ABSTRACT

SYNTHESIS AND APPLICATION OF NOVEL CHIRAL IONIC LIQUIDS DERIVED FROM α-PINENE

by
Yun Wang

Two new chiral ionic liquids of oxazolinium cations derived from α-pinene: 9,9-Dimethyl-4-propenyl-5-propyl-3-oxa-5-azonia-tricyclo [6.1.1.0 ^{2,6}] dec-4-ene tetrafluoro borate ([ChIPOZ][BF_4]) and 9,9-Dimethyl-4-propenyl-5-propyl-3-oxa-5-azonia-tricyclo [6.1.1.0 ^{2,6}] dec-4-ene hexafluoro phosphate ([ChIPOZ][PF_6]). Both these chiral ionic liquids have been applied in enantiomeric copper-catalyzed 1,4-addition reactions with diethyl zinc. The enantiomeric excess for product using [ChIPOZ][BF_4] is above 70% and for [ChIPOZ][PF_6] is above 30%. Chiral ionic liquids worked as phase transfer catalysts In this reaction.

α-Pinene was used as the "chiral pool" in the synthesis of amino alcohol through a two-step reaction, followed by conversion to an oxazoline. Reaction of oxazoline with alkyl bromide gave 9,9-Dimethyl-4-propenyl-5-propyl-3-oxa-5-azonia-tricyclo [6.1.1.$0^{2,6}$] dec-4-ene bromide ([ChIPOZ][Br]). This organic bromide was used as the starting material for synthesis of chiral ionic liquid. Three additional novel compounds were obtained during the synthesis: But-2-enoic acid (2-hydroxy-2,6,6-trimethyl-bicyclo [3.1.1] hept-3-yl)-amide (Amide), 2,9,9-Trimethyl -4-propenyl -3-oxa -5-aza -tricyclo [6.1.1.$0^{2,6}$] dec-4-ene (Oxazoline) and 9,9-Dimethyl-4-propenyl-5-propyl-3-oxa-5-azonia-tricyclo [6.1.1.$0^{2,6}$] dec-4-ene bromide ([ChIPOZ][Br]).

Products formation in each step of synthesis was confirmed by FT-IR, NMR and Mass Spectrometry analysis.

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by
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To my husband, Yulu; my parents, Mr. and Mrs. Wang; my son, Yunpeng.

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TABLE OF CONTENTS

TABLE OF CONTENTS
(Continued)

Chapter **Page**

TABLE OF CONTENTS
(Continued)

Chapter **Page**

LIST OF SCHEMES

Schemes **Pages**

LIST OF FIGURES

LIST OF FIGURES
(Continued)

Figure **Page**

LIST OF TABLES

Table **Page**

CHAPTER 1

INTRODUCTION AND OBJECTIVES

1.1 Background

Since the environment problems relating to organic solvents in the environment are becoming more and more important, organic reactions, catalytic processes and separation technologies require the development of alternative solvents and technologies. The ideal solvent should be environmentally friendly, chemically and physically stable, recyclable, safe and eventually easy to handle and inexpensive. In addition, solvents that allow more rapid mass and energy transfers and more selectivity in synthesis such as region-selectivity or stereo-selectivity will have a more significant effect. This technology was called clean (green) technology.

Water has been successfully used in many biphasic industrial metal catalyzed reactions during the last 20 years. [B. Cornils et al., 1998] However, the use of water as a catalyst immobilizing phase has its limitations: (i) it is a highly polar and coordinating protic solvent and so it can react with organometallic complexes by halide–carbon bond protolysis or metal–carbon bond split; (ii) from an environmental perspective, trace amounts of organic compounds in water are very difficult to remove; (iii) the synthesis of specially designed water-soluble ligands and/or organometallic complexes is essential for its use; (iv) its application is still limited due to the low miscibility of organic substrates in water that often conducts to low reaction rates.

More recently, perfluorinated solvents have proven their utility for many organic and catalytic reactions. [I.T. Horvath et al., 1994] Nevertheless, specific ligands still must

be designed to solubilize catalyst in the perfluorinated phase. Moreover, decomposition of fluorous solvents at high temperature yields to toxic compounds and fluorous derivatives are often detected in the organic phase.

Supercritical fluids (e.g. Sc CO_2) have also been considered as new solvents for organic and catalytic reactions. [P.G. Jessop et al., 1999] Their physical and chemical stability make them desirable as particularly green solvents. Unfortunately, critical conditions needed for their use is still a limitation.

In recent years, considerable attention has been focused on the use of the ionic liquids (ILs) as a green solvent to replace traditional environmental damaging organic solvents. Ionic liquids have many interesting properties, such as few vapor pressures, ease of reuse, absence of flammability, and tolerance for large temperature variations. There are a number of reports concerning the applications of ionic liquids in organic reactions, such as Friedel-Crafts reactions [Nara et al., 2001], Diels-Alder reactions [Choi et al., 2001], Heck reactions [Kaufmann et al., 1996], ring-closing metathesis [Sterrenburg et al., 2001] and Trost-Tsuji coupling [Monteiro et al., 1998]. There is also a great deal of interest in the application of ionic liquids as novel biphasic catalysts, extraction solvents, stationary phase for chromatography and additional use in enzyme catalysis or in multiphase bioprocess operations.

Asymmetric synthesis is one of the most important areas in organic chemistry, biochemistry, and in pharmacology. Asymmetric induction is usually achieved by use of optically active substrates, and/or reagents, chiral catalysts, enzymes or chiral solvents. Since ionic liquids can replace traditional volatile solvents, synthesis and application of chiral ionic liquids are now in process. Surprisingly, the number of published examples

for chiral ionic liquids has been very limited so far.

In this research, two new chiral ionic liquids were synthesized and applied in asymmetry synthesis. The product has also been used as chiral phase transfer catalysts.

1.2 Ionic Liquids

1.2.1 Introduction and Properties

An ionic liquid is a liquid containing only ions, but it is different from molten salt that is high viscous, high corrosive and with high melting point; while ionic liquids are with lower viscosity and lower melting points. The following table1.1 is simple comparisons of physical properties between ionic liquids, molten salts and volatile organic solvents:

Table 1.1 Simple Comparisons of Physical Properties

	Molten Salts	Ionic Liquids	Volatile Organic Solvents
Melting points	>200°C	-20 -150°C	< -20°C
Boiling points	>400°C	>400°C	30-100°C
Viscosity	High	Low	Low
Basic components	Ion pairs	Ion pairs	Molecules
Conductivity	High	High	Low
Corrosive	High	Low	High
Flammability	Low	Low	High

From this table it is easily to see that the ionic liquids have many advantages over molten salts and classic organic solvents. This is especially true for common organic solvents, which are harmful to environment due to mainly two reasons: (1) they are very volatile and difficult to be maintained because of their low boiling; (2) they are used in large amounts.

1.2.1.1 Cations. The two basic components of ionic liquids are the cation and anion. The most commonly cations are nitrogen or phosphorus containing organic ion, for example, alkylammonium, alkylphosphonium, N, N'-dialkylimidazolium (abbreviated as [RR'IM], e.g. [EMIM]= 1-ethyl-2-methyl-imidazolium) and N-alkylpyridium (abbreviated as [RPy], e.g. [EtPy]= ethylpyridium). The normal alkyl substitutions are methyl, ethyl, butyl, hexal, octyl and decyl, etc. [Malhotra et al., 2002] (Figure 1.1)

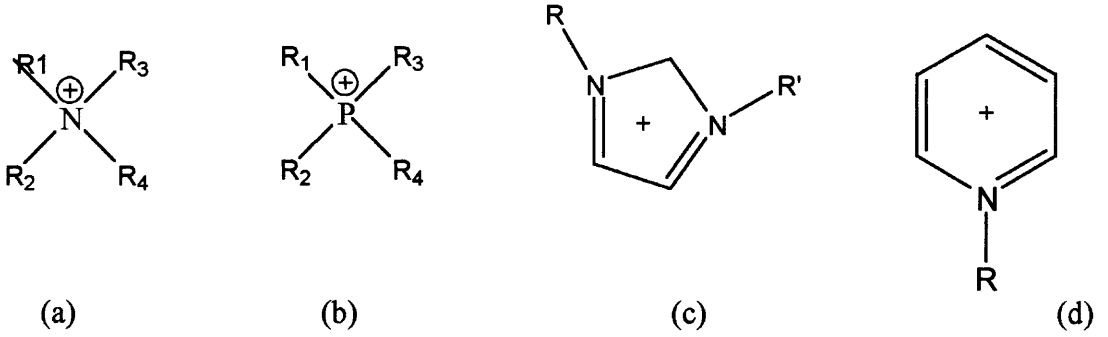


Figure 1.1 Normal types of cations in ionic liquids: (a) Tetraalkyl-ammonium, (b) Tetraalkyl- phosphonium, (c) N-N'-dialkyl-imidazolium and (d) N-alkyl-pyridine cations.

Several other cations have been also investigated. They are generally bulk, organic with low symmetry, such as pyrrolidinium (1), thiazolium (2), triazolium (3), oxazolium (4) and pyrazolium (5). (Figure 1.2)

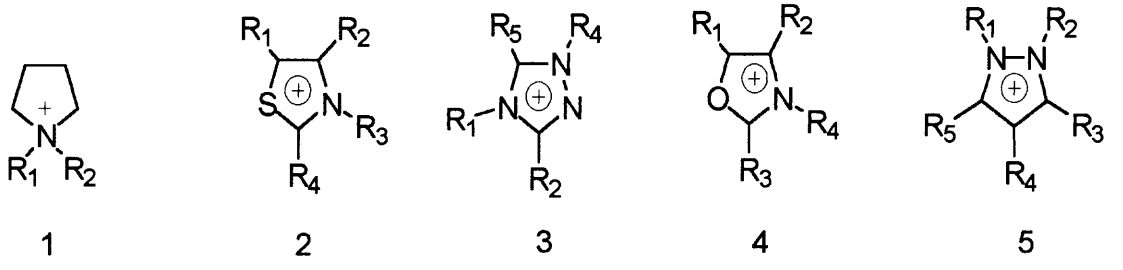
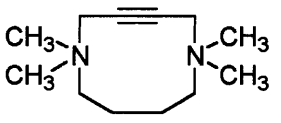


Figure 1.2 Some examples of cations in ionic liquids.

In most chemical applications of ionic liquids, cations influence the physical properties of the medium. However, a chemical effect of the cation is also possible. For example, for the hydrovinylation of styrene catalyzed by Ni organometallic complexes, 4-methylpyridinium salts proved to give higher enantioselectivity than their 1-ethyl-3-butylimidazolium homologues. [A.Bosmann, 2001] Organic polycations such as 1 and 2 in Figure 1.3 have also been envisioned.



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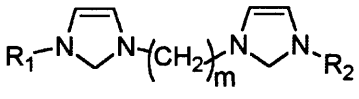


2

Figure1.3 Some examples of polycations.

Besides organic cation based ionic liquids, lithium salts are being increasingly developed particularly for secondary batteries and storage of energy. They often have lower lattice energy and, therefore, lower melting points than their neighboring elements of the periodic table. Their use to form ionic liquids can be considered. As an example, the mixture of LiCl and $EtAlCl_2$ gives a liquid, on a large range of composition, at temperatures lower than 0°C. [Y. Chauvin, 1998]

1.2.2.2 Anions. Anions can be classified into two categories: (i) those that give polynuclear anions, e.g. $Al_2Cl_7^-$, $Al_3Cl_{10}^-$, $Au_2Cl_7^-$, $Fe_2Cl_7^-$, $Sb_2F_{11}^-$. These anions are formed by the reaction of the corresponding Lewis acid, e.g. $AlCl_3$ with the mononuclear anion, e.g. $AlCl_4^-$ to form $Al_2Cl_7^-$. They are particularly air and water sensitive. (ii) the second class of anions corresponds to mononuclear anions which lead to neutral, stoichiometric ionic liquids, e.g. BF_4^-, PF_6^-, SbF_6^-, $ZnCl_3^-$, $CuCl_2^-$, $SnCl_3^-$, $N(CF_3SO_2)_2^-$, $N(C_2F_5SO_2)_2^-$, $N(FSO_2)_2^-$, $C(CF_3SO_2)_3^-$, $CF_3CO_2^-$, $CF_3SO_3^-$, $CH_3SO_3^-$, NO_3^-, NO_2^-, ClO_4^-,

etc. When using NO_3- and ClO_4- as anion, most care must be taken because organic nitrates and perchlorates are potentially explosive, especially when rigorously dried.

Of particular interest are the carborane-based salts [A.S.Larsen et al., 2000][C.a. Reed et al., 2001]. Carborane anions ($CB_{11}H_{12}^-$, Figure 1.4) are one of the most inert anions in modern chemistry. Despite their high stability, the position 1 of the $CB_{11}H_{12}^-$ anion can be alkylated leading to new derivatives having melting points just above room temperature, e.g. [EMIM][1-C_3H_7-$CB_{11}H_{11}$] salt, which melts at 45°C. It appeared also feasible to substitute the B-H bond with strong electrophiles which allows a systematic variation of properties of the anion. Moreover, their very weak nucleophilicity and redox inertness allow the exploration of new extreme cation reactivity and the isolation of new extreme cation reactivity and isolation of new superacids. [H. Olivier-Bourbigou, 2002]

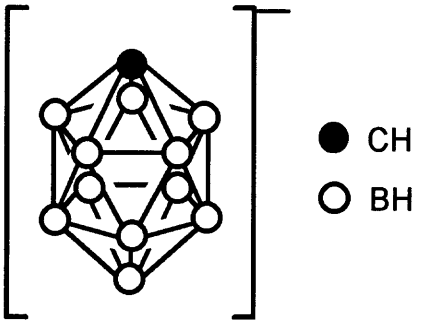


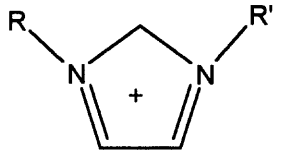
Figure 1.4 Carborane anion ($CB_{11}H_{12}^-$).

Ionic liquids developed up to now often present higher viscosities than common organic solvents used in synthesis. Driven by the need to find materials with lower viscosity, dicyanamide anions (-$N(CN)_2^-$) have recently been described. [D. Mac

Farlane, 2001] This anion gives ionic salts with melting point below –10°C. Viscosity for the [EMIM][$N(CN)_2$] liquid salt is only 21 mPa s at 25°C.

1.2.1.3 Properties. By changing the cation and/or anion, we can obtain versatility in the ionic liquids. This is one of the strong characters of ionic liquids, which can be designed according to the requirements.

Table 1.2 Melting Points (°C) of Some Ionic Liquids ([RR'IM^+][X^-]) [Peng et al., 2001][Dupont et al., 2002]



IM^+	BF_4^-	PF_6^-	$AlCl_4^-$	$CF_3SO_3^-$	$C_4F_9SO_3^-$	$(CF_3SO_2)_2N^-$
3-Me						
1-Me	39	22	62	39		22
1-Et	15	60	-80	-8	28	-3
1-n-Bu	-81	71	-88	16	20	-4
1-i-Bu						a
1-MeOEt				27		a
1-CF_3CH_2				45		a
3-Et						
1-Et				25		14
1-n-Bu				2	21	a
1-Et						
2,3-Me_2				109		20
2-Et-3-Me				113		28

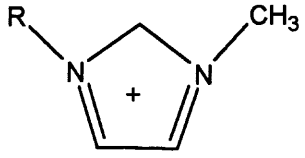
Note: 'a' means not crystallize; change to glass state at –30 to 50 ℃.

For cation it can be changed the substitution on the organic backbone, e.g., RR' IM, RPy. Different substitutions will lead to decrease or increase in melting points. The reason maybe the asymmetric random packs of ions, which lead to form crystal structure

difficultly. But further research to verify this assumption is needed because no clear rule between the substitution and the melting points (Table 1.2). Very surprisingly, 1,3-dialkylimidazolium hexafluorophosphates with dibutyl, dipentyl, dioctyl, dinonyl and didecyl substituents are found to be liquid at room temperature. [S.V. Dyzuba et al., 2001]

Different anions have differences in affinity to water, hydrophilic or hydrophobic, and in strength of coordination. For the [BMIM] cation, the BF_4^-, $CF_3SO_3^-$, $CF_3CO_2^-$, NO_3^- and halide salts have a complete miscibility with water at 25°C. On the other hand, the PF_6^-, SbF_6^-, NTf_2^-, BR_4^- anions with [BMIM] show a very low miscibility with water. The solubility with water changes with temperature and the length of the alkyl chain on the dialkylimidazolium cation. For example, at 4°C, [BMIM][BF_4]/water solution will separate a water phase and for PF_6^- based salts, the shorter symmetric substituted salt becomes water-soluble.

Table 1.3 Some Physical Characteristics of More Currently Used 1-Butyl-3-Methylimidazolium Ionic Liquids



Anion	Melting point (°C)	Density (g/cm^3)	Viscosity (mPas)	Conductivity (S/m)
BF_4	-82/-83	1.17 (30°C)	233 (30°C)	0.173 (25°C)
PF_6	-62	1.37 (30°C)	312(30°C)	0.146 (25°C)
CF_3SO_3	16	1.29 (20°C)	90 (20°C)	0.37 (20°C)
CF_3CO_2	-50/-30	1.31 (21°C)	73 (20°C)	0.32 (20°C)
NTf_2	-4	1.43 (19°C)	52 (20°C)	0.39(20°C)

It has recently been demonstrated that the viscosity of 1-alkyl-3-methylimidazolium salts can be decreased by using highly branched and compact alkyl chain; but also by changing the nature of the anion, which is more important [D. Swartling et al., 2000]. For the same cation the viscosity decreases as follows: $Cl^- > PF_6^- > BF_4^- \approx NO_3^- > N(CF_3SO_2)_2^-$ (See table 1.3). All these structure differences in combination of various cations and anions will lead to alternation of the distinct physical and chemical properties.

These properties as well as the structure of ionic liquids have been recently investigated. One example is Thomas Welton's review [Welton et al., 1999], where some simple physical properties of ionic liquids that make them interesting as potential solvents for synthesis are generalized. He shows they are good solvents for both organic and inorganic materials, and unusual combinations of reagents can lead to homogenous reaction, all reagents in the same phase. He points out they are often composed of weakly coordination anions e.g. $[BMIM]BF_4^-$ and $[BMIM]PF_6^-$ are most popular and used in biphasic catalysis system, Where they serve as highly polar but non-coordination solvents. They are also immiscible with a number of organic solvents and provide a non-aqueous, polar alternative for two-phase systems. Hydrophobic ionic liquids can also be used as immiscible polar phases with water. A last important point: ionic liquids are non-volatile, so they can be used in high-vacuum systems and eliminate many containment problems. Thus, they are environmentally friendly solvents.

1.2.2 Applications

Ionic liquids have been mainly used in two fields: electrochemical devices and solvents for organic and catalytic reactions.

