DMG][Cl]**

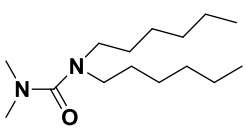


^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.14 (br s, 6H), 3.04 (s, 6H), 2.92 (br s, 2H), 1.6 (br s, 4H), 1.29 (br s, 4H), 1.72 (m, 24H), 0.75 (m, 12H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 163.12; 49.79; 49.23; 47.91; 40.61; 31.18; 31.05; 27.63; 27.26; 26.28; 26.19; 25.51; 22.27; 13.70; 13.64.

Product spectral data similar to previously reported. [50]

Characterization of **1,1-dihexyl-3,3-dimethylurea**

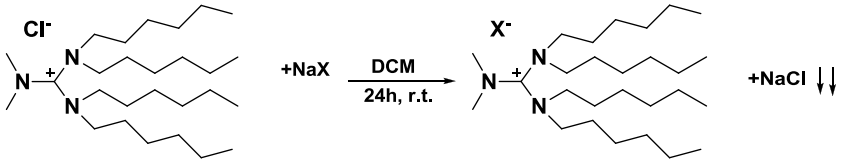


^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.09 (t, 4H, *J(H,H)*= 6Hz), 2.75 (s, 6H), 1.48 (br s, 4H), 1.27 (br s12H), 0.86 (t, 6H, J(H,H)= 3Hz).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 165.53; 48.00; 38.63; 31.55; 27.92; 26.60; 22.56; 13.97.

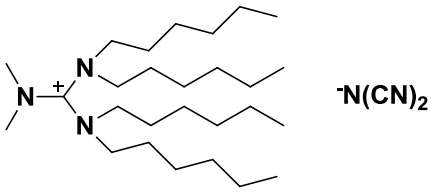
Product spectral data identical to previously reported..[287]

4.4.1.3 General procedure for the synthesis of N,N,N'N'-*tetrahexyl*-N,N-*dimethylguanidinium with different anions [(di-h)$_2$DMG][Anion] (Method C)*



To a solution of [(di-h)$_2$DMG][Cl] (1 equiv.) in dichloromethane was added NaX (1.4 equiv.) and the mixture stirred at room temperature overnight. The sodium chloride salt was removed by filtration and the organic phase evaporated under vacuum. The residue was then purified by passing through a column with silica and activated carbon, with dichloromethane as eluent. The solvent was removed under vacuum, and the IL stirred under vacuum (<1 mmHg) at 60°C overnight.

4.4.1.3.1 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium dicyanamide [(di-h)$_2$DMG][DCA]



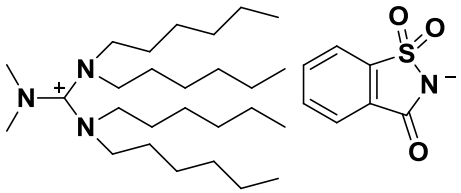
Following Method C (page 177): [(di-h)$_2$DMG][Cl] (1g, 2.1 mmol) and $NaN(CN)_2$ (0.28 g, 2.94 mmol) were stirred overnight in dichloromethane and N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium dicyanamide was obtained as a yellow oil (0.83 g, 81%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.19-2.97 (m, 8H), 1.67-1.24 (m, 44H), 0.83 (s, 6H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 163.37; 119.79; 49.42; 40.46; 31.19; 27.76; 26.51; 22.35; 13.78.

Product spectral data similar to previously reported.[154]

4.4.1.3.2 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium saccharine [(di-h)$_2$DMG][SAC]



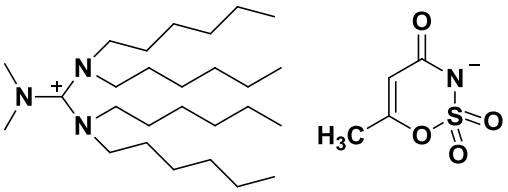
Following Method C page 177: [(di-h)$_2$DMG][Cl] (1g, 2.1 mmol) and sodium saccharin (0.64 g, 2.94 mmol) were stirred overnight in dichloromethane of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium saccharine was obtained as a yellow oil (1.02 g, 84%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 7.76 (s, 1H), 7.68 (s, 1H), 7.50 (m, 2H), 3.18-3.05 (m, 8H), 1.82-1.19 (m, 44H), 0.82 (s, 6H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 169.31; 163.43; 144.69; 131.58, 131.03; 123.20; 119.48; 49.27; 40.74; 31.08; 27.87; 26.45; 22.49; 13.80.

Product spectral data identical to previously reported.[154]

4.4.1.3.3 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium acesulfame [(di-h)$_2$DMG][ACES]



Following Method C page 177: [(di-h)$_2$DMG][Cl] (1g, 2.1 mmol) and potassium acesulfame (0.61g, 2.94 mmol) were stirred overnight in dichloromethane and N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium acesulfame was obtained as a yellow oil (0.83 g, 65.2%).

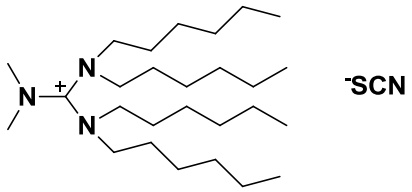
^{1}H-NMR δ (400 MHz, $CDCl_3$): 5.49 (s, 1H); 3.17–3.03 (m, 8H); 2.99 (s, 6H); 1.99 (s, 3H); 1.72–1.22 (m, 32H); 0.83 (m, 12H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 170.49; 163.32; 101.11; 49.81; 49.23; 40.55; 31.19; 31.08; 27.64; 27.29; 26.28; 25.19; 22.48; 19.86; 13.89.

Elemental analysis calc. (%) for $C_{31}H_{62}N_4O_4S{\cdot}0.5\ H_2O$: C 62.48; H 10.66; N 9.40; S, 5.38. Found: C 62.50, H 10.93; N 9.27, S 5.30.

Product spectral data identical to previously reported.[170]

4.4.1.3.4 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium thiocyanate [(di-h)$_2$DMG][SCN]



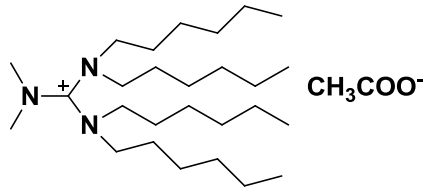
Following Method C page 177: [(di-h)$_2$DMG][Cl] (1 g, 2.1 mmol) and KSCN (0.31 g, 2.94 mmol) were stirred overnight in dichloromethane and N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium thiocyanate was obtained as a yellow oil (0.82 g, 82%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3,05-2,85 (m, 8H), 1,53-1.06 (m, 44H), 0.64 (s, 6H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 163.18; 131.29; 49.23; 40.36; 30.64; 27.26; 25.50; 22.19; 13.65.

Product spectral data identical to previously reported.[154]

4.4.1.3.5 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium Acetate [(di-h)$_2$DMG][OAc]



A solution of [(di-*h*)$_2$DMG][Cl] (1 g, 2.1 mmol) in methanol (10 mL) was passed through a column with Amberlite IRA-400 (OH) resin. A solution of acetic acid (1.1 equiv.) in methanol was slowly added to [(di-*h*)$_2$DMG][OH] extracted from the column and the mixture stirred at room temperature for 30 minutes. The solvent was removed under vacuum. The residual acetic acid was removed by stirring under vacuum (<1 mmHg) at 60°C overnight. N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium acetate was obtained as yellow oil (0.99 g, 98.2%).

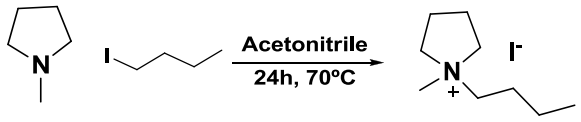
^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.17–3.05 (m, 8H); 2.86 (s, 6H); 2.03 (s, 3H); 1.68–1.29 (m, 32H); 0.90 (m, 12H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 176.00; 163.41; 49.91; 49.34; 47.5; 40.62; 31.31; 31.23; 27.79; 27.44; 26.56; 26.44; 22.82; 22.49; 13.91.

Elemental analysis calc. (%) for $C_{29}H_{62}N_3O_2 \cdot 2.5\ H_2O$: C 65.74, H 12.75, N 7.93. Found: C 65.20, H 12.70; N 7.60.

Product spectral data identical to previously reported.[170]

4.4.1.3.6 Preparation of 1-n-Butyl-1-methyl Pyrrolidinium Iodide [BMPyr][I][288]



To a suspension of 1-methyl pyrrolidine (11 mL, 0.1 mol) in acetonitrile (25 mL) under atmosphere of argon, was added drop wise 1-iodobutane (13.5 mL, 0.1 mol). The mixture was stirred at 70°C overnight. The solvent was removed by evaporation, and the resulting brown oil was washed with diethyl ether. After evaporation of the solvent, a yellow solid was obtained, that was dissolved in dichloromethane and 5 g of sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$, thiosulfate anion reacts stoichiometrically with iodine, reducing it to iodide as it is oxidized to tetrathionate). A precipitate was formed, and filtered. After solvent evaporation, 1-Butyl-1-methyl pyrrolidinium iodide was obtained as white solid crystals, with 87.3% yield (23.5 g).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.76 (m, 4H), 3.60 (m, 2H), 3.23 (s, 3H), 2.27 (m, 4H), 1.73 (m, 2H), 1.41 (sex, *J(H, H)*=7,4 Hz, 2H), 0.95 (t, *J(H, H)*=7.3 Hz, 3H).

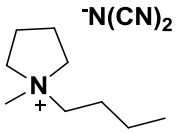
^{13}C-NMR δ (400 MHz, $CDCl_3$): 64.66; 64.12; 49.13; 25.83; 21.61; 19.56; 13.62.

Product spectral data identical to previously reported.[289]

4.4.1.4 General procedure for the synthesis of 1-n-Butyl-1-methyl Pyrrolidinium with different anions [BMPyr][Anion] (Method D)

To a solution of [BMPyr][I] (1 equiv.) in dichloromethane was added NaX (1.5 equiv.) and the mixture stirred at room temperature overnight. The sodium iodide salt was removed by filtration and the organic phase evaporated under vacuum. The residue was then purified by passing through a column with silica and activated carbon, with dichloromethane as eluent. The solvent was removed under vacuum, and the IL stirred under vacuum (<1 mmHg) at 60°C overnight.

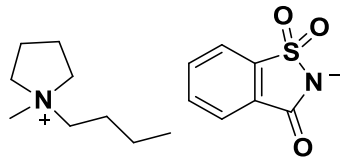
4.4.1.4.1 Preparation of 1-n-Butyl-1-methyl Pyrrolidinium Dicyanamide [BMPyr][DCA]



Following Method D (page 180): [BMPyr][I] (1.14 g, 4.2 mmol) and $NaN(CN)_2$ (0.5 g, 6.3 mmol) were stirred overnight in dichloromethane and 1-*n*-butyl-1-methyl pyrrolidinium dicyanamide was obtained as a yellow solid (0.84 g, 95%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.70 (m, 4H), 3.65 (m, 2H), 3.18 (s, 3H), 2,20 (m, 4H), 1.80 (m, 2H), 1.37 (sex, *J(H, H)*=7.4 Hz, 2H), 1.01 (t, *J(H, H)*=7.3 Hz, 3H).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 120.09; 63.66; 64.22; 49.50; 26.89; 22.60; 19.35; 13.43**.**
Product spectral data identical to previously reported.[289]

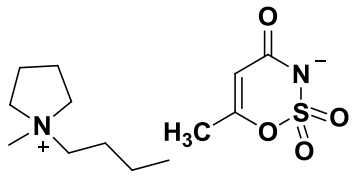
4.4.1.4.2 Preparation of1-n-Butyl-1-methyl Pyrrolidinium Saccharine [BMPyr][SAC]



Following Method D (page 180): [BMPyr][I] (1.04 g, 3.8 mmol) and sodium saccharin (1.31 g, 5.7 mmol) were stirred overnight in dichloromethane of 1-*n*-butyl-1-methyl pyrrolidinium saccharine was obtained as a yellow solid (0.93 g, 75%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 7.64 (m, 1H), 7.58 (m, 1H), 7.47 (m, 2H), 3,68 (t, 4H, J*(H, H)*=4Hz), 3.51 (m, 2H); 3.13 (s, 3H), 2.18 (br s, 4H), 1.65 (m, 2H), 1.33 (sex, 2H, *J(H, H)*= 8Hz), 0.86 (t, 3H, J*(H, H)* =8Hz).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 169.55; 144.4; 134.39; 132.07; 131.50; 123.11; 119.44; 65.67; 64.66; 49.12; 25.86; 21.64; 19.59; 13.69.
Product spectral data identical to previously reported. [290]

4.4.1.4.3 Preparation of 1-n-Butyl-1-methyl Pyrrolidinium Acesulfame [BMPyr][ACE]



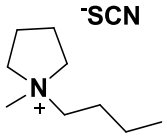
Following Method D (page 180): [BMPyr][I] (1g, 3.7 mmol) and potassium acesulfame (1.16g, 5.55 mmol) were stirred overnight in dichloromethane and 1-*n*-butyl-1-methyl pyrrolidinium acesulfame was obtained as a yellow solid (0.76 g, 70%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 5.29 (s, 1H), 3.64 (m, 2H), 3.49 (m, 2H); 3.11 (s, 3H), 2.17 (m, 4H), 1.87 (s, 3H), 1.65 (m, 2H), 1.30 (sex, 2H, J*(H, H)*= 8.2Hz), 0.85 (t, 3H, J*(H, H)* =8.3Hz).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 169.56; 160.97; 101.94; 64.65; 64.11; 49.12; 25.84; 21.63; 19.57; 13.69.

Product spectral data identical to previously reported. [290]

4.4.1.4.4 Preparation of 1-n-Butyl-1-methyl Pyrrolidinium thiocyanate [BMPyr][SCN]

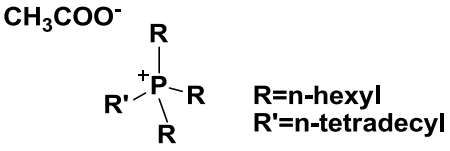


Following Method D (page 180): [BMPyr][I] (1g, 3.7 mmol) and KSCN (0.82 g, 5.55 mmol) were stirred overnight in dichloromethane and 1-*n*-butyl-1-methyl pyrrolidinium thiocyanate was obtained as a yellow solid (0.70 g, 95%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.73 (m, 4H), 3.65 (m, 2H), 3.20 (s, 3H), 2.28 (m, 4H), 1.73 (m, 2H), 1.44 (sex, *J(H, H)*=8,0 Hz, 2H), 1.0 (t, *J(H, H)* = 7.3 Hz, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 130.91, 64.67; 64.13; 49.13; 25.93; 21.71; 19.57; 13.63.

4.4.1.4.5 Preparation of Trihexyl(tetradecyl)phosphonium acetate [$P_{6,6,6,14}$][OAc]



A solution of [$P_{6,6,6,14}$][Cl] (2 g, 3.8 mmol) in methanol (10 mL) was passed through a column with Amberlite IRA-400 (OH) resin. A solution of acetic acid (0.277 g, 4.62 mmol) in methanol was slowly added to [$P_{6,6,6,14}$][OH] obtained from the column and the mixture stirred at room temperature for 30 minutes. The solvent and the residual acetic acid were removed under vacuum. The IL was stirred under vacuum (<1 mmHg) at 60°C overnight. Trihexyl(tetradecyl)phosphonium acetate was obtained as colourless oil (1.99 g, 96.6 %).

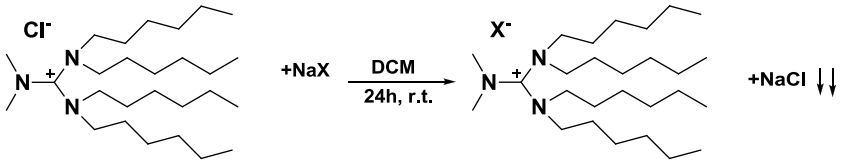
^{1}H-NMR δ (400 MHz, $CDCl_3$): 2.26 (m, 8H), 2.05 (s, 3H), 1.52 (m, 16H), 1.33 (m, 16H), 1.26 (m, 16H), 0.89 (m, 12H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 177.64; 31.91; 31.02; 30.48; 30.33; 29.67; 29.64; 29.62; 29.53; 29.35; 29.31; 28.92; 22.68; 22.34; 22.14; 21.69; 21.65; 19.12; 18.65; 14.11; 13.92.

Product spectral data similar to previously reported. [291]

4.4.2 Chiral Ionic Liquids

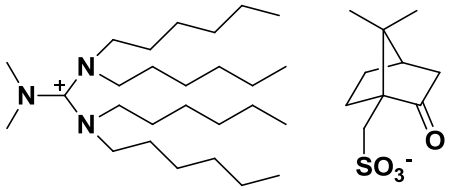
4.4.2.1 General procedure for the synthesis of different cations with different chiral anions [Cation][Chiral Anion] (Method E and F)



Method E: The chiral acid (3 equivalents relative to the IL chloride) was dissolved in a aqueous solution of NaOH (1 equivalent relatively to the chiral acid) and left stirring for 1 hour, to form the respective sodium salt. After that was added a solution of [Cation][Cl] in methanol, and the mixture was stirred at 30°C overnight. The water and methanol were evaporated, and dichloromethane was added to dissolve the IL, and precipitate the excess salts present, that were removed by filtration. The organic phase was evaporated under vacuum. The residue was then purified by passing through a column with silica and activated carbon, with dichloromethane as eluent. The solvent was removed under vacuum, and the IL stirred under vacuum (<1 mmHg) at 60°C overnight.

Method F: A solution of [Cation][Cl] (1 equivalent) in methanol was passed through a column with Amberlite IRA-400 (OH) resin. A solution of chiral acid (1.1 equiv.) in methanol was slowly added to [Cation][OH] extracted from the column and the mixture stirred at room temperature for 30 minutes. The solvent was removed under vacuum. The residue was then purified by passing through a column with silica and activated carbon, with dichloromethane as eluent. The solvent was removed under vacuum, and the IL stirred under vacuum (<1 mmHg) at 60°C overnight.

4.4.2.1.1 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium (1S)-(+)-Camphor-10-sulfonate [(di-h)$_2$DMG][(S)-CSA]



Following Method E (page 183): (1S)-(+)-Camphor-10-sulfononic acid (1.6 g, 3 equiv.) was dissolved in a aqueous solution of NaOH (252 mg, 3 equiv.) were stirred for 1 hour. [(di-h)$_2$DMG][Cl] (1 g, 2.1 mmol) in methanol was added and the mixture was stirred overnight.

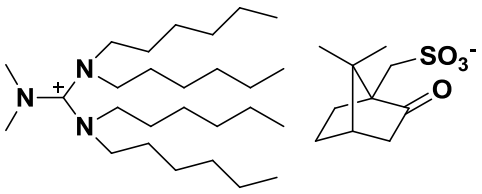
N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium (1S)-(+)-Camphor-10-sulfonate was obtained as a yellow oil (0.825 g, 60%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.30 (d, 1H, *J(H, H)* =9Hz), 3.03 (s, 6H), 2.74 (d, 1H, *J(H, H)* = 10Hz), 2.26 (d, 1H, *J(H, H)* =15Hz), 1.93 (m, 1H), 1.89 (m, 1H), 1.85 (m, 1H), 1.66 (m, 1H, 4H), 1.55 (m, 1H), 1.34 (m, 1H), 1.21 (br s, 28H), 1.12 (s, 3H), 0.80 (t, 12H, *J(H, H)* =6 Hz), 0.76 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 218.87; 163.36; 58.81; 49.75; 49.26; 48.17; 46.98; 43.03; 42.65; 40.81; 31.45; 31.26; 27.72; 27.39; 26.95; 26.52; 26.39; 24.60; 22.47; 22.44; 19.82; 18.33; 13.91; 13.85.

Product spectral data similar to previously reported.[57]

4.4.2.1.2 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium (1R)-(−)-Camphor-10-sulfonate [(di-h)$_2$DMG][(R)-CSA]

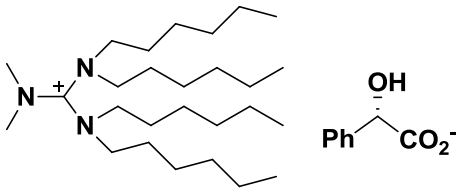


Following Method E (page 183): (1R)-(+)-Camphor-10-sulfononic acid (1.6 g, 3 equiv.) was dissolved in a aqueous solution of NaOH (252 mg, 3 equiv.) were stirred for 1 hour. [(di-h)$_2$DMG][Cl] (1 g, 2.1 mmol) in methanol was added and the mixture was stirred overnight. N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium (1R)-(+)-Camphor-10-sulfonate was obtained as a yellow oil (1.0 g, 73%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.56 (d, 1H, *J(H, H)* =9.3Hz), 3.32 (s, 1H), 3.12 (s, 1H), 2.96 (s, 6H), 2.70 (s, 1H), 2.56 (d, 1H, *J(H, H)* =10Hz), 2.21 (d, 1H, *J(H, H)* =15Hz), 1.88 (m, 1H), 1.86 (m, 1H), 1.79 (m, 1H), 1.73 (m, 1H), 1.62 (m, 1H), 1.48 (m, 1H), 1.30-1.15 (m, 32H), 0.95 (s, 3H), 0.75 (t, 12H, *J(H, H)* =6 Hz), 0.76 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 218.50; 163.19; 58.60; 49.67; 49.12; 48.00; 46.82; 42.85; 42.48; 40.57; 31.28; 31.12; 27.59; 27.24; 26.82; 26.35; 26.24; 24.44; 22.31; 22.28; 19.79; 19.65; 18.16; 13.76; 13.71.

4.4.2.1.3 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium (S)-Mandelate [(di-h)$_2$DMG][(S)-Mand]



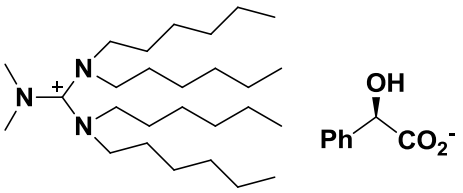
Following Method E (page 183): (S)-Mandelic acid (1.09 g, 3 equiv.) was dissolved in an aqueous solution of NaOH (252 mg, 3 equiv.) were stirred for 1 hour. [(di-h)$_2$DMG][Cl] (1 g, 2.1 mmol) in methanol was added and the mixture was stirred overnight. N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium (S)-mandelate was obtained as a yellow oil (0.91 g, 76%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 7.31 (m, 2H), 7.04 (m, 2H), 6.94 (m, 1H), 4.7 (br s, 1H), 3.01 (m, 6H), 2.75 (s, 6H), 2.47 (br s, 2H), 1.50-1.37 (m, 8H), 1.09 (s, 24H), 0.69 (m, 12H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 176.21, 163.09; 142.93; 127.51; 126.66; 126.29; 74.29; 49.88; 49.22; 47.35; 40.31; 31.25; 31.14; 31.07; 27.69; 27.27; 26.34; 26.28; 25.58; 22.31; 13.81; 13.78; 13.74.

Product spectral data similar to previously reported.[57]

4.4.2.1.4 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium (R)-Mandelate [(di-h)$_2$DMG][(R)-Mand]

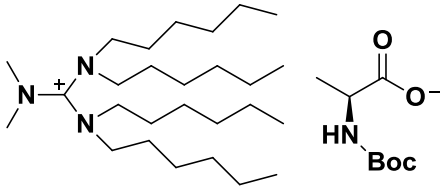


Following Method E (page 183): (R)-Mandelic acid (1.09 g, 3 equiv.) was dissolved in an aqueous solution of NaOH (252 mg, 3 equiv.) were stirred for 1 hour. [(di-h)$_2$DMG][Cl] (1 g, 2.1 mmol) in methanol was added and the mixture was stirred overnight. N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium (R)-mandelate was obtained as a yellow oil (0.88 g, 73%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 7.43 (m, 2H), 7.29 (m, 3H), 5.07 (m, 1H), 3.11 (m, 6H), 2.81 (s, 6H), 2.76 (m, 2H), 1.55 (br s, 8H), 1.24 (s, 24H), 0.85 (m, 12H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 176.06, 163.09; 143.34; 127.26; 126.41; 125.88; 74.14; 49.68; 49.03; 47.17; 40.15; 31.05; 30.96; 27.51; 27.09; 26.14; 26.11; 25.42; 22.13; 13.58.

4.4.2.1.5 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium N-(tert-Butoxycarbonyl)-(L)-alaninate [(di-h)$_2$DMG][Boc-L-Ala]



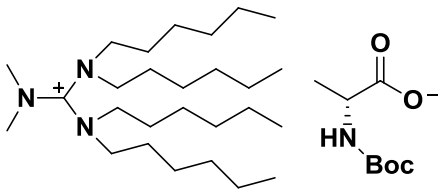
Following Method E (page 183): N-(tert-Butoxycarbonyl)-(L)-alanine (1.33 g, 3 equiv.) was dissolved in an aqueous solution of NaOH (252 mg, 3 equiv.) were stirred for 1 hour. [(di-h)$_2$DMG][Cl] (1 g, 2.1 mmol) in methanol was added and the mixture was stirred overnight. N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium N-(tert-Butoxycarbonyl)-(L)-alaninate was obtained as a yellow oil (0,99g, 77%).

^{1}H-NMR δ (400 MHz, CDCl$_3$): 3.93 (m, 1H), 3.15 (m, 6H), 2.98 (s, 6H), 2.74 (m, 2H), 1.62-1.52 (m, 8H), 1.31 (s, 24H), 1.19 (s, 9H), 0.79 (m, 12).

^{13}C-NMR δ (400 MHz, CDCl$_3$): 177.52; 163.40; 155.36; 78.40; 50.86; 50.00; 49.41; 47.52; 40.60; 31.42; 31.29; 31.27; 28.46; 27.84; 27.47; 26.55; 26.51; 26.45; 25.92; 22.49; 22.48; 22.44; 19.70; 13.92; 13.89.

Product spectral data similar to previously reported.[57]

4.4.2.1.6 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium N-(tert-Butoxycarbonyl)-(D)-alaninate [(di-h)$_2$DMG][Boc-D-Ala]

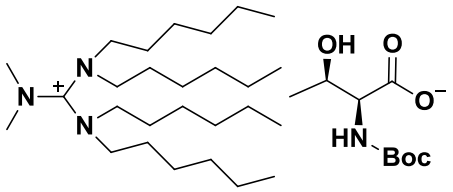


Following Method E (page 183): N-(tert-Butoxycarbonyl)-(D)-alanine (1.33 g, 3 equiv.) was dissolved in an aqueous solution of NaOH (252 mg, 3 equiv.) were stirred for 1 hour. [(di-h)$_2$DMG][Cl] (1 g, 2.1 mmol) in methanol was added and the mixture was stirred overnight. N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium N-(tert-Butoxycarbonyl)-(D)-alaninate was obtained as a yellow oil (0.93g, 71%).

^{1}H-NMR δ (400 MHz, CDCl$_3$): 3.99 (m, 1H), 3.19 (m, 6H), 3.11 (s, 6H), 2.79 (m, 2H), 1.66-1.55 (m, 8H), 1.37 (s, 24H), 1.24 (s, 9H), 0.83 (m, 12).

^{13}C-NMR δ (400 MHz, CDCl$_3$): 177.03; 163.46; 155.39; 78.35; 50.04; 49.46; 47.61; 40.67; 31.48; 31.34; 28.52; 27.89; 27.53; 26.60; 26.58; 26.50; 26.01; 22.53; 22.50; 19.86; 13.98; 13.95.

4.4.2.1.7 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium N-(tert-Butoxycarbonyl)-(L)-threoninate [(di-h)$_2$DMG][Boc-L-Thr]



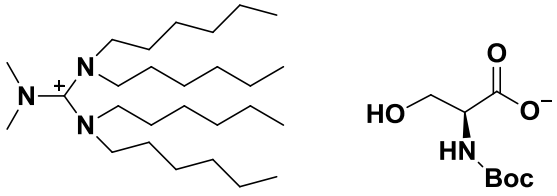
Following Method E (page 183): N-(tert-Butoxycarbonyl)-(L)-threonine (1.51 g, 3 equiv.) was dissolved in an aqueous solution of NaOH (252 mg, 3 equiv.) were stirred for 1 hour. [(di-h)$_2$DMG][Cl] (1 g, 2.1 mmol) in methanol was added and the mixture was stirred overnight. N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium N-(tert-Butoxycarbonyl)-(L)-threoninate was obtained as a yellow oil (1.08 g, 80%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 5.56 (br s, 1H), 4.31 (m, 1H), 3.41 (br s, 1H), 3.08 (br s, 6H), 2.98 (s, 6H), 2.76 (m, 2H), 1.74-1.48 (m, 8H), 1.15 (s, 24H), 0.70 (m, 12H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 177.67, 163.21; 155.53; 80.21; 68.03; 58.15; 54.18; 49.86; 49.32; 47.82; 40.66; 31.26; 31.12; 31.05; 28.23; 28.09; 27.71; 27.31; 26.37; 25.61; 22.32; 13.85; 13.80; 13.75.

