ABSTRACT

STUDY OF ORGANIC REACTIONS IN PYRIDINIUM-BASED IONIC LIQUIDS

by
Ying Xiao

Recently, ionic liquids have attracted a lot of attention as novel materials for organic transformations. This is due to their unique properties, which make them suitable substitutes for organic solvents. Most of the available literature is focused on the application of imidazolium-based ionic liquids for organic reactions, while very limited information is available on the application of pyridinium-based ionic liquids.

In this study, two different ionic liquids, 1-ethyl-pyridinium tetrafluoroborate ($[EtPy]^+[BF_4]^-$) and 1-ethyl-pyridinium trifluoroacetate ($[EtPy]^+[CF_3COO]^-$) have been investigated. Compared to previous reports, the synthetic technique for preparation of N-ethyl-pyridinium-based ionic liquids has been improved. Systematic studies of five reactions in both these ionic liquids have yielded a greater understanding. These reactions include (i) Diels-Alder reaction; (ii) Friedel-Crafts alkylation; (iii) Friedel-Crafts acylation; (iv) asymmetric Friedel-Crafts reaction; and (v) asymmetric reduction of ketones. Moreover, the effects of various catalysts, solvents and temperatures have been studied. Also, the reusability of ionic liquids for these reactions has been tested and the optimal reaction conditions have been determined. These studies have led to the development of new methodologies for all of these reactions in both these N-ethyl-pyridinium-based ionic liquids.

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by
Ying Xiao

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STUDY OF ORGANIC REACTIONS IN PYRIDINIUM-BASED IONIC LIQUIDS

Ying Xiao

Dr. Sanjay V. Malhotra, Dissertation Advisor — Date
Assistant Professor of Chemistry, NJIT

Dr. Edgardo T. Farinas, Committee Member — Date
Assistant Professor of Chemistry, NJIT

Dr. Tamara Gund, Committee Member — Date
Professor of Chemistry, NJIT

Dr. Zafar Iqbal, Committee Member — Date
Research Professor of Chemistry, NJIT

Dr. Sharon Lall-Ramnarine, Committee Member — Date
Assistant Professor of Chemistry
Queensborough Community College, NY

BIOGRAPHICAL SKETCH

Author: Ying Xiao

Degree: Doctor of Philosophy

Date: January 2006

Undergraduate and Graduate Education:

- Doctor of Philosophy in Chemistry,
  New Jersey Institute of Technology, Newark, NJ, 2006

- Bachelor of Engineering in Chemical Engineering,
  East China University of Science and Technology, Shanghai, P. R. China, 1997

Major: Chemistry

Presentations and Publications:

Ying Xiao and Sanjay V. Malhotra,
"Friedel-Crafts acylation in pyridinium based ionic liquids,"
Journal of Organometallic Chemistry, 15, 3609-3613, 2005.

Ying Xiao and Sanjay V. Malhotra,
"Friedel-Crafts alkylation in pyridinium based ionic liquids,"
Journal of Molecular Catalysis A: Chemical, 230(1-2), 129-133, 2005.

Ying Xiao and Sanjay V. Malhotra,
"Diels-Alder reactions in pyridinium based ionic liquids,"
Tetrahedron Letters, 45(45), 8339-8342, 2004.

Ying Xiao, Dawoon Jung, Tamara Gund, and Sanjay V. Malhotra,
"A Theoretical and Experimental Study of the Enantioselective Deprotonation of Cyclohexene Oxide with Isopinocampheyl Based Chiral Lithium Amides,"
Accepted by Journal of Molecular Modeling.

Sanjay V. Malhotra and Ying Xiao,
"Enantioselective Friedel-Crafts reaction of aromatic amines in pyridinium-based ionic liquids,"
Presented at the 230th ACS National Meeting, Washington, DC, United States, Aug 28-Sept 1, 2005.

Ying Xiao and Sanjay V. Malhotra,
"Diels-Alder reactions in pyridinium-based room temperature ionic liquids,"
Presented at the 228th ACS National Meeting, Philadelphia, PA, United States, August 22-26, ORGN-717, 2004.

Ying Xiao and Sanjay V. Malhotra,
"Alkylation/acylation reactions in pyridinium-based ionic liquids,"
Presented at the 228th ACS National Meeting, Philadelphia, PA, United States, August 22-26, ORGN-718, 2004.