The increasing need for high performance batteries in various applications (portable electronics, cellular phones, electrical vehicles, etc.) has promoted the research for non-aqueous improved electrolytes solutions. For example, the conductivities can be five times higher than that obtained by non-aqueous solvent/salt combinations used in Li-batteries. In addition, their electrochemical window can be in excess of 4.5V compared with 1.2V for aqueous electrolytes. At the same time they offer greater thermal stability and greater solubility than quaternary ammonium commonly used. [J. Caja et al., 2000]

The applications of ionic liquids continue to expand. In the solvent areas they can be classified in three classes: solvents for organic reactions (nucleophilic and electrophilic reactions including acidic catalyzed reactions), solvents for reactions catalyzed by transition metal complexes and solvents for biocatalysis. Many review papers have given the summary for applications of ionic liquids in organic and catalyzed reactions. [Malhotra et al., 2002] [H.Olivier-Bourbigou, 2002] From a chemical point of view, the main potential benefits of using ionic liquids are to enhance reaction rates and improve chemo- and regio-selectivities relative to other organic solvents. From an economic and practical point of view, the use of ionic liquids can of course be beneficial if the separation of the products and the recovery of the catalyst are simple enough.

The ideal case of operability is when the ionic liquid is able to dissolve the catalyst and displays a partial miscibility with the substrate and when the products have a negligible miscibility in the ionic liquid and can be removed by simple decantation without extracting the catalyst. This mode of operation does not require heating and therefore results in energy saving and reduced loss of catalyst by thermal decomposition..

If the products are partially or totally miscible in the ionic liquid, separation is

more complicated. For highly volatile products distillation can be simple used to separate ionic liquids with products. For low volatile products extraction with a co-solvent poorly miscible with ionic liquids is often used although cross-contamination may occur. $ScCO_2$ extraction is an efficient separation technique but it remains technically demanding. [T. Schafer, 2001]

A more complex example of separation of the products can be illustrated by the nucleophilic cyanide displacement on benzyl chloride to yield phenylacetonitrile. This reaction is usually performed using phase transfer catalyst, e.g. a tetra-alkyl ammonium salt, to facilitate the reaction between the organic reagents and the inorganic KCN salt that provides the nucleophile. Ionic liquids, e.g. [BMIM][PF_6] can act as both the solvent and the catalyst in promoting the contact of the reagents and providing the activation of the nucleophile. In the first step, the reaction proceeds. The products are removed in a second step *via* vaporization or supercritical fluid extraction. Washing with water can be used to remove the inorganic salt by-product. The ionic liquid can be reused after decantation. [H.Olivier-Bourbigou, 2002]

1.3 Chiral Ionic Liquids

1.3.1 Introduction

There are only four papers describing the synthesis of chiral ionic liquids even though the applications of ionic liquids are growing.

Seddon et.al. [Earle et.al., 1999] investigated Diels-Alder reactions in lactate ionic liquids. Howarth and co-workers [Howarth et.al. 1997] described the use of chiral imidazolium cations in Diels-Alder reactions (Figure 1.5). However, the synthesis of

these systems required an expensive chiral alkylating agent; furthermore, two symmetrical chiral centers may not be favorable to chiral inducement because they did not observe good chiral induction.

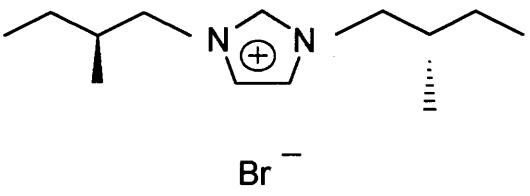
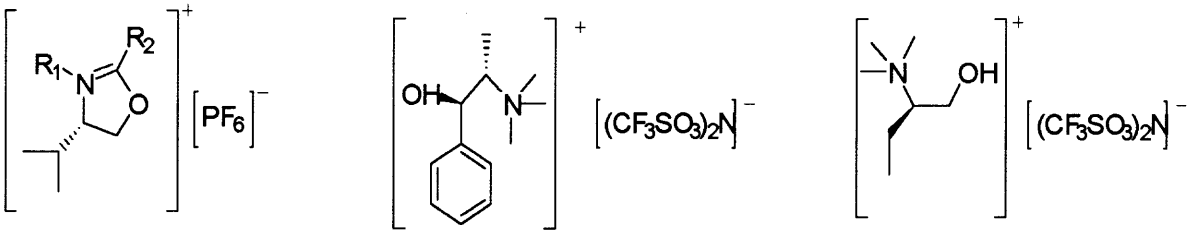


Figure 1.5 Imidazolium chiral ionic liquid.

Peter Wasserscheid and co-workers [P. Wasserscheid et al., 2002] synthesized three different classes of chiral ionic liquids (1-3 in Figure 1.6). However under acidic conditions, the oxazoline ring of 1 has lower stability than the imidazole ring, and 2 and 3 are not very similar to the popular ionic liquids encompassing imidazolium cations. These traditional imidazolium cations are favorable species for investigation because of their facile and inexpensive preparation, their air and water stability, their wide liquid range, and their relatively favorable viscosity and density characteristics.



1 **2** **3**

Figure 1.6 Three chiral ionic liquids synthesized by Wasserscheid and co-workers.

Weiliang Bao et al. [Bao et al., 2003] first synthesized chiral imidazolium ionic liquids containing one chiral carbon from the natural amino acids. (Figure 1.7) There are many merits in this ionic liquid: (a) low melting point <80°C; (b) good thermal stability; (c) starting materials are commercially available and synthetic procedures are straightforward. Application of these new chiral ionic liquids in asymmetric synthesis is however not illustrated.

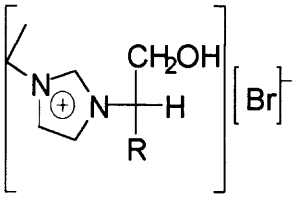


Figure 1.7 Imidazolium chiral ionic liquids with one chiral center.

Recently two new chiral ionic liquids 1- ((-)-menthoxy carbonyl methylene) – 3 – methyl imidazolium hexa- fluorophosphate and 1- ((-) – menthoxy carbonyl methylene)-3-hexadecylimidazolium hexafluorophosphate have been synthesized. [Ma, Hong-yang et al., 2003] Reverse atom transfer radical polymerization of Methyl methacrylate (MMA) in these two ionic liquids was carried out using AIBN/$CuCl_2$/bipy as the initiating system. The resultant well-defined polymethyl methacrylate (PMMA) was employed as a macro initiator to induce the atom transfer radical polymerization of methyl methacrylate (MnMA) in chlorobenzene, which yielded a PMMA-b-PMnMA diblock copolymer with narrow polydispersity.

1.3.2 Application

There are only three reports on the application of these chiral ionic liquids. Joshus Howarth and co-workers [Howarth et al., 1997] synthesized homochiral dialkylimidazolium salts , which gave less than 5% e.e. product in a Diels-Alder reaction. Wasserscheid et al. [Peter Wasserscheid, 2002] investigated diastereomeric interactions between racemic substrate and chiral ionic liquid. Using it has shown that the substrate has been dissolved in a chiral environment. The extend of peak splitting is related to the strength of the diastereomeric interactions. Recently another report [Ma, Hong-yang et al., 2003] have synthesized two chiral imidazolium ionic liquids and applied them in radical polymerization.

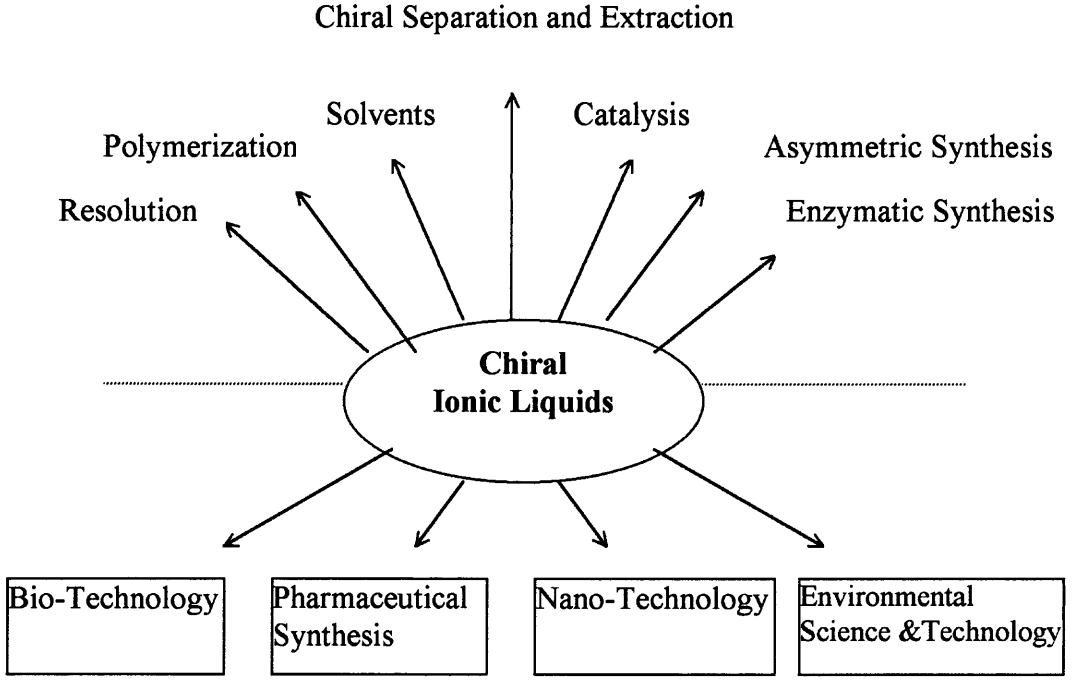


Figure 1.8 Proposed applications of chiral ionic liquids.

The successful synthesis and characterization of chiral ionic liquids will lead to research focused on the application of chiral ionic liquids in many synthetic and analytical applications. These applications include: resolution, polymerization, chiral solvents, chiral separation and extraction, enzyme synthesis, asymmetric synthesis and catalysis. Chiral ionic liquids will also see use in bio-, nano-, pharmaceutical and environmental technology. Some possible applications of chiral ionic liquids are described as following. (Figure 1.8)

1.3.2.1 Chiral Solvents. Chiral ionic liquids could be used as chiral solvents for asymmetric synthesis and catalysis as well as NMR spectroscopy.

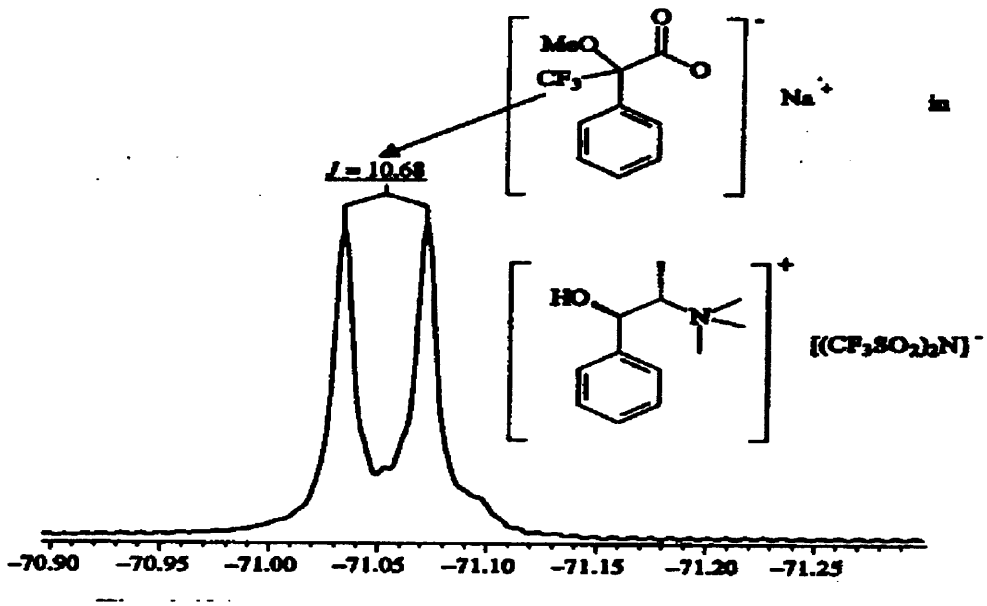


Figure 1.9 Chiral ionic liquids used for chiral resolution.

Peter Wasserscheid and co-workers [P. Wasserscheid, 2002] have verified the use of chiral ionic liquids for diastereomeric resolution. Here the split of the signal related to

the CF_3-group of ^{19}F-NMR shows the racemic substrate has been dissolved in a chiral environment. The degree of peak splitting is related to the strength of the diastereomeric interactions.

During the last decade, a number of powerful catalytic asymmetric reactions have emerged as a result of growing need to develop more efficient and practical synthetic methods for biogically active compounds. [Jacobsen et al., 1999] Although a number of homogeneous chiral catalysts have gained wide acceptance in terms of their efficiency and selectivity. The high cost and toxicity of these catalysts and the possible contamination of the product with the catalyst has, however, restricted the use of asymmetric catalytic reactions in industry. The development of an efficient immobilization method for chiral homogenous catalysts is, therefore, highly desirable. For catalyst recycling, homogenous chiral catalysts can be immobilized either by anchoring the catalyst on a solid support or by using aqueous or fluorous biphasic system. [Fan et al., 2002] In these solvents, catalysts having a polor or ionic character can be immobilized without additional structural modification and thus the ionic solutions containing the catalyst can easily be separated from the reagents and reaction products, and then, be used.

Research in this field focused on the achiral ionic liquids until now. The author has synthesized new chiral ionic liquids. It is expected that use chiral ionic liquids can be used as both chiral auxiliaries and solvents.

1.3.2.2 Chiral Phase Transfer Catalysts. Phase transfer catalysis (PTC) is a powerful methodology for the preparation of numerous classes of non-chiral and chiral compounds. Some nucleophilic reactions are frequently carried out in two phases system

using PTC. The PTC facilitates the reaction between the organic reaction in the organic phase and the nucleophile in the aqueous phase as an inorganic salt. In conventional reaction using PTC, the organic solvents such as dichloromethane or toluene are considered environmentally unfriendly compounds. Ecker et al. [Wheeler et al. 2001] already demonstrated the use of the ionic liquid [BMIM][PF_6] as a catalyst and solvent for the cyanide displacement of benzyl chloride and alkylation of benzyl cyanide under solid- IL PTC conditions. Nuno et al. [Nuno et al., 2003] reported the ionic liquid [BMIM][PF_6] is an efficient catalyst and solvent for several representative nucleophilic displacement reactions carried out under aqueous –RTIL PTC conditions.

The PTCs are generally quaternary ammonium salts and most of the ionic liquids are ammonium salts. So it is reasonable to use chiral ionic liquids as chiral phase transfer catalysts.

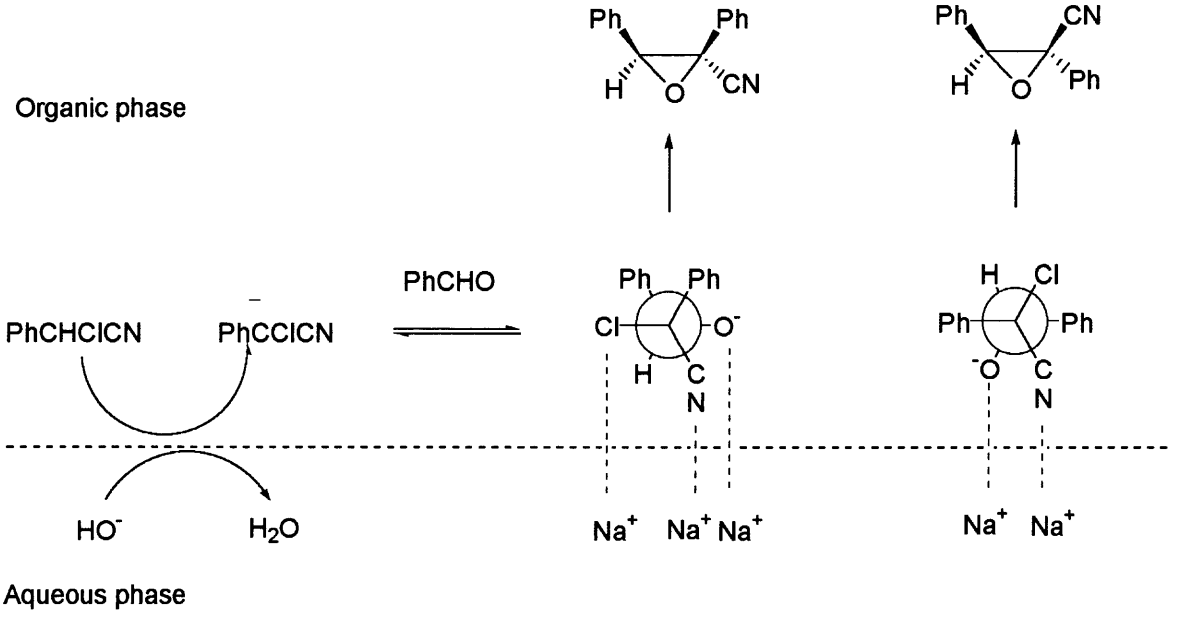


Figure 1.10 Mechanism of stereoselective control in phase transfer catalyst.

A degree of stereoselective control of the course of reaction, which is absent or different from that prevalent when the reaction is conducted in the absence of quaternary ammonium salts, maybe achieved under usual a 'standard' phase transfer catalyst. These involve anionic intermediates whose preferred conformations or configurations can be controlled by the cationic species across the interface of the two-phase system. For example, in the base-catalyzed Darzens condensation of aromatic aldehydes with α-chloroacetonitriles to produce oxirans, the intermediate anion may adopt either of the two conformers, which are stabilized by interaction across the interface by the cations [JP Masse et al, 1976]. Obtained from chloroacetonitrile and asymmetrically substituted ketons [Colonna et al., 1978] react specifically with aldehydes to yield only the *trans*-substituted oxiranes.[Dehemlow et al., 1981](Figure1.10)

1.3.2.3 Chiral Mobile or Stationary Phase in Chromatography. Based on the sales of chiral drugs and rapid growth of chiral drugs, the market size for chiral compounds is likely to surpass $100 billion in the year 2000. Accurate assessment of the isomeric purity of substances is critical, since isomeric impurities may have unwanted toxicologic, pharmacologic, or other effects. Such impurities may be carried through a synthesis and react preferentially at one or more steps, yielding an desirable level of another impurity. Frequently, one isomer of series produces a desired effect, while another is inactive or even toxic. Large differences in activity between stereoisomers point out the need to accurately assess isomeric purity of pharmaceuticals. Often these differences exist between enantiomers, the stereoisomers most difficult to separate. [Ahuja, 2000]

Chromatographic methods are considered most useful for enantiomeric resolution (def. Separation of the enantiomers.) for a number of reasons, the most important being the ease of separation. Chromatographic methods can be direct or indirect. [Ahuja, 2000] Indirect methods entail derivatization of a given enatiomeric mixture with a chiral reagent, leading to a pair of diastereomers that can be resolved by a given chromatographic method. In the indirect approach, the enantiomer may be converted into covalent, diastereomeric compounds by a reaction with a chiral reagent; and these diastereomers are typically separated on a routine achiral stationary phase.

The direct methods are chiral stationary or mobil-phase systems and are used more frequently because of ease of operation; however, selection of right combination still remains an intriguing process. In the last 30 years, systematic research was initiated for design of chiral stationary phases functioning to separate enatiomers by gas chromatography. More recently, efforts have been directed to finding new types of chiral and mobile phases on the basis of stereochemical viewpoint, resulting in the technical evolution of modern liquid chromatography.

Either direct or indirect method requires a chiral discriminator or selector. During the last few years, a number of research publications have focused on use of ionic liquids in chromatography separation. Since chiral ionic liquids can be used as chiral auxiliaries and have high boiling points compared with normal organic compounds, the application in chiral separation will increase.