Product spectral data identical to previously reported.[290]

4.4.2.1.8 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium N-(tert-Butoxycarbonyl)-(L)-serinate [(di-h)$_2$DMG][Boc-L-Ser]

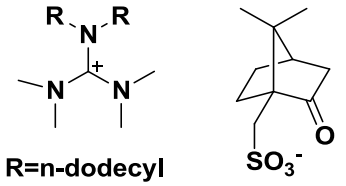


Following Method E (page 183): N-(tert-Butoxycarbonyl)-(L)-serine (1.29g, 3 equiv.) was dissolved in an aqueous solution of NaOH (252 mg, 3 equiv.) were stirred for 1 hour. [(di-h)$_2$DMG][Cl] (1 g, 2.1 mmol) in methanol was added and the mixture was stirred overnight. N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium N-(tert-Butoxycarbonyl)-(L)-serinate was obtained as a yellow oil (1.04 g, 79%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 6.99 (m, 1H), 6.88 (m, 1H), 3.71 (br s, 1H), 3.12 (m, 6H), 2.90 (s, 6H), 2.83 (m, 2H), 1.49 (m, 8H), 1.24 (s, 24H, 9H), 0.84 (m, 12H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 177.39, 163.32; 155.35; 80.21; 58.38; 49.89; 49.38; 48.07; 47.73; 40.64; 38.72; 37.16; 31.58; 31.46; 31.28; 30.45; 28.38; 27.95; 27.80; 27.43; 26.55; 25.82; 22.50; 13.95.

4.4.2.1.9 Preparation of N,N,N'N'-tetramethyl-N,N-didodecylguanidinium (1S)-(+)-Camphor-10-sulfonate [C_{12}TMG][(S)-CSA]

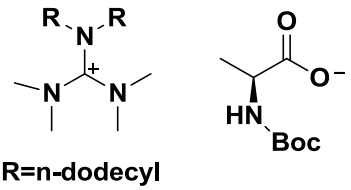


Following Method E (page 183): (1S)-(+)-Camphor-10-sulfononic acid (1.07 g, 3 equiv.) was dissolved in a aqueous solution of NaOH (206.9 mg, 3 equiv.) were stirred for 1 hour. [C_{12}TMG][I] (1 g, 1.72 mmol) in methanol was added and the mixture was stirred overnight. *N,N,N'N'*-tetramethyl-*N,N*-didodecylguanidinium (1S)-(+)-Camphor-10-sulfonate was obtained as dark brown solid (0.87g, 83%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.48 (s, 1H), 3.20 (s, 1H), 3.08 (s, 1H), 3.06 (m, 4H), 3.03 (s, 6H), 2.98 (s, 6H), 2.44 (m, 1H), 2.39 (m, 1H), 2.19 (m, 1H), 2.06 (m, 1H), 1.81 (m, 1H), 1.25 (m, 40H), 1.04 (s, 3H), 0.87 (s, 6H), 0.84 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 163.12; 58.68; 49.64; 49.64; 48.81; 48.36; 43.03; 42.66; 40.98; 40.80; 33.55; 31.88; 30.48; 29.52; 29.40; 29.31; 28.52; 27.69; 26.91; 26.81; 26.62; 22.66; 19.83; 19.53; 14.12.

4.4.2.1.10 Preparation of N,N,N'N'-tetramethyl-N,N-didodecylguanidinium N-(tert-Butoxycarbonyl)-(L)-alaninate [C_{12}TMG][Boc-L-Ala]

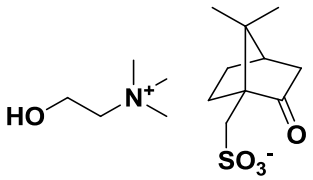


Following Method E (page 183): N-(tert-Butoxycarbonyl)-(L)-alanine (0.97 g, 3 equiv.) was dissolved in a aqueous solution of NaOH (206.9 mg, 3 equiv.) were stirred for 1 hour. [C_{12}TMG][I] (1 g, 1.7 mmol) in methanol was added and the mixture was stirred overnight. of *N,N,N'N'*-tetramethyl-*N,N*-didodecylguanidinium N-(tert-Butoxycarbonyl)-(L)-alaninate was obtained as yellow solid (0.74g, 67%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 4.08 (s, 1H), 3.32-3.09 (m, 12H), 3.00 (s, 4H), 1.37 (s, 9H), 1.24 (m, 40H), 0.83 (m, 6H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 179.06; 163.20; 155.66; 79.59; 50.32; 49.80; 41.52; 41.19; 33.51; 31.84; 30.44; 29.56; 29.50; 29.42; 29.36; 29.28; 29.22; 28.48; 28.29; 27.71; 26.74; 22.62; 18.47; 14.07.

4.4.2.1.11 Preparation of N,N,N-trimethyl ethanolammonium (1S)-(+)-Camphor-10-sulfonate [Choline][(S)-CSA]

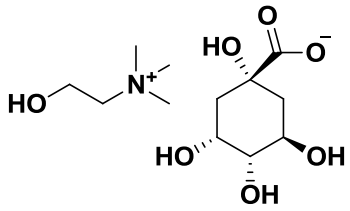


To a solution of [Choline][OH] (8.2 mmol) in methanol, was slowly added an aqueous solution of (1S)-(+)-Camphor-10-sulfonic acid (1.91 g, 8.2 mmol) and left stirring overnight. The solvent mixture was evaporated, and the IL was stirred under vacuum (<1 mmHg) at 60°C overnight. *N,N,N*-trimethyl ethanolammonium (1S)-(+)-Camphor-10-sulfonate was obtained as yellow solid (2.6 g, 95%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.91 (br s, 2H), 3.56-3.54 (m, 2H), 3.24 (s, 9H), 3.10 (d, 1H, *J(H, H)* = 15Hz), 2.61 (d, 1H, *J(H, H)* =16Hz), 2.50 (m, 1H), 2.45 (m, 1H), 2.20 (m, 1H), 1.91 (m, 1H), 1.77 (s, 1H), 1.52 (m, 1H), 1.29 (m, 1H), 0.94 (s, 3H), 0.69 (s, 3H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 216.84; 67.63; 58.67; 56.07; 54.22; 54.17; 54.12; 49.73; 47.14;42.83; 42.45; 26.92; 24.38; 19.38; 19.78; 19.76.

4.4.2.1.12 Preparation of N,N,N-trimethylethanolammonium Quinate [Choline][Quinic]

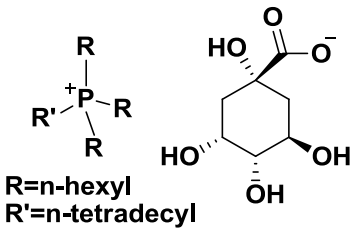


To a solution of [Choline][OH] (8.2 mmol) in methanol, was slowly added an aqueous solution of quinic acid (1.58 g, 8.2 mmol) and left stirring overnight. The solvent mixture was evaporated, and the IL was stirred under vacuum (<1 mmHg) at 60°C overnight. *N,N,N*-trimethylethanolammonium quinate was obtained as yellow solid (2.22 g, 92%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 4.03 (br s, 2H), 3.95-3.89 (m, 4H), 3.45 (m, 1H), 3.24 (s, 9H), 1.97-1.71 (m, 4H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 181.29; 76.93; 75.17; 70.36; 67.49; 67.45; 67.41; 66.99; 55.57; 53.86; 53.81; 53.76; 40.61; 37.38.

4.4.2.1.13 Preparation of Trihexyl(tetradecyl)phosphonium Quinate [$P_{6,6,6,14}$][Quinic]

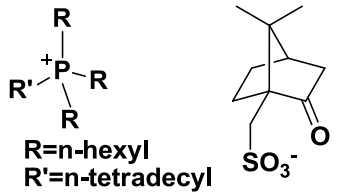


Following Method F (page 183): [$P_{6,6,6,14}$][Cl] (9.3 g, 17.9 mmol) in methanol was pass through a Amberlite column and was added an aqueous solution of quinic acid (3.6 g, 1.05 equiv.) the mixture was stirred overnight. Trihexyl(tetradecyl)phosphonium quinate was obtained as a yellow oil (10g, 87%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 4.00 (m, 3H), 3.45 (m, 1H), 2.27 (m, 8H), 1.93 (m, 4H), 1.46 (m, 16H), 1.26 (m, 32H), 0.85(m, 12H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 207.08, 75.62; 69.51; 39.15; 31.00; 31.98; 31.12; 30.91; 30.77; 30.58; 30.44; 29.75; 29.71; 29.68; 29.60; 29.42; 29.02; 22.75; 22.4; 21.88; 21.84; 19.26; 18.79; 14.19; 14.01.

4.4.2.1.14 Preparation of Trihexyl(tetradecyl)phosphonium (1S)-(+)-Camphor-10-sulfonate [$P_{6,6,6,14}$] [(S)-CSA]

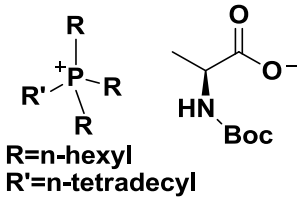


Following Method F (page 183): [$P_{6,6,6,14}$][Cl] (9.3 g, 17.9 mmol) in methanol was pass through a Amberlite column and was added an aqueous solution of (1S)-(+)-Camphor-10-sulfonic acid (4.78 g, 1.05 equiv.) the mixture was stirred overnight. Trihexyl(tetradecyl)phosphonium (1S)-(+)-Camphor-10-sulfonate was obtained as a yellow oil (9.5 g, 73%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.24(d, 1H, *J(H,H)*=15Hz), 2.73-2.87(m, 2H), 2.22-2.36 (m, 9H), 1.91-2.02 (m, 2H), 1.80 (d, 1H, *J(H,H)*=18Hz), 1.61-1.70(m, 1H), 1.46-1.54 (m, 16H), 1.22-1.30 (m, 32H), 1.11(s, 3H), 0.8-0.88 (m, 15H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 192.57; 58.70; 47.85; 47.02; 43.08; 42.77; 31.99; 31.19; 30.65; 30.46; 29.75; 29.72; 29.61; 29.42; 29.08; 27.22; 24.56; 22.75; 22.44; 21.93; 21.91; 20.35; 19.94; 19.38; 18.75; 14.19; 14.02.

4.4.2.1.15 Preparation of Trihexyl(tetradecyl)phosphonium N-(tert-Butoxycarbonyl)-(L)-alaninate [$P_{6,6,6,14}$][Boc-L-Ala]



Following Method F (page 183): [$P_{6,6,6,14}$][Cl] (9.3 g, 17.9 mmol) in methanol was pass through a Amberlite column and was added an aqueous solution of N-(tert-Butoxycarbonyl)-(L)-alanine (3.97 g, 1.05 equiv.) the mixture was stirred overnight. Trihexyl(tetradecyl)phosphonium N-(tert-Butoxycarbonyl)-(L)-alaninate was obtained as a yellow oil (10.7g, 89%).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 4.08 (m, 1H), 2.34 (m, 8H), 1.49 (m, 16H), 1.26 (m, 32H), 1.28 (s, 3H), 1.23 (s, 9H), 0.87 (m, 12H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 176.49; 155.21; 78.34; 50.60; 50.25; 31.02; 30.81; 30.66; 30.48; 30.33; 29.63; 29.60; 29.57; 29.48; 29.31; 29.26; 28.92; 28.41; 22.64; 22.29; 21.80; 21.75; 19.64; 19.25; 18.78; 14.08; 13.89.

4.4.2.2 Asymmetric induction by CILs

In a 3 mL NMR tube was introduced a mixture of 300 mg of the CIL and 3 mg of the NMR probe in study. This NMR tube was introduced in a 5 mL NMR tube with $CDCl_3$ as deuterated solvent. ^{19}F NMR spectra were recorded.

4.4.3 Magnetic Ionic Liquids

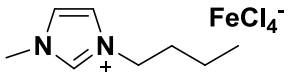
4.4.3.1 General procedure for the synthesis of tetrachloroferrate(III) with different cations [Cation][$FeCl_4$] (Method G)

$$Cation^{+}\ Cl^{-} + FeCl_3 \xrightarrow[24h,\ r.t.]{DCM} Cation^{+}FeCl_4^{-}$$

Method G: To a solution of IL with chloride as anion (1 equiv.) in dichloromethane (to ensure efficient mixing) was added iron (III) chloride hexahydrate (1.2 equiv.). The solution was left stirring at room temperature for 24h. After that, two layers were formed, and the aqueous

phase was decanted. The organic phase was evaporated, and the residue was purified by passing through a column with silica and activated carbon, with dichloromethane as eluent. The solvent was removed under vacuum, and the IL stirred under vacuum (<1 mmHg) at 60°C overnight.

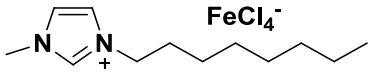
4.4.3.1.1 Preparation of 1-Butyl-3-methyl imidazolium tetrachloroferrate (III) [BMIM][$FeCl_4$]



Following Method G (page 191): [BMIM][Cl] (12.13 g) and $FeCl_3 \cdot 6H_2O$ (25.93 g) were stirred overnight in dichloromethane and 1-butyl-3-methyl imidazolium tetrachloroferrate (III) was obtained as dark brown liquid (17.28 g, 74.3%).

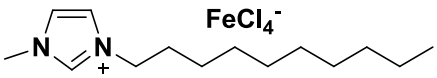
Prepared according with the procedure previously reported.[292]

4.4.3.1.2 Preparation of 1-Octyl-3-methyl imidazolium tetrachloroferrate (III) [C_8MIM][$FeCl_4$]



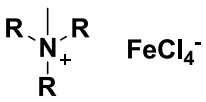
Following Method G (page 191): [C_8MIM][Cl] (43 g, 0.18 mol) and $FeCl_3 \cdot 6H_2O$ (60.6 g, 0.22 mmol) were stirred overnight in dichloromethane and 1-octyl-3-methyl imidazolium tetrachloroferrate (III) was obtained as dark brown liquid (60 g, 82%).

4.4.3.1.3 Preparation of 1-Decyl-3-methyl imidazolium tetrachloroferrate (III) [C_{10}MIM][$FeCl_4$]



Following Method G (page 191): [C_{10}MIM][Cl] (4.81g, 18.5 mmol) and $FeCl_3 \cdot 6H_2O$ (6.02 g, 22.3 mmol) were stirred overnight in dichloromethane and 1-decyl-3-methyl imidazolium tetrachloroferrate (III) was obtained as dark brown liquid (5.89 g, 75.8%).

4.4.3.1.4 Preparation of Aliquat® tetrachloroferrate (III) [Aliquat][$FeCl_4$]

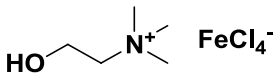


R= *n*-octyl
***n*-decyl**

Following Method G (page 191): [Aliquat][Cl] (50 g, 0.11 mol) and $FeCl_3 \cdot 6H_2O$ (37.5 g, 0.14 mol) were stirred overnight in dichloromethane and Aliquat® tetrachloroferrate (III) was obtained as dark brown liquid (59.2 g, 84.4%).

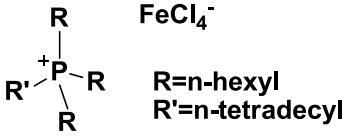
Prepared according with the procedure previously reported.[290]

4.4.3.1.5 Preparation of N,N,N-trimethylethanolammonium tetrachloroferrate (III) [Choline][$FeCl_4$]



Following Method G (page 191): [Choline][Cl] (5 g, 35 mmol) and $FeCl_3 \cdot 6H_2O$ (11.6 g, 43.1 mmol) were stirred overnight in dichloromethane and N,N,N-trimethylethanolammonium tetrachloroferrate (III) was obtained as dark brown solid (8.7 g, 80.7%).

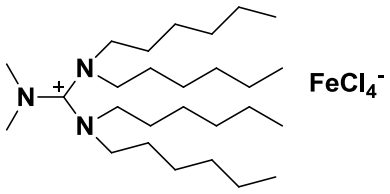
4.4.3.1.6 Preparation of Trihexyl(tetradecyl)phosphonium tetrachloroferrate (III) [$P_{6,6,6,14}$][$FeCl_4$]



Following Method G (page 191): [$P_{6,6,6,14}$][Cl] (50 g, 0.096 mol) and $FeCl_3 \cdot 6H_2O$ (31.22g, 0.11 mol) were stirred overnight in dichloromethane and trihexyl(tetradecyl)phosphonium tetrachloroferrate (III) was obtained as dark brown liquid (61.8 g, 94%).

Prepared according with the procedure previously reported. [68]

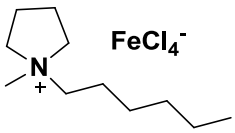
4.4.3.1.7 Preparation of N,N,N'N'-tetrahexyl-N,N-dimethylguanidinium tetrachloroferrate (III) [(di-h)$_2$DMG][$FeCl_4$]



Following Method G (page 191): [(di-h)$_2$DMG][Cl] (2.74 g, 5.9 mmol) and $FeCl_3 \cdot 6H_2O$ (1.93 g, 7.1 mmol) were stirred overnight in dichloromethane and *N,N,N'N'*-tetrahexyl-*N,N*-dimethylguanidinium tetrachloroferrate (III) was obtained as dark brown liquid (3.2 g, 87.5%).

Prepared according with the procedure previously reported.[290]

4.4.3.1.8 Preparation of 1-n-Hexyl-1-methyl Pyrrolidinium tetrachloroferrate (III) [C_6MPyr][$FeCl_4$]



Following Method G (page 191): [C_6MPyr][Cl] (2 g, 9.7 mmol) and $FeCl_3 \cdot 6H_2O$ (3.15 g, 11.6 mmol) were stirred overnight in dichloromethane and N,N,N-trimethylethanol ammonium tetrachloroferrate (III) was obtained as dark brown solid (3.0 g, 84%).

4.5 Ionic Liquids & Carbohydrates

4.5.1 General procedure for solubility studies of carbohydrates in ionic liquids

To a 1 mL seal vial was added 250 mg of IL. With a controlled temperature of 35 °C was added several portions of 5 mg additions of carbohydrate until saturation. The sample was centrifuged and the supernatant was analyzed in a HPLC system with a reverse phase C_{18} column (Hichrom, Lichrosorb RP18-5, 25cm×4.6mm id) and a refractive index detector; the mobile phase consisted of water (100%) and 1.0 mL/min flow rate. For ILs insoluble in water the IL plus carbohydrate sample was dissolved in DCM, precipitating the carbohydrates, and extracted with water. The aqueous phase was evaporated till dryness and was added a known amount of water. The final concentration was determined by HPLC analysis. The water content of all IL was measured before and after solubility experiments.

4.5.2 General procedure for the extraction of carbohydrates by ionic liquids from aqueous phase

In a 10 mL vial was added 2 mL of a 500 mg/mL aqueous solution of carbohydrate, and then added 2 g of the IL. The mixture was stirred for 8 days at 35°C. The two phases were separated and was added 10 mL of dichloromethane to the organic phase. The carbohydrate was filtered and washed with 2 mL of dichloromethane. For [Aliquat®][Cl] was made a supplemental experiment with a large amount of IL: in a 20 mL vial was added 5 mL of a 500 mg/mL aqueous solution of carbohydrate, and then added 5 g of the IL. The mixture was stirred for 8 days at 35°C. The two phases were separated and was added 60 mL of dichloromethane to the organic phase. The carbohydrate was filtered and washed with 2 mL of dichloromethane. The carbohydrate or mixtures of carbohydrates were recovered without traces of the IL (by ^{1}HNMR analysis). For [(di-*h*)$_2$DMG][DCA] the process of extraction was recycled three times with the same IL without lost of efficiency.

4.6 *Trans*-dihydroxylation of olefins

For the following compounds the concentrations used in all experiments were:

Hydrochloric acid – 37% aqueous solution;

Sulfuric acid – 97-98% aqueous solution;

Hydrogen peroxide – 30% aqueous solution.

(1R,2S)-cis-1-amino-indane-2-ol, octyl 4-methylbenzenesulfonate, 5α-cholestan-3-yloxy (methoxy)ethyl trimethylsilane and octan-2-yloxy(methoxy)methylbenzene were obtained from our laboratory collection.

4.6.1 Synthesis of *trans*-cyclohexan-1,2-diol (42)

4.6.1.1 General procedure for trans-dihydroxylation of cyclohexene with different catalysts (Method H)

Method H: Catalyst (30 mol%) and H_2O_2 (30% aq., 2 equiv.) were stirred for five minutes and cyclohexene (1 or 2.5 mmol) was added. The reaction mixture was stirred for 21 h at 20°C. In the end of the reaction was added chloroacetic acid as internal standard for the yield calculation by ^{1}H NMR, as follows (Internal standard (**IS**) is chloroacetic acid):

$$mol(diol) = \frac{Integration\ of\ diol\ NMR\ peack\ (2.9\ ppm)}{Integration\ of\ IS\ NMR\ peack\ (3.8\ ppm)} * \frac{IS\ mass\ added}{IS\ Molecular\ Weight}$$

The experiments results are described in Table 3.2.1 and Table 3.2.2 (please see section 3.2.1 , page 129 and 130).

Following Method H (page 196): **H_2SO_4** (29.4 mg, 30 mol%), H_2O_2 (30% aq., 226.7 mg, 2 equiv.) and cyclohexene (101 µL, 1 mmol) were left to stir for 21 hours at 20°C.

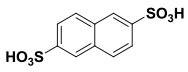
Following Method H (page 196): **$MeSO_3H$** (28.8 mg, 30 mol%), H_2O_2 (30% aq., 226.7 mg, 2 equiv.) and cyclohexene (101 µL, 1 mmol) were left to stir for 21 hours at 20°C.

Following Method H (page 196): **$PhSO_3H$** (113.9 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5 mmol) were left to stir for 21 hours at 20°C.

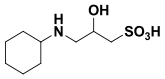
Following Method H (page 196): **CF_3SO_3H** (45.0 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5 mmol) were left to stir for 21 hours at 20°C.

Following Method H (page 196): **PSA** (117.5 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5 mmol) were left to stir for 21 hours at 20°C.

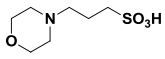
Following Method H (page 196): **PESA** (138.2 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5 mmol) were left to stir for 21 hours at 20°C.



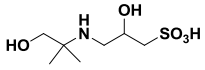
Following Method H (page 196): **NDSA** (212.7 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5 mmol) were left to stir for 21 hours at 20°C.



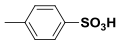
Following Method H (page 196): **CAPSO** (71.2 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5 mmol) were left to stir for 21 hours at 20°C.



Following Method H (page 196): **MOPS** (157 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5 mmol) were left to stir for 21 hours at 20°C.

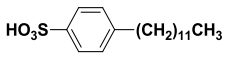


Following Method H (page 196): **AMPSO** (170.4 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5 mmol) were left to stir for 21 hours at 20°C.



Following Method H (page 196): **PTSA** (140.4 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5 mmol) were left to stir for 21 hours at 20°C.

Following Method H (page 196): **CSA** (177.3 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5mmol) were left to stir for 21 hours at 20°C.



Following Method H (page 196): **DBSA** (266.6 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5mmol) were left to stir for 21 hours at 20°C.

Following Method H (page 196): **HCOOH** (33.9 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5mmol) were left to stir for 21 hours at 20°C.

Following Method H (page 196): **Nafion®** (152.5 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5mmol) were left to stir for 21 hours at 20°C.

Following Method H (page 196): **Amberlyst®** (125.5 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2.5mmol) were left to stir for 21 hours at 20°C.

4.6.1.2 General procedure for trans-dihydroxylation of cyclohexene with different oxidants (Method I and J)

Method I: PTSA or CSA (30 mol%) and the oxidant were stirred for five minutes and cyclohexene (1, 2.5 mmol) was added. The reaction mixture was stirred for 21h at 20°C (or 50°C). In the end of the reaction was added chloroacetic acid as internal standard for the yield calculation by ^{1}H NMR, as follows (Internal standard (**IS**) is chloroacetic acid):

$$mol(diol) = \frac{Integration\ of\ diol\ NMR\ peack\ (2.9\ ppm)}{Integration\ of\ IS\ NMR\ peack\ (3.8\ ppm)} * \frac{IS\ mass\ added}{IS\ Molecular\ Weight}$$

Method J: PTSA or CSA (30 mol%) and the oxidant were stirred for five minutes and cyclohexene (25 mmol) was added. The reaction mixture was stirred for 21h at 20°C (or 50°C). After that the final product was isolated by extraction of the crude reaction with diethylether, without the need of chromatography techniques to purify it.

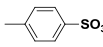
The results with different oxidants are described in Table 3.2.3 (please see section 3.2.1, page 132):

Following Method I (page 198): CSA (171.4 mg, 30 mol%), **Oxone®** (1.51 g ,2 equiv.) plus 200 mg **H_2O or** 150 mg **[C_{10}MIM][BF_4]** were stirred for five minutes, and then cyclohexene (253 µL, 2.5 mmol) was added. The reaction mixture was left to stir for 21 hours at 20°C.

Following Method I (page 198): **Oxone®** (607.2 mg ,2 equiv.) plus 200 mg of **water** were stirred for five minutes, and then cyclohexene (101 µL, 1 mmol) was added. The reaction mixture was left to stir for 21 hours at 20°C.

Following Method I (page 198): **Oxone®** (607.2 mg, 30 mol%) and H_2O_2 (30% aq., 566.7 mg, 2 equiv.) were stirred for five minutes, and then cyclohexene (101 µL, 1 mmol) was added. The reaction mixture was left to stir for 21 hours at 20°C.

Following Method I (page 198): CSA (171.4 mg, 30 mol%), **Urea peroxide** (231.6 mg, 2 equiv.) plus 200 mg of **H_2O** or 150 mg of **[C_{10}MIM][BF_4]** were stirred for five minutes, and then cyclohexene (253 µL, 2.5 mmol) was added. The reaction mixture was left to stir for 21 hours at 20°C.



Following Method J (page 198): PTSA (456.5 mg, 1 equiv.), H_2O_2 (30% aq., 340.0 mg, 1.2 equiv., or 566.7 mg, 2 equiv.) and cyclohexene (2.53 mL, 25 mmol) were left to stir for 21 hours at 20°C.

4.6.1.3 General procedure for trans-dihydroxylation of cyclohexene by using different catalyst loading, or different temperatures (Method K and L)

Method K: PTSA (20-100 mol%) and H_2O_2 (30% aq. 2 equiv.) were stirred for five minutes and cyclohexene (2.5, 25 or 250 mmol) was added. The reaction mixture was stirred for 21 h. In the end of the reaction was added chloroacetic acid as internal standard for the yield calculation by ^{1}H NMR, as follows (Internal standard (**IS**) is chloroacetic acid):

$$mol(diol) = \frac{Integration\ of\ diol\ NMR\ peack\ (2.9\ ppm)}{Integration\ of\ IS\ NMR\ peack\ (3.8\ ppm)} * \frac{IS\ mass\ added}{IS\ Molecular\ Weight}$$

Method L: PTSA (20-100 mol%) and H_2O_2 (30% aq. 2 equiv.) were stirred for five minutes and cyclohexene (2.5, 25 or 250 mmol) was added. The reaction mixture was stirred for 21 h. The final product was isolated by extraction of the crude reaction with diethylether, without the need of chromatography techniques to purify it.

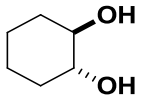
The results with different catalyst loading, or different temperatures are described in Table 3.2.5 (please see section 3.2.1, page 134).

4.6.1.4 General procedure for trans-dihydroxylation of several olefins (Method M)

Method M: In a sealed flask was added PTSA (951.1 mg, 20 mol%) and H_2O_2 (30% aq. sol., 5.7 g, 2 equiv.) that were stirred for 5 minutes, then was added the substrate (25 mmol). After 21 hours stirring at 50°C, the reaction mixture was neutralized with sodium bicarbonate, and reduced with Na_2SO_3, and then extracted with diethyl ether.