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"The computational study of the deprotonation of cyclohexene oxide catalyzed by isopinocampheyl based chiral lithium amides,"
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To my beloved family

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CHAPTER 1

INTRODUCTION AND OBJECTIVES

1.1 Ionic Liquids

What is an ionic liquid? An ionic liquid is a class of solvent that contains only ions. In the broad sense, this term formerly was known as molten salts (Seddon, 1997). Traditional molten salts exhibit a high melting point (e.g., 800 °C for sodium chloride and 614 °C for lithium chloride), which greatly limits their use as solvents in most applications. The term "ionic liquids" is used for the salts whose melting points are lower than 100°C. Similarly, the salts that melt at or around room temperature are called "room-temperature ionic liquids" (RTILs).

The traditional organic solvents such as diethyl ether, THF, benzene, dichloromethane etc. used in organic synthesis, particularly in industrial production, generate a large amount of waste and cause environmental and health problems. Handling and treating this waste is a difficult problem, not only to separate them, but also to destruct them, thereby dramatically increasing the cost of producing chemicals. In view of this, searching for alternatives to the traditional solvents and developing cleaner technologies has become a critical topic for both industry and academia. The emergence of ionic liquids provides a new approach to green chemistry.

The first ionic liquid, ethylammonium nitrate $[EtNH_3]^+[NO_3]^-$ (m.p. 12°C), was discovered by Walden in 1914. Since then, a number of ionic liquids with m.p. lower than 100 °C have been synthesized and various properties of ionic liquids have been investigated. Recently, much attention has been focused on ionic liquids as 'green' substitutes for commonly used molecular solvents, in particular volatile organic compounds (VOCs), a major source of industrial pollutants. Ionic Liquids possess excellent dissolution properties for many organic and inorganic substances but do not show any measurable vapor pressure, which can greatly reduce the risk associated with traditional solvents. Ionic liquids are also able to improve reaction rates, selectivities and yields in a large number of reactions. In addition, their properties are tunable by the choice of the cation-anion combination and therefore, have been described as designable solvents. Herein, a comparison of properties between ionic liquids and general organic solvents is shown in Table 1.1 (Dzyuba, 2002; Wasserscheid and Welton, 2003).

Table 1.1 The Comparison of Properties Between Ionic Liquids and Organic Solvents

Ionic Liquids	Organic Solvents
1) Bronsted or Lewis acid	1) Neutral
2) Non-volatile	2) Volatile
3) Non-flammable	3) Flammable
4) High thermal stability	4) Non-thermal stability
5) A liquid phase range up to 400°C	5) A liquid phase range << 400°C
6) High ionic conductivity	6) Non-ionic conductivity
7) Highly solvating, yet non-coordinating	7) Non-recyclable
8) Easy to prepare and recycle	

These properties suggest that ionic liquids could be good solvents for many organic and inorganic materials, therefore, they have been investigated as reaction media in many organic and organometallic synthesis (Welton, 1999; Zhao et al., 2002; Zhao and Malhotra, 2002a; Wasserscheid and Welton, 2003; Sheldon, 2001) such as Heck reactions, Friedel-Crafts reactions, hydrogenation, hydroformylation, dimerization, condensation, acylative cleavage of cyclic and acyclic ethers, polymerization, etcetera.

These solvents are found to be more effective in enhancing the reaction rate and product yields than the organic solvents.