1.4 Asymmetry Synthesis

1.4.1 Introduction

The world is chiral! Most organic compounds are chiral. Chemists working with perfumes, cosmetics, nutrients, flavors, pesticides, vitamins, and pharmaceuticals, to name a few examples, require access to enantiomerically pure compounds. In the pharmaceutical industry, more than half of the drugs available on the market are chiral, and roughly half of those are sold as a single enantiomer.

The most quoted definition of an asymmetric synthesis is that of Marckwald [Marckwald, 1904]. The core of this definition is the conversion of an achiral substance into a chiral, nonracemic one by the action of a chiral reagent. By this criterion, the chemical, biochemical and enzymatic processes are all included in this field.

This research focused on the synthesis of chiral product and application in the asymmetry reaction. Copper-catalyzed enantioselective reactions and α-pinene as chiral pool compounds are introduced because this is important for the design of the research in synthesis of chiral ionic liquids.

1.4.2 Copper-catalyzed Enantioselective Reactions

Organocopper reagents are one of the most valuable tools of synthetic organic chemistry within the last decade major shifts in the research directions of copper-catalyzed chemistry have focused on new reagents and methods for conducting stereoselective transformations (conjugate additions, substitutions and cyclopropanations); particularly striking is the recent discovery of a new class of chiral copper catalysts by Feringa et al. which gives high enantioselection in the 1,4-addition of organozinc reagents to many cyclic enones. Likewise, the development of new organocopper reagents (which started almost 50 years ago with Gilman's discovery of organocuprates) and unconventional applications in the synthesis of natural and non-natural target molecules are an important

part of the field.

1.4.3 α-Pinene as Chiral Pool

The ready availability of both enantiomers of α-pinene makes this compound unique among natural sources of chirality. Its derivatives such as pinanediol [Matterson et al., 1989], 2-hydroxypinan-3one [Oguri et al., 1978], Alpine-Borane [Midland et al., 1980], B-chlorodidiopinocampheylborane [Brown et al 1988], 3-amino-2-hydroxypinane [Burak et al., 1978] and oxazaborolidine [Moriyasu Masui et.al., 1995] have been used for chiral reagents in asymmetric synthesis. 2-α- hydroxypinan-3-one, synthesized by treatment of α-pinene with potassium permanganate in aqueous acetone solution has been successfully used as a chiral auxiliary in the asymmetric alkylation of ketoimines for over 20 years.[Carlson et al., 1971] It can be used in numerous syntheses, especially of amino acids, α, α-disubstituted amino acids and sphingosines.[Solladie et al., 1989]

1.5 Objectives

Based on the advantages of chiral ionic liquids and chiral phase transfer catalysts introduced above, this research focuses on conducting enantioselective copper-catalyzed 1,4-addition of organozinc reagents to enones by using new chiral ionic liquids as reaction media. By tuning the structure of cation and anion it would also be possible to investigate and develop their application such as solvents in asymmetric catalysis, extraction, separation, asymmetric organic and enzymatic synthesis etc.

The conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is an attractive and widely used tool for C-C bond formation. A number of

chiral auxiliaries and stoichiomeric reagents are known that allow high stereo control in the 1,4-addition. By comparing this reaction in organic solvents using chiral ligand and chiral-ionic liquids-solvent mixtures, the effectiveness of using ionic liquids as chiral solvents and chiral phase transfer catalysts will be investigated.

CHAPTER 2

EXPERIMENTAL SECTION

2.1 Chemicals and Equipments

2.1.1 Chemicals

Reagents were all purchased from Aldrich company: (1S)-(-)-Alpha-pinene (CAS 7785-26-4), potassium permanganate (CAS 7722-64-7), sodium acetate trihydrate (CAS 6131-90-4), hydroxylamine hydrochloride (CAS 5470-11-1), lithium aluminum hydride (CAS 16853-85-3), triethylamine (CAS 121-44-8), methanesulfonyl chloride (CAS 124-63-0), trans-Crotonyl chloride (CAS 625-35-4), 1-bromopropane (B7810-6), hexafluorophosphoric acid (CAS 16853-85-3), tetrafluoroboric acid (CAS 16853-85-3), diethyl-zinc (CAS557-20-0), copper(II) trifluoromethanesulfonate((CAS 34946-82-2), 2-cyclohexen-1-one (CAS930-66-7), 2-cyclopenten-1-one (C112909) and copper trifluoromethanesulfonate (CAS 34946-82-2).

Solvents including acetone, ethyl alcohol, hexane, ether, petroleum ether, chloroform, dichloromethane, tetrahydrofuran, ammonium hydroxide and 1,1,1-trichloroethane were all from Aldrich, Baker or Fisher Scientific Company.

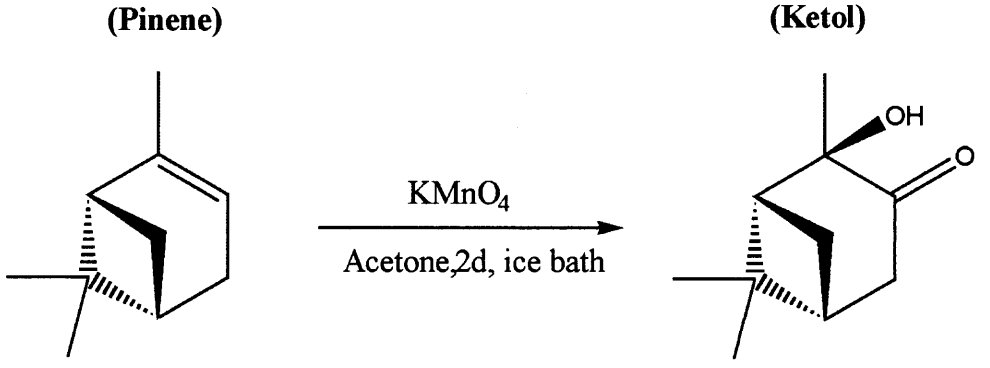
Sodium carbonate, sodium bicarbonate, magnesium sulphate, activated carbon and molecular sieve were from Brothers chemical or Aldrich company.

2.1.2 Equipment

Polarimeter (AUTOPOL IV) was from Rudolph Research Analytical Company. FT-IR (model 1605) was from Perkin Elmer. Gas Chromatograph (CP-3800) was from Varian. NMR spectrometer 60MHz were from Anasazi Instrument Inc.

2.2 Synthesis of New Chiral Ionic Liquids

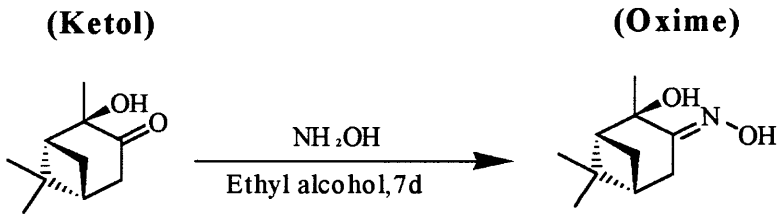
2.2.1 Preparation of 2-Hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]heptan-3-one



Scheme 2.1 Synthesis of ketol

Procedure: 200g pulverized potassium permanganate was added to a cold 90% aqueous acetone solution with continuously stirring in an ice bath. Then add 100g cold (1S)-(-)-α-pinene to the mixture slowly. The reaction mixture, after stirring in ice bath for 2 days, was filtered, acetone evaporated under reduced pressure (<35°C) and the residue extracted with ether (3×200 ml). The combined extracts were washed with water (4×200 ml) and saturated aqueous sodium bicarbonate, dried over magnesium sulphate and concentrated in vacuum to give yellow oil which was distilled to give 98g ketol (2-Hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]heptan-3-one): b.p.= 126°C (10mmHg); n_D^{20}=1.4895 (overcooled liquid), $[\alpha]_D^{20}$=-25.9 (*c* 0.5, $CHCl_3$). Yield 40–45%. FTIR(NaCl): [-OH] ν(O-H)=3428.42cm^{-1}; [-CH_3] ν(C-H as)=2924.28cm^{-1} ; [-C=O] ν(C-O)=1713.31cm^{-1}; [-CH_3,-CH_2] δ (C-H as)=1459.69cm^{-1} ; [-CH_3] δ (C-H s)=1372.13cm^{-1} . (See APPENDIX Figure A.1)

2.2.2 Preparation of 2-Hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]heptan-3-one oxime



2-Hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]heptan-3-one

2-Hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]heptan-3-one oxime

Scheme 2.2 Synthesis of oxime.

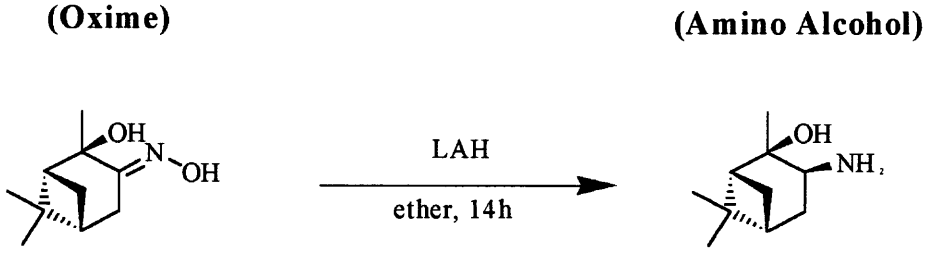
Procedure: A sample of ketol (84g) was dissolved in ethanol (250 ml), then a solution of $NH_2OH{\cdot}HCl$ (51 g) and $AcONa{\cdot}3H_2O$ (103 g) in water (70 ml) was added. The reaction mixture, after mixing in a shaker for 7 days at room temperature, was diluted with water (200 ml). The ethanol was evaporated under reduced pressure (<35°C) and the residue extracted with $CHCl_3$ (3×200 ml). The combined extracts were washed with water (4×200 ml), dried over magnesium sulphate and concentrated in vacuum. Colorless or pale yellow product (containing 3–5% $CHCl_3$) solidified after 1–2 days at -18°C. After crushing the solid and washing it with cold hexane (50 ml), the solvents were evaporated, and the crude oxime (91 g, 99%) was obtained.

The crude oxime (91 g) was extracted by heating under reflux in hexane (700 ml) for 15 min. This procedure was repeated three times. The combined hexane extracts crystallized on cooling to room temperature. The mixture was filtered to afford the crystalline oxime (56.1 g). The mother liquor yielded after condensation, a further 9 g of oxime was obtained. The yellow oily residue (1 g) contained mostly the oxime. Crystallization of oxime from a mixture of diethyl ether–hexane (1:10) afforded a product

with $[\alpha]_D^{20}$=-18.5, and recrystallization afforded the enantiomerically pure oxime in the form of needles: mp 119°C, $[\alpha]_D^{20}$=-32.340 (0.9779%, ethyl acetate), e.e. >99% (determined by ^{1}H NMR); FT-IR(KBr): [-OH] ν(O-H)=3312.67cm^{-1}; [-CH_3] ν(C-H as)=2925.60cm^{-1} ; [-C=N-OH] ν(C-N)=956.35cm^{-1}; [-CH_3,-CH_2] δ (C-H as)=1458.84cm^{-1} ; [-CH_3] δ (C-H s)=1379.34cm^{-1} (See APPENDIX Figure A.2) . ^{1}H NMR δ: 0.86 (s, 3H, $^9CH_3$), 1.30 (s, 3H, $^8CH_3$), 1.55 (s, 3H, $^{10}CH_3$), 1.59 (d, 1H, $^{7\text{-}1}$CH, J=10.6), 2.00 (m, 2H, ^{1}CH and $^{7\text{-}2}$CH), 2.32 (m, 1H, ^{5}CH), 2.73 (m, 2H, $^4CH_2$), 3.35 (1H, OH), 9.00 (1H, =NOH).

Total yield from over ten experiments carried out in the range of 42–128 g of used ketol, calculated, as the sum of enantiomerically pure and racemic crystalline oxime, was 93%.

2.2.3 Preparation of 3-Amino-2,6,6-trimethyl-bicyclo[3.1.1]heptan-2-ol



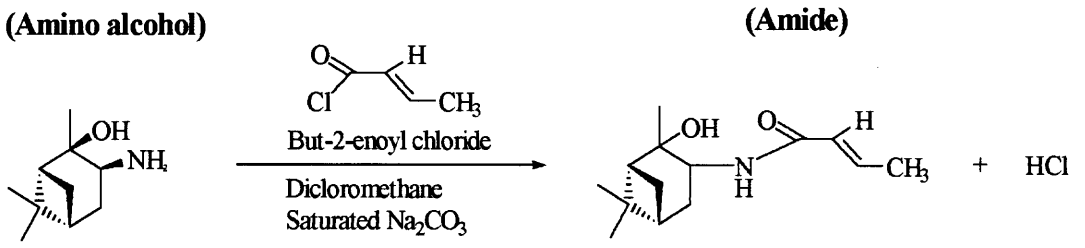
Scheme 2.3 Synthesis of amino alcohol

Procedure: In 100ml of ether 3.1g of LAH was placed and boiled for 30min. To solution, 5.0g of oxime 2 in 70ml of ether were introduced. The mixture was heated for 14 hours. The excess of LAH was decomposed by careful dropwise addition of water. $Al(OH)_3$

precipitate was filtered off and washed 3 times (50ml) with ether. Combined ethereal extracts were dried over anhydrous Na_2SO_4 and after distilling off the solvent, 3.0g of oily product was obtained. After a distillation under reduced pressure (b.p. 110°C/1.5mmhg) 2.9g (64.4%) of chromatographically homogeneous amino alcohol (TLC system: *iso*-PrOH---Me_2CO 1:1 ; developer: ninhydrin-*n*-BuOH), crystallizing in freezer was obtained. This preparation after a single crystallization from n-heptanes showed m.p. 67-68°C. FT-IR (KBr): (See APPENDIX Figure A.3) [-OH] ν(O-H)=3355.46cm^{-1}; [-CH_3] ν(C-H, as)=2913.03cm^{-1} ; [-NH_2] ν(N-H, s&as)≈3200cm^{-1},3300cm^{-1}; [-NH_2] δ (N-H)=1591.94cm^{-1}; [-CH_3,-CH_2] δ (C-H as)=1461.12cm^{-1} ; [-CH_3] δ (C-H s)=1378.34cm^{-1} . ^{1}H NMR δ: 0.51 (m, 2H, $^{7\text{-}1}CH_2$), 0.94 (s, 3H, $^{12}CH_3$), 1.02 (s, 3H, $^{9}CH_3$), 1.28 (s, 3H, ^{11}CH), 1.60 (m, 2H, $^{7}CH_2$), 1.80 (m, 2H, $^{3\text{-}2}CH$), 2.17 (m, 1H, ^{4}CH), 2.71 (1H, CH); ^{5}J= 0.25(^{2}CH, $^{7}CH_2$), ^{4}J= 1.79(^{2}CH, $^{9}CH_3$), ^{6}J=0.04(^{2}CH, $^{11}CH_3$), ^{6}J= 0.04(^{2}CH, $^{12}CH_3$), ^{3}J= 5.00(^{2}CH, $^{3\text{-}2}CH_2$), ^{4}J= 1.40($^{3\text{-}2}$CH, $^{7}CH_2$), ^{5}J= 0.11($^{3\text{-}2}$CH, $^{11}CH_3$), ^{5}J= 0.11($^{3\text{-}2}$CH, $^{12}CH_3$), ^{3}J= 10.50(^{2}CH, $^{3\text{-}1}CH_2$), ^{2}J= -13.24($^{3\text{-}1}CH_2$, $^{3\text{-}2}CH_2$), ^{4}J= 1.4($^{3\text{-}1}CH_2$, $^{7}CH_2$), ^{5}J= 0.11($^{3\text{-}1}CH_2$, $^{11}CH_3$), ^{5}J= 0.11(^{2}CH, $^{12}CH_3$), ^{4}J= 1.2(^{2}CH, ^{4}CH), ^{3}J= 6.17($^2CH_2$, $^{7}CH_2$), ^{3}J= 5.52(^{4}CH, $^{7\text{-}2}CH_2$), ^{3}J= 2.60(^{2}CH, $^{7\text{-}1}CH_2$), ^{4}J= 0.19(^{4}CH, $^{11}CH_3$), ^{4}J= 0.19(^{4}CH, $^{12}CH_3$), ^{4}J= 1.20(^{6}CH, ^{2}CH), ^{4}J= 5.03(^{6}CH, ^{4}CH), ^{3}J= 5.52(^{6}CH, $^{7\text{-}2}CH_2$), ^{3}J= 2.60(^{6}CH, $^{7\text{-}1}CH_2$), ^{4}J= 1.79(^{6}CH, $^{9}CH_3$), ^{4}J= 0.19(^{6}CH, $^{11}CH_3$), ^{4}J= 0.19(^{6}CH, $^{12}CH_3$), ^{5}J= 0.05($^{7\text{-}2}CH_2$, $^{11}CH_3$), ^{5}J= 0.05($^{7\text{-}2}CH_2$, $^{12}CH_3$), ^{2}J= 9.00($^{7\text{-}1}CH_3$, $^{7\text{-}2}CH_3$), ^{5}J= 0.10($^{7\text{-}1}CH_3$, $^{11}CH_3$), ^{5}J= 0.10($^{7\text{-}1}CH_3$, $^{12}CH_3$), ^{2}J= 1.33($^{9}CH_3$, $^{9}CH_3$), ^{2}J= 1.33($^{11}CH_3$, $^{11}CH_3$), ^{4}J= 1.09($^{11}CH_3$, $^{12}CH_3$), ^{2}J= 1.33($^{12}CH_3$, $^{12}CH_3$).