The results with different olefins are described in Table 3.2.6 and Table 3.2.7 (please see section 3.2.1, page 136 and 138, respectively).

*4.6.1.4.1 Preparation of (±)-*trans*-1,2-cyclohexanediol (**42**)*

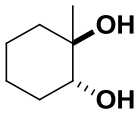


Following Method M (page 199), PTSA (951.1 mg, 20 mol%), H_2O_2 (30% aq. sol.,5.7 g, 2 equiv.) and cyclohexene (2.53 mL, 25 mmol) were stirred for 21h, at 50°C. **(±)-*trans*-1,2-cyclohexanediol** was obtained as a white solid with 95.5% yield.

^{1}H-NMR δ (400 MHz, $CDCl_3$): 5.35 (s, 2H, OH); 3.27 (s, 2H); 1.87 (s, 2H); 1.61 (s, 2H); 1.17 (s, 4H)
^{13}C-NMR δ (400 MHz, $CDCl_3$): 75.53; 32.82; 24.32.

Product obtained with the same spectral data as described previously.[272]

*4.6.1.4.2 Preparation of (±)-1-Methylcyclohexane-1,2-diol (**45**)*

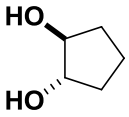


Following Method M (page 199), PTSA (951.1 mg, 20 mol%), H_2O_2 (30% aq. sol.,5.7 g, 2 equiv.) and 1-methyl-1-cyclohexene (2.96 mL, 25 mmol) were stirred for 21h, at 50°C. After purification by column chromatography with hexane and ethyl acetate (1:1) as mobile phase **(±)-1-methylcyclohexane-1,2-diol** was obtained a white solid in 82.9 % yield.

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.43 (m, 1H); 1.76-1.53 (m, 4H); 1.22-1.21 (m, 4H); 1.20 (s, 3H).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 77.02; 74.27; 38.57; 31.06; 24.19; 23.17; 19.14.

Product obtained with the same spectral data as described previously. [293]

*4.6.1.4.3 Preparation of (±)-*Trans*-1,2-Cyclopentanediol (**46**)*

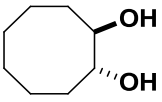


Following Method M (page 199): PTSA (951.1 mg, 20 mol%), H_2O_2 (30% aq. sol.,5.7 g, 2 equiv.) and cyclopentene (2.20 mL, 25 mmol) were stirred for 21h, at 50°C. **(±)-*Trans*-1,2-cyclopentanediol** was obtained in 95.7% yield as a white solid.

^{1}H-NMR δ (400 MHz, $CDCl_3$): 5.05 (br, 2H); 3.90 (m, 2H); 1.91 (m, 2H); 1.64 (m, 2H); 1.47 (m, 2H).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 78.85; 30.98; 19.61.

Product obtained with the same spectral data as described previously. [240c, 294]

*4.6.1.4.4 Preparation of (±)-*Trans*-1,2-Cyclooctanediol (**47**)*



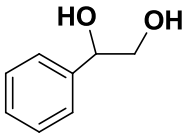
Following Method M (page 199): PTSA (951.1 mg, 20 mol%), H_2O_2 (30% aq. sol.,5.7 g, 2 equiv.) and cyclooctene (3.24 mL, 25 mmol) were stirred for 21h, at 50°C. After purification by column chromatography with hexane and ethyl acetate (1:1) as mobile phase **(±)-*trans*-1,2-cyclooctanediol (47)** was obtained as a viscous yellow liquid in 75.5% yield.

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.51 (br, 4H); 1.99-1.78 (m, 4H); 1.76-1.63 (m, 4H); 1.50-1.41 (m, 4H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 76.08; 31.82; 26.15; 23.75.

Product obtained with the same spectral data as described previously. [294]

*4.6.1.4.5 Preparation of (±)-1-phenyl-1,2-ethanediol (**48**)*

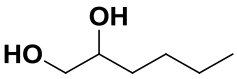


Following Method M (page 199): PTSA (951.1 mg, 20 mol%), H_2O_2 (30% aq. sol.,5.7 g, 2 equiv.) and styrene (2.86 mL, 25 mmol) were stirred for 21h, at 50°C. **(±)-1-Phenyl-1,2-ethanediol** was obtained in 91.6% yield as a brown solid.

^{1}H-NMR δ (400 MHz, $CDCl_3$): 7.35-7.27 (m, 5H); 4.77-4.74 (m, 1H); 3.68-3.57 (m, 2H).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 140.52; 128.47; 127.87; 126.15; 74.75; 67.96.

Product obtained with the same spectral data as described previously.[240c, 294]

*4.6.1.4.6 Preparation of (±)-1,2-Hexanediol (**49**)*

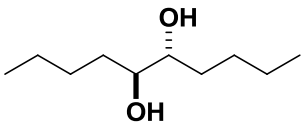


Following Method M (page 199): PTSA (951.1 mg, 20 mol%), H_2O_2 (30% aq. sol.,5.7 g, 2 equiv.) and 1-hexene (3.12 mL, 25 mmol) were stirred for 21h, at 50°C. **(±)-1,2-Hexanediol** was obtained in 86.8% yield as a colourless liquid.

^{1}H-NMR δ (400 MHz, $CDCl_3$): 4.41 (br, 2H); 3.57-3.52 (m, 2H); 3.35-3.30 (m, 1H); 1.29-1.23 (m, 6H); 0.83 (m, 3H).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 72.26; 66.57; 32.72; 27.73; 22.67; 13.91.

Product obtained with the same spectral data as described previously. [294]

*4.6.1.4.7 Preparation of (±)-*Trans*-5,6-decanediol (**50**)*



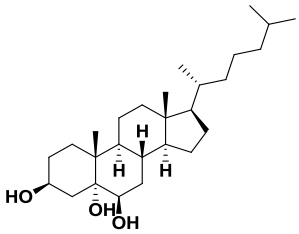
Following Method M (page 199): PTSA (50.17 mg, 20 mol%), H_2O_2 (30% aq. sol.,298.9 mg, 2 equiv.) and *trans*-5-decene (250 µL, 2.5 mmol) were stirred for 21h, at 50°C. After purification

by column chromatography with hexane and ethyl acetate (95:5) as mobile phase **(±)-*trans*-5,6-decanediol** was obtained as a white solid in 65% yield.

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.65-3.62 (m, 2H); 1.49-1.28 (m, 12H); 0.94-0.91 (m, 6H)
^{13}C-NMR δ (400 MHz, $CDCl_3$): 74.76; 30.81; 28.20; 22.73; 14.02.

Product obtained with the same spectral data as described previously. [295]

*4.6.1.4.8 Preparation of Cholestane-3,5,6-triol (**53**)*



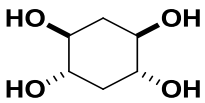
PTSA (49.1 mg, 20 mol%), H_2O_2 (30% aq. sol., 293.1 mg, 2 equiv.) and a solution of cholesterol (500 mg, 1.29 mmol) in 5 ml of propan-1-ol, hexan-1-ol, octan-1-ol or dodeca-1-nol were stirred for 21h, at 50°C. After purification by column chromatography with hexane and ethyl acetate (1:1) as mobile phase **cholestane-3,5,6-triol** was obtained as a white solid.

The results of the reaction with cholesterol and different co-solvents are described in Table 3.2.7 (please see section 3.2.1, page 138).

^{1}H-NMR δ (400 MHz, DMSO-d_6): 4.38 (d, 1H, J(H,H)= 4.4 Hz), 4.15 (d, 1H, J(H,H)= 5.6 Hz), 3.79, (q, 1H, J(H,H)= 5.6 Hz), 3.6 (s, 1H), 3.2 (s, 1H), 3.17 (s, 1H). From 1.9-0.6 ppm the peaks are overlap is not possible to identify it.
^{13}C-NMR δ (400 MHz, DMSO-d_6): 74.76; 74.60; 66.21; 60.20; 56.26; 45.01; 42.73; 41.37; 39.41; 39.36; 38.24; 36.14; 35.75; 34.94; 32.47; 31.55; 30.46; 28.33; 27.86; 24.36; 23.75; 23.13; 22.85; 21.21; 18.99; 16.742; 12.80; 12.39.

Product obtained with the same characterization as previously reported.[277c]

*4.6.1.4.9 Preparation of (±)-*Trans, trans-*Cyclohexane-1,2,4,5-tetraol (**51**)*



Following Method M (page 199): PTSA (951.1 mg, 20 mol%), H_2O_2 (30% aq. sol.,5.7 g, 2 equiv.) and 1-hexene (2.4 mL, 25 mmol) were stirred for 21h, at 50°C. **(±)-*trans, trans*-Cyclohexane-**

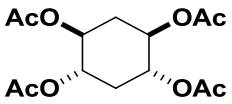
1,2,4,5-tetraol was obtained as only product, and the yield of 76.7% was calculated by ^{1}HNMR by using chloroacetic acid as internal standard.

^{1}H-NMR δ (400 MHz, $CDCl_3$): 3.59 (m, 4H); 1.67 (s, 4H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 69.78; 33.60.

Product obtained with the same spectral data as described previously.[296]

*4.6.1.4.10 Preparation of (±)-*Trans, trans-*cyclohexane-1,2,4,5-tetrayl tetra acetate (**52**)*



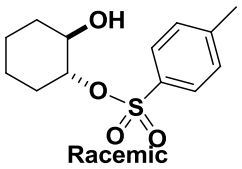
To the crude product of cyclohexane-1,2,4,5-tetraol (1.19 g, 8.01 mmol) was added triethylamine (9.03 mL, 8 equiv.) and Ac_2O (4.56 mL, 6 equiv.), and left stirring for one day under argon atmosphere at room temperature. Then, the triethylamine excess was removed by evaporation under vacuum, and was added 10 mL of aqueous HCl 10% (v/v), and extracted with 2×25mL of dichloromethane. The organic layer was dried with Na_2SO_4 and evaporated the solvent under vacuum. The final product was purified by column chromatography (EtOAc / Hexane 80:20), providing *trans, trans*-cyclohexane-1,2,4,5-tetrayl tetra acetate as a white solid (1.85g, 73.3%), with a melting point of 136-140°C (lit.[297] 138-139°C). The yield of acetylation was calculated according the yield (determined by ^{1}H-NMR) of cyclohexane-1,2,4,5-tetraol.

^{1}H-NMR δ (400 MHz, $CDCl_3$): 4.93 (m, 4H); 1.92 (s, 16H).

^{13}C-NMR δ (400 MHz, $CDCl_3$): 169.52, 68.9; 29.99, 20.55.

Product obtained with the same characterization as previously reported. [297]

*4.6.1.4.11 Preparation of trans-2-hydroxycyclohexyl-p-toluenesulfonate (**44**)*



In a sealed flask was added PTSA (951.1 mg, 20 mol%) and H_2O_2 (30% aq. sol., 5.7 g, 2 equiv.) that were stirred for 5 minutes, then was added cyclohexene (2.53 mL, 25 mmol). After 21 hours stirring at 0°C, was added water to the reaction mixture. Almost immediately *trans*-2-hydroxycyclohexyl-*p*-toluenesulfonate (44) precipitated from the crude reaction. After filtration and washed with water the *trans*-2-hydroxycyclohexyl-*p*-toluenesulfonate (44) was isolated.

The results of several experiments to prepare *trans*-2-hydroxycyclohexyl-*p*-toluenesulfonate are described in Table 3.2.5 (please see section 3.2.1, page 134).

^{1}H-NMR δ (400 MHz, $CDCl_3$): 7.85 (s, 1H); 7.84 (s, 1H), 7.37 (s, 1H), 7.35 (s, 1H), 4.3 (m, 1H), 3.59 (m, 1H), 2.02-2.01 (m, 2H), 1.70-1.66 (m, 2H), 1.29-1.25 (m, 2H), 1.23-1.22 (m, 2H).
^{13}C-NMR δ (400 MHz, $CDCl_3$): 144.40; 133.93; 129.90; 127.76; 86.73; 72.00; 32.35; 30.80; 23.89; 23.27; 21.68.

Product obtained with the same spectral data as described previously. [298]

4.6.1.5 General procedure for trans-dihydroxylation of cyclohexene in the presence of several substrates (Method N)

Method N: In a sealed flask was added PTSA (20 mol%) and H_2O_2 (30% aq. sol., 2 equiv.) that were stirred for 5 minutes, then was added cyclohexene (1-2.5 mmol) and the substrate (50 or 100 mol%). After 21 hours stirring at 50°C, the reaction mixture was neutralized with sodium bicarbonate, and reduced with Na_2SO_3, and then extracted with diethyl ether. The mixture was separated by column chromatography on silica gel, and the substrate stability was made based on TLC, crude ^{1}H and ^{13}C-NMR analysis and recovered substrate by preparative TLC/column chromatography.

4.6.1.6 Preparation of ^{18}O enriched p-toluenesulfonic acid

In a sealed flask was added 4-toluenesulfonyl chloride (500 mg, 2.6 mmol) and 5 mL of toluene. After total dissolution was added 4 equiv. of $^{18}OH_2$ (209 µL, 10.4 mmol) and left overnight in reflux. Then the reaction was cooled till room temperature, and immediately enriched ^{18}O PTSA precipitated. The white solid was filtered and washed with dichloromethane. The obtained yield was 1.6% (6.9 mg).

4.6.1.7 General procedure for trans-dihydroxylation of styrene in the presence of chiral inductors (Method O)

Method O: In a sealed flask was added (S)-CSA (171.4 mg, 30 mol%) and/or [(di-*h*)$_2$DMG][(S)-CSA] (200 mg) and H_2O_2 (30% aq. sol., 566.7 g, 2 equiv.) that were stirred for 5 minutes, then was added styrene (286 µL, 2.5 mmol). After 21 (or 48) hours stirring at 50 (or 20)°C, the reaction mixture was extracted with diethyl ether.

The results are described in Table 3.2.9 (please see section 3.2.4, page 144).

The obtained mixture was analyzed by chiral HPLC in order to determine the enantiomeric excess (Chiral LUX, Hexane/*iso*-Propanol 95:5, 1 mL/min, Enantiomers retention time: 39.68 and 46.85 min).

4.6.1.8 General procedure for the reuse of the catalyst (PTSA) in the trans-dihydroxylation of cyclohexene (Method P)

Method P: In a sealed flask was added PTSA (20 mol%, 951.1 mg) and 2 equiv. H_2O_2 (2 equiv., 30% aq. sol., 5.66 g) that were stirred for 5 minutes, then was added cyclohexene (25 mmol, 2.5 mL). After 21 hours stirring at 50°C, the crude aqueous phase was extracted with diethylether (3x100 mL). The aqueous phase was concentrated by water evaporation, and the next cycle started by adding H_2O_2 (30% aq. sol., 2 equiv., 5.66 g) and the substrate (25 mmol, 2.5 mL). Diethylether was removed from the organic layer, and the diol **42** was obtained in very high purity.

The results with of the different cycles are described in Table 3.2.10 (please see section 3.2.5, page 145):

4.6.1.9 Preparation of (±)-trans-1,2-cyclohexanediol using a organic solvent free protocol (Method Q and R)

Method Q: In a 50 mL round-bottomed flask (calibrated) was added 4.56 g (25 mmol) PTSA, and 5.09 mL of H_2O_2 (30 wt.% aq. sol., 2 eq.) and stirrer at room temperature for 5 minutes. Then was added 2.5 mL (25 mmol) of cyclohexene. It is possible to observe two phases. The mixture was stirred for 24 hours, at 50°C. After that was slowly added 2.1 g $NaHCO_3$ to neutralize the solution, and 1.6 g of Na_2SO_3 to reduce the H_2O_2 excess. The reaction mixture was distilled under reduced pressure (34 mmHg, 30°C). After complete water removal, the remain solid was mill with a mortar and transfer to a sublimation equipment with a magnetic stir bar. Then the (±)-*trans*-1,2-cyclohexanediol was isolated from the reaction mixture by sublimation (2 mmHg, 70°C with stirring), overnight.

Method R: In a 50 mL round-bottomed flask (calibrated) was added 1.9 g (10 mmol) PTSA, and 2.67 mL of H_2O_2 (30 wt.% aq. sol., 2 eq.) and stirrer at room temperature for 5 minutes. Then was added 1.0 mL (10 mmol) of cyclohexene. It is possible to observe two phases. The mixture was stirred for 4 hours, at 75°C . After that was slowly added 1.2 g $NaHCO_3$ to neutralize the solution, and 1.0 g of Na_2SO_3 to reduce the H_2O_2 excess. The reaction mixture was distilled under reduced pressure (34 mmHg, 30°C). After complete water removal, the remaining solid was mill with a mortar and transfer to a sublimation equipment with a magnetic stir bar. Then the (±)-

trans-1,2-cyclohexanediol was isolated from the reaction mixture by sublimation (2 mmHg, 70°C with stirring), for 4 hours.

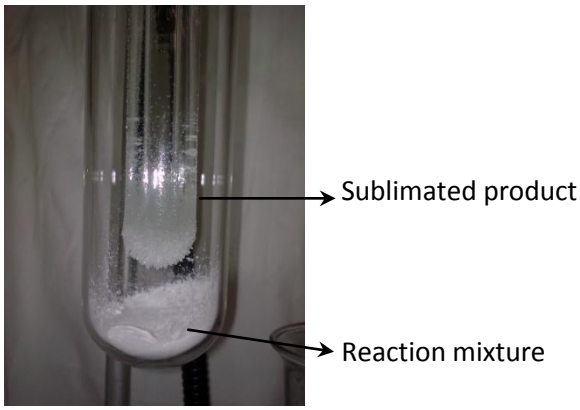
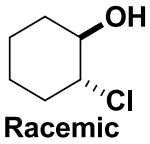


Figure 4.6.1 – Separation of *trans*-1,2-cyclohexanediol from the reaction mixture by sublimation.

The results with of the different experiments performed are described in Table 3.2.11 (please see section 3.2.6, page 147).

4.6.2 Synthesis of *trans*-2-chloro-cyclohexanol (43)



Racemic

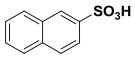
4.6.2.1 General procedure for trans-dihydroxylation of cyclohexene with different catalysts (Method S)

Method S: Sodium salt (30 mol%) and 1 equiv. of HCl were stirred for five minutes, and then was added H_2O_2 (30% aq., 2 equiv.) and again stirred for five minutes. After that cyclohexene (1 or 2.5 mmol) was added. The reaction mixture was stirred for 21 h at 20°C. In the end of the reaction was added chloroacetic acid as internal standard for the yield calculation by ^{1}H NMR. The product yield was calculated by NMR as follows (Internal standard (**IS**) is chloroacetic acid):

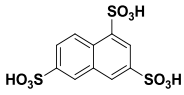
$$mol(diol) = \frac{Integration\ of\ diol\ NMR\ peack\ (2.9\ ppm)}{Integration\ of\ IS\ NMR\ peack\ (3.8\ ppm)} * \frac{IS\ mass\ added}{IS\ Molecular\ Weight}$$

The results for the catalysts tested are described in Table 3.2.1 (please see section 3.2.1, page 129).

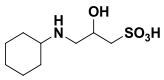
Following Method S (page 206): **HCl** (72.6 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2 mmol) were left to stir for 21 hours at 20°C.



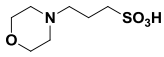
Following Method S (page 206): **NSA** (169.9 mg, 30 mol%), HCl (84.9 mg, 2x30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2 mmol) were left to stir for 21 hours at 20°C.



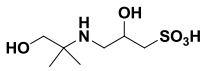
Following Method S (page 206): **NTSA** (320.5 mg, 30 mol%), HCl (217.8 mg, 3×30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2 mmol) were left to stir for 21 hours at 20°C.



Following Method S (page 206): **CAPSO** (71.19 mg, 30 mol%), HCl (49 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2 mmol) were left to stir for 21 hours at 20°C.



Following Method S (page 206): **MOPS** (62.8 mg, 30 mol%), HCl (45.8 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2 mmol) were left to stir for 21 hours at 20°C.



Following Method S (page 206): **AMPSO** (68.1 mg, 30 mol%), HCl (49.2 mg, 30 mol%), H_2O_2 (30% aq., 566.7 mg, 2 equiv.) and cyclohexene (253 µL, 2 mmol) were left to stir for 21 hours at 20°C.

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6 Appendix

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6.1 Rheology

Rheology studies the response of a material when it is applied a strength (tension). Rheological properties report us how a material responds when is subject to a mechanic solicitation, this response is nothing more than the material structure expression due to their chemical composition.[150] Other possible definition for rheology is the science of flow and deformation of materials.[151] The definition of flow can be described with a simple example: if water is carried carefully in a bucket, it is certainly moving, but it is not flowing, however if the water is poured out, it is flowing. The difference is that, in flow, elements of the liquid are deforming, and adjacent points in the liquid are moving relative to one another.[299] There are two basic kinds of flow, depending on the relative movement of adjacent particles of the liquid: shear flow and extensional flow. In shear flow adjacent particles move over or past each other, and in extensional flow adjacent particles move away from each other (Figure 6.1.1).

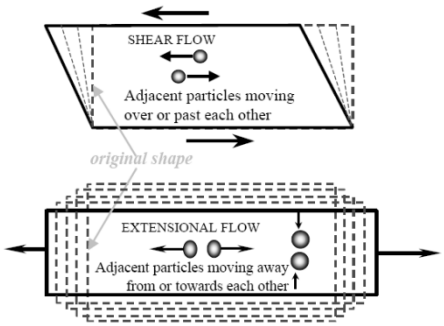


Figure 6.1.1 – Particle motion in shear and extensional flows[299].

Instead of a particle consider now a hypothetic layer as an ensemble of particles (Figure 6.1.2). The movement of several hypothetic layers sliding over each other is such as the velocity of each layer increases linearly with respect to its neighbour bellow. It is possible to define (Figure 6.1.3):

- **Shear or shear strain**[300] ($\gamma=\delta/h$, adimensional) – the deformation caused by a force (F);
- **Shear rate** ($\dot{\gamma}=V/h$, unit s^{-1}) – the gradient of the velocity, in the direction at right angles to the flow;
- **Shear stress** ($\sigma=F/A$, unit Pa) as the force per unit area creating or produced by the flow.

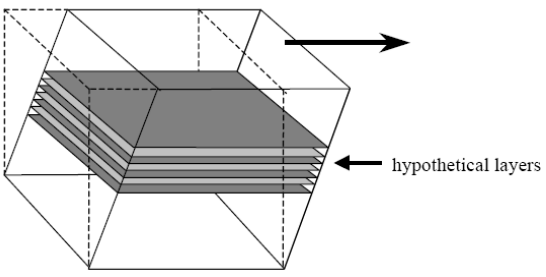


Figure 6.1.2 – Hypothetical layers in shear flow[299]

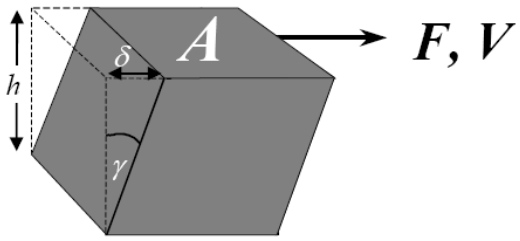


Figure 6.1.3 – Definition diagram for shear flow[299]; h – separation height; A – area; F – force; V – velocity; δ – displacement; γ – angle of shear (if the deformation is sufficiently small the angle of shear γ (expressed in rad) equals the shear strain).[301]

The rheological behaviour of materials is diverse and very complex. In addition to its nature, the materials may have different behaviours according to the conditions to which they are subjected, such as the tension and speed of deformation, or the time of solicitation and temperature. In this way, it is shown to be impossible describe the behaviour of materials by a unique law which takes into account all these variables (deformation (γ, shear), tension (σ, shear stress), shear rate ($\dot{\gamma}$), time (t), temperature (T), …) and adaptable to every situations: f(γ, σ, $\dot{\gamma}$, t, T,…)[150, 302]. In this context, scientists have proposed several rheological models that describe the mechanical behaviour of various materials correlating some rheological properties. These models have underlying the definition of three theoretical states of materials: linear elastic solid (Hooke solid), perfect fluid (Newtonian liquid) or viscoelastic material[151].

In linear elastic solids, or Hooke solids there is a proportional relation between the tension and the deformation, time independent ($\sigma=E\cdot\gamma$, where E (unit Pa) is the elastic or the Young constant that depends on the interactions between the solid molecules). The behaviour of these materials is purely elastic, any deformation reverses spontaneously when an applied force is removed. The energy is stored by the system, and then released.

The perfect fluid has a plastic behaviour where any deformation ceases when the applied force is removed and the material don't reverse to the original form. Energy performs work on the material.[151] The physical property that describes its resistance to flow resulting from the inter layers friction is called viscosity (η). The simplest model was proposed by Newton where the force, or resistance (shear stress) is proportional to the velocity of movement (shear rate), ($\sigma=\eta\cdot\dot{\gamma}$, where the proportional constant η is the viscosity, Pa.s). Several liquids follow the Newton law, so they are called Newtonian liquids. For these materials the viscosity does not vary with deformation rate or time (although varying with the temperature and pressure).

Both models represent's properties of many real materials and work well in describing their behaviour with considerably high degree of accuracy. However, there are numerous other real materials which are not described by the above-mentioned Newton and Hooke laws. Rheology

relies on the idea that non-Newtonian and non-Hookean materials exist in reality[299, 302]. In between elastic and viscous behaviour are viscoelastic materials. This non-Newtonian behaviour normally results from suspensions of particles with flexibility and various forms which may form temporary links between them or, internal structures more or less complex establishing networks more or less organized in the form of emulsion or gel[150]. The viscosity of a non-Newtonian fluid is not intrinsic from the material, can be shear rate dependent (η=f(γ̇)) or time depending (η=f(t)), so is called apparent viscosity (η_0) to differentiate from the shear viscosity (η) of Newtonians fluids. When the apparent viscosity is shear rate dependent, the material can be shear-thickening (apparent viscosity increases with increased stress), or shear-thinning (apparent viscosity decreases with increased stress)[303], Figure 6.1.4a. If the apparent viscosity is time dependent, the material can be thixopropic (apparent viscosity decreases with duration of stress) or, rheopectic (apparent viscosity increases with duration of stress)[303], Figure 6.1.4b.

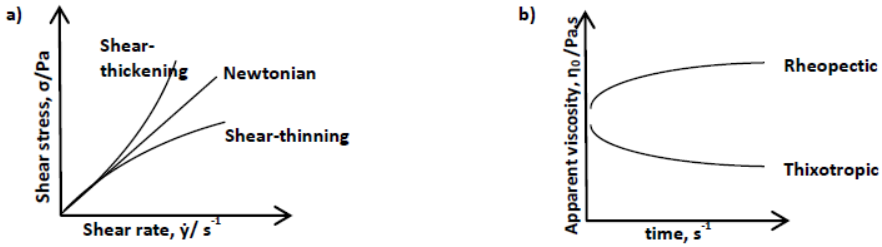


Figure 6.1.4 – Classification of fluids based on variation of: a) shear stress (σ/Pa) with shear rate (γ̇/s-1); b) apparent viscosity (η_0/Pa.s) with time (γ̇/s-1) with constant shear rate, (figures adapted from [150]).

The aim of this part of the work is to characterize some ILs, so some properties of these fluids will be further described. In summary, a Newtonian behaviour follow some characteristics: the shear viscosity (η) does not vary with shear rate (γ̇), (Figure 1.2.6a) and the shear rate is proportional to the shear stress of the material (Figure 1.2.6b)[151].

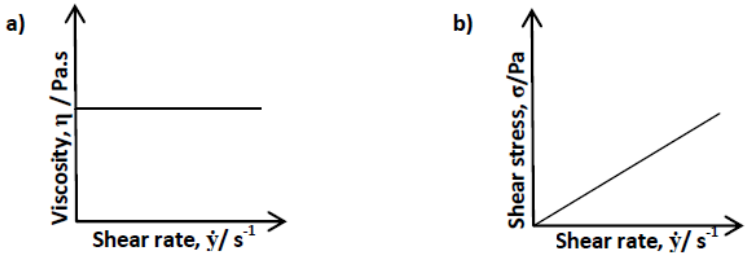


Figure 6.1.5 – Variation of: a) viscosity, η/Pa.s with shear rate γ̇/s-1, and b) shear stress, σ/Pa with shear rate γ̇/s-1.