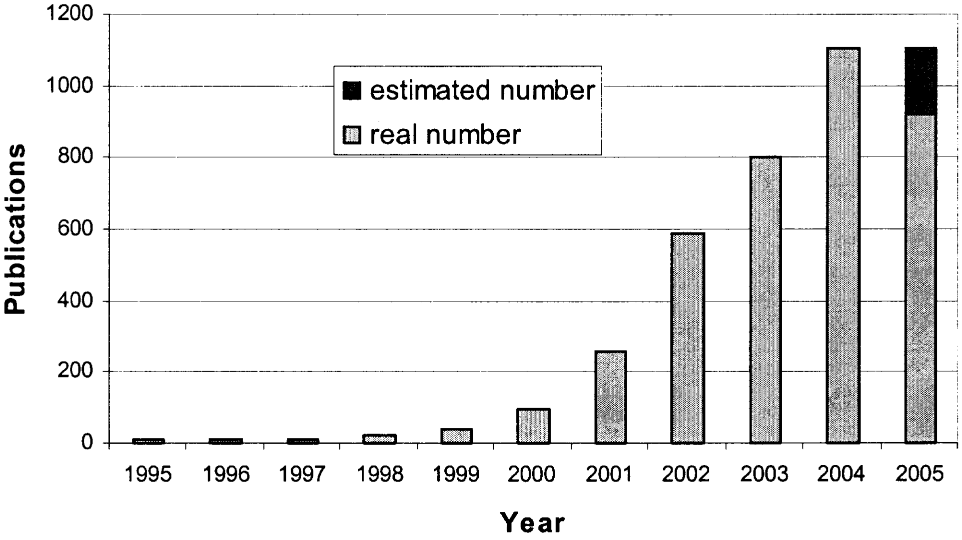
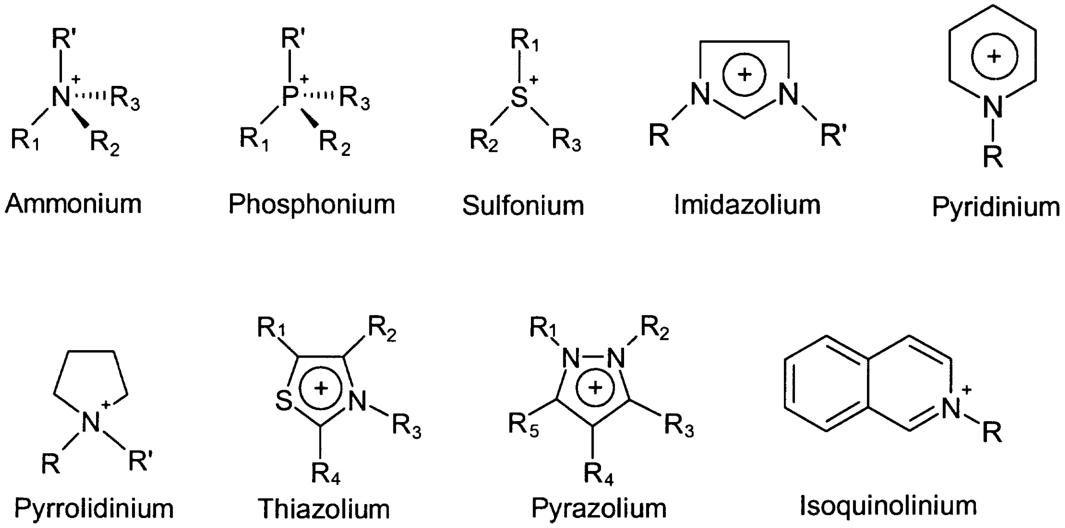


Figure 1.1 The rise of publications concerning ionic liquids as a function of time

Figure 1.1 shows the growth of publications on ionic liquids searched by SciFinder based on articles containing the phrase 'ionic liquids' in the title, abstract or keywords (the number of publications in 2005 is estimated based on the real number by November 2005). The increasing trend of relative publications in this area clearly reflects an increasing progress and based on the continuing commitment to excellent and innovative research from both industry and academia the prospects for the future are bright. Commercial availability, however, is a drawback for ionic liquids research. Therefore, seeking a rapid and inexpensive route to synthesize ionic liquids is an urgent demand.

Generally, ionic liquids are salts, which are composed completely of ions, cations, and anions. The properties such as 'no measurable vapor pressure', 'non-flammability', and 'good electrical conductivity' are common to all ionic liquids. Physical-chemical properties such as melting point, viscosity, polarity and solubility depend on the cation-anion combination. For example, $[BMIM]^+[PF_6]^-$ is totally hydrophobic, whereas, $[BMIM]^+[BF_4]^-$ is hydrophilic at room temperature. This illustrates that by only changing the counter anion, the hydrophobic character changes to hydrophilic.

The most commonly used cations in ionic liquids are alkylammonium, alkylphosphonium, alkylsulfonium, dialkylimidazolium [RR'IM] (for example, 1-butyl-3-methylimidazolium as [BMIM]), N-alkylpyridinium, dialkylpyrrolidinium, thiazolium, pyrazolium and N-alkylisoquinolinium (Figure 1.2). Typically, the alkyl chains involved are methyl, ethyl, propyl, butyl, hexyl, octyl and so on.


Ammonium Phosphonium Sulfonium Imidazolium Pyridinium

Pyrrolidinium Thiazolium Pyrazolium Isoquinolinium

Figure 1.2 Commonly used cations in ionic liquids

Typically used anions have been listed in Table 1.2. Various combinations of cations and anions provide a huge number of ionic liquids including room temperature ionic liquids and non-room temperature ionic liquids. In comparison to the other combinations, room temperature ionic liquids attract much attention because they can provide relatively mild reaction conditions.