2.2.4 Preparation of Oxazoline

2.2.4.1 Preparation of Amide.



3-Amino-2,6,6-trimethyl-bi cyclo[3.1.1]heptan-2-ol

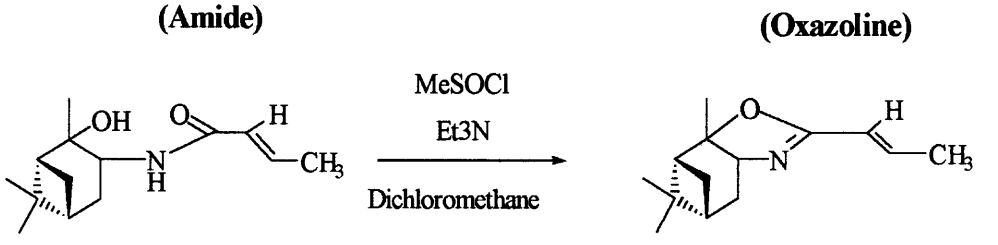
But-2-enoic acid (2-hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide

Scheme 2.4 Synthesis of amide

(E)-Crotonyl chloride (17.26g, 0.17mol) was added to a mixture of amino alcohol (13.38g, 0.15mol) in dichloromethane(200ml) and saturated aqueous sodium carbonate solution (120)ml). The mixture was stirred overnight then the aqueous layer was saturated with sodium chloride and extracted three times with dichloromethane (75ml). The combined organic layers were dried over MgSO4, filtered and the solvent was removed in vacuum to afford amide. A white solid product was obtained. [α]=12.813 (c=1.623%, dichloromethane); m.p.= 169°C; (See Figure A.4) FT-IR (KBr): [-OH] ν(O-H)=3312.67cm^{-1}; [-CH_3] ν(C-H, as)=2925.00cm^{-1} ; [-NH-] ν(N-H)≈3280cm^{-1}; [-RCON] δ (C-O)=1616.77cm^{-1}; [-CH_3,-CH_2] δ (C-H as)=1458.84cm^{-1} ; [-CH_3] δ (C-H s)=1379.34cm^{-1}; [E, $R_1C{=}CR_2$] γ(C-H)=956.35cm^{-1} . ^{1}H NMR **δ**: 0.51 (m, 2H, $^{7\text{-}1}CH_2$), 0.94 (s, 3H, $^{14}CH_3$), 1.18 (s, 3H, $^{9}CH_3$), 1.28 (s, 3H, $^{13}CH_3$), 1.88 (s, 3H, $^{17}CH_3$), 2.01 (m, 1H, ^{6}CH), 2.22 (m, 2H, $^{3\text{-}1}CH$), 2.26 (m, 1H, $^{3\text{-}2}CH$), 3.97 (m, 1H, ^{2}CH), 4.98 (m, 1H, ^{8}OH, ^{10}NH), 5.81 (m, 1H, ^{15a}H), 5.85 (m, 1H, ^{15a}H), 6.72 (m, 1H, ^{16a}H); ^{5}J= 0.25(^{2}CH, $^7CH_2$), ^{4}J= 1.79(^{2}CH, $^9CH_3$), ^{6}J=0.04(^{2}CH, $^{13}CH_3$), ^{6}J= 0.04(^{2}CH, $^{14}CH_3$), ^{3}J= 5.00(^{2}CH, $^{3\text{-}}$

$^{2}CH_2$), ^{4}J= 1.40($^{3\text{-}2}CH$, $^{7}CH_2$), ^{5}J= 0.11($^{3\text{-}2}CH$, $^{13}CH_3$), ^{5}J= 0.11($^{3\text{-}2}CH$, $^{14}CH_3$), ^{3}J= 10.50(^{2}CH, $^{3\text{-}1}CH_2$), ^{2}J= -13.24($^{3\text{-}1}CH_2$, $^{3\text{-}2}CH_2$), ^{4}J= 1.4($^{3\text{-}1}CH_2$, $^{7}CH_2$), ^{5}J= 0.11($^{3\text{-}1}CH_2$, $^{13}CH_3$), ^{5}J= 0.11(^{2}CH, $^{14}CH_3$), ^{4}J= 1.2(^{2}CH, ^{4}CH), ^{3}J= 6.17($^{2}CH_2$, $^{7}CH_2$), ^{3}J= 5.52(^{4}CH, $^{7\text{-}2}CH_2$), ^{3}J= 2.60(^{2}CH, $^{7\text{-}1}CH_2$), ^{4}J= 0.19(^{4}CH, $^{13}CH_3$), ^{4}J= 0.19(^{4}CH, $^{14}CH_3$), ^{4}J= 1.20(^{6}CH, ^{2}CH), ^{4}J= 5.03(^{6}CH, ^{4}CH), ^{3}J= 5.52(^{6}CH, $^{7\text{-}2}CH_2$), ^{3}J= 2.60(^{6}CH, $^{7\text{-}1}CH_2$), ^{4}J= 1.79(^{6}CH, $^{9}CH_3$), ^{4}J= 0.19(^{6}CH, $^{13}CH_3$), ^{4}J= 0.19(^{6}CH, $^{14}CH_3$), ^{5}J= 0.05($^{7\text{-}2}CH_2$, $^{13}CH_3$), ^{5}J= 0.05($^{7\text{-}2}CH_2$, $^{14}CH_3$), ^{2}J= 9.00($^{7\text{-}1}CH_3$, $^{7\text{-}2}CH_3$), ^{5}J= 0.10($^{7\text{-}1}CH_3$, $^{13}CH_3$), ^{5}J= 0.10($^{7\text{-}1}CH_3$, $^{14}CH_3$), ^{2}J= 1.33($^{9}CH_3$, $^{9}CH_3$), ^{2}J= 1.33($^{13}CH_3$, $^{13}CH_3$), ^{4}J= 1.09($^{13}CH_3$, $^{14}CH_3$), ^{2}J= 1.33($^{14}CH_3$, $^{14}CH_3$), ^{3}J= 15.67(^{15a}H, ^{16a}H), ^{3}J= 1.6($^{17}CH_3$, ^{15a}H), ^{3}J= 6.60($^{17}CH_3$, ^{16a}H), ^{3}J= 2.09($^{17}CH_3$, $^{17}CH_3$).

2.2.4.2 Preparation of Oxazoline.



But-2-enoic acid (2-hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide

2,9,9-Trimethyl-4-propenyl-3-oxa-5-aza-tricyclo[6.1.1.$0^{2,6}$]dec-4-ene

Scheme 2.5 Synthesis of oxazoline.

Amide (4.21g, 27mmol) in dichloromethane (75ml) was cooled to 5°C. Trimethyl-amine (5.42g, 54mmol) and methanesulfonyl chloride (3.07g, 27mmol) were added and the solution was stirred overnight. The solution was then washed twice with saturated $NaHCO_3$ (50ml), dried over MgSO4, filtered and concentrated in vacuum. The product

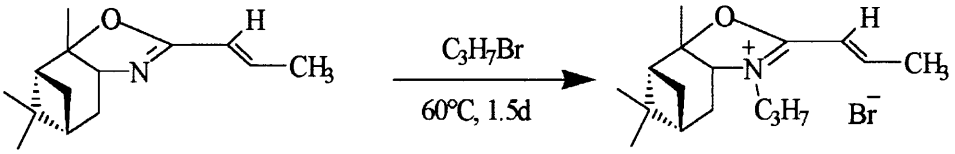
was purified by recrystallizing to afford the oxazoline as a red solid. Yield: 90% M.P.= 122-134°C. [α]=4.651 (c=0.3%, ethyl acetate); (See APPENDIX Figure A.5) FT-IR(KBr): [-OH] ν(O-H)=3312.80cm^{-1}; [-CH_3] ν(C-H, as)=2932.42cm^{-1} ; [-C-O-C=N] δ (-C=N)=1671.42cm^{-1},δ (C-O-C)=1171.47cm^{-1}; [-CH_3,-CH_2] δ (C-H as)=1455.17cm^{-1} ; [-CH_3] δ (C-H s)=1379.21cm^{-1} ;[E, $R_1C=CR_2$] γ(C-H)=956.35cm^{-1} . ^{1}H NMR **δ**: 0.90/6.68 (3H, $^{15}CH_3$), 1.19/6.60 (3H, $^{14}CH_3$), 1.73/4.43 (3H, $^{13}CH_3$), 2.16/0.22 (2H, $^{10\text{-}2}CH_2$), 4.21/0.37 (1H, $^{3\text{-}1}$CH), 4.25/0.84 (1H, $^{3\text{-}2}$CH), 4.46/1.02 (1H, ^{2}CH), 5.47/1.24 (1H, ^{11a}H), 6.32/1.04 (1H, ^{12a}H), 6.34/0.38 (1H, ^{12a}H); ^{4}J= 1.82(^{2}CH, $^{10}CH_3$), ^{3}J=7.45(^{3}CH, ^{2}CH), ^{4}J= 1.82(^{8}CH, ^{3}CH), ^{3}J= 6.17(^{8}CH, $^9CH_2$), ^{3}J= 5.52(^{8}CH, $^{10\text{-}2}CH_3$), ^{3}J= 2.60(^{8}CH, $^{10\text{-}1}CH_3$), ^{4}J= 0.19(^{8}CH, $^{14}CH_3$), ^{4}J= 0.19(^{8}CH, $^{15}CH_3$), ^{4}J= 1.82($^{9\text{-}2}CH_2$, ^{2}CH), ^{3}J= 8.85($^{9\text{-}2}CH_2$, ^{3}CH), ^{4}J= 2.01($^{9\text{-}2}CH_2$, $^{10\text{-}2}CH_3$), ^{4}J= 0.92($^{9\text{-}2}CH_2$, $^{10\text{-}1}CH_3$), ^{5}J= 0.11($^{9\text{-}2}CH_2$, ^{14}CH), ^{5}J= 0.11($^{9\text{-}2}CH_2$, $^{15}CH_2$), ^{4}J= 1.82($^{9\text{-}1}CH_2$, ^{2}CH), ^{3}J= 8.85($^{9\text{-}1}CH_2$, ^{3}CH), ^{2}J= -13.24($^{9\text{-}1}CH_2$, $^{9\text{-}2}CH_2$), ^{4}J= 0.92($^{9\text{-}1}CH_2$, $^{10\text{-}2}CH_3$), ^{4}J= 0.28($^{9\text{-}1}CH_2$, $^{10\text{-}1}$CH), ^{5}J= 0.11($^{9\text{-}1}CH_2$, $^{14}CH_3$), ^{5}J= 0.11($^{9\text{-}1}CH_2$, $^{15}CH_3$), ^{5}J= 0.05($^{10\text{-}2}CH_2$, $^{14}CH_3$), ^{5}J= 0.05($^{10\text{-}2}CH_2$, $^{15}CH_3$), ^{2}J= -9.22($^{10\text{-}1}CH_2$, $^{10\text{-}2}CH_3$), ^{5}J= 0.10($^{10\text{-}1}CH_2$, $^{15}CH_3$), ^{5}J= 0.10($^{10\text{-}1}CH_2$, $^{14}CH_3$), ^{3}J= 14.17(^{11a}H, ^{12a}H), ^{4}J= -1.5($^{13}CH_3$, ^{11a}H), ^{3}J= 6.08($^{13}CH_3$, ^{12a}H), ^{2}J= 2.09($^{13}CH_3$, $^{13}CH_3$), ^{2}J= 1.33($^{14}CH_3$, $^{14}CH_3$),), ^{4}J= 1.09($^{14}CH_3$, $^{15}CH_3$), ^{2}J= 1.33($^{15}CH_3$, $^{15}CH_3$).

2.2.5 Preparation of Chiral Ionic Liquids

2.2.5.1 Preparation of [ChIPOZ][Br] Ionic Liquid.

Oxazoline (3.0g) was mixed with 1-bromopropane (20ml) for 2 days under stirring and heating with reflux at 60°C. The remaining bromopropane was removed under vacuum to yield 4.2g oxazolium bromide (90%yield). [α]=4.651 (c=0.3%, ethyl acetate); m.p. 162°C; (See Figure A.6) FT-IR(KBr): [-OH] ν(O-H)=3312.80cm^{-1}; [-CH_3] ν(C-H,

(Oxazoline) **([ChIPOZ][Br])**



2,9,9-Trimethyl-4-propenyl-3-oxa-5-aza-tricyclo[6.1.1.$0^{2,6}$]dec-4-ene

9,9-Dimethyl-4-propenyl-5-propyl-3-oxa-5-azonia-tricyclo[6.1.1.$0^{2,6}$]dec-4-ene; bromide

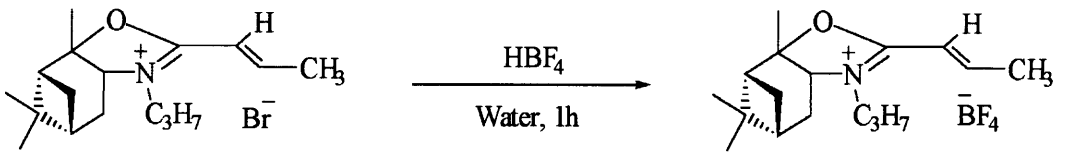
Scheme 2.6 Synthesis of Bromide ionic liquid.

as)=2932.42cm^{-1} ; [-C-O-C=N] δ (-C=N)=1671.42cm^{-1},δ (C-O-C)=1171.47cm^{-1}; [-CH_3,-CH_2] δ (C-H as)=1455.17cm^{-1} ; [-CH_3] δ (C-H s)=1379.21cm^{-1} ;[E, $R_1C=CR_2$] γ(C-H)=956.35cm^{-1} . ^{1}H NMR δ: 0.86/0.88(m, 3H, $^{13}CH_3$), 0.90(s, 3H, $^{18}CH_3$), 1.19(s, 3H, $^{17}CH_3$), 1.69(s, 3H, $^{16}CH_3$), 2.12/2.14 (1H, $^8CH_2$), 3.36/3.38 (1H, ^3CH), 3.91 (1H, ^2CH), 5.31/5.36/5.37 (1H, ^{14a}H), 5.43/5.48/5.46 (1H, ^{15a}H), 5.82/5.84 (1H, ^5H); ^4J= 0.95(^2CH, ^5CH), ^4J= 1.82(^2CH, $^{10}CH_3$), ^3J=7.45(^3CH, ^2CH), ^4J=1.56(^3CH, ^5CH), ^4J=0.99(^3CH, $^{11}CH_2$), ^4J=0.99(^5CH, $^{11}CH_2$), ^5J=0.42(^5CH, ^{12}CH), ^3J=5.34(^5CH, ^{14a}H), ^4J=0.50(^5CH, ^{15a}H), ^3J=5.33(^6CH, ^2CH), ^4J=1.82(^6CH, ^3CH), ^4J=5.03(^6CH, ^8CH), ^3J=5.52(^6CH, $^{10\text{-}2}CH_2$), ^3J=2.60(^6CH, $^{10\text{-}1}CH_2$), ^4J=0.19(^6CH, $^{17}CH_3$), ^4J=0.19(^6CH, $^{18}CH_3$), ^4J= 1.82(^8CH, ^3CH), ^3J= 6.17(^8CH, $^9CH_2$), ^3J= 5.52(^8CH, $^{10\text{-}2}CH_3$), ^3J= 2.60(^8CH, $^{10\text{-}1}CH_3$), ^4J= 0.19(^8CH, $^{17}CH_3$), ^4J= 0.19(^8CH, $^{18}CH_3$), ^4J= 1.82($^{9\text{-}2}CH_2$, ^2CH), ^3J= 8.85($^{9\text{-}2}CH_2$, ^3CH), ^4J= 2.01($^{9\text{-}2}CH_2$, $^{10\text{-}2}CH_3$), ^4J= 0.92($^{9\text{-}2}CH_2$, $^{10\text{-}1}CH_3$), ^5J= 0.11($^{9\text{-}2}CH_2$, $^{17}CH_3$), ^5J= 0.11($^{9\text{-}2}CH_2$, $^{18}CH_3$), ^4J= 1.82($^{9\text{-}1}CH_2$, ^2CH), ^3J= 8.85($^{9\text{-}1}CH_2$, ^3CH), ^2J= -13.24($^{9\text{-}1}CH_2$, $^{9\text{-}2}CH_2$), ^4J= 0.92($^{9\text{-}1}CH_2$, $^{10\text{-}2}CH_3$), ^4J= 0.28($^{9\text{-}1}CH_2$, $^{10\text{-}1}CH$), ^5J= 0.11($^{9\text{-}1}CH_2$, $^{17}CH_3$), ^5J= 0.11($^{9\text{-}1}CH_2$, $^{18}CH_3$), ^5J= 0.05($^{10\text{-}2}CH_2$, $^{17}CH_3$), ^5J= 0.05($^{10\text{-}2}CH_2$, $^{18}CH_3$), ^2J= -9.22($^{10\text{-}1}CH_2$, $^{10\text{-}2}CH_3$), ^5J= 0.10($^{10\text{-}1}CH_2$, $^{17}CH_3$), ^5J= 0.10($^{10\text{-}1}CH_2$, $^{18}CH_3$), ^3J= 7.08($^{11\text{-}2}CH_2$, $^{12}CH_2$), ^4J= -0.51($^{11\text{-}2}$

CH_2, $^{13}CH_3$), ^2J= 14.00($^{11\text{-}1}CH_2$, $^{11\text{-}2}CH_2$), ^3J= 7.08($^{11\text{-}1}CH_2$, $^{12}CH_2$), ^4J= -0.37($^{11\text{-}1}CH_2$, $^{13}CH_3$), ^2J= -13.47($^{12}CH_2$, $^{12}CH_2$), ^3J= 7.24($^{12}CH_2$, $^{13}CH_3$), ^2J= 4.24($^{13}CH_3$, $^{13}CH_3$), ^5J= 12.20(^{14a}H, $^{11}CH_2$), ^3J= 15.00(^{14a}H, ^{15a}H), ^3J= 15.00($^{16}CH_3$,, ^{14a}H), ^2J= 15.00($^{16}CH_3$, ^{15a}H), ^2J= 2.09($^{16}CH_3$, $^{16}CH_3$), ^2J= 1.33($^{17}CH_3$, $^{17}CH_3$), ^4J= 1.09($^{17}CH_3$, $^{18}CH_3$), ^2J= 1.33($^{18}CH_3$, $^{18}CH_3$).