Variation of Newtonian viscosity with temperature

The viscosity of all simple liquids decreases with increase in temperature because of the increasing Brownian motion of their constituent molecules. Generally the higher the viscosity, the greater is the rate of decrease[300]. Many attempts have been made to describe the viscosity/temperature dependence mathematically, so that by 1951 Partington had listed nearly 50[299]. The most widely-used expression is that due to Andrade $\log_{10} \eta = A + B/T$ (where T is the temperature in K). This equation is also known by other names, for instance the Arrhenius law where B is replaced by E_a/R where E_a is an activation energy for viscous flow and R is the universal gas constant[151]. The activation energy E_a is said to be a measure of the height of a potential energy barrier associated with the force needed to produce elemental quantum steps in the movement of molecules. Another equation used to describe this temperature dependence of viscosity is the Vogel-Fulcher-Tamman (VFT) equation ($\eta = \eta_0 \exp(B/(T-T_0))$, where B and T are adjustable parameters).

The effect of pressure on viscosity

The effect of pressure on viscosity is such that as the pressure goes up, the viscosity increases. However the changes are quite small for pressures differing from atmospheric pressure by about one bar[151], therefore, for most practical purposes, the pressure effect is ignored by rheometers users.

Limit of Newtonian behaviour

At a high enough shear rate, all liquids become non-Newtonian[151, 299] (Figure 6.1.6). At high shear rate values, the intermolecular binding can be broken and then the Newtonian behaviour of the material is not possible any more.

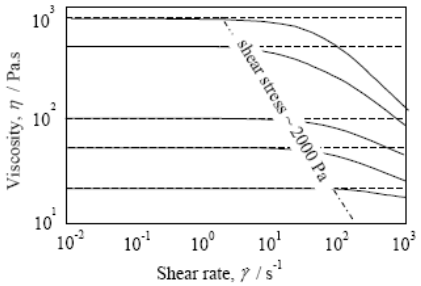


Figure 6.1.6 – Flow curves for a series of silicone oils[299]. The Newtonian fluid has a non-Newtonian behaviour at a shear stress of around 2000 Pa[299].

Rheometry refers to the experimental techniques used to determine the rheological properties of materials. That is, the quantitative and qualitative relationships between deformations and

stresses and their derivatives, along the time.[304] The choice of the adequate experimental technique depends on the rheological property which has to be determined, for example steady shear viscosity and linear viscoelastic, among others. There are three fundamental rheological tests to evaluate the rheological behaviour of the material: steady, oscillatory and static.[150] The steady tests consist in the application of a gradient of tension (rheometers with controlled tension) or a gradient of deformation (rheometers with controlled deformation), linear or logarithmic, unidirectional in the sample. These tests are used for the determination of apparent viscosity at several rates of deformation, allowing the determination of flow curves (representation of shear stress *vs.* shear rate) and viscosity curves (representation of viscosity *vs.* shear rate)[152]. For Newtonian fluids the steady tests are sufficient to characterize the material, on the contrary, for the characterization of non-Newtonian materials is necessary several others, more complex tests.

A rheometer is a laboratory device used to measure the way in which a liquid, suspension or slurry flows in response to applied forces. In this work was used a shear stress rheometer with controlled stress fitted with a cone-plate geometry. The sample is placed between the bottom plate fixed, which incorporates the system of temperature control, and a mobile system of measurement above (cone), whose axis is perpendicular to the plate plane (Figure 6.1.7). The system cone-plate allows a more uniform stress throughout the sample and lower values of inertia when compared with other systems. [152]

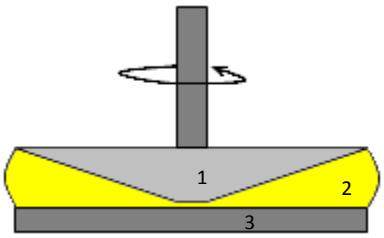


Figure 6.1.7 – Scheme of the cone(1)-plate(3) system with the sample (2).

The main difference of a rheometer and a simple viscosimeter is that with a viscosimeter is only possible to perform steady tests (viscosity determination), whereas with rheometer is possible to perform steady and oscillatory tests, to measure the viscoelasticity of the material.

6.2 Carbohydrates extraction from aqueous phase using ILs

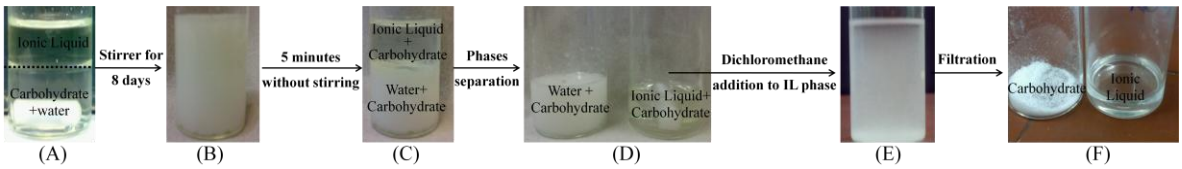


Figure 6.2.1 – Scheme of the extraction experiments (photographs of example made for the extraction of glucose from the IL [Aliquat®][Cl]). The sugar (or sugar mixture) is dissolved in the aqueous solution (A), and mixed with the hydrophobic IL for one week (B). The two phases are separated (C). Dichloromethane is added to the organic layer (D), in which sugar (or sugar mixture) dissolved in the IL precipitate immediately (E). Following filtration and washing with dichloromethane the sugar (or sugar mixture) recovered shows no trace of IL (F). After evaporation of the solvent, the IL is recovered without any traces of carbohydrates (F), and can be recycled for, at least, three times (the recycling experiments was made only with the [(di-*h*)$_2$DMG][DCA]).

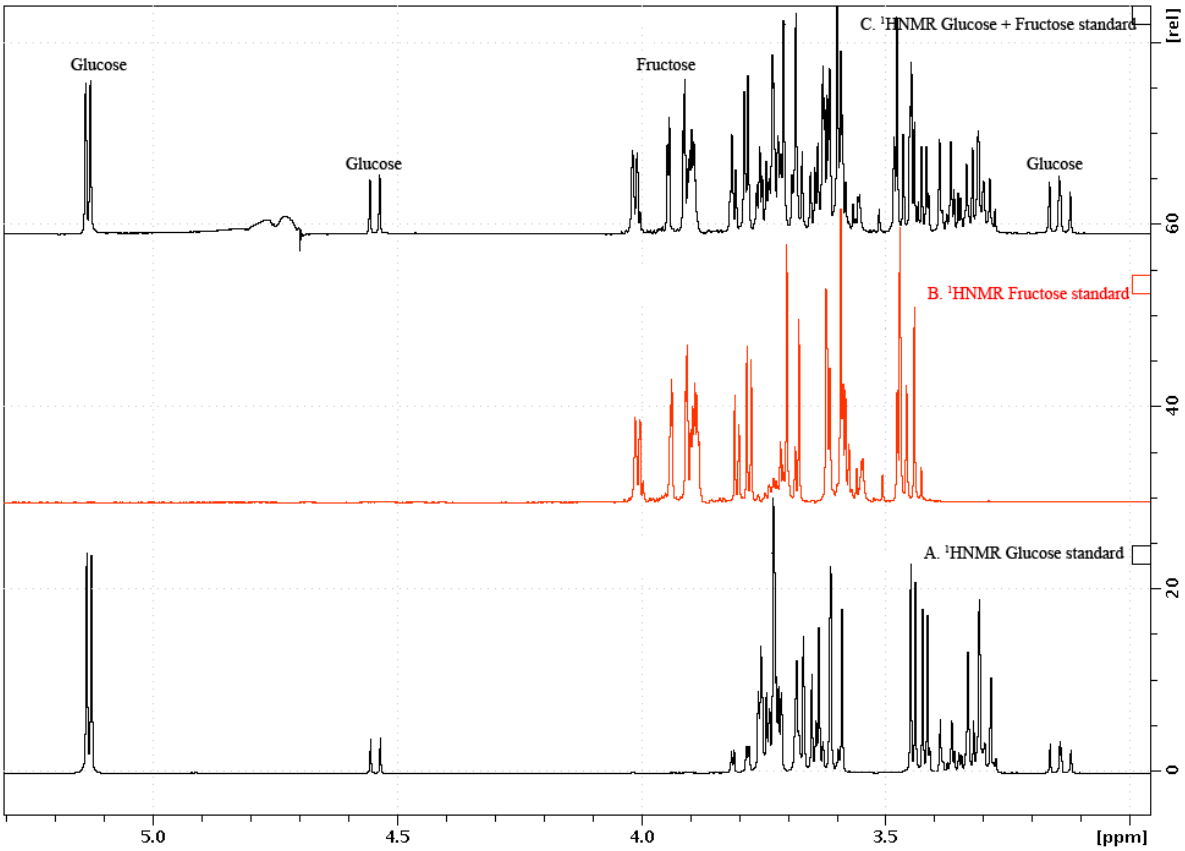


Figure 6.2.2 – ^{1}HNMR spectrum of monosaccharide glucose (A), monosaccharide fructose (B) and a mixture glucose and fructose (1:1 wt.) (C).

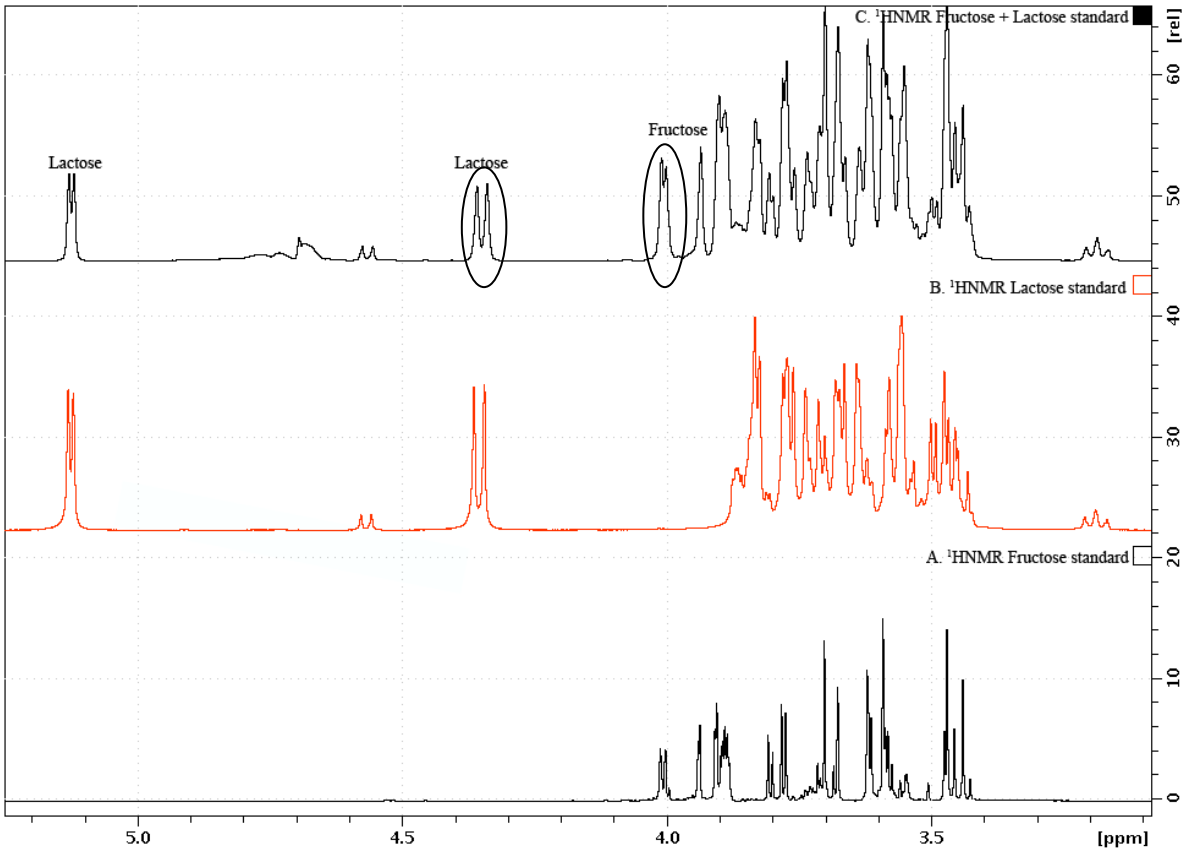


Figure 6.2.3 – ^{1}HNMR spectrum of monosaccharide fructose (A), disaccharide lactose (B) and a mixture of fructose and lactose (1:1 wt.) (C).

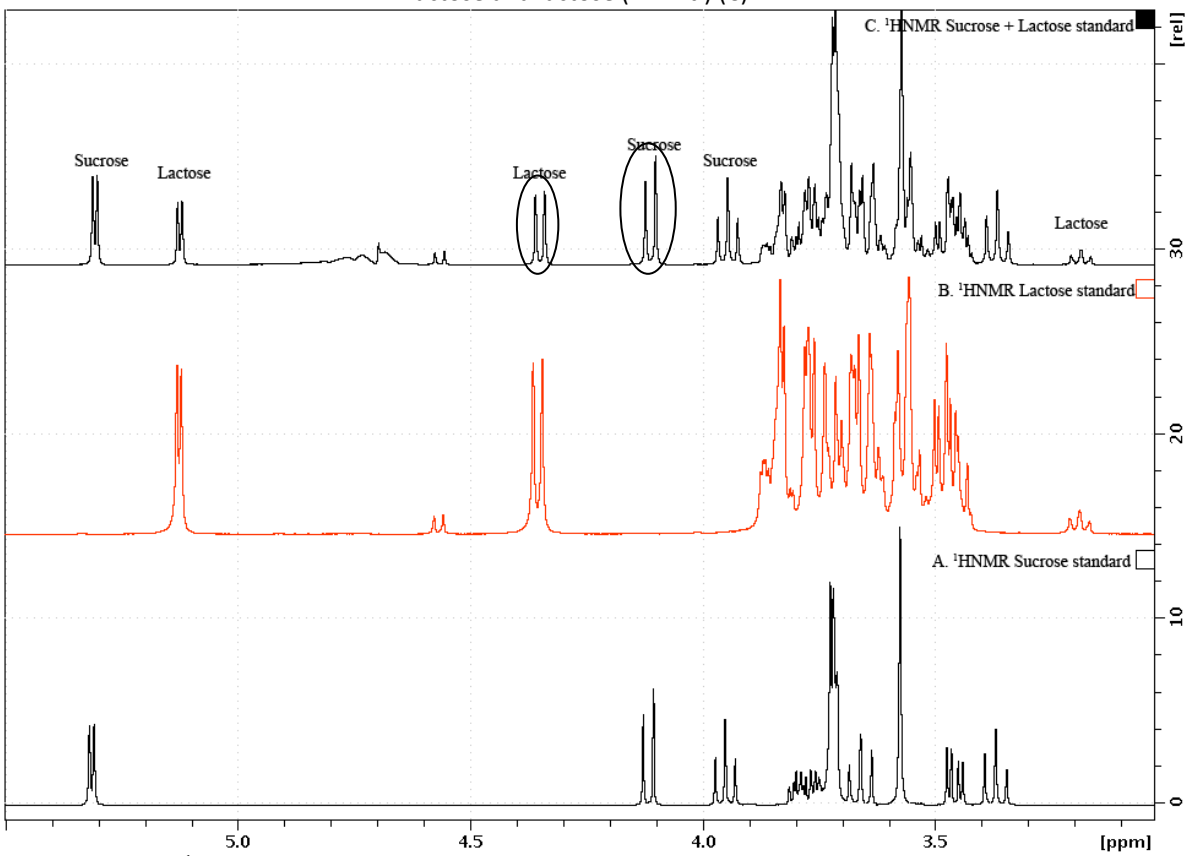


Figure 6.2.4 – ^{1}HNMR spectrum of disaccharide sucrose (A), disaccharide lactose (B) and a mixture of sucrose and lactose (1:1 wt.) (C).

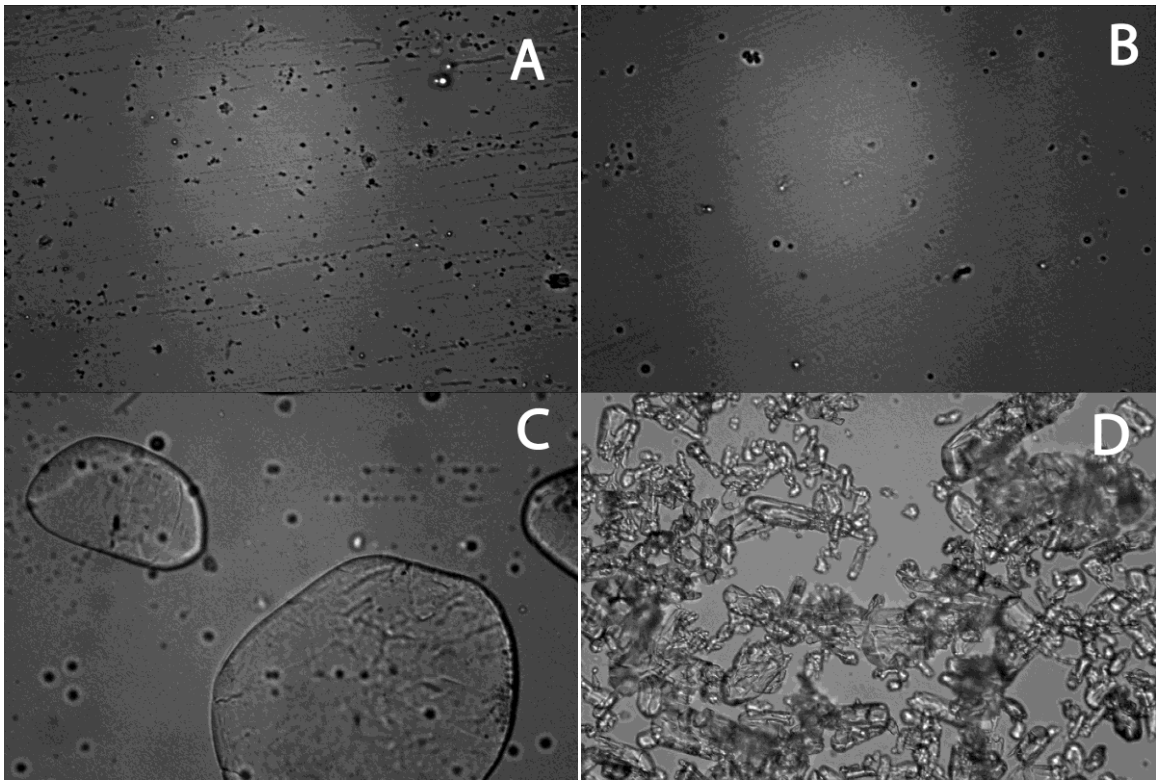


Figure 6.2.5 **–** Optical microscopic image (200x magnification) of: **A** – [MOEOEMIM][Cl] without glucose dissolved (dots are air bubbles and layer imperfections); **B** – [MOEOEMIM][Cl] with glucose dissolved without saturation; **C** – [MOEOEMIM][Cl] saturated with glucose; **D** – Water saturated with glucose. From the comparison of images A and B there is no difference in the IL with (B) or without (A) glucose dissolved; images C and D show glucose crystals when saturated in IL (C) or in water (D).

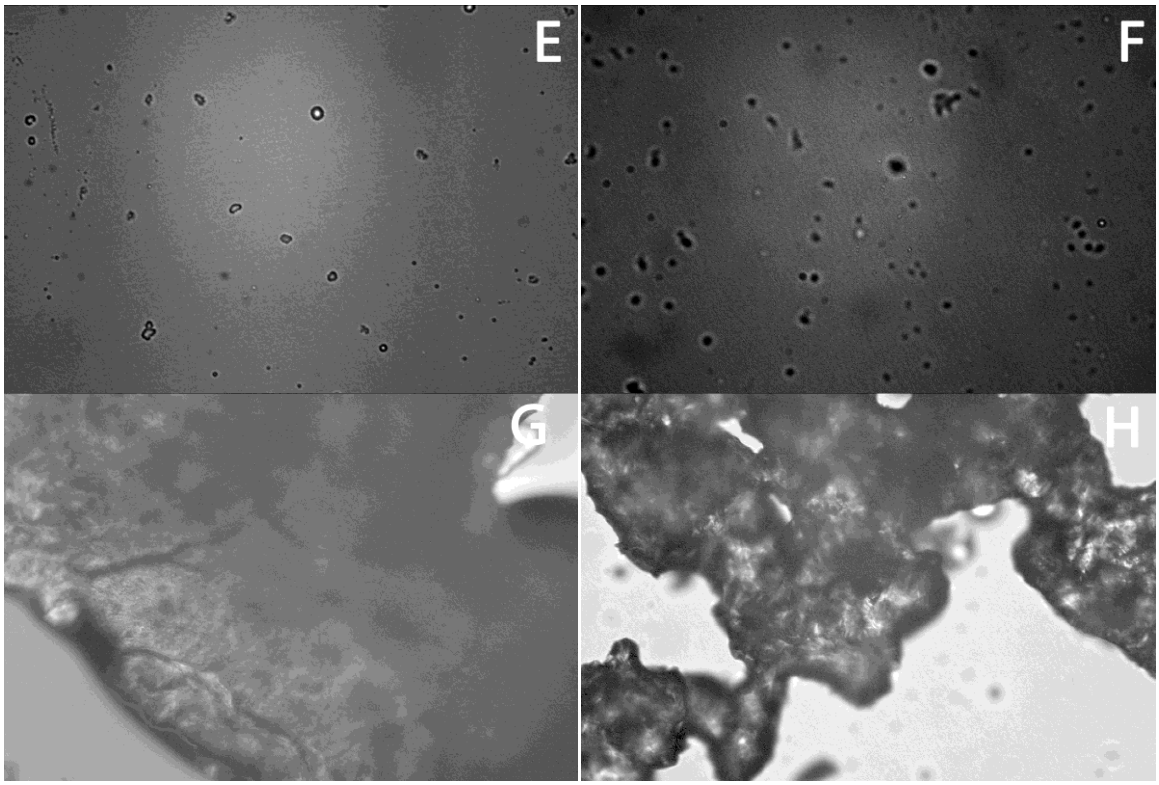


Figure 6.2.6 **–** Optical microscopic image (200x magnification): **E** – [$P_{6,6,6,14}$] [DCA] before extraction experiments (dots are air bubbles in the layer); **F** – [$P_{6,6,6,14}$] [DCA] after extraction experiments (with

glucose dissolved); **G** – Glucose precipitated from the [$P_{6,6,6,14}$] [DCA] with dichloromethane (not crystalline); **H** – Glucose in dichloromethane (not crystalline). From the comparison of images E and F there is no difference in the IL with (F) or without (E) glucose dissolved; image G show that glucose after precipitation from the IL, with dichloromethane, is not crystalline; in image H is possible to see that glucose in dichloromethane is amorphous.

6.3 NMR Spectra of the crude reaction regarding to substrate tolerance under the optimized conditions

6.3.1 ^{1}H and ^{13}C NMR of crude reaction in the presence of *tert*-butyl benzylcarbamate (55)

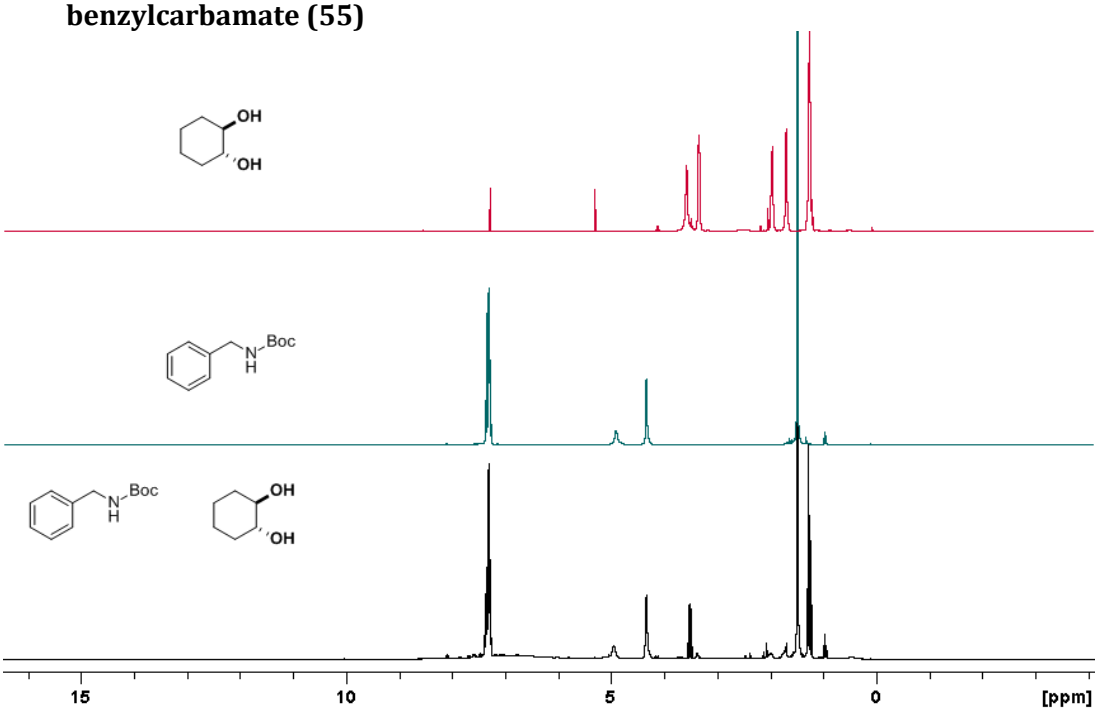


Figure 6.3.1 –^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence of *tert*-butyl benzylcarbamate. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and *tert*-butyl benzylcarbamate (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

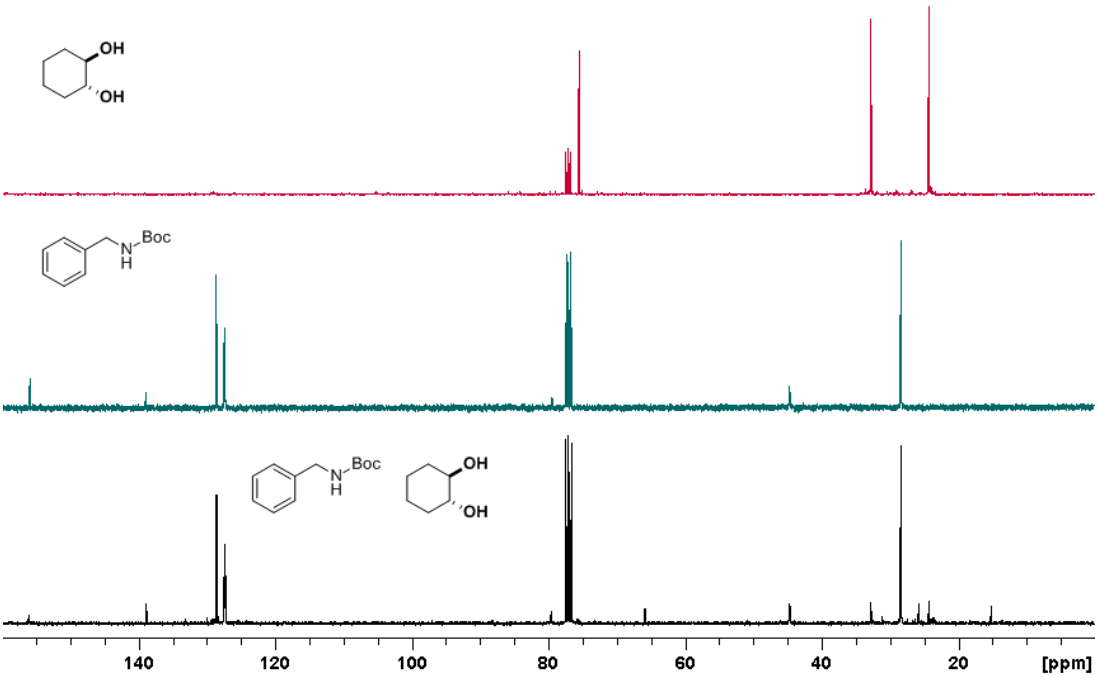


Figure 6.3.2 – ^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence of *tert*-butyl benzylcarbamate. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and *tert*-butyl benzylcarbamate (middle) ^{13}C-NMR NMR spectrum show the

occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

6.3.2 ^{1}H and ^{13}C NMR of crude reaction in the presence of *(+)-cis*-2-benzylaminocyclohexanemethanol (56)

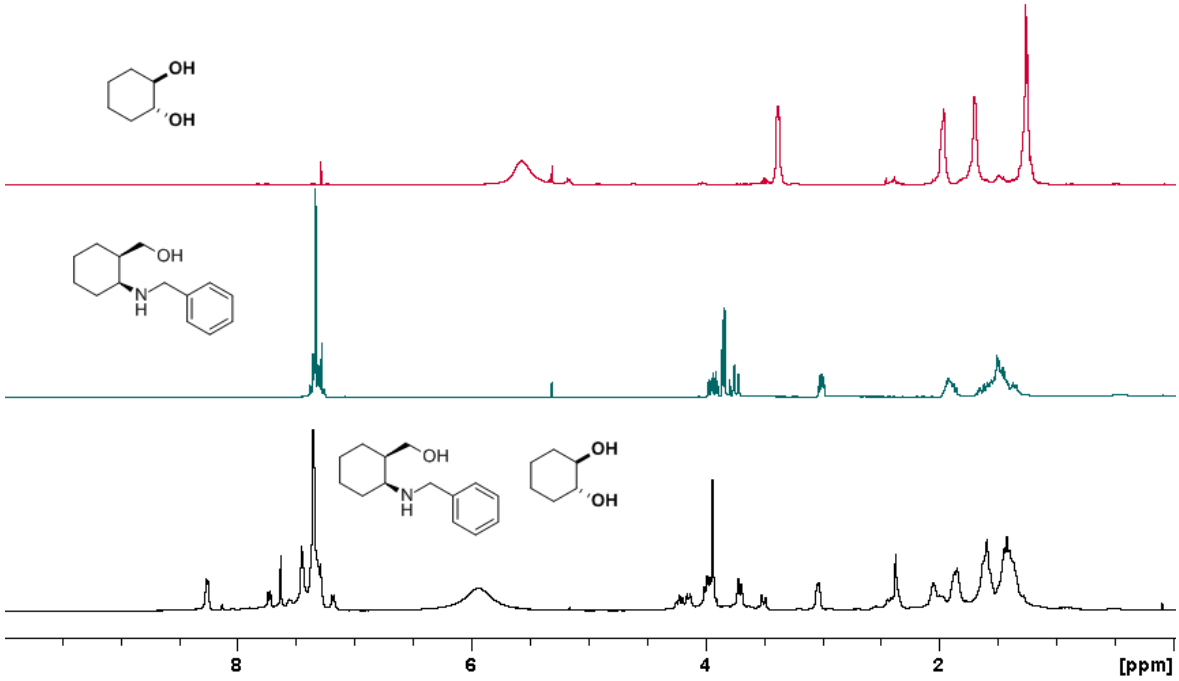


Figure 6.3.3 – ^{1}H-NMR (400MHz, $CDCl_3$) of *trans*-dihydroxylation of cyclohexene in the presence (+)-*cis*-2-benzylaminocyclohexanemethanol. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and (+)-*cis*-2-benzylaminocyclohexanemethanol (middle) ^{1}H-NMR spectrum show no occurrence of dihydroxylation and no stability of this substrate under the reaction conditions.