Table 1.2 Some Commonly Used Anions in Ionic Liquids

Anions	Reference	Anions	Reference
$AlCl_4^-$	Wilkes et al., 1982	$(CN)_2N^-$	MacFarlane et al., 2001
$AuCl_4^-$	Hasan et al., 1999	Cl^-	Wilkes et al., 1982
$B(Et_3Hex)^-$	Ford et al.,1973	$CH_3CO_2^-$	Wilkes and Zaworatko, 1992
BF_4^-	Wilkes and Zaworatko, 1992	$GaCl_4^-$	Wicelinski et al., 1987
Br^-	Chan et al., 1977	HSO_4^-	Keim et al., 2000
$CF_3CO_2^-$	Bonhote et al., 1996	I^-	Chan et al., 1977
$(CF_3SO_2)_2N^-$	Bonhote et al., 1996	NO_2^-	Wilkes and Zaworatko, 1992
$CF_3SO_3^-$	Bonhote et al., 1996	NO_3^-	Wilkes and Zaworatko, 1992
$n\text{-}C_8H_{17}OSO_3^-$	Wasserscheid et al., 2002	PF_6^-	Fuller et al., 1994
Carborane anions $(1\text{-}R\text{-}CB_{11}H_6X_6)^-$	Larsen et al., 2000	SbF_6^-	Chauvin and Oliver-Bourbigon, 1995

Various combinations of cations and anions would produce thousands of ionic liquids. This study focuses only on pyridinium-based ionic liquids. The properties and applications of this class of ionic liquids are introduced in detail.

1.2 Properties of Pyridinium-based Ionic Liquids

1.2.1 Composition

As the name indicates, pyridinium-based ionic liquids are composed of N-alkyl pyridinium cation and an anion, which varies widely from a simple halide to a complex polyatomic ion. The typically involved alkyl chains are methyl, ethyl, butyl, hexyl, octyl and so on; and those alkyl groups can attach to different positions (Figure 1.3).

Commonly used anions are listed in Table 1.3. Different combinations of cations and anions provide various pyridinium-based ionic liquids.

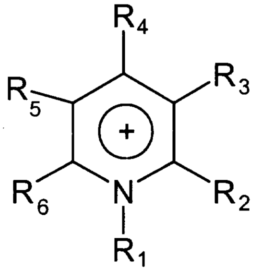
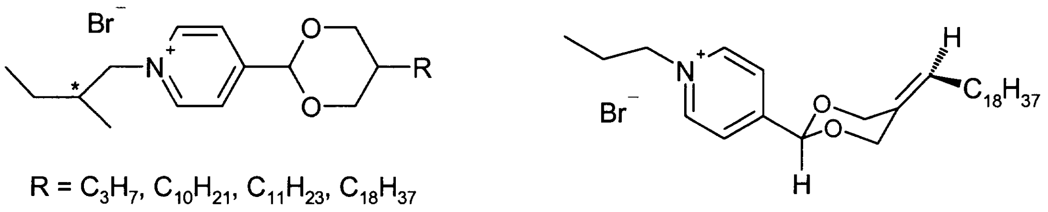


Figure 1.3 The structure of pyridinium cation

Table 1.3 Reported anions in Pyridinium-based Ionic Liquids

Anions	Reference
$AlCl_4^-$	Robinson and Osteryoung, 1979
BF_4^-	Noda and Watanabe., 2000
Br^-	Ray and Bhattacharya, 1936
$CF_3CO_2^-$	Zhao, 2002
$[(C_2F_5)_2PO_2]^-$	Ignatyev et al., 2005
$[(CF_3SO_2)_2N]^-$	Noda et al, 2001
$[CH_3(CH_2)_{11}SO_3]^-$	Anderson and Braatz, 2004
$[C_2H_5OC_2H_4SO_4]^-$	Kato and Gmehling, 2004
$[CH_3SO_3]^-$	Uzagare et al., 2003
Cl^-	Robinson and Osteryoung, 1979
$CoCl_4^{2-}$	Felloni et al., 2004
$[HSO_4]^-$	Baumgarten, 1926
I^-	Magidson and Menshikov, 1926
PF_6^-	Marshall et al., 1986

In 2002, Haramoto et al. reported the first example of synthesizing chiral pyridinium-based ionic liquids, (+)-*N*-2-methylbutyl-4-(5-alkyl-1,3-dioxan-2-yl) pyridinium bromides, which have a 1,3-dioxane ring in the central core (Figure 1.4 a). Four new ionic liquids were prepared in four steps with yields ranging from 28 to 48% and melting points from 11 to 73°C. Paralleling this work, Baudoux et al. proposed a new chiral pyridinium-based ionic liquid with axial chirality settled on the 1,3-dioxane ring (Figure 1.4 b). The authors emphasized that this type of chiral ionic liquids were not obtained from the chiral pool but were synthesized *via* an enantioselective reaction with excellent enantioselectivity and yield (Baudequin et al., 2003).