2.2.5.2 Preparation of [ChIPOZ] [BF_4] Ionic Liquid.

[ChIPOZ][Br] **[ChIPOZ][BF_4]**



ChIP-Oxazolium bromide **ChIP-Oxazolium tetrafluoro borate**

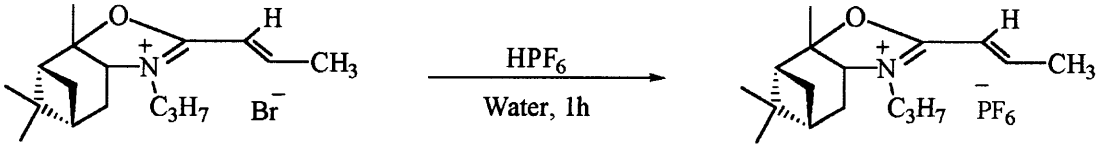
Scheme 2.7 Synthesis of tetrafluoro borate chiral ionic liquid

Tetrofluoroboric acid (48% wt% solution in water, 0.7402g) was added dropwise to a cooled, stirred solution of oxazolium bromide (1.0498g) in 100ml water over 10 minutes. The product was precipated as a waxy solid. After wash with water, product 0.9083g(83.7%yield) was obtained. Melting point: 120°C. [α]=28.329 (c=0.06%, ethyl acetate) FT-IR(KBr): [-OH] ν(O-H)=3312.80cm^{-1}; [$-CH_3$] ν(C-H, as)=2932.42cm^{-1} ; [-C-O-C=N] δ (-C=N)=1671.42cm-1,δ (C-O-C)=1171.47cm^{-1}; [$-CH_3$,$-CH_2$] δ (C-H as)=1455.17cm^{-1} ; [$-CH_3$] δ (C-H s)=1379.21cm^{-1} ; [PF_6] δ =1288.67cm^{-1} ; [E, $R_1C=CR_2$] γ(C-H)=956.35cm^{-1} . ^{1}H NMR δ: 0.86/0.88(m, 3H, $^{13}CH_3$), 0.90(s, 3H, $^{18}CH_3$), 1.19(s, 3H, $^{17}CH_3$), 1.69(s, 3H, $^{16}CH_3$), 2.12/2.14 (1H, $^8CH_2$), 3.36/3.38 (1H, ^3CH), 3.91

(1H, ^{2}CH), 5.31/5.36/5.37 (1H, ^{14a}H), 5.43/5.48/5.46 (1H, ^{15a}H), 5.82/5.84 (1H, ^{5}H); ^{4}J= 0.95(^{2}CH, ^{5}CH), ^{4}J= 1.82(^{2}CH, ^{10}CH$_3$), ^{3}J=7.45(^{3}CH, ^{2}CH), ^{4}J=1.56(^{3}CH, ^{5}CH), ^{4}J=0.99(^{3}CH, ^{11}CH$_2$), ^{4}J=0.99(^{5}CH, ^{11}CH$_2$), ^{5}J=0.42(^{5}CH, ^{12}CH), ^{3}J=5.34(^{5}CH, ^{14a}H), ^{4}J=0.50(^{5}CH, ^{15a}H), ^{3}J=5.33(^{6}CH, ^{2}CH), ^{4}J=1.82(^{6}CH, ^{3}CH), ^{4}J=5.03(^{6}CH, ^{8}CH), ^{3}J=5.52(^{6}CH, $^{10\text{-}2}$CH$_2$), ^{3}J=2.60(^{6}CH, $^{10\text{-}1}$CH$_2$), ^{4}J=0.19(^{6}CH, ^{17}CH$_3$), ^{4}J=0.19(^{6}CH, ^{18}CH$_3$), ^{4}J= 1.82(^{8}CH, ^{3}CH), ^{3}J= 6.17(^{8}CH, ^{9}CH$_2$), ^{3}J= 5.52(^{8}CH, $^{10\text{-}2}$CH$_3$), ^{3}J= 2.60(^{8}CH, $^{10\text{-}1}$CH$_3$), ^{4}J= 0.19(^{8}CH, ^{17}CH$_3$), ^{4}J= 0.19(^{8}CH, ^{18}CH$_3$), ^{4}J= 1.82($^{9\text{-}2}$CH$_2$, ^{2}CH), ^{3}J= 8.85($^{9\text{-}2}$CH$_2$, ^{3}CH), ^{4}J= 2.01($^{9\text{-}2}$CH$_2$, $^{10\text{-}2}$CH$_3$), ^{4}J= 0.92($^{9\text{-}2}$CH$_2$, $^{10\text{-}1}$CH$_3$), ^{5}J= 0.11($^{9\text{-}2}$CH$_2$, ^{17}CH$_3$), ^{5}J= 0.11($^{9\text{-}2}$CH$_2$, ^{18}CH$_3$), ^{4}J= 1.82($^{9\text{-}1}$CH$_2$, ^{2}CH), ^{3}J= 8.85($^{9\text{-}1}$CH$_2$, ^{3}CH), ^{2}J= -13.24($^{9\text{-}1}$CH$_2$, $^{9\text{-}2}$CH$_2$), ^{4}J= 0.92($^{9\text{-}1}$CH$_2$, $^{10\text{-}2}$CH$_3$), ^{4}J= 0.28($^{9\text{-}1}$CH$_2$, $^{10\text{-}1}$CH), ^{5}J= 0.11($^{9\text{-}1}$CH$_2$, ^{17}CH$_3$), ^{5}J= 0.11($^{9\text{-}1}$CH$_2$, ^{18}CH$_3$), ^{5}J= 0.05($^{10\text{-}2}$CH$_2$, ^{17}CH$_3$), ^{5}J= 0.05($^{10\text{-}2}$CH$_2$, ^{18}CH$_3$), ^{2}J= -9.22($^{10\text{-}1}$CH$_2$, $^{10\text{-}2}$CH$_3$), ^{5}J= 0.10($^{10\text{-}1}$CH$_2$, ^{17}CH$_3$), ^{5}J= 0.10($^{10\text{-}1}$CH$_2$, ^{18}CH$_3$), ^{3}J= 7.08($^{11\text{-}2}$CH$_2$, ^{12}CH$_2$), ^{4}J= -0.51($^{11\text{-}2}$ CH$_2$, ^{13} CH$_3$), ^{2}J= 14.00($^{11\text{-}1}$ CH$_2$, $^{11\text{-}2}$ CH$_2$), ^{3}J= 7.08($^{11\text{-}1}$ CH$_2$, ^{12}CH$_2$), ^{4}J= -0.37($^{11\text{-}1}$ CH$_2$, ^{13}CH$_3$), ^{2}J= -13.47(^{12} CH$_2$, ^{12}CH$_2$), ^{3}J= 7.24(^{12} CH$_2$, ^{13}CH$_3$), ^{2}J= 4.24(^{13} CH$_3$, ^{13}CH$_3$), ^{5}J= 12.20(^{14a}H, ^{11}CH$_2$), ^{3}J= 15.00(^{14a}H, ^{15a}H), ^{3}J= 15.00(^{16}CH$_3$,, ^{14a}H), ^{2}J= 15.00(^{16}CH$_3$, ^{15a}H), ^{2}J= 2.09(^{16}CH$_3$, ^{16}CH$_3$), ^{2}J= 1.33(^{17}CH$_3$, ^{17}CH$_3$), ^{4}J= 1.09(^{17}CH$_3$, ^{18}CH$_3$), ^{2}J= 1.33(^{18}CH$_3$, ^{18}CH$_3$).

2.2.5.3 Preparation of [ChIPOZ] [PF_6] Ionic Liquid.

[ChIPOZ][Br] → **[ChIPOZ][PF_6]**



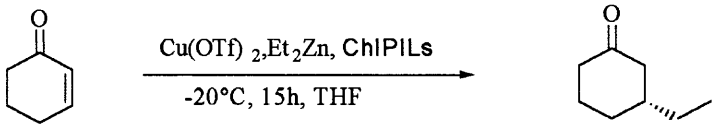
Oxazolium bromide **Oxazolium hexafluoro phosphate**

Scheme 2.8 Synthesis of hexafluoro phosphate chiral ionic liquid.

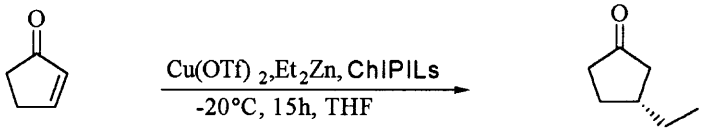
Hexafluorophosphoric acid (60% wt% solution in water, 0.499g) was added dropwise to a cooled, rapidly stirred solution of oxazolium bromide (0.5615g) in 100ml water over 10 minutes. The product was precipated as a waxy solid. After wash with water product 0.5683g(88.1%yield) was obtained. Melting point: 140°C. [α]=4.166 (c=0.09%, ethyl acetate) FT-IR(KBr): [-OH] ν(O-H)=3312.80cm^{-1}; [-CH_3] ν(C-H, as)=2932.42cm^{-1} ; [-C-O-C=N] δ (-C=N)=1671.42cm^{-}1,δ (C-O-C)=1171.47cm^{-1}; [-CH_3,-CH_2] δ (C-H as)=1455.17cm^{-1} ; [-CH_3] δ (C-H s)=1379.21cm^{-1} ; [PF_6] δ =1288.67cm^{-1}; [E, $R_1C{=}CR_2$] γ(C-H)=956.35cm^{-1} . ^{1}H NMR δ: 0.86/0.88(m, 3H, $^{13}CH_3$), 0.90(s, 3H, $^{18}CH_3$), 1.19(s, 3H, $^{17}CH_3$), 1.69(s, 3H, $^{16}CH_3$), 2.12/2.14 (1H, $^{8}CH_2$), 3.36/3.38 (1H, ^{3}CH), 3.91 (1H, ^{2}CH), 5.31/5.36/5.37 (1H, ^{14a}H), 5.43/5.48/5.46 (1H, ^{15a}H), 5.82/5.84 (1H, ^{5}H); ^{4}J= 0.95(^{2}CH, ^{5}CH), ^{4}J= 1.82(^{2}CH, $^{10}CH_3$), ^{3}J=7.45(^{3}CH, ^{2}CH), ^{4}J=1.56(^{3}CH, ^{5}CH), ^{4}J=0.99(^{3}CH, $^{11}CH_2$), ^{4}J=0.99(^{5}CH, $^{11}CH_2$), ^{5}J=0.42(^{5}CH, ^{12}CH), ^{3}J=5.34(^{5}CH, ^{14a}H), ^{4}J=0.50(^{5}CH, ^{15a}H), ^{3}J=5.33(^{6}CH, ^{2}CH), ^{4}J=1.82(^{6}CH, ^{3}CH), ^{4}J=5.03(^{6}CH, ^{8}CH), ^{3}J=5.52(^{6}CH, $^{10\text{-}2}CH_2$), ^{3}J=2.60(^{6}CH, $^{10\text{-}1}CH_2$), ^{4}J=0.19(^{6}CH, $^{17}CH_3$), ^{4}J=0.19(^{6}CH, $^{18}CH_3$), ^{4}J= 1.82(^{8}CH, ^{3}CH), ^{3}J= 6.17(^{8}CH, $^{9}CH_2$), ^{3}J= 5.52(^{8}CH, $^{10\text{-}2}CH_3$), ^{3}J= 2.60(^{8}CH, $^{10\text{-}1}CH_3$), ^{4}J= 0.19(^{8}CH, $^{17}CH_3$), ^{4}J= 0.19(^{8}CH, $^{18}CH_3$), ^{4}J= 1.82($^{9\text{-}2}CH_2$, ^{2}CH), ^{3}J= 8.85($^{9\text{-}2}CH_2$, ^{3}CH), ^{4}J= 2.01($^{9\text{-}2}CH_2$, $^{10\text{-}2}CH_3$), ^{4}J= 0.92($^{9\text{-}2}CH_2$, $^{10\text{-}1}CH_3$), ^{5}J= 0.11($^{9\text{-}2}CH_2$, $^{17}CH_3$), ^{5}J= 0.11($^{9\text{-}2}CH_2$, $^{18}CH_3$), ^{4}J= 1.82($^{9\text{-}1}CH_2$, ^{2}CH), ^{3}J= 8.85($^{9\text{-}1}CH_2$, ^{3}CH), ^{2}J= -13.24($^{9\text{-}1}CH_2$, $^{9\text{-}2}CH_2$), ^{4}J= 0.92($^{9\text{-}1}CH_2$, $^{10\text{-}2}CH_3$), ^{4}J= 0.28($^{9\text{-}1}CH_2$, $^{10\text{-}1}CH$), ^{5}J= 0.11($^{9\text{-}1}CH_2$, $^{17}CH_3$), ^{5}J= 0.11($^{9\text{-}1}CH_2$, $^{18}CH_3$), ^{5}J= 0.05($^{10\text{-}2}CH_2$, $^{17}CH_3$), ^{5}J= 0.05($^{10\text{-}2}CH_2$, $^{18}CH_3$), ^{2}J= -9.22($^{10\text{-}1}CH_2$, $^{10\text{-}2}CH_3$), ^{5}J= 0.10($^{10\text{-}1}CH_2$, $^{17}CH_3$), ^{5}J= 0.10($^{10\text{-}1}CH_2$, $^{18}CH_3$), ^{3}J= 7.08($^{11\text{-}2}CH_2$, $^{12}CH_2$), ^{4}J= -0.51($^{11\text{-}2}$ CH_2, ^{13} CH_3), ^{2}J= 14.00($^{11\text{-}1}$ CH_2, $^{11\text{-}2}$ CH_2), ^{3}J= 7.08($^{11\text{-}1}$ CH_2, $^{12}CH_2$), ^{4}J= -0.37($^{11\text{-}1}$ CH_2, $^{13}CH_3$), ^{2}J= -13.47(^{12} CH_2, $^{12}CH_2$), ^{3}J= 7.24(^{12} CH_2,

$^{13}CH_3$), ^{2}J= 4.24(^{13} CH_3, $^{13}CH_3$), ^{5}J= 12.20(^{14a}H, $^{11}CH_2$), ^{3}J= 15.00(^{14a}H, ^{15a}H), ^{3}J= 15.00($^{16}CH_3$,, ^{14a}H), ^{2}J= 15.00($^{16}CH_3$, ^{15a}H), ^{2}J= 2.09($^{16}CH_3$, $^{16}CH_3$), ^{2}J= 1.33($^{17}CH_3$, $^{17}CH_3$), ^{4}J= 1.09($^{17}CH_3$, $^{18}CH_3$), ^{2}J= 1.33($^{18}CH_3$, $^{18}CH_3$).

2.3 Application of Chiral Ionic Liquids in Copper-Catalyzed Asymmetric Reactions



Cyclohex-2-enone **(+)-3-Ethyl-cyclohexanone**



Cyclopent-2-enone **(+)-3-Ethyl-cyclopentanone**

Scheme 2.9 Copper-catalyzed 1,4-addition reaction using chiral ionic liquids as phase transfer catalyst.

2.3.1 Cyclohexenone in [IP-oxazolinium][BF_4] Ionic Liquid

Copper trifluoromethanesulfonate (55.4 mg, 0.15 mmol, 3.0 mol%) was weighed in the glove box. IP-oxazolium BF_4 (60.3mg, 0.18 mmol, 3.6 mol%) and dry THF (10 mL) were added. The solution was stirred for 1 h at room temperature under a Helium atmosphere. The reaction was cooled to -20°C. Cyclohexenone (480.65 mg, 5 mmol) was added followed by Et_2Zn (6.5 mL, 1.3 equiv., 1 M in Hexane), which was added dropwise within 2 min. After stirring for 15 h at -20°C the reaction mixture was hydrolyzed by addition of saturated NH_4Cl and NH_3 (32%) solutions (10 mL each). *n*-Undecane (194 mg, 1.2 mmol) as internal standard was added and the mixture was allowed to warm up to room temperature. After dilution with water and Et_2O (2 mL each)

and stirring for 10 min., an aliquot of the organic phase was taken, filtered through a pad of cotton and analyzed by GC (95% yield). The aqueous phase was separated and extracted with Et_2O (3×3 mL). The combined organic phases were dried over $MgSO_4$. Most of the solvent was removed at reduced pressure. The crude product was purified by gradient flash column chromatography (silica-gel, 2×15 cm, going from pentane (to remove the toluene) to pentane/diethyl ether 4:1) to afford 0.5679g (90%) of 3-ethylcyclohexanone as a colorless liquid. [α]= 119.68 (c=1%, chloroform); e.e.=76% (Compared with [α]=156.0 in chloroform.[Posner et al. 1984])

2.3.2 Cyclohexenone in [IP-oxazolinium] [PF_6] Ionic Liquid

Copper trifluoromethanesulfonate (55.4 mg, 0.15 mmol, 3.0 mol%) was weighed in the glove box. IP-oxazolium PF_6 (70.8mg, 0.18 mmol, 3.6 mol%) and dry THF (10 mL) were added. The solution was stirred for 1 h at room temperature under a Helium atmosphere. The reaction was cooled to -20°C. Cyclohexenone (480.65 mg, 5 mmol) was added followed by Et_2Zn (6.5 mL, 1.3 equiv., 1 M in Hexane), which was added dropwise within 2 min. After stirring for 15 h at -20°C the reaction mixture was hydrolyzed by addition of saturated NH_4Cl and NH_3 (32%) solutions (10 mL each). *n*-Undecane (194 mg, 1.2 mmol) as internal standard was added and the mixture was allowed to warm up to room temperature. After dilution with water and Et_2O (2 mL each) and stirring for 10 min., an aliquot of the organic phase was taken, filtered through a pad of cotton and analyzed by GC (95% yield). The aqueous phase was separated and extracted with Et_2O (3×3 mL). The combined organic phases were dried over $MgSO_4$. Most of the solvent was removed at reduced pressure. The crude product was purified by gradient flash column chromatography (silica-gel, 2×15 cm, going from pentane (to remove the toluene) to pentane/diethyl ether 4:1) to afford 0.5679g (90%) of 3-ethylcyclohexanone as a colorless liquid. [α]= 53.5 (c= 1%, chloroform); e.e.=34.29% (Compared with [α]=156.0 in chloroform.[Posner et al. 1984])

2.3.3 Cyclopentenone in [IP-oxazolinium] [BF_4] Ionic Liquid

Copper trifluoromethanesulfonate (55.4 mg, 0.15 mmol, 3.0 mol%) was weighed in the

glove box. IP-oxazolium BF_4 (60.3mg, 0.18 mmol, 3.6 mol%) and dry THF (10 mL) were added. The solution was stirred for 1 h at room temperature under a Helium atmosphere. The reaction was cooled to -20°C. Cyclopentenone (410.65 mg, 5 mmol) was added followed by Et_2Zn (6.5 mL, 1.3 equiv., 1 M in Hexane), which was added dropwise within 2 min. After stirring for 15 h at -20°C the reaction mixture was hydrolyzed by addition of saturated NH_4Cl and NH_3 (32%) solutions (10 mL each). *n*-Undecane (194 mg, 1.2 mmol) as internal standard was added and the mixture was allowed to warm up to room temperature. After dilution with water and Et_2O (2 mL each) and stirring for 10 min., an aliquot of the organic phase was taken, filtered through a pad of cotton and analyzed by GC (49% yield). The aqueous phase was separated and extracted with Et_2O (3×3 mL). The combined organic phases were dried over $MgSO_4$. Most of the solvent was removed at reduced pressure. The crude product was purified by gradient flash column chromatography (silica-gel, 2×15 cm, going from pentane (to remove the toluene) to pentane/diethyl ether 4:1) to afford 0.2243g (40%) of 3-ethylcyclopentanone as a colorless liquid. [α]=128.6 (c= 1%, chloroform); e.e.=73.14% (Compared with [α]=175.0 in chloroform.[Posner et al. 1984])

2.3.4 Cyclopentenone in [IP-oxazolinium] [PF_6] Ionic Liquids

Copper trifluoromethanesulfonate (55.4 mg, 0.15 mmol, 3.0 mol%) was weighed in the glove box. IP-oxazolium PF_4 (70.8mg, 0.18 mmol, 3.6 mol%) and dry THF (10 mL) were added. The solution was stirred for 1 h at room temperature under a Helium atmosphere. The reaction was cooled to -20°C. Cyclopentenone (410.65 mg, 5 mmol) was added followed by Et_2Zn (6.5 mL, 1.3 equiv., 1 M in Hexane), which was added dropwise within 2 min. After stirring for 15 h at -20°C the reaction mixture was hydrolyzed by addition of saturated NH_4Cl and NH_3 (32%) solutions (10 mL each). *n*-Undecane (194 mg, 1.2 mmol) as internal standard was added and the mixture was allowed to warm up to room temperature. After dilution with water and Et_2O (2 mL each) and stirring for 10 min., an aliquot of the organic phase was taken, filtered through a pad of cotton and analyzed by GC (49% yield). The aqueous phase was separated and extracted with Et_2O (3×3 mL). The combined organic phases were dried over $MgSO_4$. Most of the solvent was removed at reduced pressure. The crude product was purified by gradient flash

column chromatography (silica-gel, 2×15 cm, going from pentane (to remove the toluene) to pentane/diethyl ether 4:1) to afford 0.2243g (40%) of 3-ethylcyclopentanone as a colorless liquid. [α]= 34.0 (c=1%, ether); e.e. .=19.4% (Compared with [α]=175.0 in chloroform.[Posner et al., 1984])

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Synthesis of Chiral Ionic Liquids