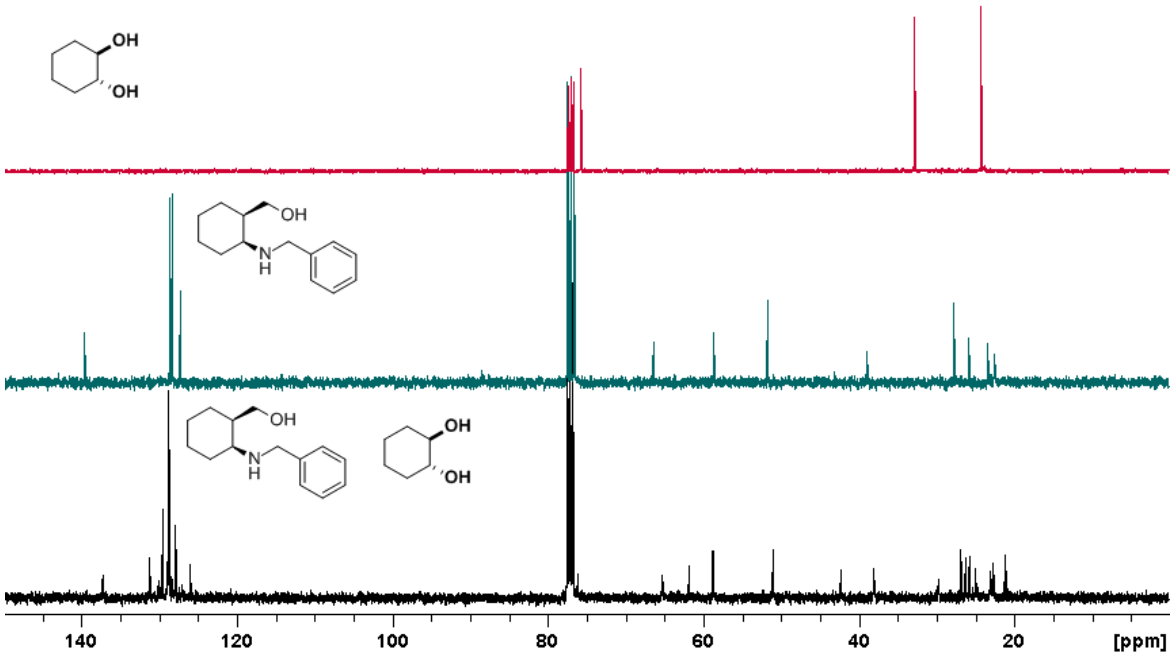


Figure 6.3.4 –– 13C-NMR (400MHz, CDCl3) of the trans-dihydroxylation of cyclohexene in the presence (+)-cis-2-benzylaminocyclohexanemethanol. The comparison of the crude reaction (bottom) with trans-1,2-cyclohexanediol (top) and (+)-cis-2-benzylaminocyclohexanemethanol (middle) 13C-NMR spectrum show no occurrence of dihydroxylation and no stability of this substrate under the reaction conditions.

6.3.3 ^{1}H and ^{13}C NMR of crude reaction in the presence of *of N,N-dimethylbenzamide (57)*

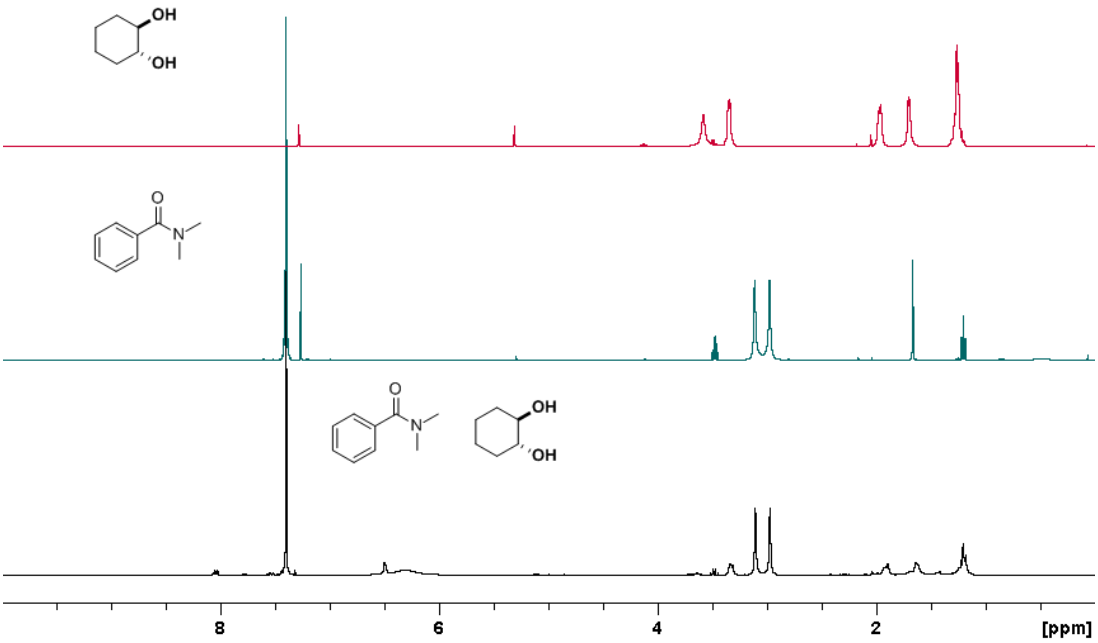


Figure 6.3.5 –^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence of *N,N*-dimethylbenzamide. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and *N,N*-dimethylbenzamide (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

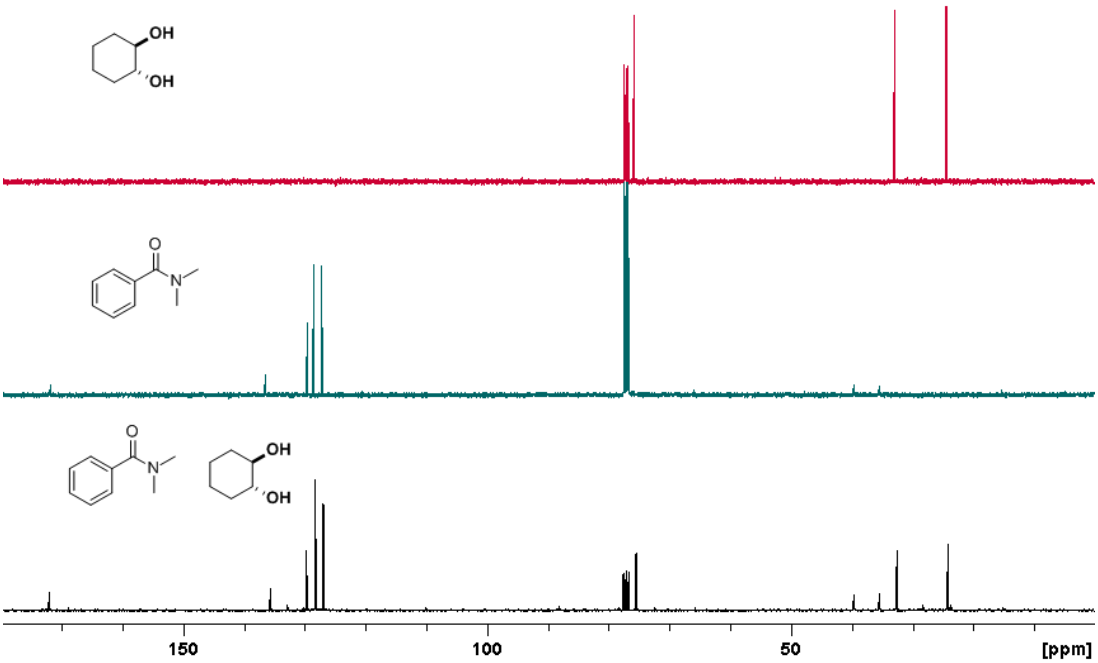


Figure 6.3.6 –^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence of *N,N*-dimethylbenzamide. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and of of *N,N*-dimethylbenzamide (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

6.3.4 ^{1}H and ^{13}C NMR of crude reaction in the presence of *(1R,2S)-cis*-1-amino-indane-2-ol (58)

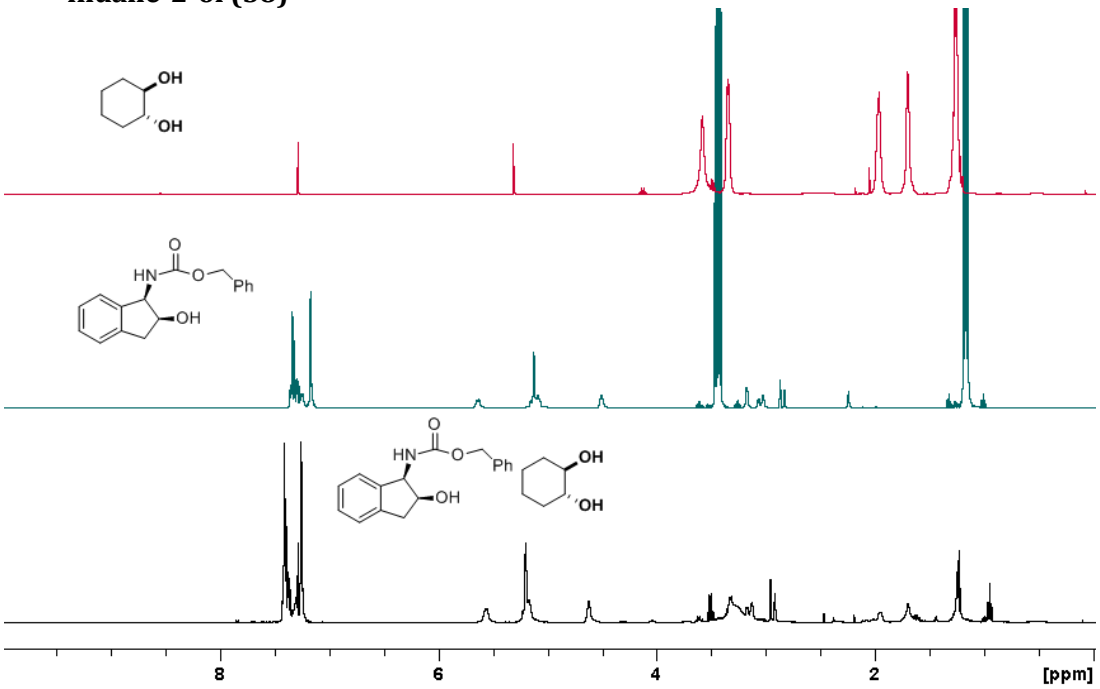


Figure 6.3.7 –^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence of (1R,2S)-*cis*-1-amino-indane-2-ol. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and (1R,2S)-*cis*-1-amino-indane-2-ol (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.. NOTE: ^{1}H-NMR spectrum of (1R,2S)-*cis*-1-amino-indane-2-ol was made in D_2O and ethanol, due to their insolubility in D_2O.

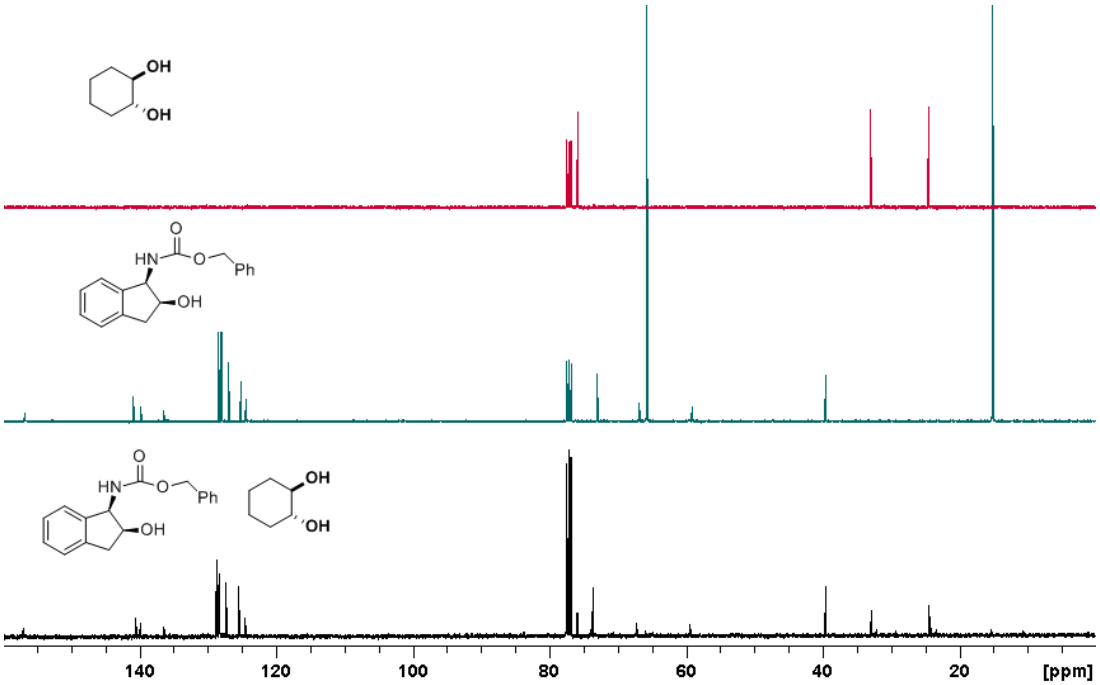


Figure 6.3.8 –^{13}C-NMR (400MHz, CDCl3) of the *trans*-dihydroxylation of cyclohexene in the presence of (1R,2S)-*cis*-1-amino-indane-2-ol. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and of (1R,2S)*cis*-1-amino.indane-2-ol (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction

conditions. NOTE: ^{13}C-NMR spectrum of (1R,2S)-*cis*-1-amino-indane-2-ol was made in D_2O and ethanol, due to their insolubility in water.

6.3.5 ^{1}H and ^{13}C NMR of crude reaction in the presence of *(+)*-taddol (59)

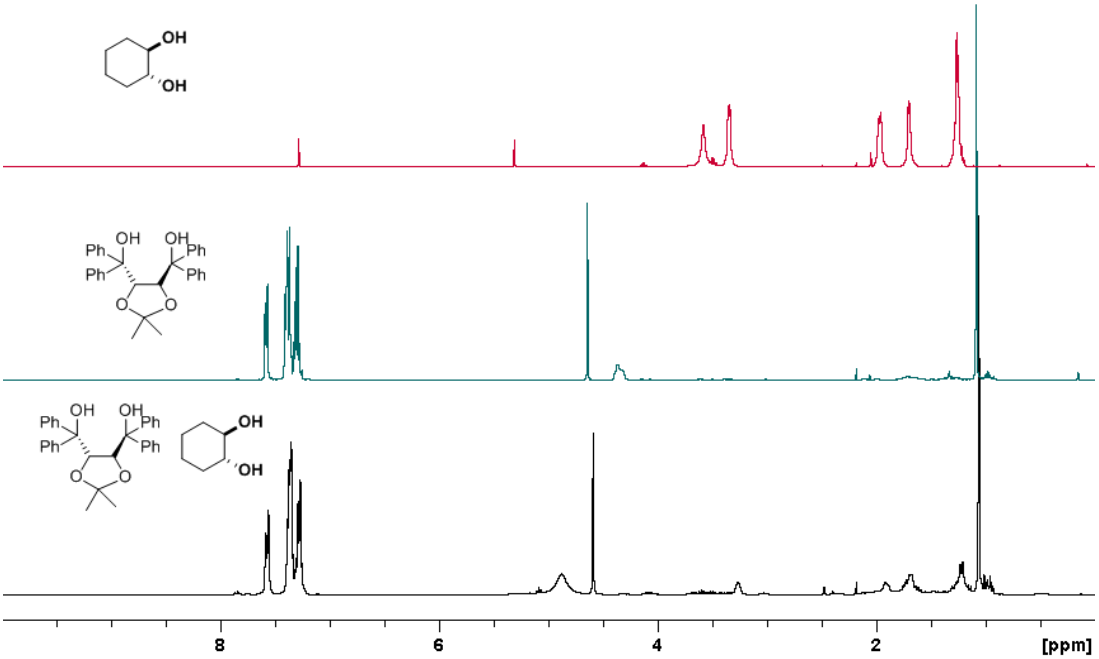


Figure 6.3.9 – ^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence of (+)-taddol. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and (+)-taddol (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

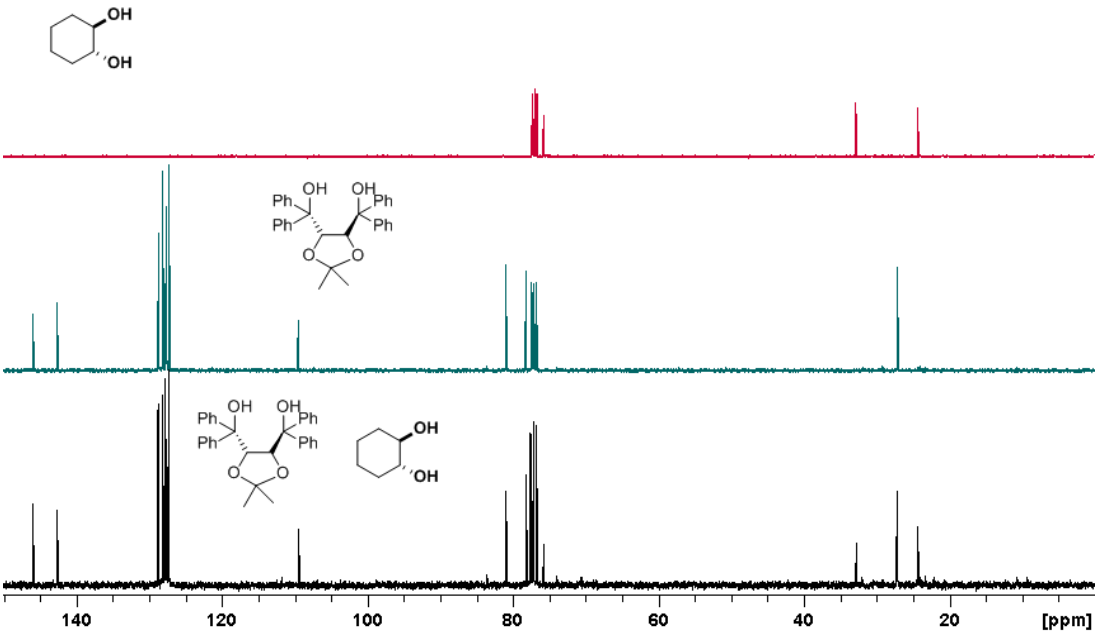


Figure 6.3.10 –^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence (+)-taddol. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and (+)-taddol (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

6.3.6 ^{1}H and ^{13}C NMR of crude reaction in the presence of Fmoc-L-valine (60)

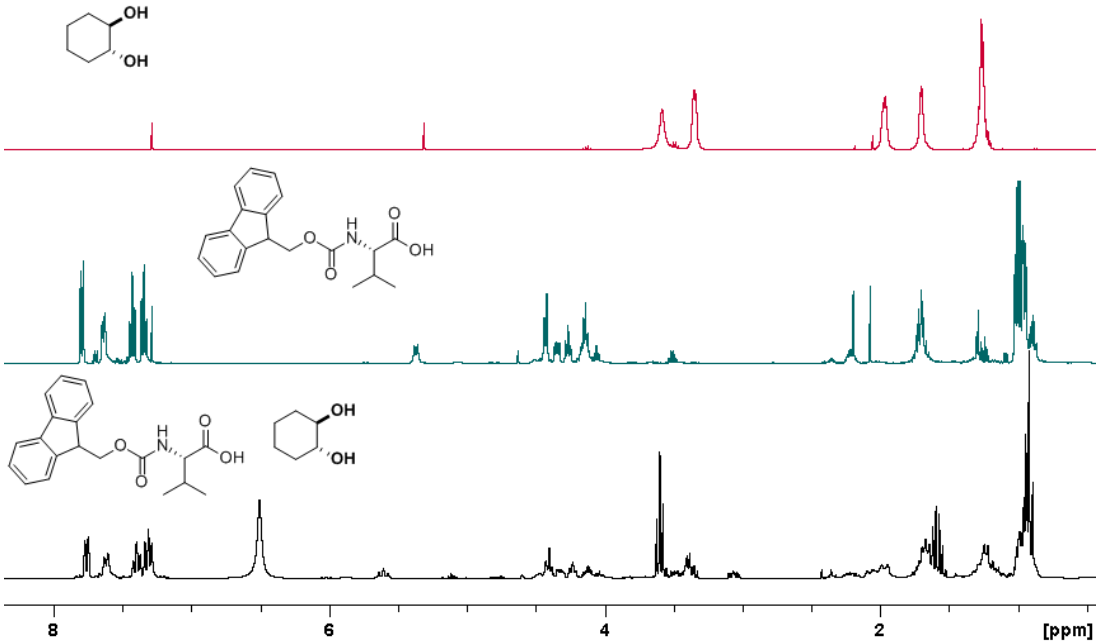


Figure 6.3.11 – ^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence Fmoc-L-valine. The comparison of the crude reaction (bottom) with *trans*-1,2-cyclohexanediol (top) and Fmoc-L-valine (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

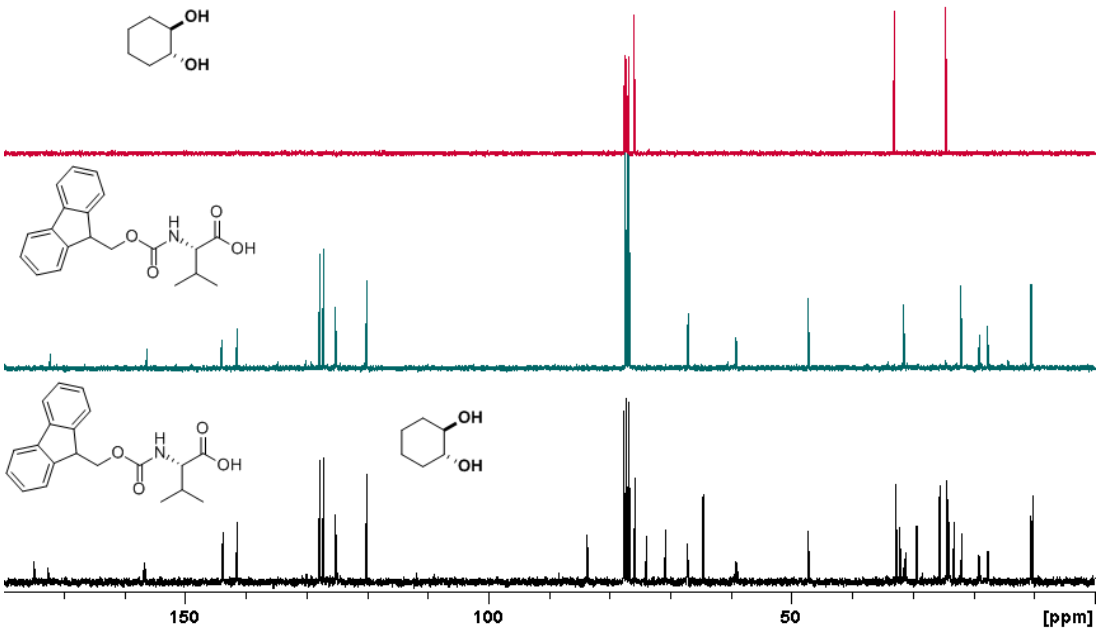


Figure 6.3.12 – ^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence Fmoc-L-valine. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and Fmoc-L-valine (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

6.3.7 ^{1}H and ^{13}C NMR of crude reaction in the presence of *O*-benzyl serine (61)

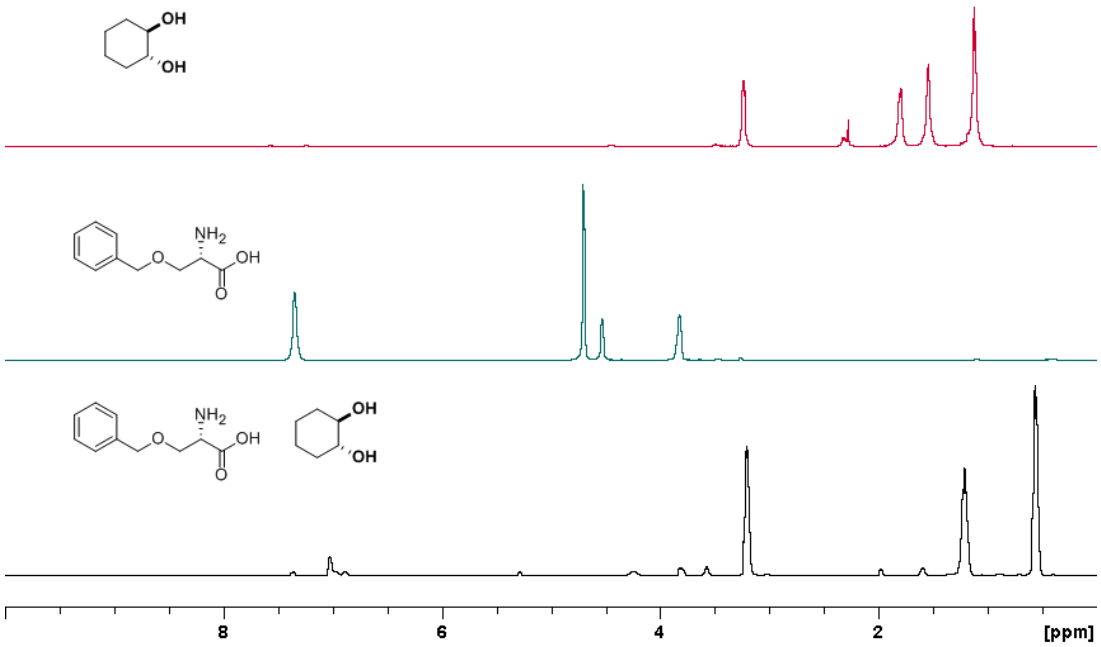


Figure 6.3.13 – ^{1}H-NMR (400MHz, D_2O) of the *trans*-dihydroxylation (20 mol% PTSA)of cyclohexene in the presence *O*-benzyl serine and 1-propanol (3.58, 1.57, 0.94 ppm) as co-solvent. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and *O*-benzyl serine (middle) ^{1}H-NMR spectrum show no occurrence of dihydroxylation although was observed the complete stability of this substrate under the reaction conditions.

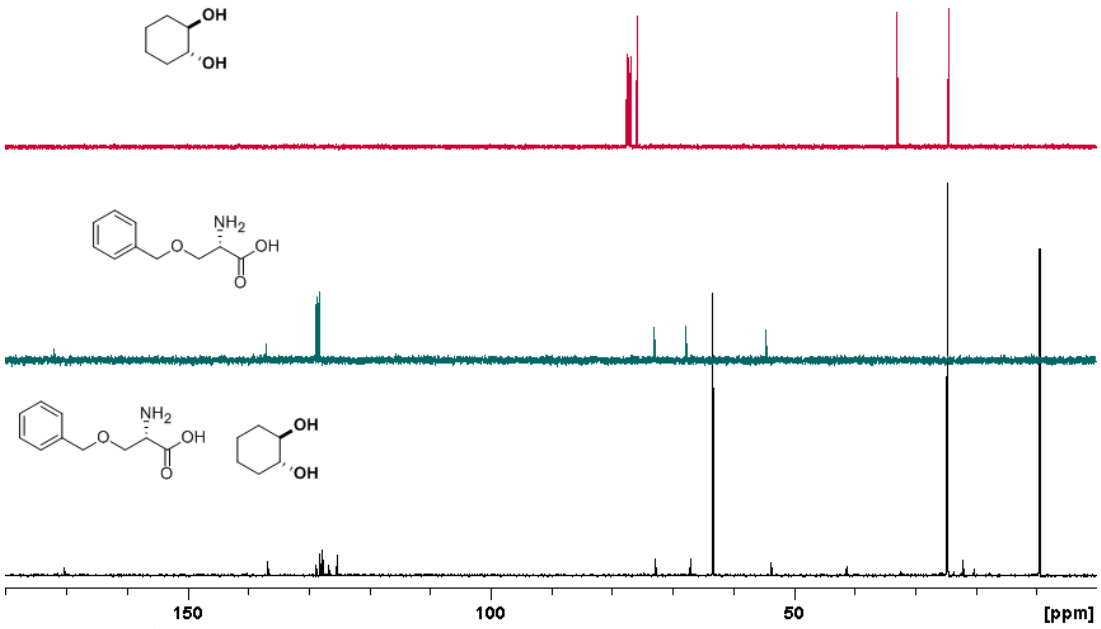


Figure 6.3.14 – ^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation (20 mol% PTSA)of cyclohexene in the presence *O*-benzyl serine and 1-propanol as co-solvent (64.25, 25.89, 10.28 ppm). The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and *O*-benzyl serine (middle) ^{13}C-NMR spectrum show no occurrence of dihydroxylation although was observed the complete stability of this substrate under the reaction conditions.

6.3.8 ^{1}H and ^{13}C NMR of crude reaction in the presence of *O*-benzyl serine (61)

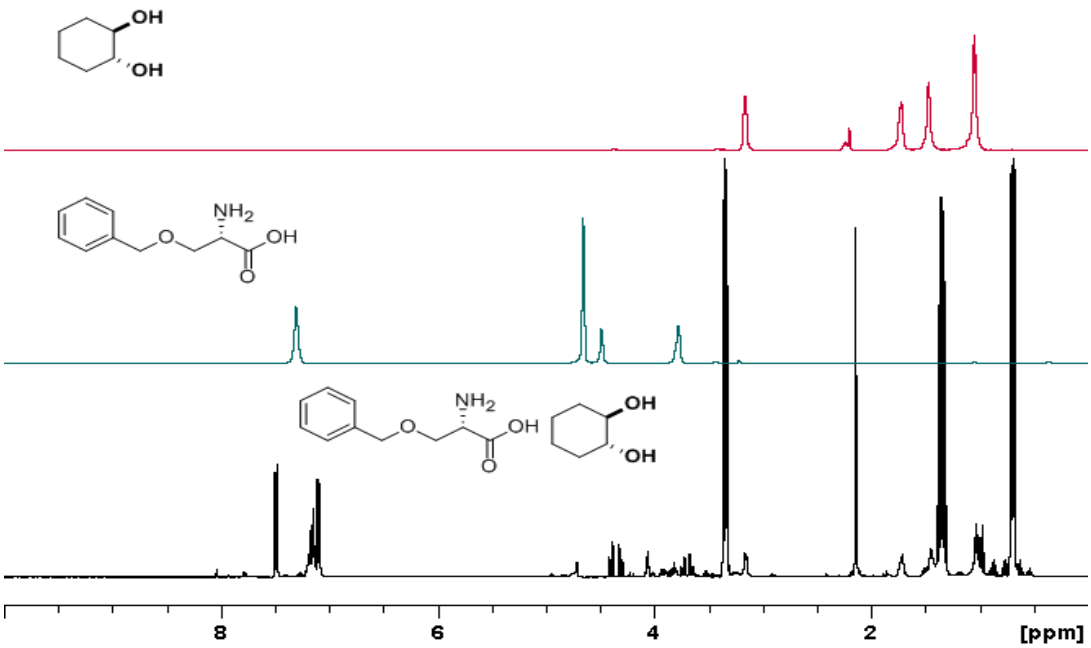


Figure 6.3.15 – ^{1}H-NMR (400MHz, D_2O) of the *trans*-dihydroxylation (70 mol% PTSA) of cyclohexene in the presence *O*-benzyl serine and 1-propanol (3.58, 1.57, 0.94 ppm) as co-solvent. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and O-benzyl serine (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

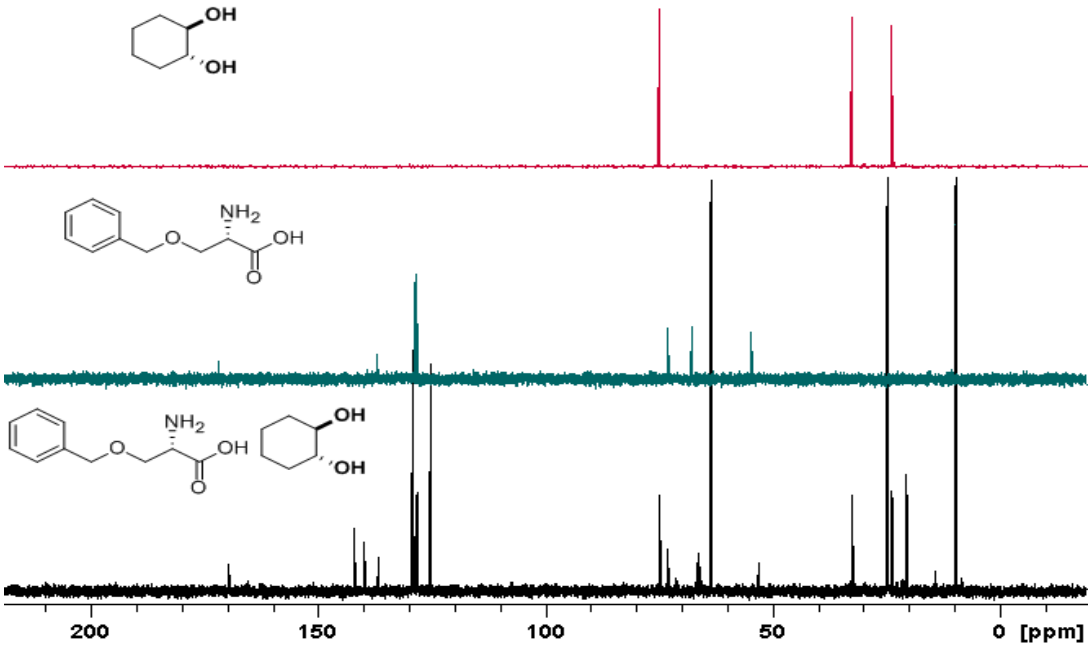


Figure 6.3.16 – ^{13}C-NMR (400MHz, D_2O) of the *trans*-dihydroxylation (70 mol% PTSA) of cyclohexene in the presence *O*-benzyl serine and 1-propanol (64.25, 25.89, 10.28 ppm) as co-solvent. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and O-benzyl serine (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

6.3.9 ^{1}H and ^{13}C NMR of crude reaction in the presence of octyl 4-methylbenzenesulfonate (62)

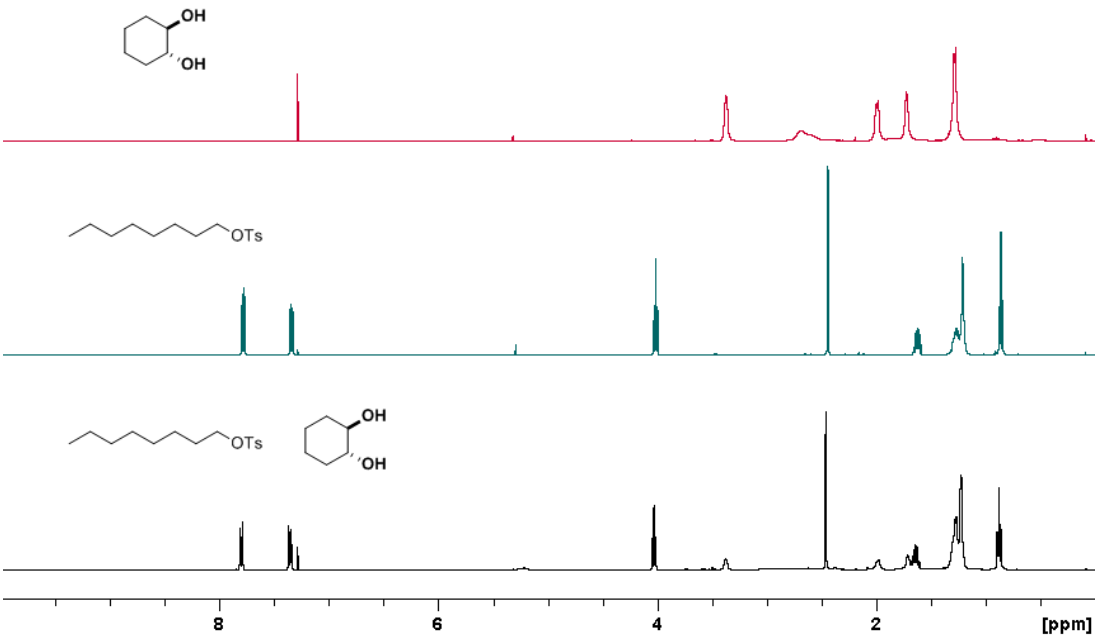


Figure 6.3.17 –^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence octyl 4-methylbenzenesulfonate. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and octyl 4-methylbenzenesulfonate (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

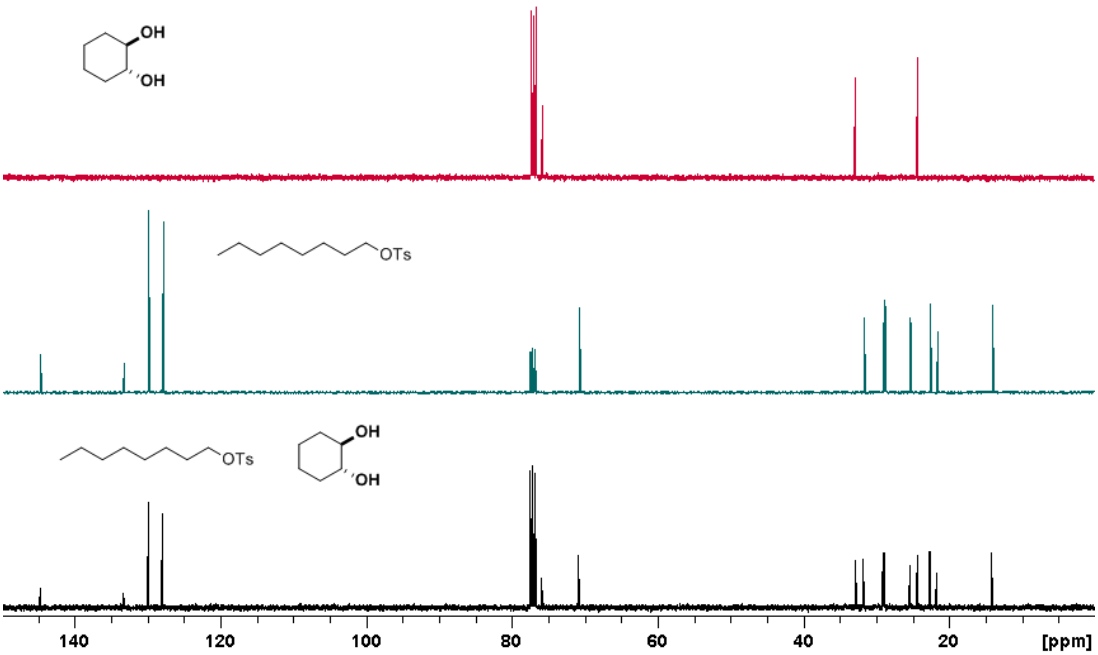


Figure 6.3.18 –^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence octyl 4-methylbenzenesulfonate. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and octyl 4-methylbenzenesulfonate (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

6.3.10 ^{1}H and ^{13}C NMR of crude reaction in the presence of *tert*-butyldimethyl(1-phenylethoxy)silane (63)

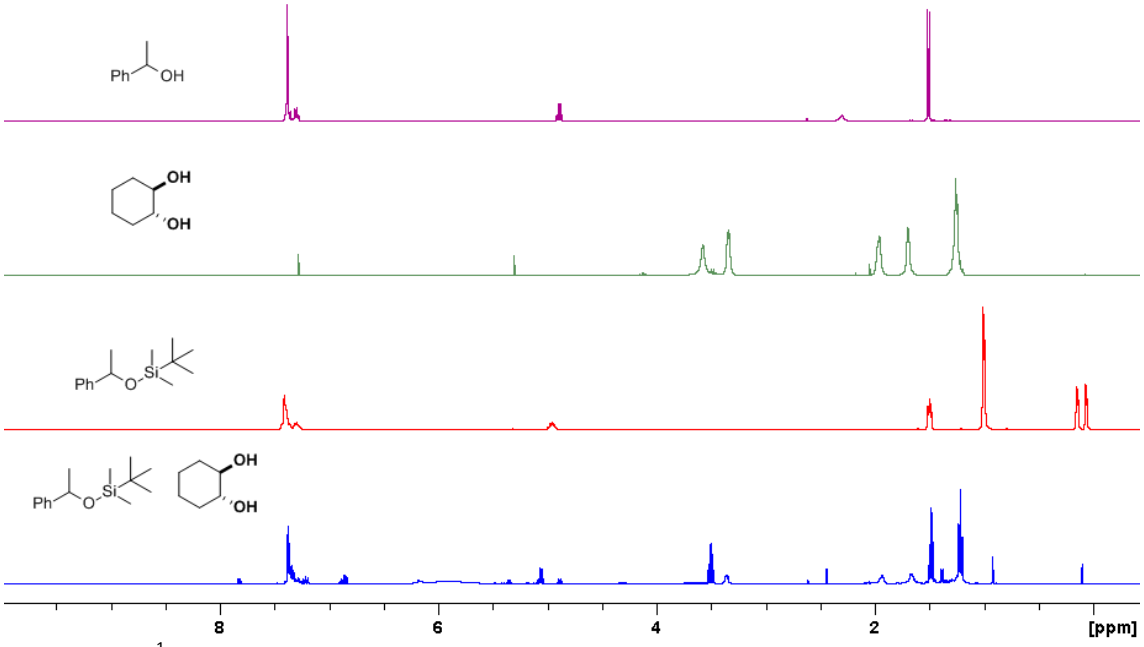


Figure 6.3.19 –^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence *tert*-butyldimethyl(1-phenylethoxy)silane. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (middle) and *tert*-butyldimethyl(1-phenylethoxy)silane (middle) ^{1}H-NMR spectrum show the occurrence of dihydroxylation although this substrate was not stable under the reaction conditions. It was possible to isolate phenylethanol (top) from the crude reaction.

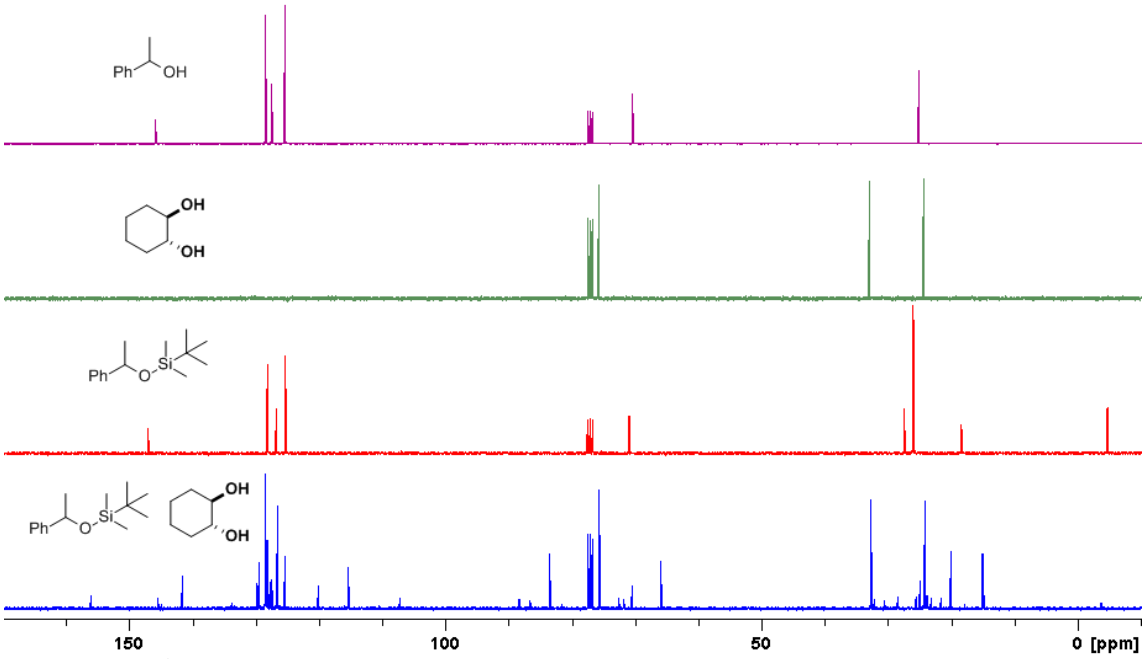


Figure 6.3.20 –^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence *tert*-butyldimethyl(1-phenylethoxy)silane The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and *tert*-butyldimethyl(1-phenylethoxy)silane (middle) ^{13}C-NMR spectrum show the occurrence of dihydroxylation although this substrate was not stable under the reaction conditions. It was possible to isolate phenylethanol (top) from the crude reaction.

6.3.11 ^{1}H and ^{13}C NMR of crude reaction in the presence of *5α*-cholestan-3-one (64)

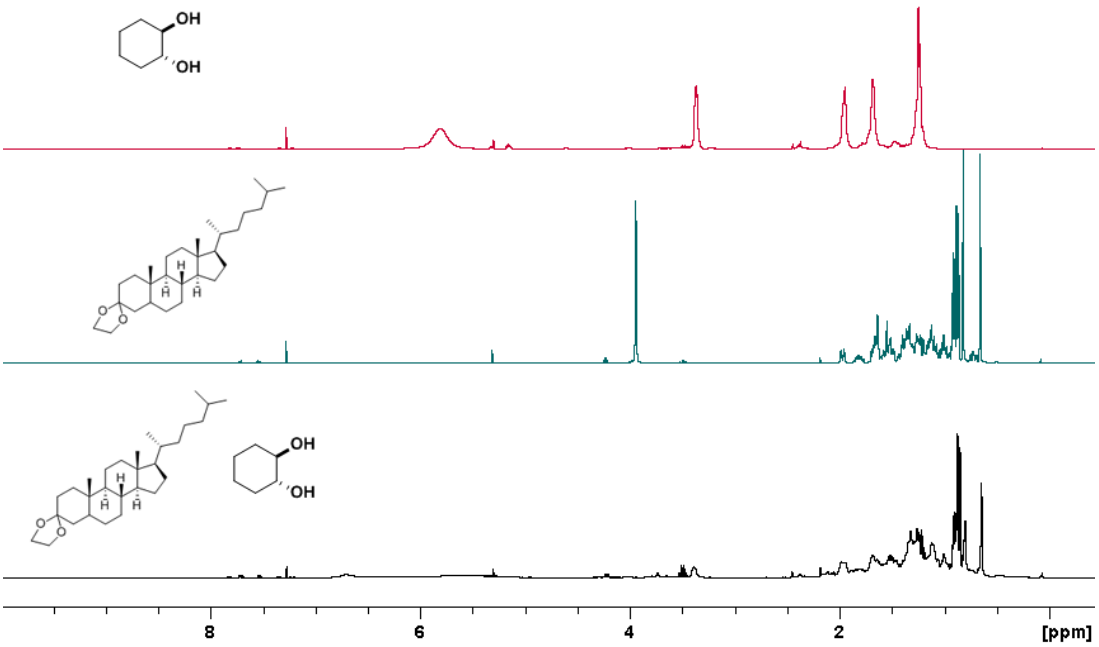


Figure 6.3.21 – ^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence 5α-cholestan-3-one ethylene ketal. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and 5α-cholestan-3-one ethylene ketal (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation although this substrate was not stable under the reaction conditions.

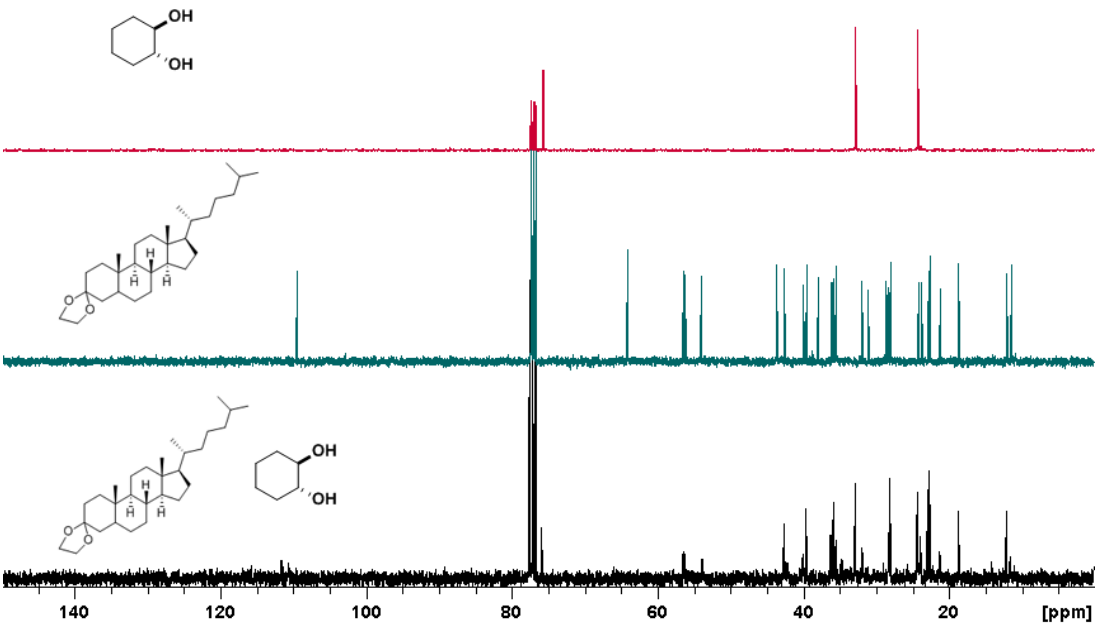


Figure 6.3.22 – ^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence 5α-cholestan-3-one ethylene ketal. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and 5α-cholestan-3-one ethylene ketal (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation although this substrate was not stable under the reaction conditions.

6.3.12 ^{1}H and ^{13}C NMR of crude reaction in the presence of *5α*-cholestan-3-yloxy(methoxy)ethyl trimethylsilane (65)

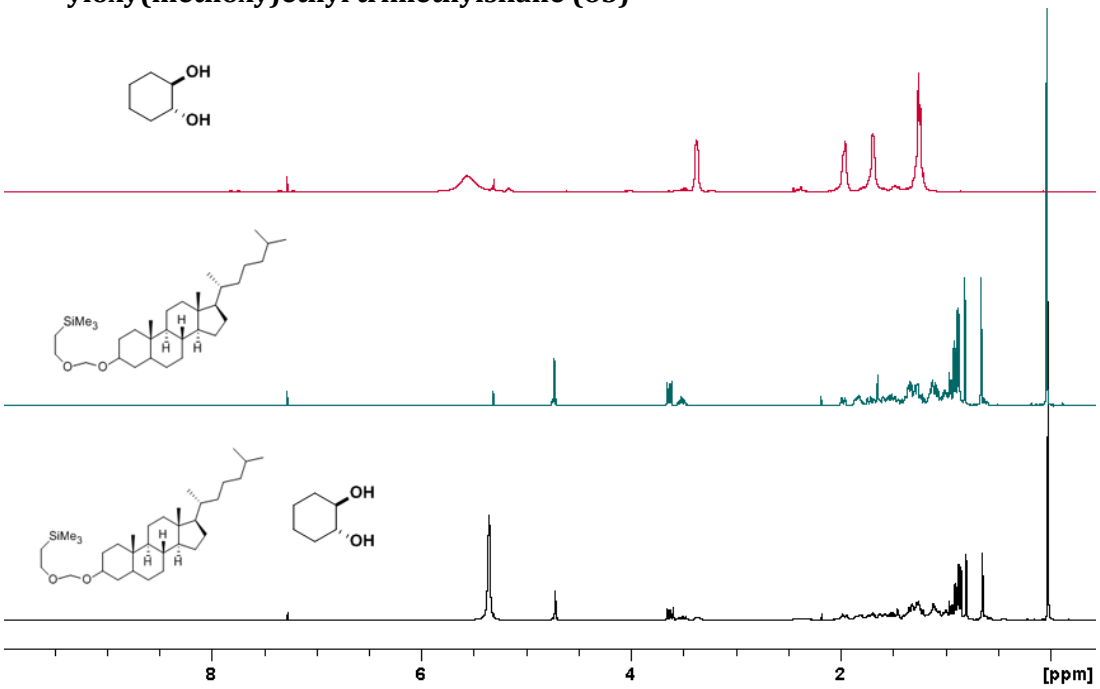


Figure 6.3.23 – ^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence 5α-cholestan-3-yloxy(methoxy)ethyl trimethylsilane. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and 5α-cholestan-3-yloxy(methoxy)ethyl trimethylsilane (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

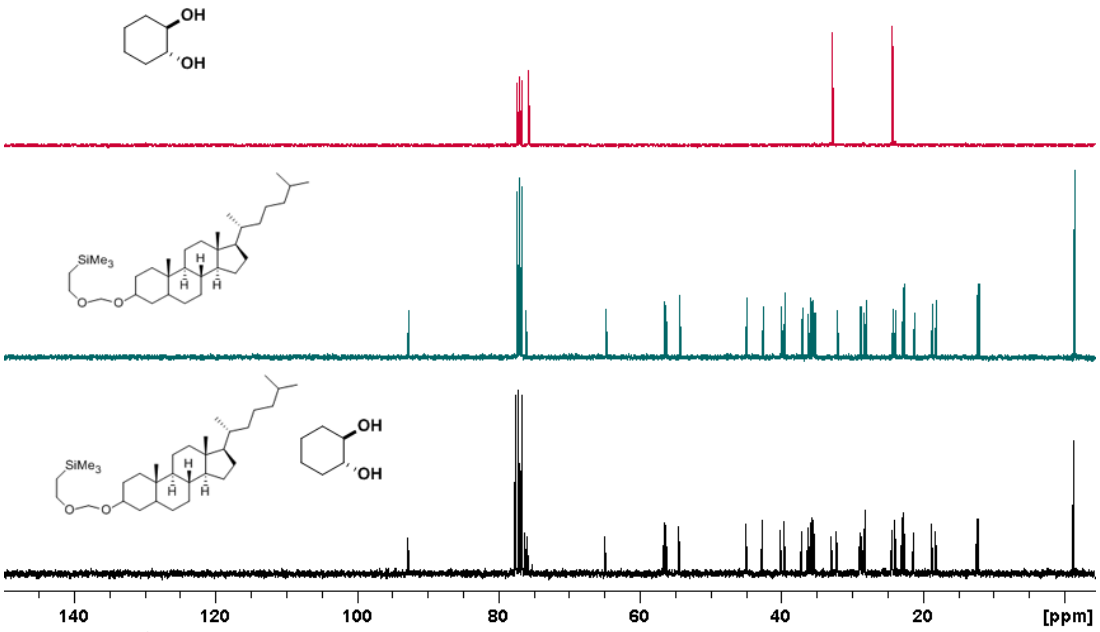


Figure 6.3.24 – ^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence 5α-cholestan-3-yloxy(methoxy)ethyl trimethylsilane. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and 5α-cholestan-3-yloxy(methoxy)ethyl trimethylsilane (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

6.3.13 ^{1}H and ^{13}C NMR of crude reaction in the presence of octan-2-yloxy(methoxy)methylbenzene (67)

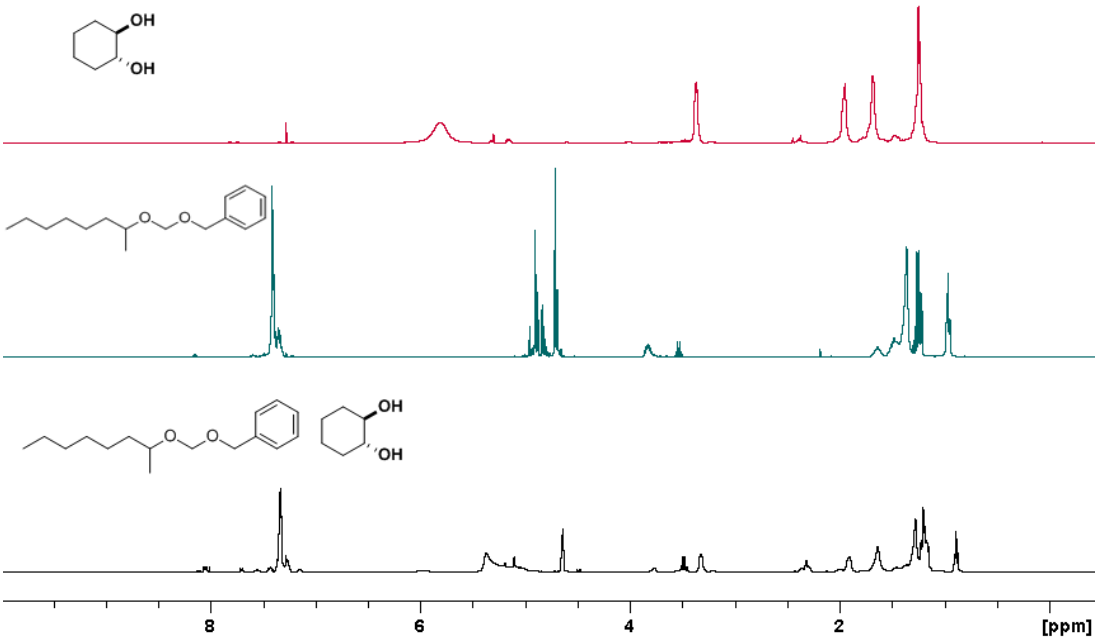


Figure 6.3.25 –^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence octan-2-yloxy(methoxy)methylbenzene. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and octan-2-yloxy(methoxy)methylbenzene (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation although this substrate was not stable under the reaction conditions.