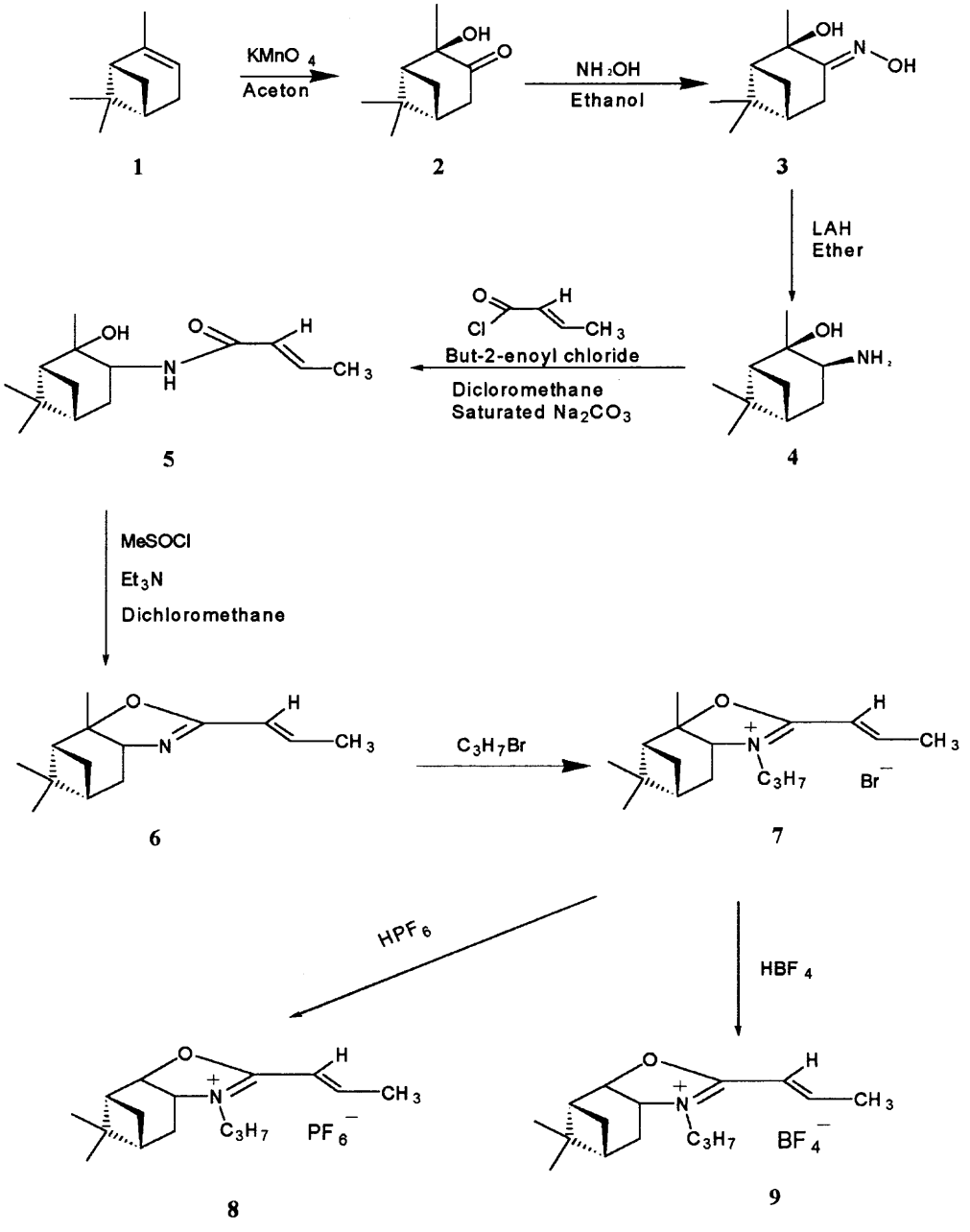
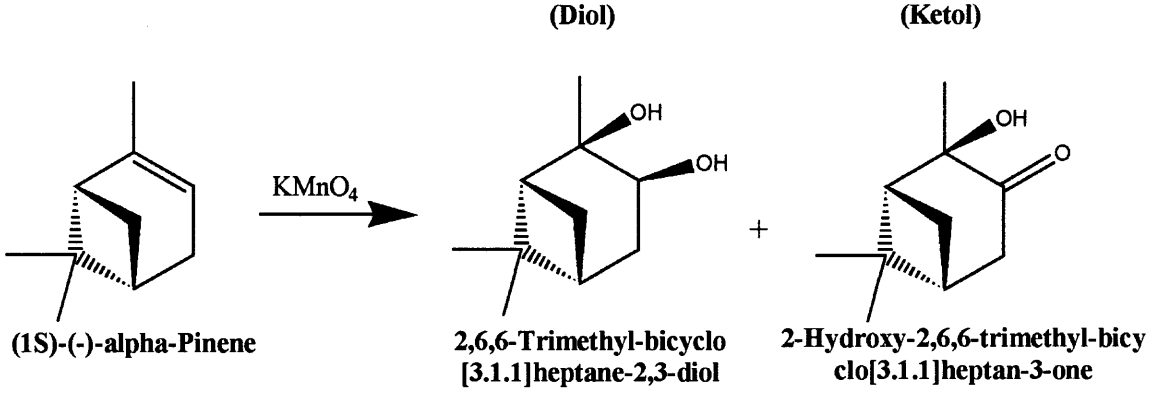


Figure 3.1 Overall steps in synthesis of chiral ionic liquids.

3.1.1 Preparation of 2-Hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]heptan-3-one (2 ketol)

Carlson and coworkers have showed that oxidation of α-pinene with potassium permanganate under neutral conditions gives a modest yield of ketol, whereas oxidation under basic conditions gives the diol. This reaction is highly steoroselective and the attack of the oxidant occurs from the side opposite the gem-dimethyl bridge. [R.G. Carlson et al. 1971]



Scheme 3.1 Formation of ketol.

The IR result showed there is a extremely broad peak at 3428cm^{-1}, which is the vibration absorbance of O-H bond due to the existence of hydrogen bond in the dimeric form in the pure liquid. (Figure 3.1) Combined with a carbonyl peak at 1713.31cm^{-1}, this makes identification of the ketol. The yield is lower than expected due to the possible explosion during reaction and separate difficulty after reaction.

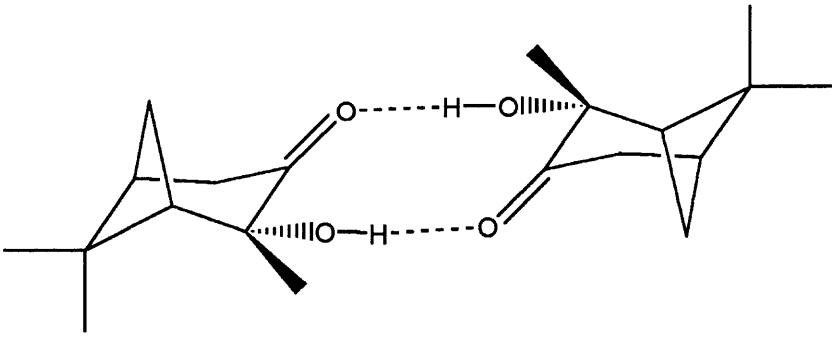


Figure 3.2 Dimeric form of ketol.

3.1.2 Preparation of 2-Hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]heptan-3-one oxime (3 oxime)

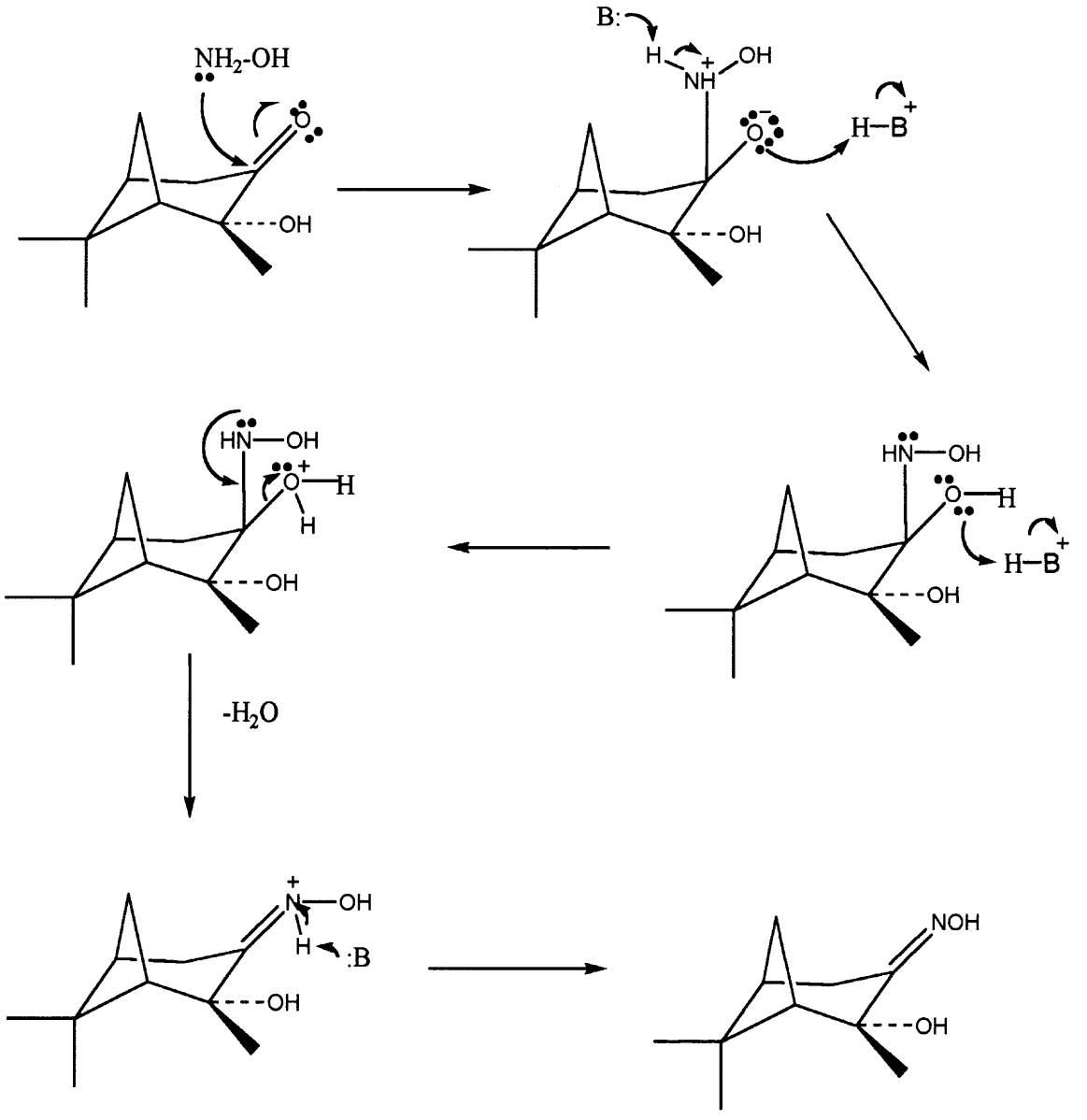


Figure 3.3 Mechanism for reaction to form oxime.

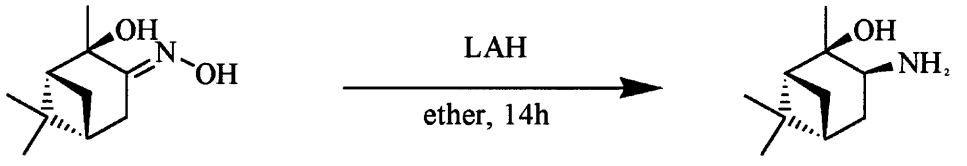
The reaction takes place in two main steps. In the first step, the nucleophile attacks the carbonyl group. The intermediate that forms loses a proton from the positively charged nitrogen atom and an amino group on the same carbon atom loses water easily, and a carbon-nitrogen double bond forms. As the loss of water is catalyzed by acid and is the rate determining step for the reaction at moderate acidity. The second step is the

elimination of water from the addition compound. In this step the hydroxyl group is converted into a good leaving group by protonation, and the water molecule is displaced by the nonbonding electrons on the nitrogen atom. Removal of a proton from the nitrogen atom gives the oxime.

During the Course of experiments it appeared that the crystalline state oxime is difficult to obtain in larger quantity. The reason is probably due to strong internal hydrogen bonding and spatial hindrances of pinane skeleton. Total yield from over ten experiments carried out in the range of 5–168 g of ketol used, calculated, as the sum of enantiomerically pure and racemic crystalline oxime, was 83%.

3.1.3 Preparation of 3-Amino-2,6,6-trimethyl-bicyclo[3.1.1]heptan-2-ol (4 Amino alcohol)

(Oxime) (Amino Alcohol)

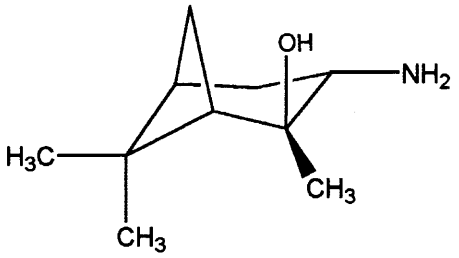


2-Hydroxy-2,6,6-trimethyl-bi cyclo[3.1.1]heptan-3-one oxime

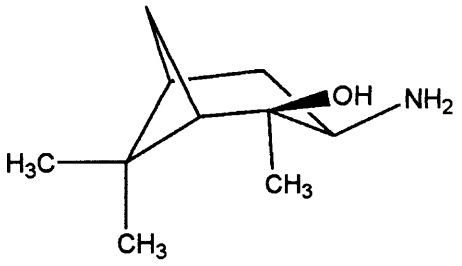
3-Amino-2,6,6-trimethyl-bi cyclo[3.1.1]heptan-2-ol

Amino alcohol was obtained by reduction of enantiomerically pure oxime with LAH, according to the procedure of Chabudziński [K. Burak et al., 2002] at 0.05 and 0.2 mol scale. After recrystallization from hexane/ether: mp 45–47°C, $[\alpha]_D^{20}$=-14.1 (*c* 1, $CHCl_3$).

Amino alcohol formation the acidic medium favors the axial amine formation, while in the basic medium the main products of the reduction are equatorial amines. [Anziani P. et al., 1948]



A: Equtorial amine



B: Axial amine

3-Amino-2,6,6-trimethyl-bicyclo[3.1.1]heptan-2-ol

Figure 3.4 Equtorial and axial structure of amino alcohol.

Burak and coworkers evaluated five methods to make reduction of oxime: sodium in *n*-AmOH, 5% Pd/C, Raney nickel, PtO_2 and LAH in ether. [Burak K, 1978] He reported LAH in ether is the best method to obtain one amino alcohol B (Figure 3.5) with axial amine. An analysis of Deriding stereo models indicates that a complex of LAH with reduced oxime is formed from α-side of molecule, because of the presence of –OH group at C_2. Such an intermediate stats causes that attack of hydride on C_2 from the β-side is favored. In this case, α-side is additionally hindered by =NOH-LAH complex, and in such an arrangement attack of hydride from α-side becomes so difficult that the reaction proceeds stereo specifically.

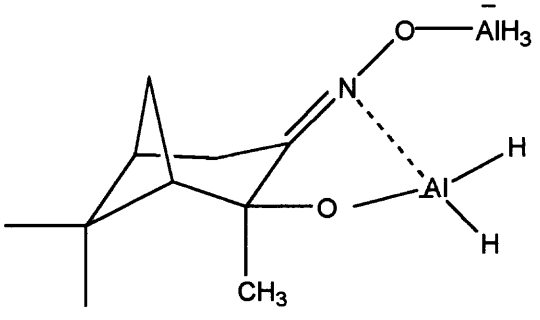


Figure 3.5 Intermediate to form amino alcohol.

The mechanism is shown in the Figure 3.6. There are two times reduction of the C=N bond by aluminum hydride. Firstly, it lose hydroxyl group and add one hydrogen atom by attack on the nitrogen. Secondly, by the aid of cation the aluminum attack nitrogen-carbon double bond again. This time the double bond break and another hydrogen was added.

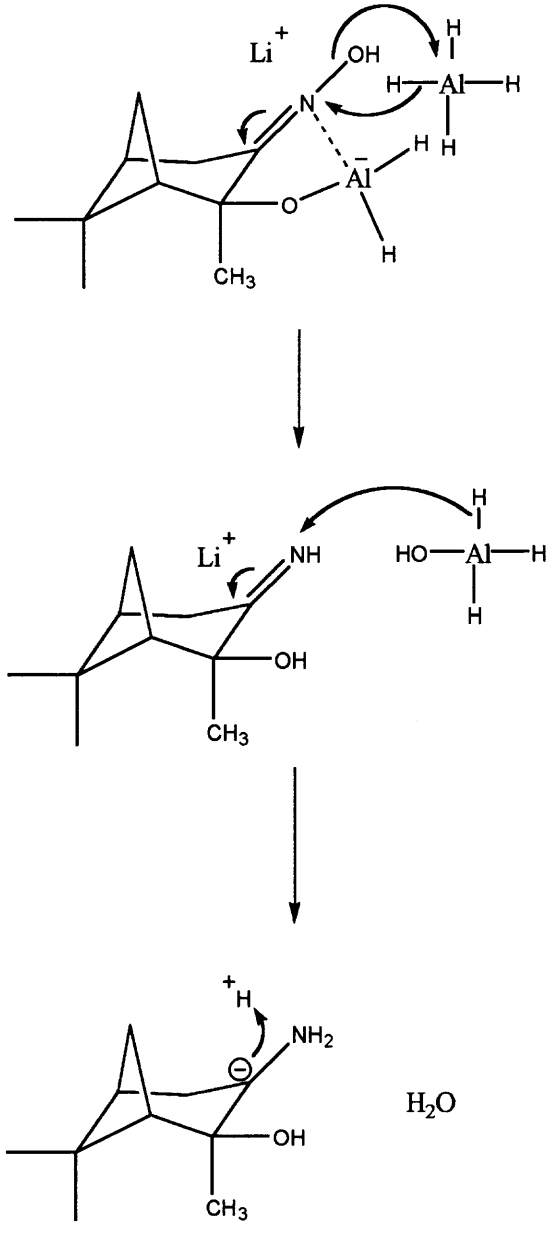
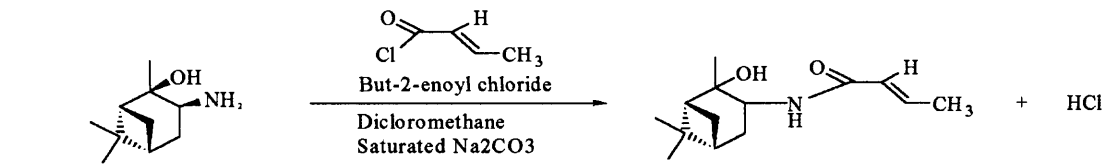


Figure 3.6 Form of amino alcohol.

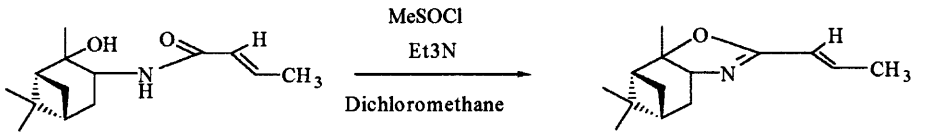
The IR spectrum shows a strong broad vibration absorbance peak in the range of 3100-3400 cm^{-1}, which includes 3355.46 cm^{-1} peak of hydroxyl group when hydrogen bond exists and two peaks of $-NH_2$ in the range of 3200-3300cm^{-1}. These bands combined with 1591.94 cm^{-1} ($-NH_2$) peak identified the amino alcohol. Spectral data (IR, ^1H NMR) were identical to that reported. [King F.E et al., 1945]

3.1.4 Preparation of Oxazoline (6)



3-Amino-2,6,6-trimethyl-bicyclo[3.1.1]heptan-2-ol

But-2-enoic acid (2-hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide



But-2-enoic acid (2-hydroxy-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl)-amide

2,9,9-Trimethyl-4-propenyl-3-oxa-5-aza-tricyclo[6.1.1.$0^{2,6}$]dec-4-ene

There are a number of methods for the preparation of oxazolines. A two-step route involving formation and cyclization of the corresponding amides was chosen in this research. Starting with amino alcohol (4), the amide (5) was obtained in 62-91% yield from addition of the appropriate acid chloride under Schotten-Baumann conditions according to the procedure of Langlois et al [Langlois et al., 1990]. The amide was used to synthesis oxazoline. In IR spectrum the two peaks in the range of 3200-3300cm^{-1} disappeared and one 3280cm^{-1} peak due to vibration of –NH- exist. Also 1616.77cm^{-1} peak due to the existence of RCON and 956.35cm^{-1} peak due to existence of E, $R_1C=CR_2$ confirmed the structure of amide. NMR verified the structure.