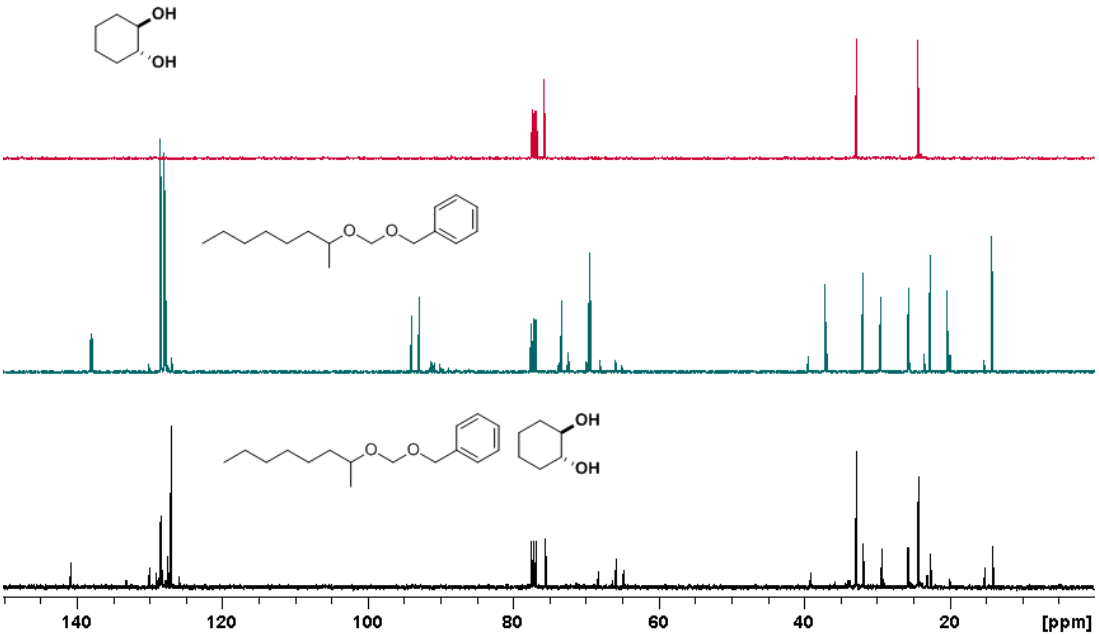


Figure 6.3.26 –^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence octan-2-yloxy(methoxy)methylbenzene. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and octan-2-yloxy(methoxy)methylbenzene (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation although this substrate was not stable under the reaction conditions.

6.3.14 ^{1}H and ^{13}C NMR of crude reaction in the presence of ethyl benzoate (68)

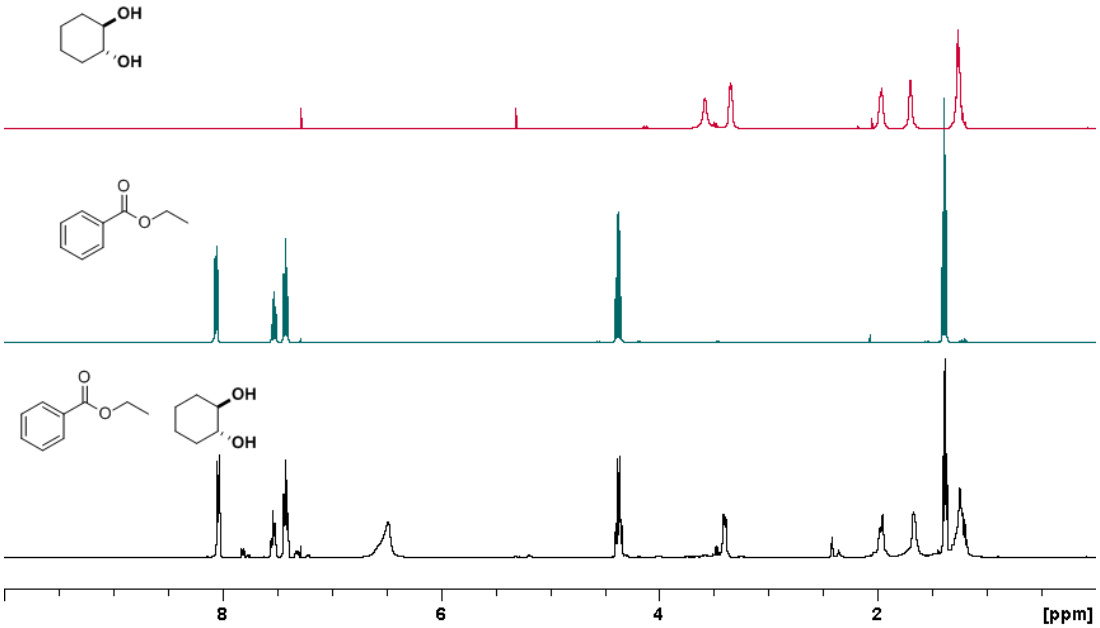


Figure 6.3.27 – ^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence of ethyl benzoate. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and ethyl benzoate (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

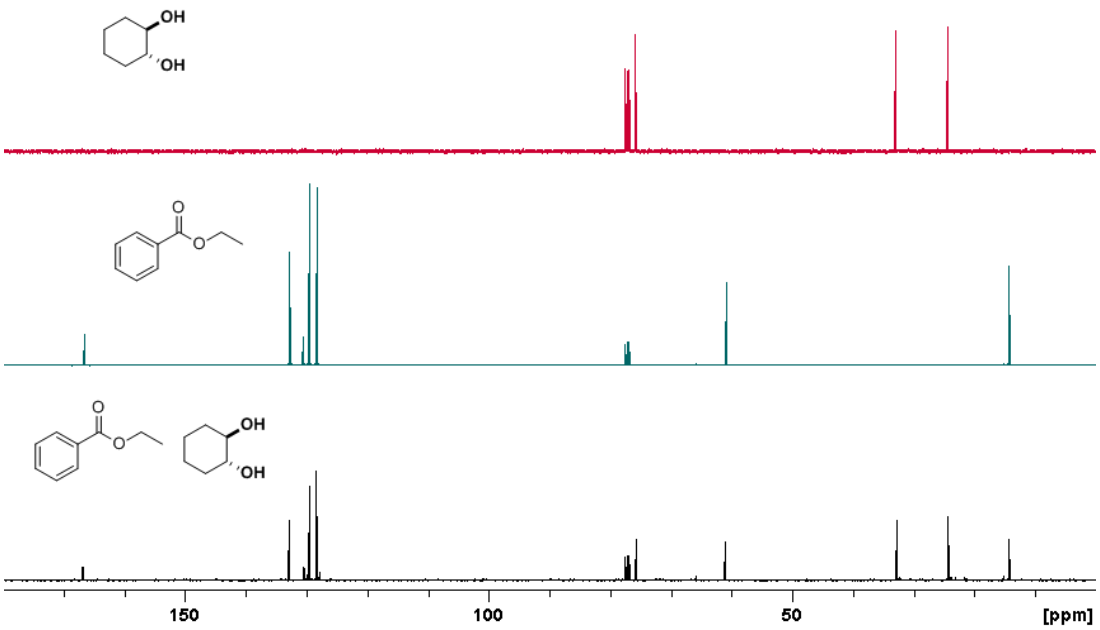


Figure 6.3.28 – ^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene in the presence of ethyl benzoate. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and ethyl benzoate (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation and the complete stability of this substrate under the reaction conditions.

6.3.15 ^{1}H and ^{13}C NMR of crude reaction in the presence of ethyl butyrate (69)

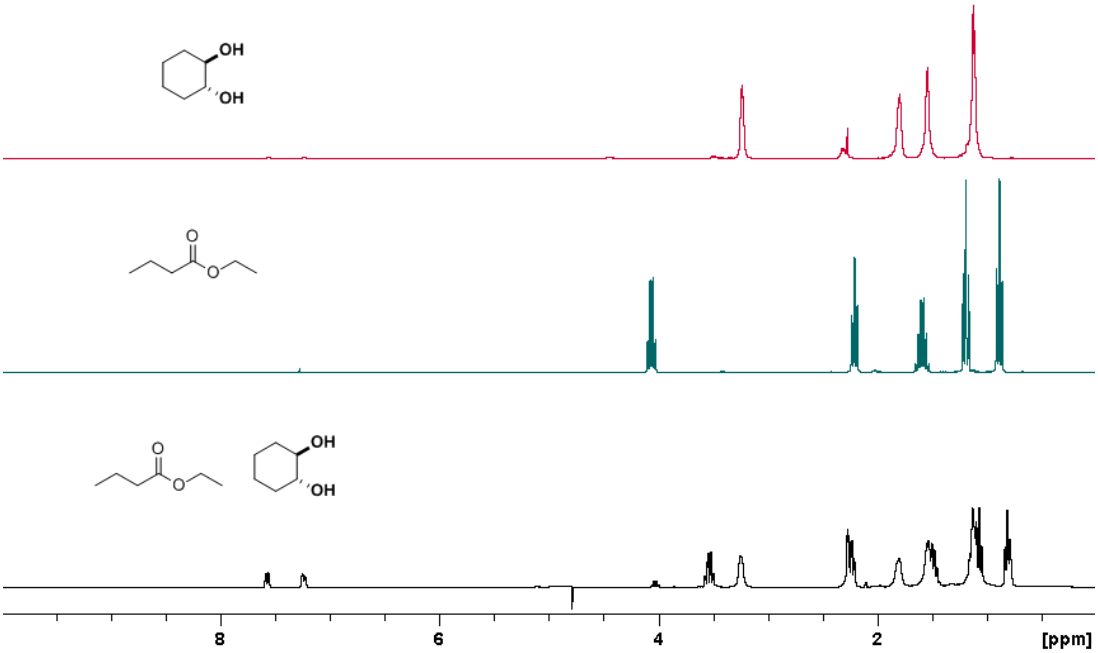


Figure 6.3.29 – ^{1}H-NMR (400MHz, D_2O) of the *trans*-dihydroxylation of cyclohexene in the presence of ethyl butyrate. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and ethyl butyrate (middle) ^{1}H-NMR spectrum show the occurrence of clean dihydroxylation although this substrate was not stable under the reaction conditions. NOTE: the crude reaction and the cyclohexanediol ^{1}H-NMR spectra were made in D_2O, but ethyl butyrate was not soluble in this solvent, so the ^{1}H-NMR spectrum was made in $CDCl_3$.

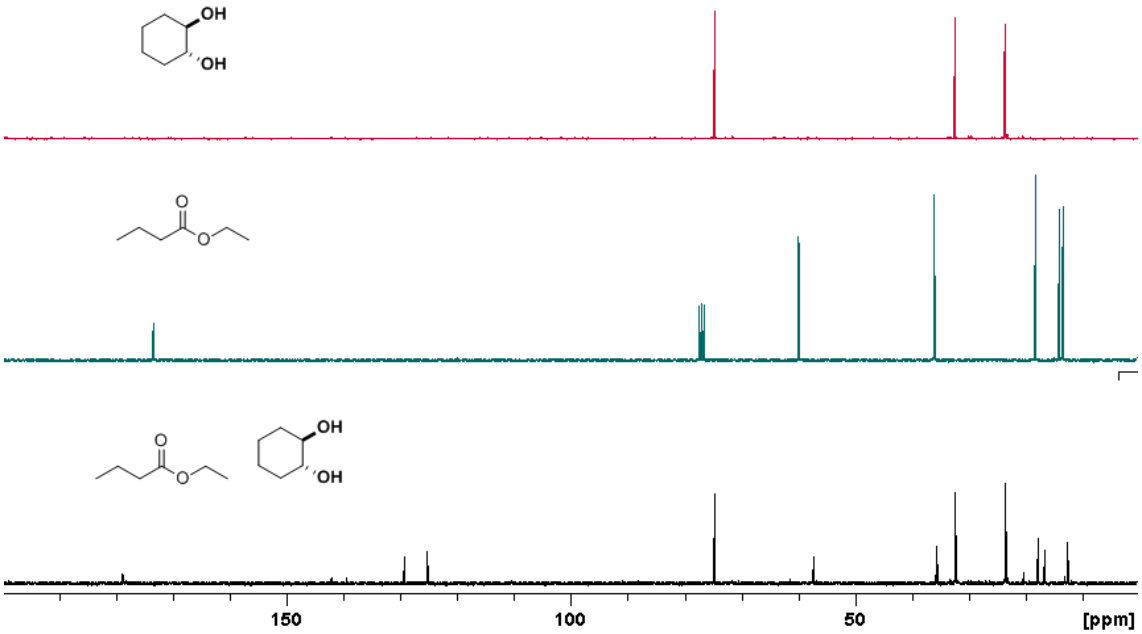


Figure 6.3.30 – ^{13}C-NMR (400MHz, D_2O) of the *trans*-dihydroxylation of cyclohexene in the presence of ethyl butyrate. The comparison of the crude reaction (bottom) with t*rans*-1,2-cyclohexanediol (top) and ethyl butyrate (middle) ^{13}C-NMR spectrum show the occurrence of clean dihydroxylation although this substrate was not stable under the reaction conditions. NOTE: the crude reaction and the *trans*-1,2-cyclohexanediol ^{13}C-NMR spectra were made in D_2O, but ethyl butyrate was not soluble in this solvent, so the ^{13}C-NMR spectrum was made in $CDCl_3$.

6.4 NMR spectra of the *trans*-1,2-cyclohexanediol obtained by catalyst recycling:

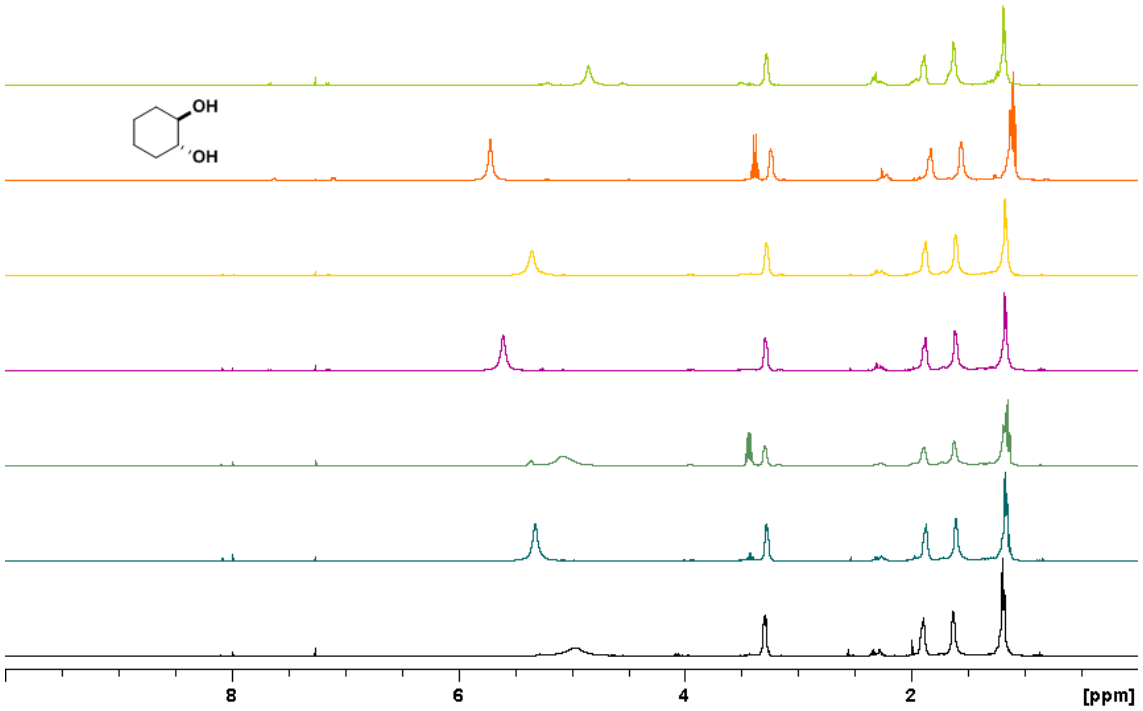


Figure 6.4.1 – ^{1}H-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene after recycling the catalyst for 7 cycles. From top to bottom: cycle 1 to cycle 7.

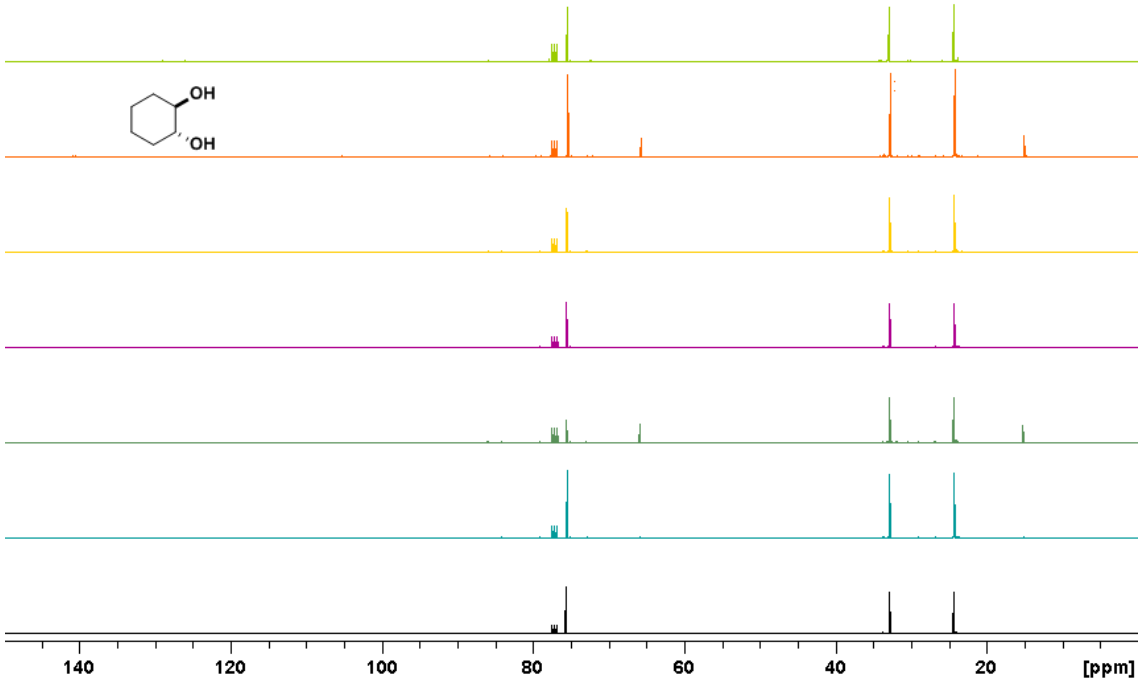


Figure 6.4.2 – ^{13}C-NMR (400MHz, $CDCl_3$) of the *trans*-dihydroxylation of cyclohexene after recycling the catalyst for 7 cycles. From top to bottom: cycle 1 to cycle 7.

6.5 Mass Spectra of ^{18}O enriched PTSA before and after trans-dihydroxylation

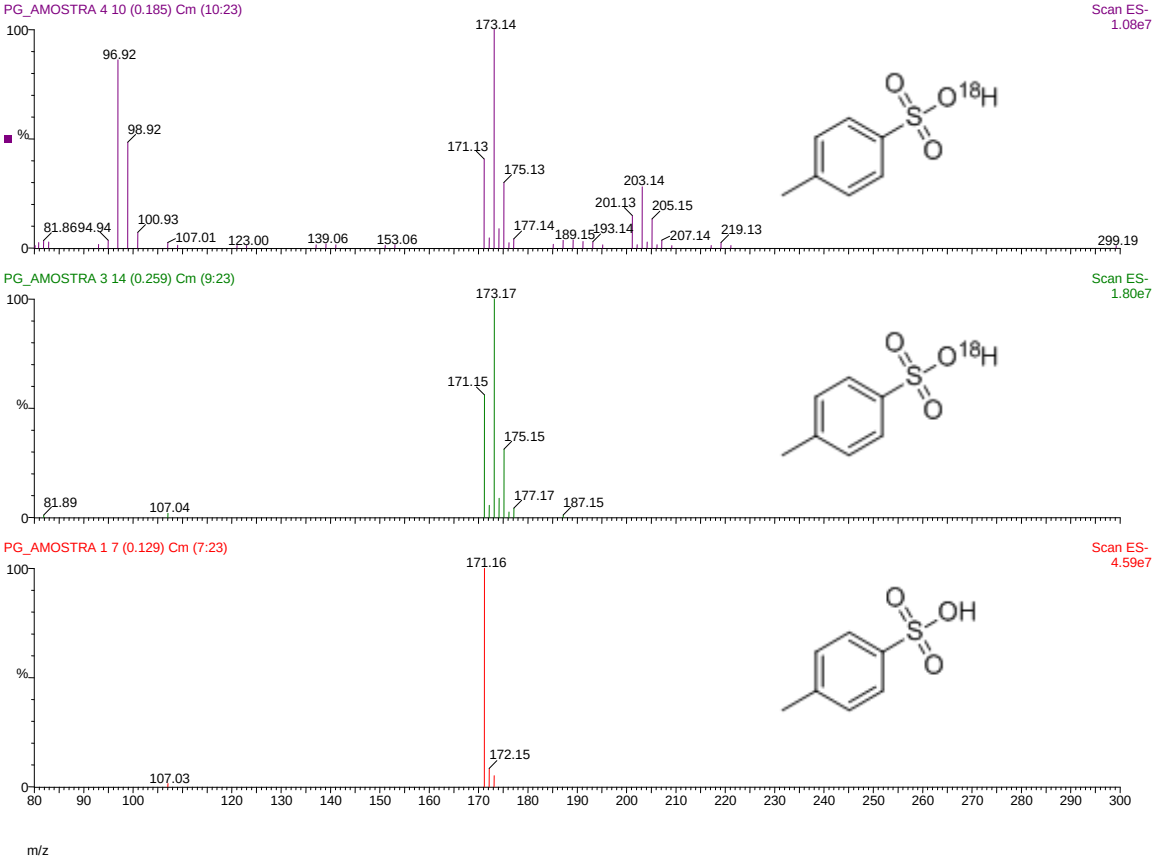
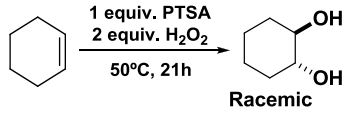


Figure 6.5.1 – Mass spectrum of *p*-toluenesulfonic acid (bottom), and enriched ^{18}O *p*-toluenesulfonic acid before (middle), and after (top) dihydroxylation reaction with hydrogen peroxide and cyclohexene. It is possible to observe that the enriched ^{18}O *p*-toluenesulfonic acid remain in the end of the reaction.

6.6 Synthesis and isolation of *trans*-1,2-cylohexanediol using an organic solvent free protocol



41 **42**

Figure 6.6.1 – Model reaction of cyclohexene transformation to *trans*-1,2-cyclohexanediol with 1 equivalent of PTSA, 2 equivalents of H_2O_2, at 50°C for 21 hours.

Calculation of the *trans*-1,2-cyclohexanediol conversion by NMR (Internal standard (**IS**) – chloroacetic acid):

$$mol\ (diol) = \frac{diol\ NMR\ peack(2.9\ ppm)}{IS\ NMR\ peack\ (3.8\ ppm)} * \frac{IS\ mass\ (m3)}{IS\ MW}$$

$$Diol\ total\ mass = mol\ diol * diol\ MW * \frac{Total\ sample\ (m1)}{NMR\ sample\ (m2)}$$

Example for Figure 6.6.2:

$$mol\ (diol) = \frac{2.19}{1.0} * \frac{0.010}{94.5} = 0.234\ mmol$$

$$Diol\ mass = 0.234 * 116.16 * \frac{14.64}{0.14} = 2.84\ g$$

$$Diol\ conversion(\%) = \frac{Obtained\ mass\ (g)}{Theoretic\ value\ (g)} = \frac{2.84}{2.90} * 100 = 97.9\%$$

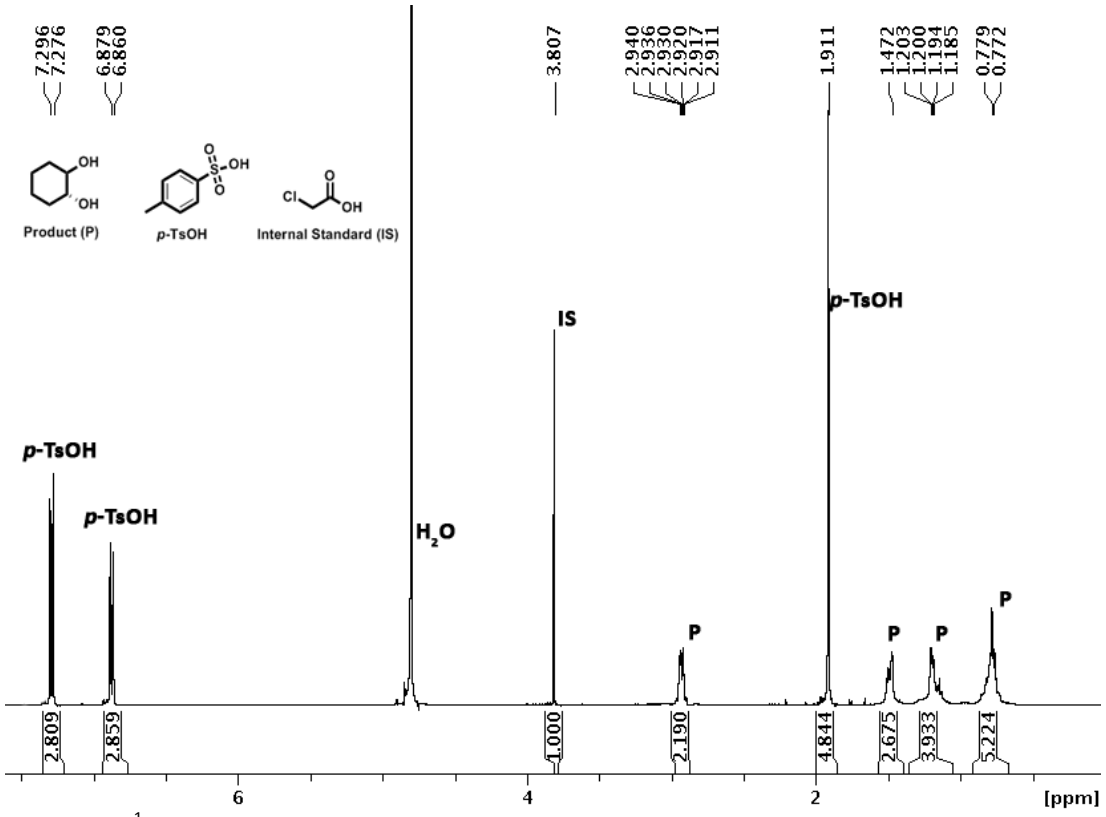


Figure 6.6.2 – ^{1}H NMR spectrum (400MHz, D_2O) of the crude mixture after 21h of reaction at 50°C, with chloroacetic acid (IS) as internal standard. Total reaction mass (m1) 14.64g; reaction sample (m2) 0.14 g; IS mass (m3) 10.1 mg.