For the cyclization, it was found that the use of methanesulfonyl chloride and triethylamine in dichloromethane to be most convenient [Langlois et al., 1990]. From IR spectrum, it is easy to see the appearance or increase of two peaks: 1671.42cm^{-1} due to the existence of -C-O-C=N group and 1171.47cm^{-1} due to C-O-C bond, which can confirm the structure of oxazoline.

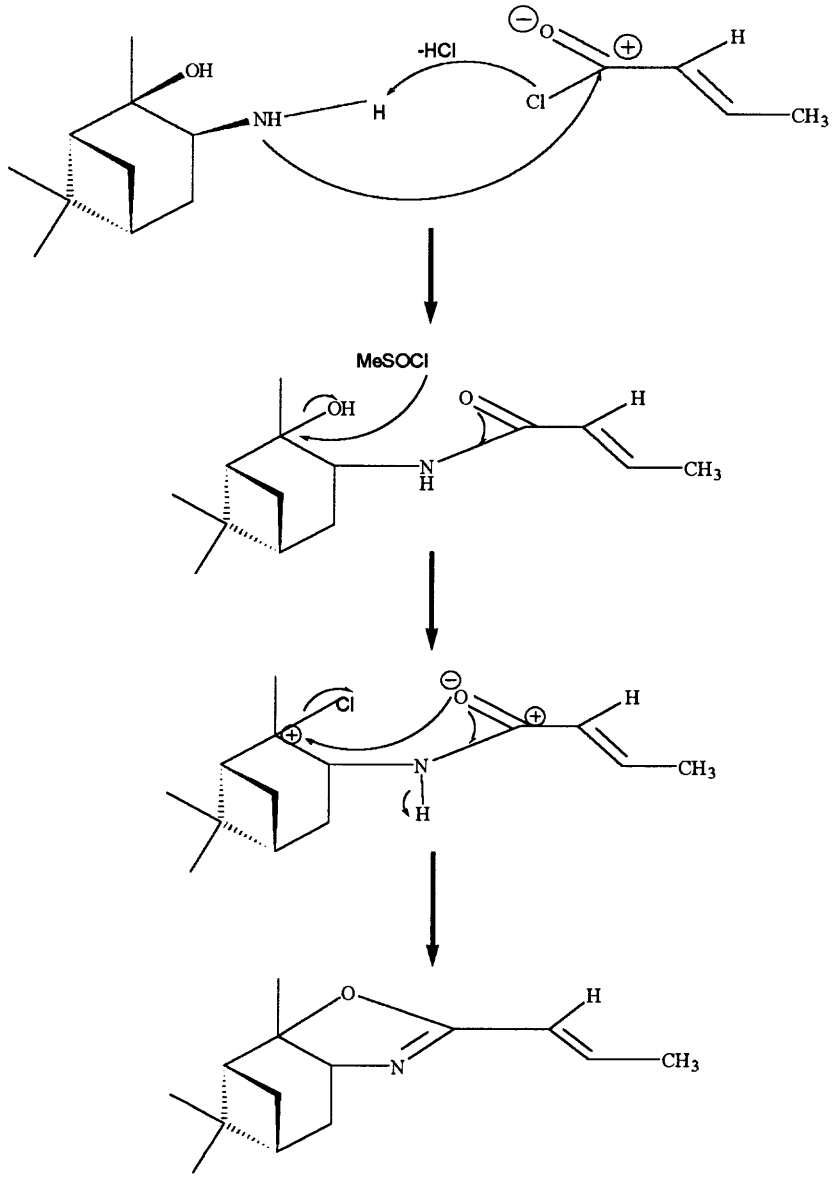
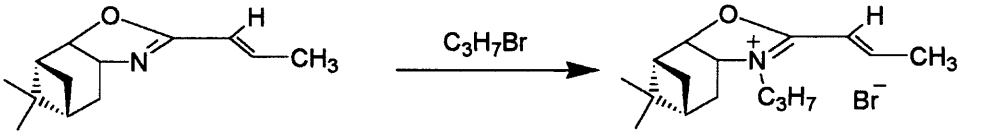


Figure 3.7 Mechanism for synthesis of oxazoline.

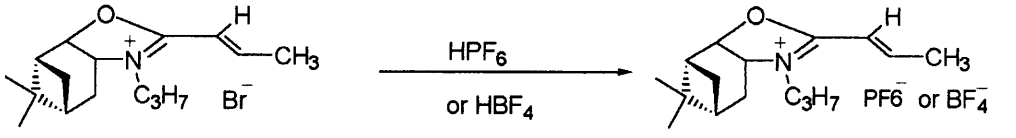
The possible mechanism is shown in figure 3.5. Nucliphilic attack of carbon atom in the carbonyl group by nitrogen atom causes the loss of HCl. The Cl atom on the methanesulfonyl chloride then replaces the –OH group and facilitates the cyclization.

3.1.5 Preparation of Ionic Liquids



2,9,9-Trimethyl-4-propenyl-3-oxa-5-aza-tricyclo[6.1.1.$0^{2,6}$]dec-4-ene

9,9-Dimethyl-4-propenyl-5-propyl-3-oxa-5-azonia-tricyclo[6.1.1.$0^{2,6}$]dec-4-ene; bromide



9,9-Dimethyl-4-propenyl-5-propyl-3-oxa-5-azonia-tricyclo[6.1.1.$0^{2,6}$]dec-4-ene; bromide

3.1.5.1 Preparation of [ChIPOZ][Br] Ionic Liquid (7). In this research the bromopropane was used directly as reagent and solvent to synthesis bromide ionic liquids. The reaction requires heating at about 60°C. The yield is 90%. IR spectrum shows the product oxazoline because no obviously appearance of the propyl group in IR spectrum. But the NMR shows the addtion of a propyl group. Melting point is 162°C.

Mark et al. [Mark et al., 1985] found the reactivity of allylic bromide was depend on the degree of C(3) olefin substitution. 3,3-disubstituted olefin will give high yield of oxazolinium salt. In contrast, 3-monosubstituted olefin reacts sluggishly, giving 45% reaction after 4-days at room temperature. No substitute failed to react appreciable with

oxazoline even when stirred at elevated temperature for several days. According to this later the author will try to use disubstituted butenol chloride in synthesis of oxazoline, which will improve the yield of oxazolinium salt.

3.1.5.2 Preparation of [ChIPOZ] [BF_4] Ionic Liquids (9). The general procedure to synthesis tetrafluoro borate ionic liquids is to use Ag_2O react with HBF_4 to form $AgBF_4$, and then $AgBF_4$ with RBr to form AgBr as precipate plus the product of RBF_4. While in this research this method cannot be used because the main product of [ChIPOZ] [BF_4] is also a solid at room temperature. Therefore the directly usage of HBF_4 as starting material was applied. The yield was 60-80%. [α]=28.329 (c=0.06%, ethyl acetate). But under acid condition the oxazoline underwent ring opening reaction. In future $NaBF_4$ will be used as starting material.

In IR spectrum δ =1288.67cm^{-1} verified the fluorine atom exist. Also NMR verifies the product.

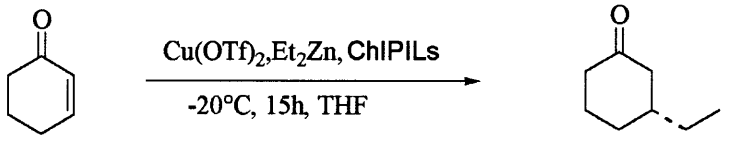
3.1.5.3 Preparation of [ChIPOZ] [PF_6] Ionic Liquids (8). Normally the hexaflorophosphate ionic liquids do not dissolve in water. The general procedure for synthesis hexaflorophosphate ionic liquids is to use HPF_6 react with RBr. This method was followed and the yield of 70-90% was obtained. The melting point is 140-144°C, which is higher than normal ionic liquids. In the following research smaller substitute in the oxazoline ring will be tried to break the symmetry of crystal or decrease the molecular weight, and thus decrease the melting point.

3.1.6 Summary

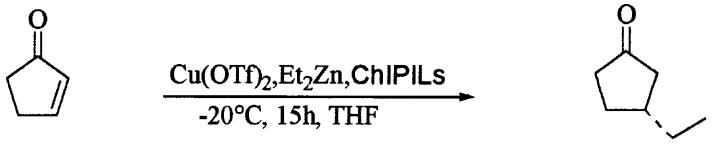
Two new chiral ionic liquids were synthesized. The IR, NMR and MS data can verify the structure of the products. The melting point is higher than expected (normally the ionic

liquids' melting point is below 100°C). These new chiral ionic liquids can also be used as phase transfer catalysts. During the synthesis process three additional new compounds **5**, **6** and **7** were also synthesized. The application of these compounds will be investigated in the future.

3.2 Application of Chiral Ionic liquids



Cyclohex-2-enone **(+)-3-Ethyl-cyclohexanone**



Cyclopent-2-enone **(+)-3-Ethyl-cyclopentanone**

The chiral ionic liquids were used to study the copper catalyzed 1,4-addition reaction to cyclohexenone and cyclopentenone with diethylzinc. For cyclohexenone we got 76%e.e. in [ChIPOZ] [BF_4] and 34.29% e.e. in [ChIPOZ] [PF_6]; for cyclohexenone we got 73.14% e.e. in [ChIPOZ] [BF_4] and 19.4% e.e. in [ChIPOZ] [PF_6]. These results verified these chiral ionic liquids work as phase transfer catalysts and induce the stereochemistry control.

CHAPTER 4

CONCLUSIONS AND RECOMMENDATIONS

4.1 Conclusions

1. Two different novel chiral ionic liquids derived from α-pinene were prepared. They are isopinocarirphenyl tetrafluoroborate([ChIPOZ][BF_4])-**9** and isopinocarirphenyl hexafluorophosphate ([IP][PF_6])-**8**. The total yield from α-pinene is 50-70%.
2. The chiral ionic liquids were purified and used as chiral phase transfer catalysts in the enantioselective copper-catalyzed 1,4-addition reactions with diethyzinc to enones. The enantiomeric excess for [ChIPOZ][BF_4] is above 70% and for [ChIPOZ][PF_6] is above 30%.
3. During synthesis of chiral ionic liquids there were additional three novel compounds synthesized and purified: amide-**5**, oxazoline-**6**, and oxazolium bromide-**7**.

4.2 Recommendations

1. In the last step to synthesis chiral ionic liquids $NaBF_4$ and $NaPF_6$ could be used to replace HBF_4 and HPF_6 since oxazoline ring is not stable in acidic condition.
2. Small substitution on the oxazoline substitutes should be tried in order to change the crystal structure by changing the degree of symmetry. Therefore the melting point will be close to room tempetature.
3. Different anion can be used to improve the physical properties.

APPENDIX A

FT-IR SPECTRUM OF PRODUCTS DURING SYNTHESIS

The IR spectrums of all products in the synthesis are showed in the following pages.

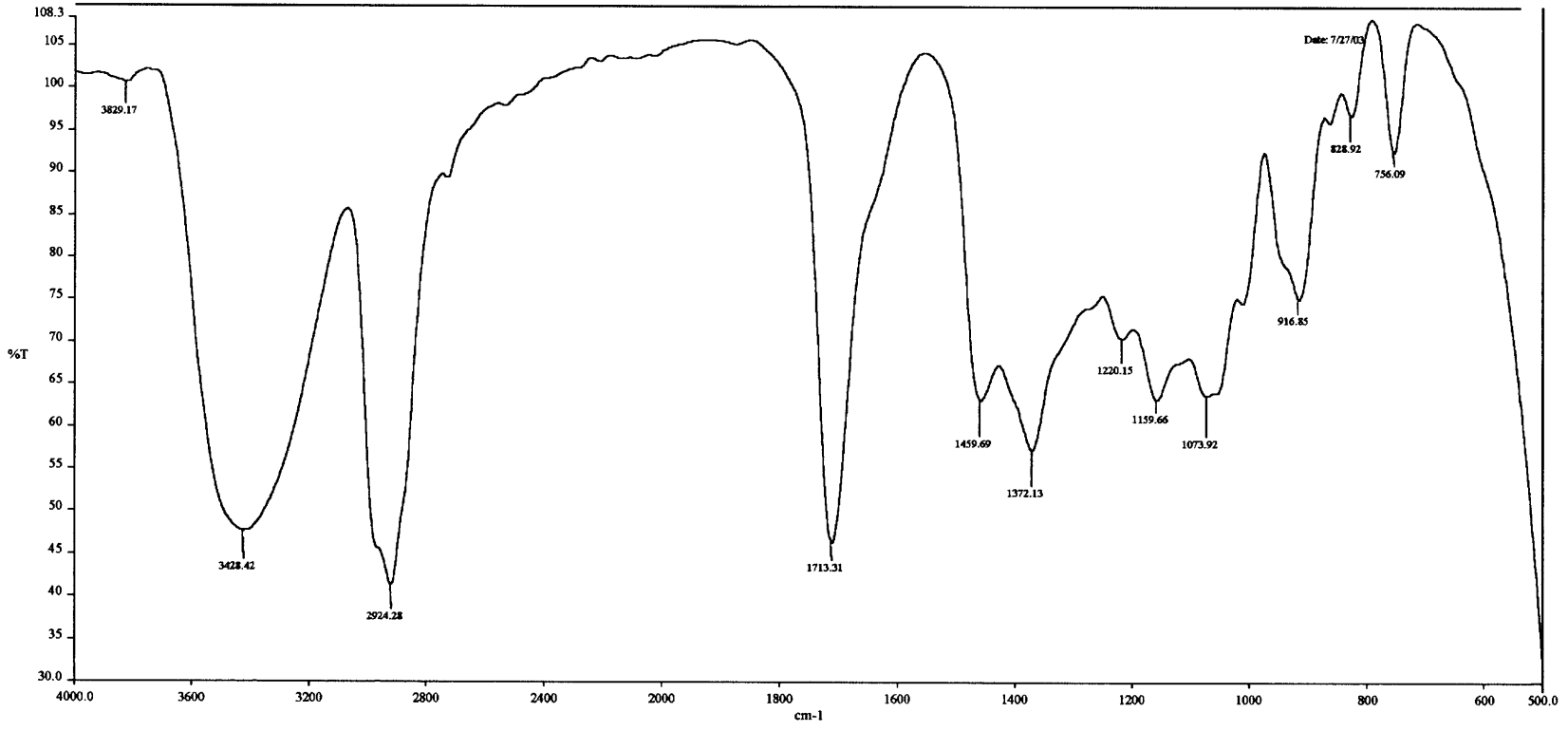


Figure A.1 FT-IR spectrum of ketol.

Figure A.2 FT-IR spectrum of oxime.

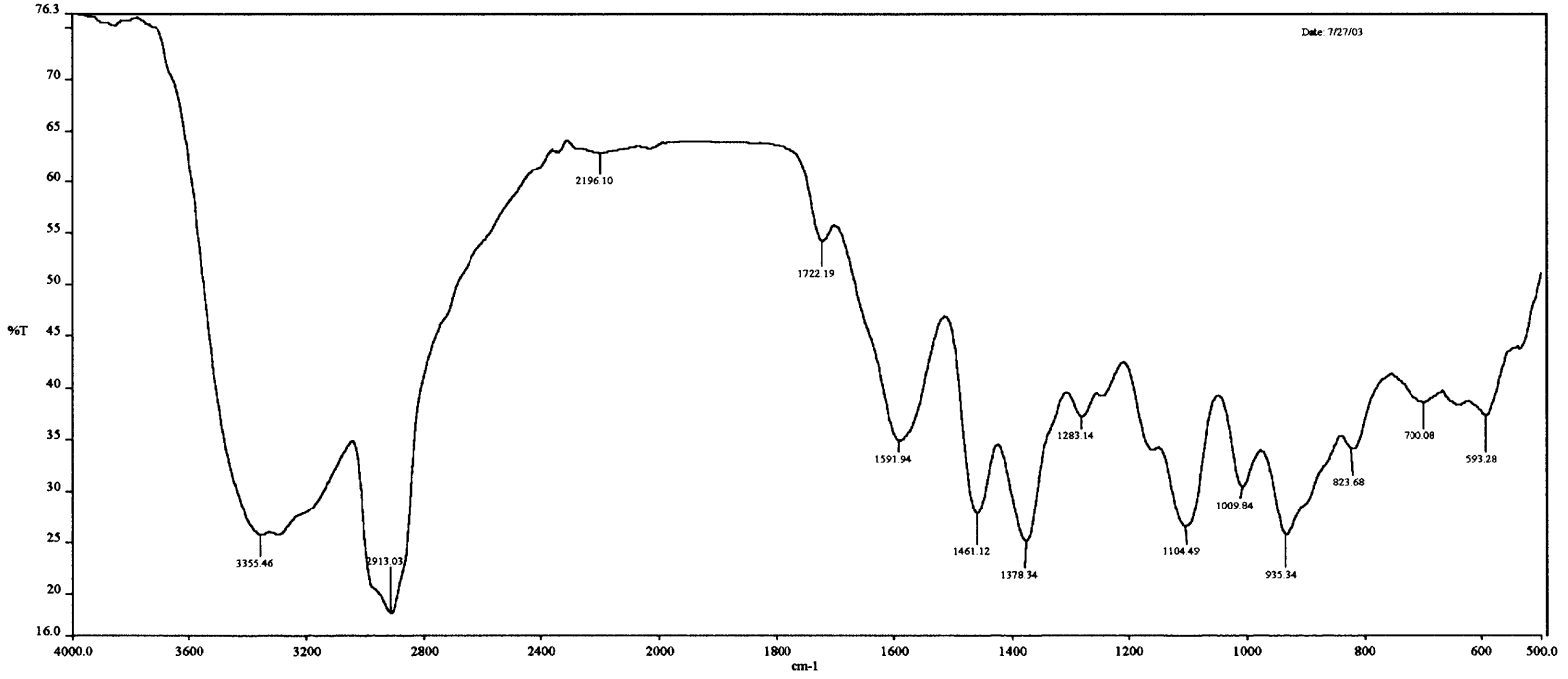


Figure A.3 FT-IR spectrum of amino alcohol.

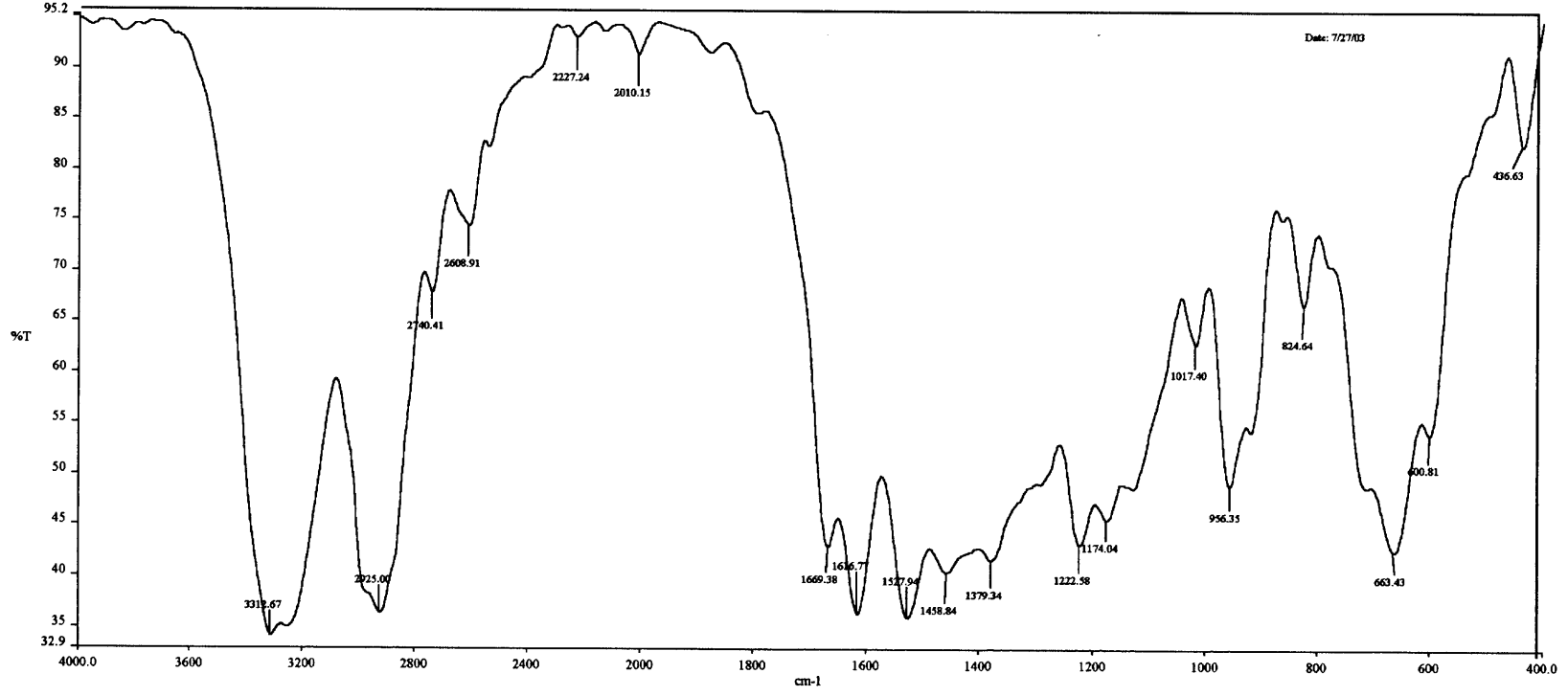


Figure A.4 FT-IR spectrum of amide.

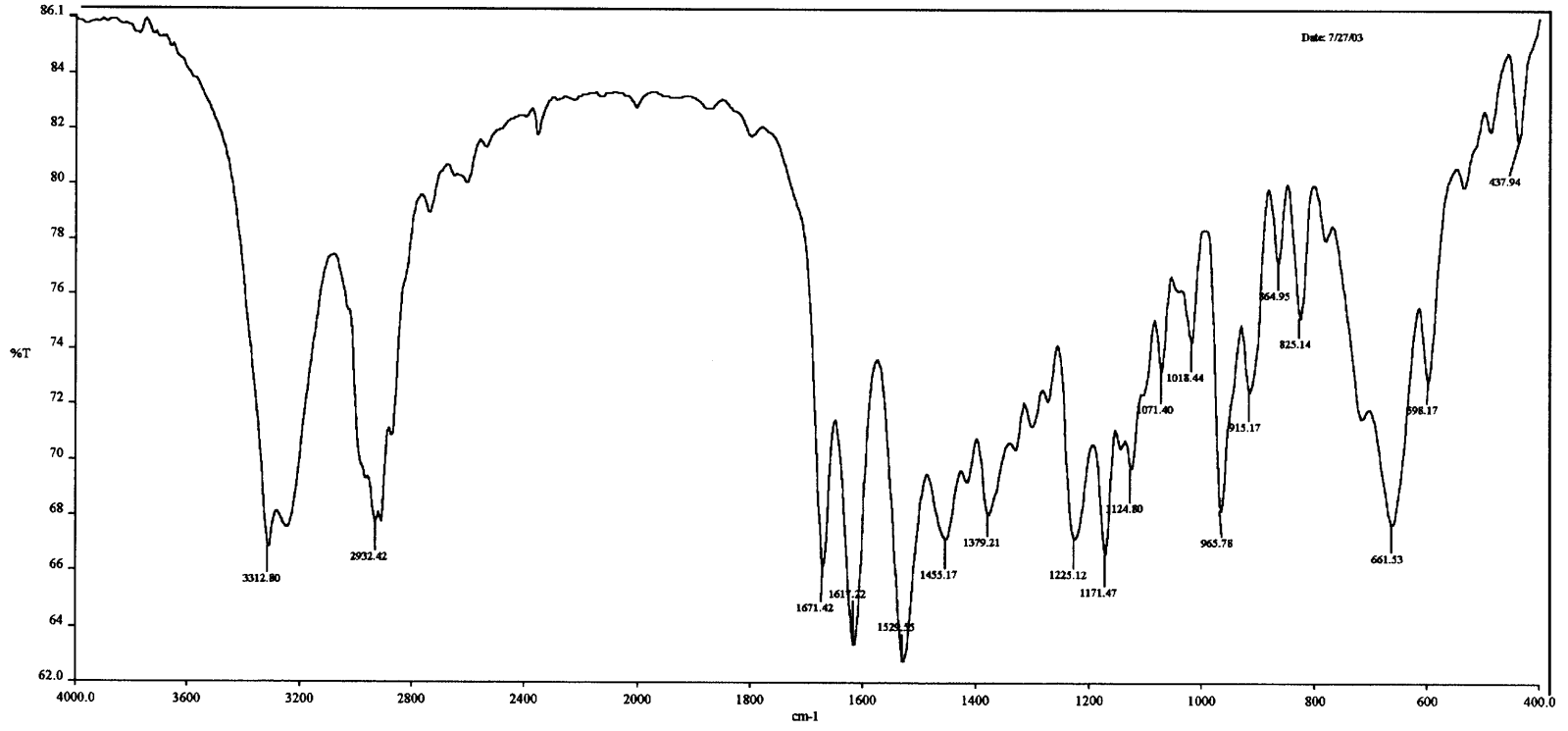


Figure A.5 FT-IR spectrum of oxazoline.

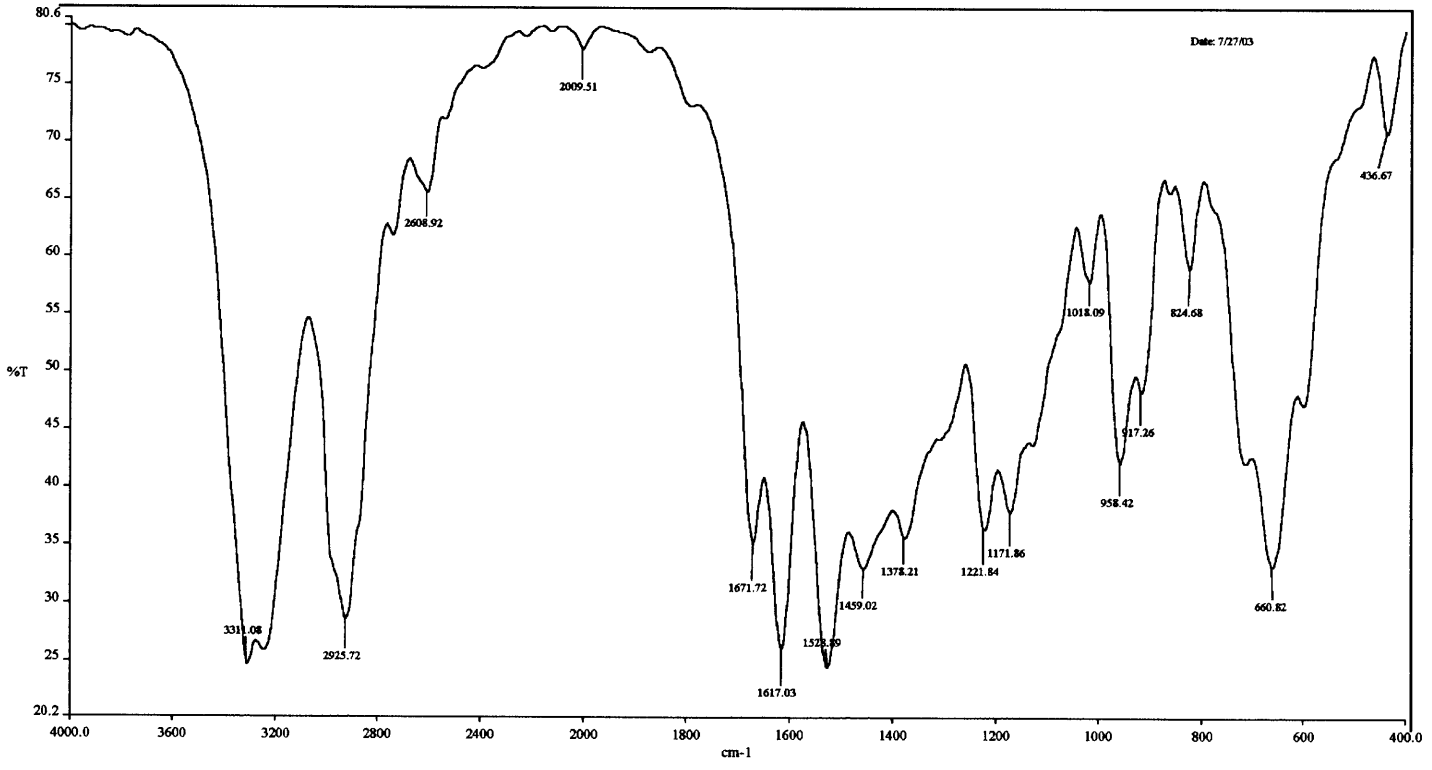


Figure A.6 FT-IR spectrum of α-pinene derived oxazolium bromide.

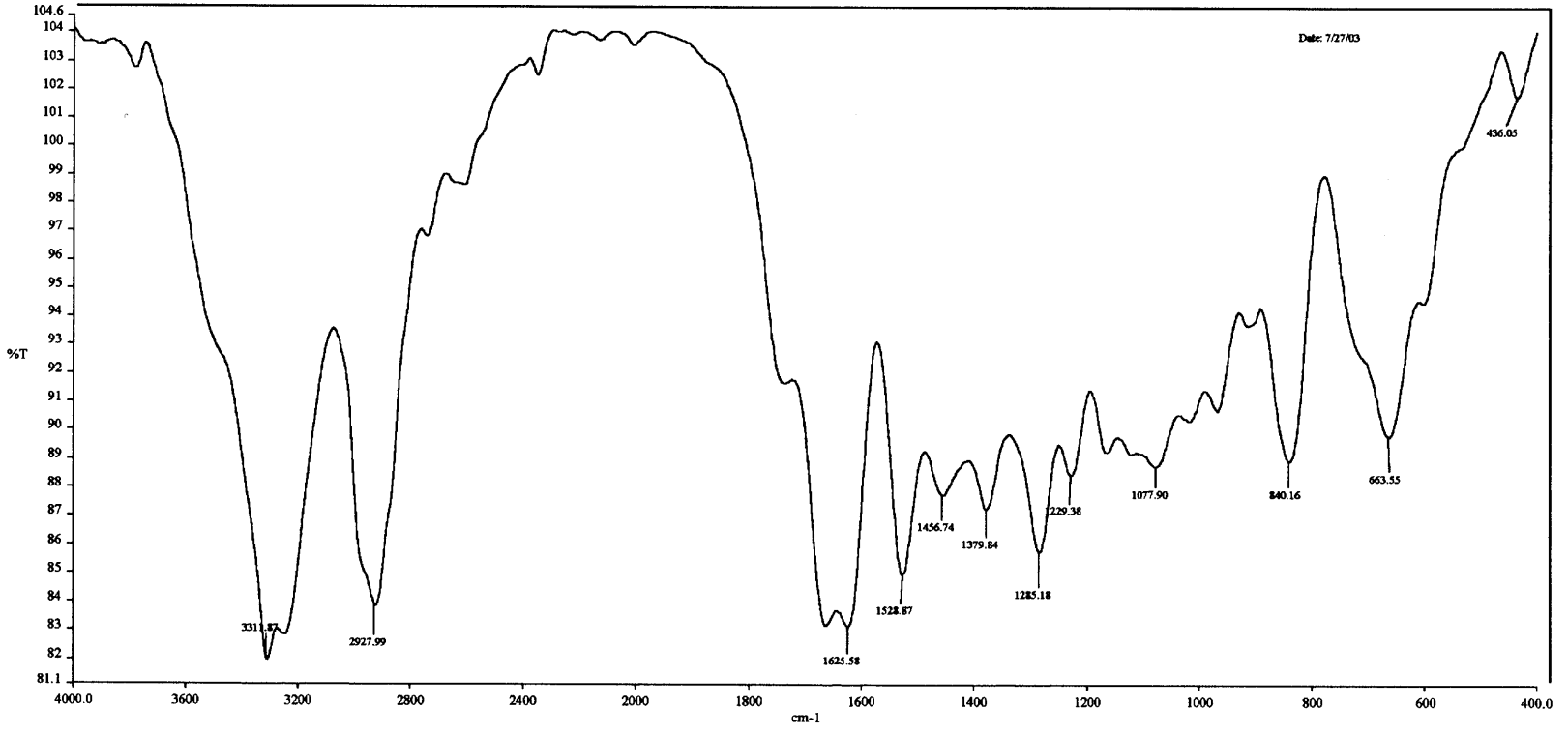


Figure A.7 FT-IR spectrum of α-pinene derived oxazolium tetrafluoroborate.

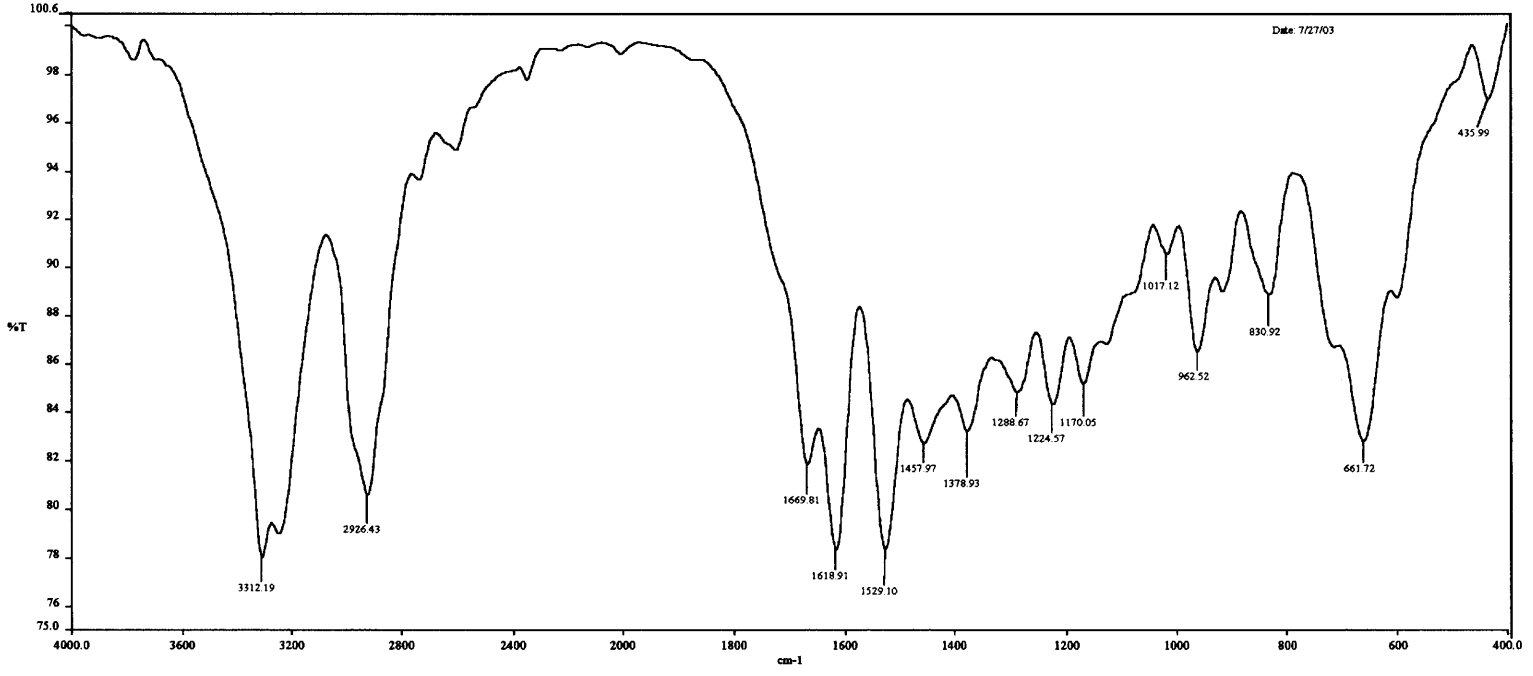


Figure A.8 FT-IR spectrum of α-pinene derived oxazolium hexafluorophosphate.

APPENDIX B

SOME CONCEPTS IN CHIRAL CHEMISTRY

The following terms are the most often used concepts in asymmetric chemistry.

1. **CHIRALITY** is handedness. An object is *chiral* if it cannot be superimposed upon its mirror image.
2. **ENANTIOMER**: One of a pair of molecular entities, which are mirror images of each other and non-superposable.
3. **ENANTIOMERIC EXCESS**: For a mixture of (+)- and (-)-enantiomers, with composition given as the mole or weight fractions $F_{(+)}$ and $F_{(-)}$ (where $F_{(+)} + F_{(-)} = 1$) the enantiomer excess is defined as $|F_{(+)} - F_{(-)}|$ (and the percent enantiomer excess by $100|F_{(+)} - F_{(-)}|$). Frequently this term is abbreviated as e.e..
4. **DIASTEREOMER** is a chiral molecule with more than one stereogenic unit (center, axial and planar). Diastereoisomers (or diastereomers) are stereoisomers not related as mirror images. Diastereoisomers are characterized by differences in physical properties, and by some differences in chemical behavior towards achiral as well as chiral reagents.
5. **SPECIFIC ROTATION** is defined as

$$[\alpha]_{\lambda}^{t} = 100\ \alpha' / l\ c$$

where α' is observed rotation, l is the cell path in dm, c is the concentration of sample in g per 100 cm^3, t is temperature of Celsius, and λ is the wavelength of incident light (nm).

6. **RACEMATE (or RACEMIC MIXTURE)**: An equimolar mixture of a pair of enantiomers. It does not exhibit optical activity. The chemical name or formula of a racemate is distinguished from those of the enantiomers by the prefix (±)- or *rac*- (or *racem*-) or by the symbols *RS* and *SR*.
7. **RESOLUTION:** The separation of a racemate into the component enantiomers.

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