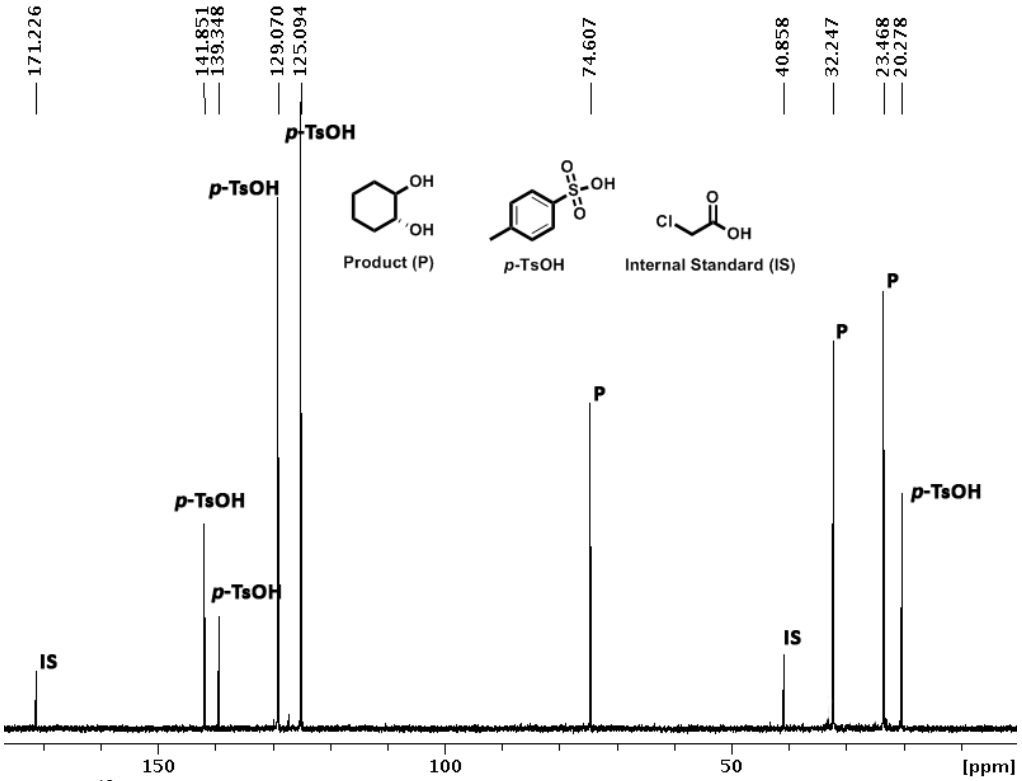


Figure 6.6.3 –^{13}C NMR spectrum (400MHz, D_2O) of the crude mixture after 21h of reaction at 50°C, with chloroacetic acid as internal standard.

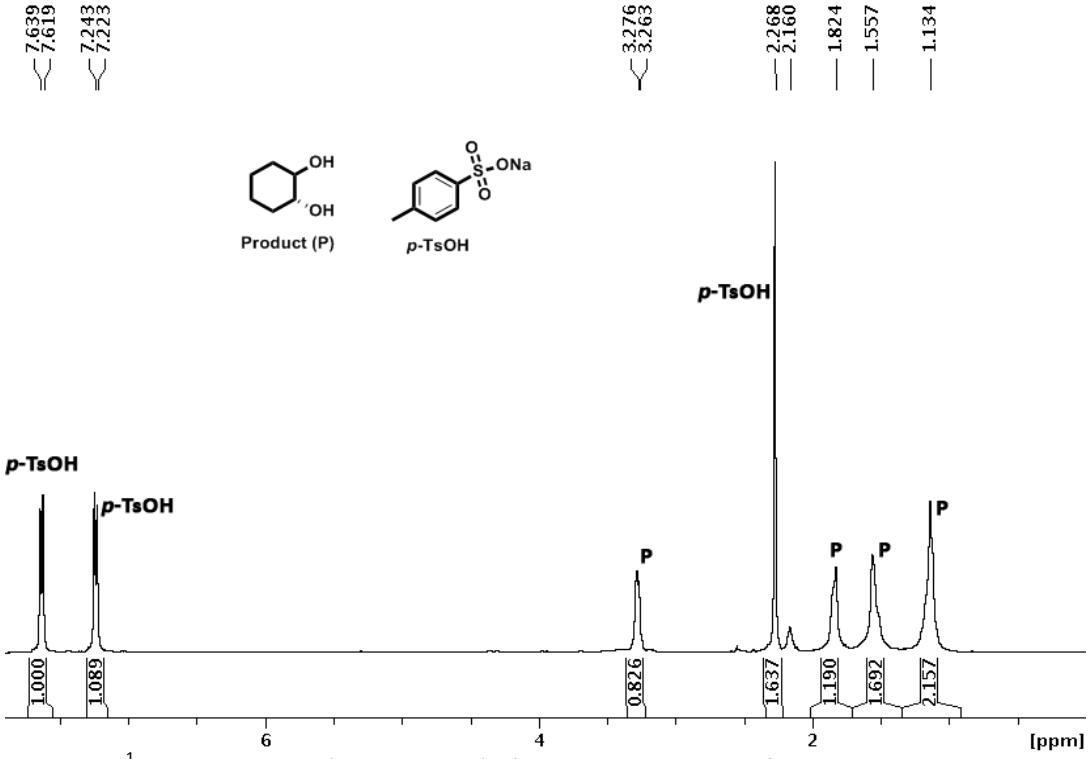


Figure 6.6.4 – ^{1}H NMR spectrum (400MHz, D_2O) of the reaction mixture after neutralization with $NaHCO_3$ and reduction with Na_2SO_3.

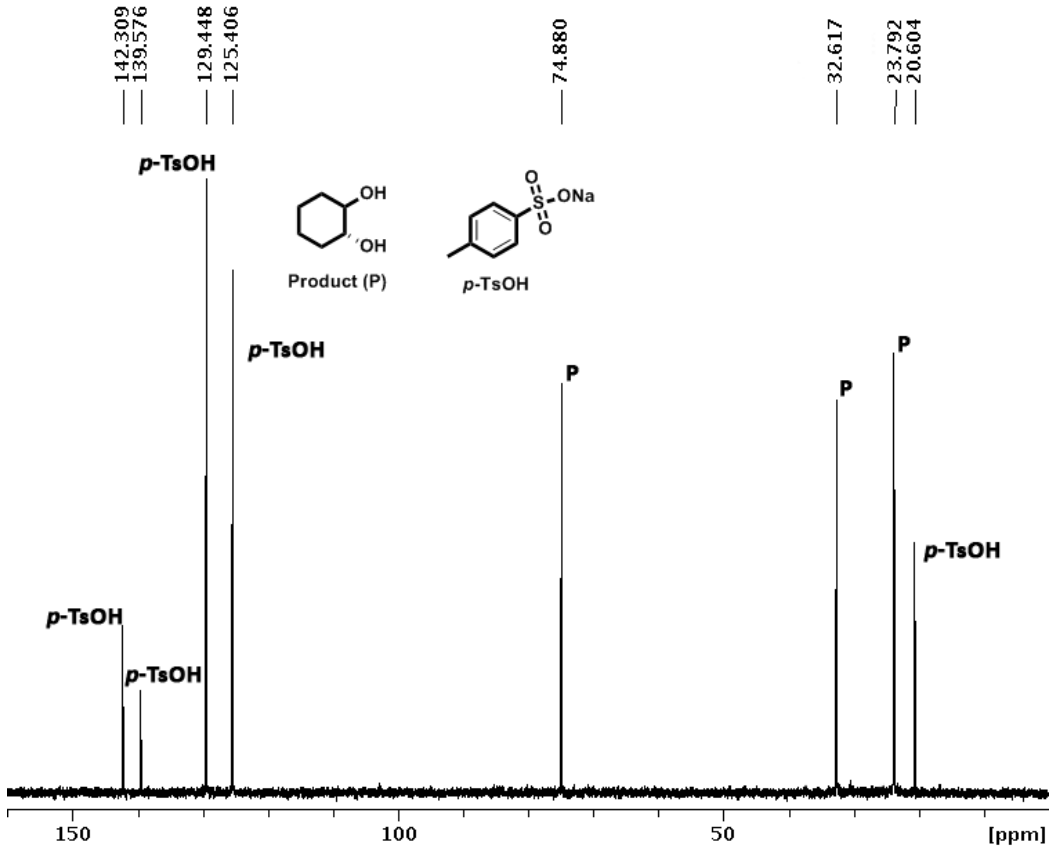


Figure 6.6.5 – ^{13}C NMR spectrum (400MHz, D_2O) of the reaction mixture after neutralization with $NaHCO_3$ and reduction with Na_2SO_3.

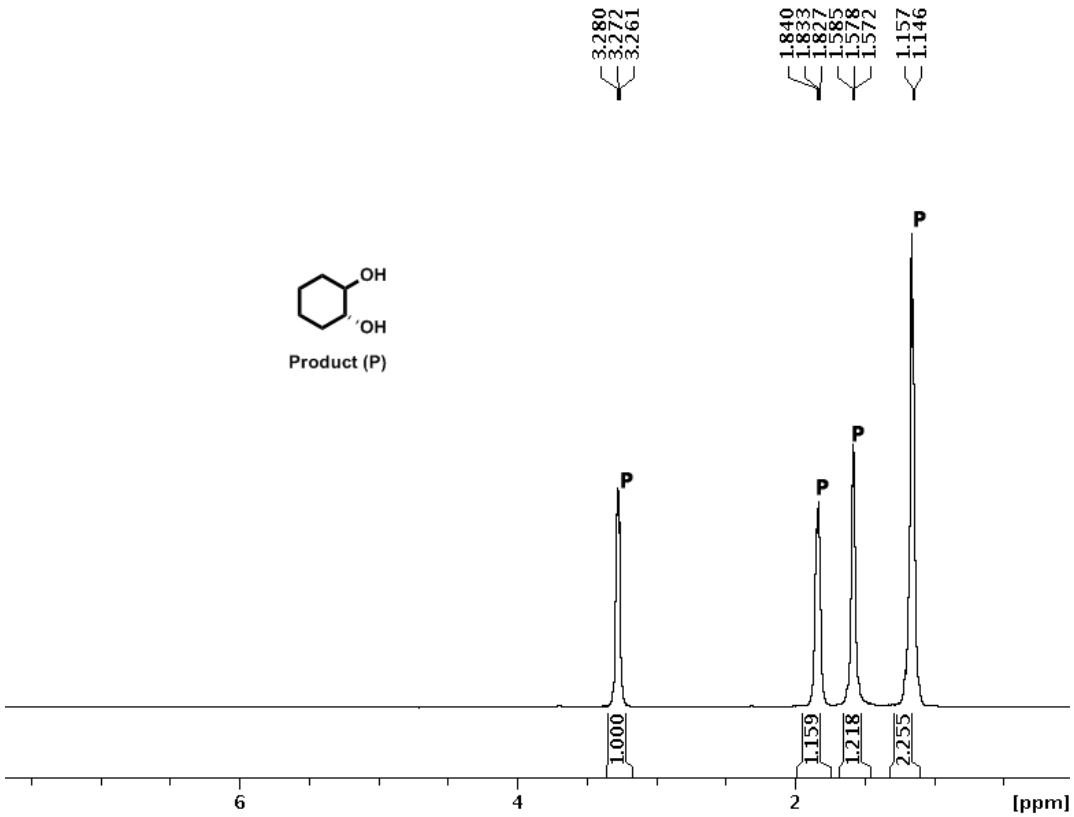


Figure 6.6.6 – ^{1}H NMR Spectrum (400MHz, D_2O) of *trans*-1,2-cyclohexanediol.

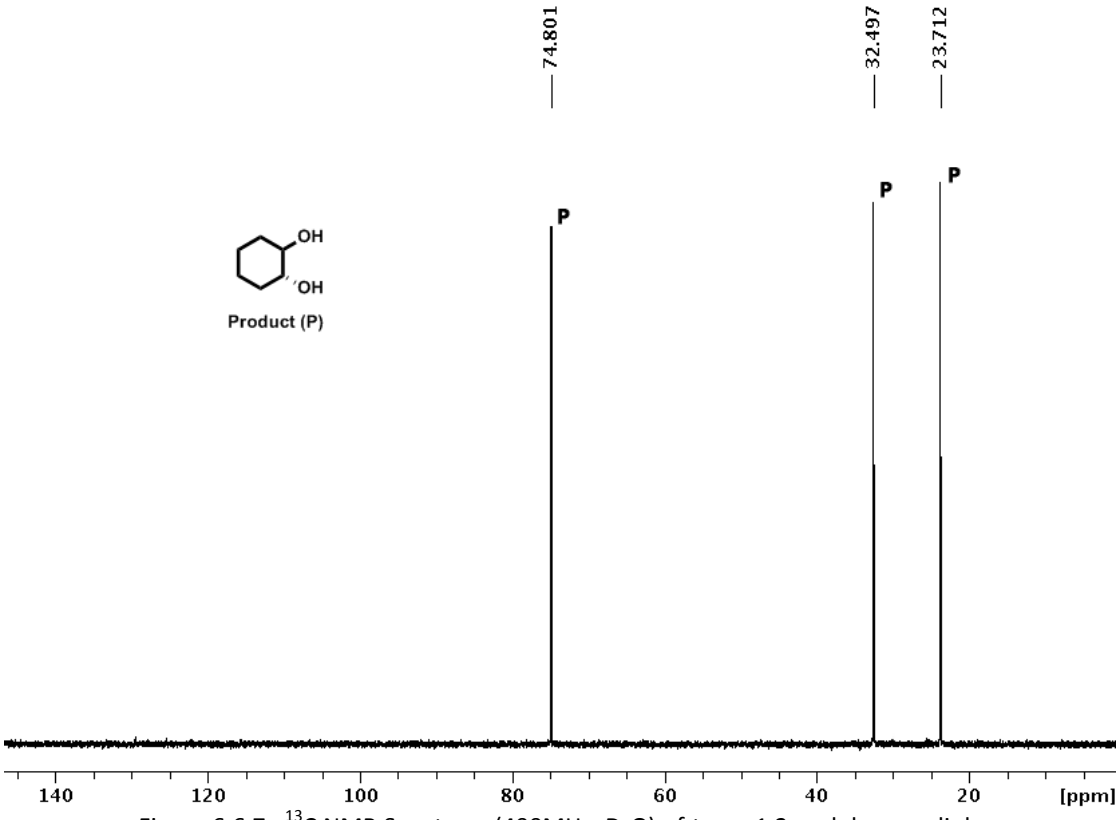


Figure 6.6.7 – ^{13}C NMR Spectrum (400MHz, D_2O) of *trans*-1,2-cyclohexanediol.

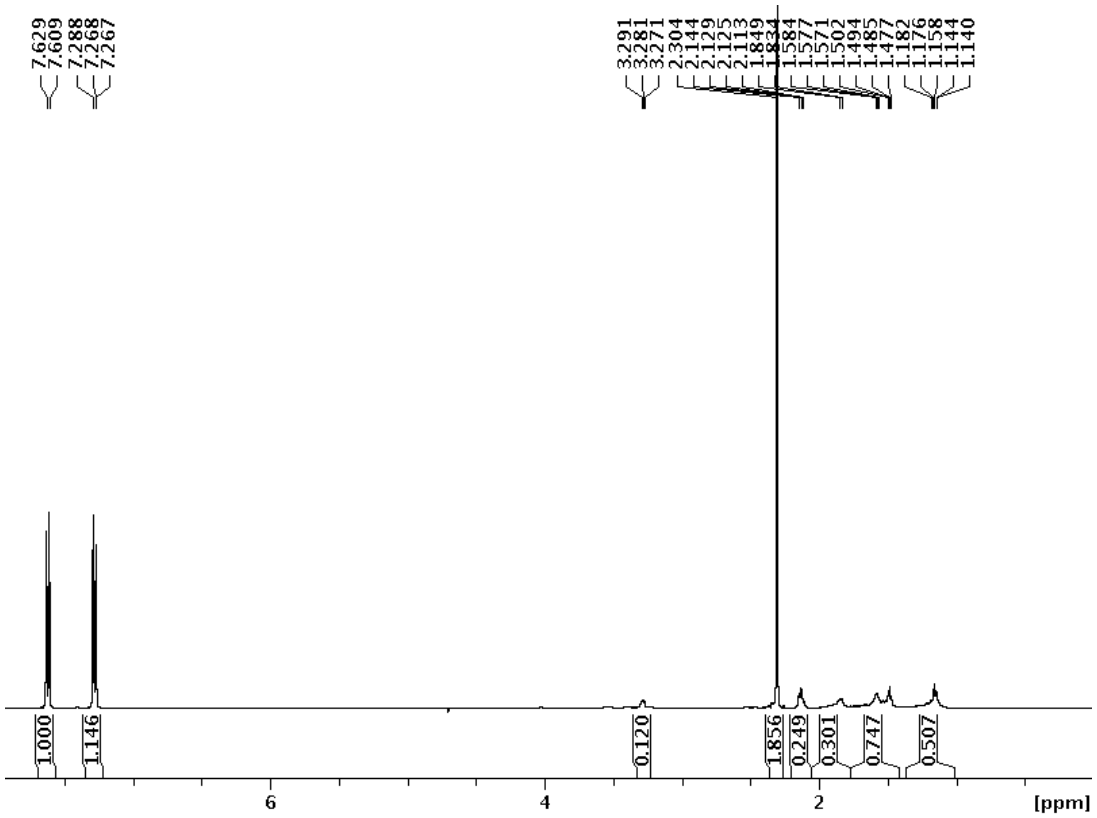


Figure 6.6.8 –^{1}H NMR spectrum (400MHz, D_2O) of the remainder solid after trans-1,2-cyclohexanediol sublimation.

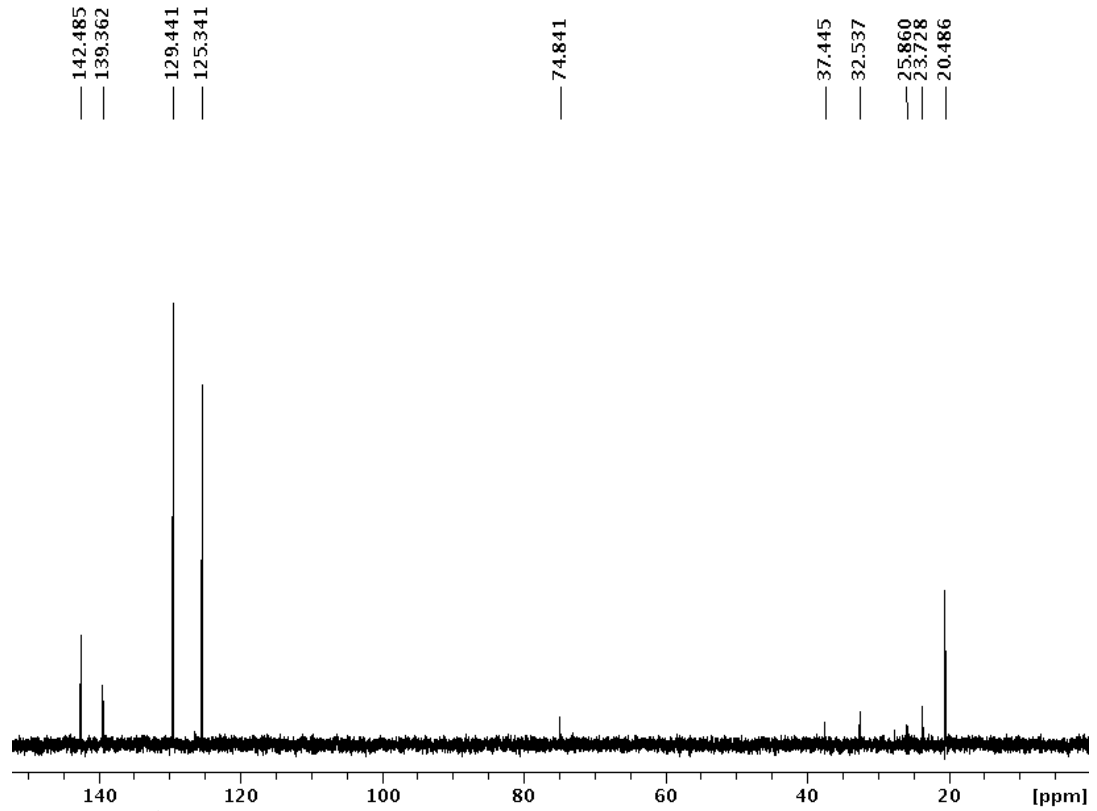


Figure 6.6.9 – ^{13}C NMR spectrum (400MHz, D_2O) of the remainder solid after trans-1,2-cyclohexanediol sublimation.

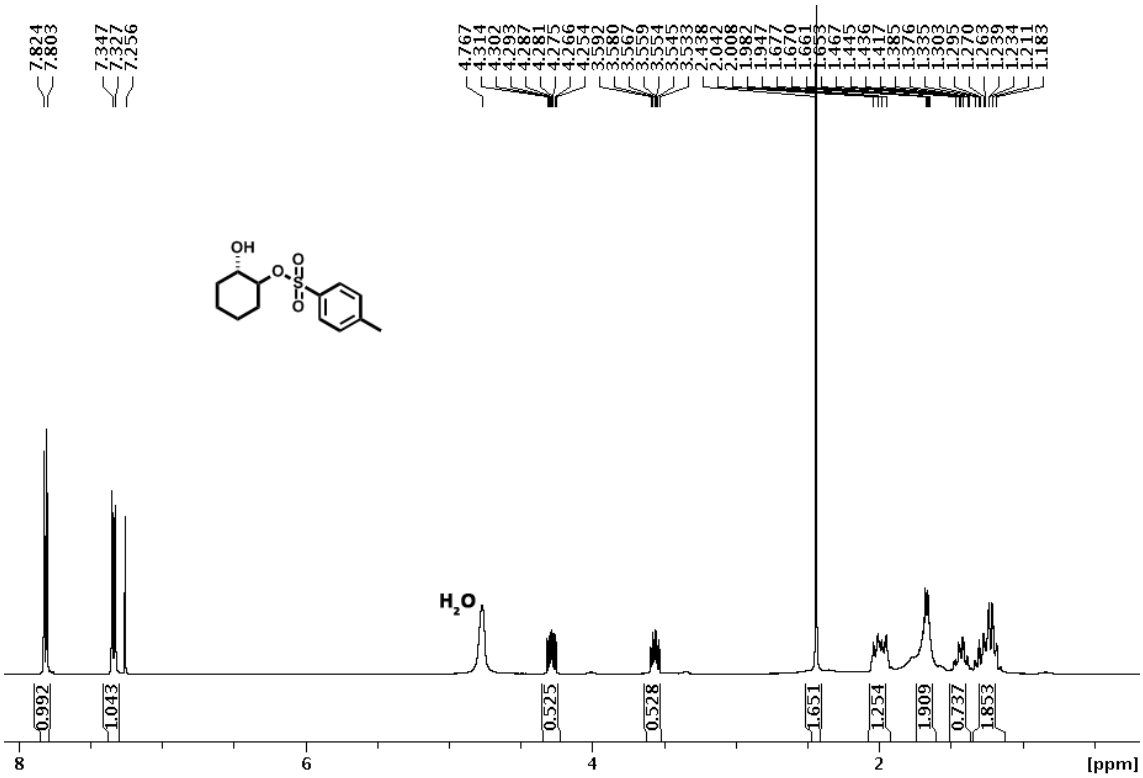


Figure 6.6.10 – ^{1}H NMR Spectrum (400MHz, $CDCl_3$) of *trans*-2-hydroxycyclohexyl-*p*-toluenesulfonate.

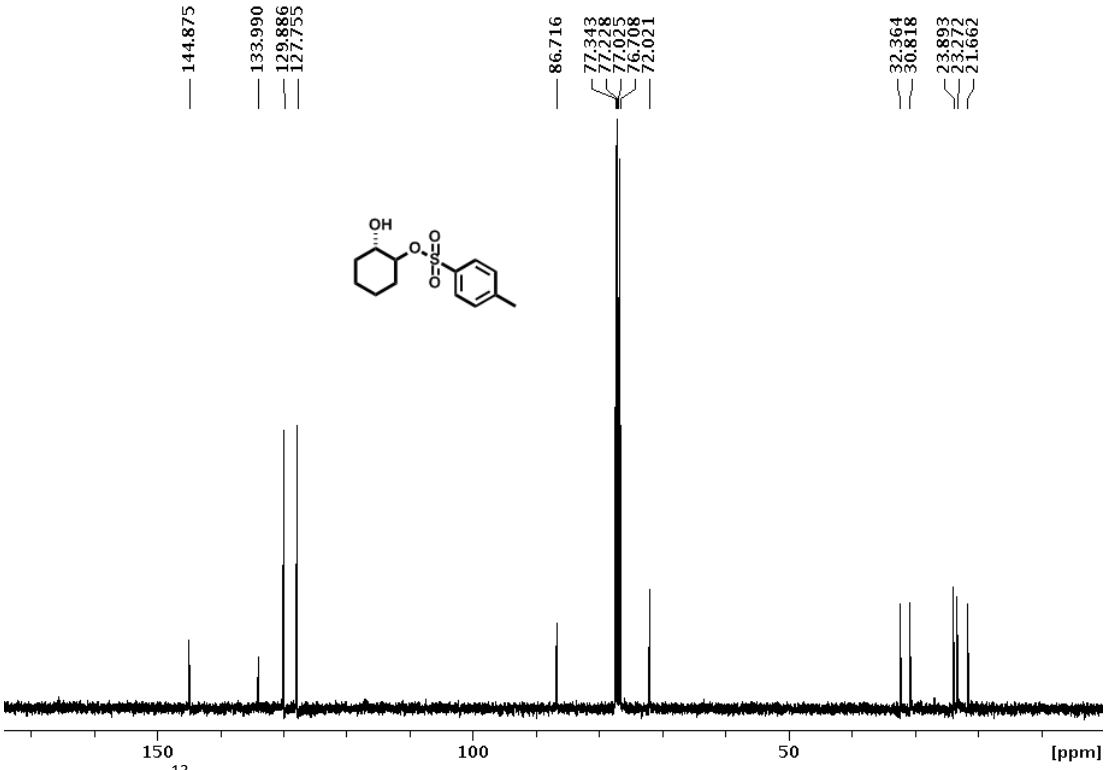


Figure 6.6.11 – ^{13}C NMR Spectrum (400MHz, $CDCl_3$) of *trans*-2-hydroxycyclohexyl-*p*-toluenesulfonate.