(a)

(b)

Figure 1.4 The structure of chiral pyridinium-based ionic liquids

Several other new chiral pyridinium-based ionic liquids were also synthesized from pyridine and 1-chloro-2,4-dinitrobenzene, with chiral primary amine (Patrascu et al., 2004). The corresponding enantiopure ionic liquids were obtained, which contained the same alkylpyridinium cation and different anions (Figure 1.5). The physical properties of those salts were determined; and 1-(1-Phenylethyl)pyridinium bis(trifluoromethane-sulfonyl)imide has been found as a room temperature ionic liquid, which is thermally stable up to 215°C and suitable for organic synthesis.

Most recently, a new type of pyridinium-based ionic liquids containing polycation and various counter-anions has been synthesized by Marcilla et al. (2005) (Figure 1.6). Polycation ionic liquids such as Poly 1-ethyl-4-vinylpyridinium ionic liquids were obtained by using a simple anion exchange reaction; and the reaction can be facilitated by the phase separation of the resulting products. The properties of the new ionic liquids have been investigated and the authors mentioned that the solubility and thermalstability of this type of ionic liquids depend on the nature of the counter-anion. Increased thermalstability was observed in the order $CF_3SO_3^- > (CF_3CF_2SO_2)_2N^- > C_{12}H_{25}C_6H_4SO_3^- > PF_6^- > Br^- > C_{16}H_{34}PO_4^-$.

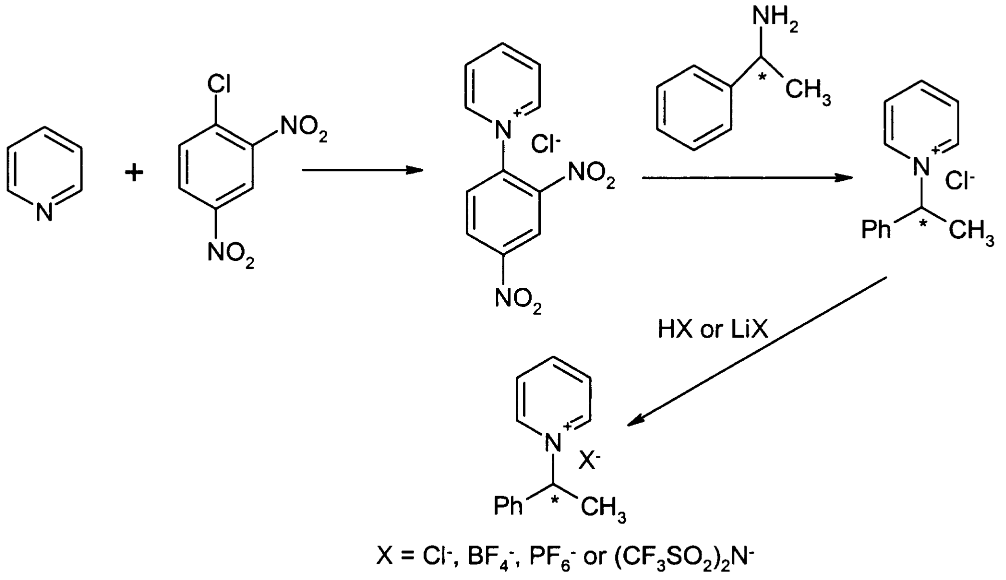


Figure 1.5 Synthesis of chiral pyridinium-based ionic liquids

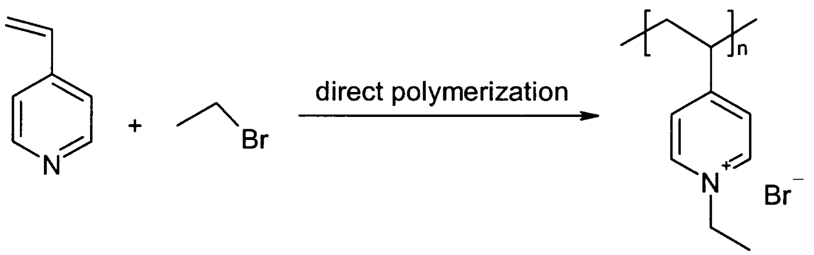


Figure 1.6 Synthesis of polycation pyridinium-based ionic liquids

1.2.2 Melting Point

Ionic liquids consist of completely ionized components and display as three-dimensional networks of cations and anions linked together by weak interactions such as hydrogen bonds, Van der Waals, and Coulombic forces. They are liquid salts, which means they exist as liquid phase naturally, not simply as salts dissolved in liquid. In contrast to traditional organic solvents, the maximum liquidus temperature of ionic liquids is the thermal decomposition point rather than boiling point.

The dominant force in ionic liquids is the Coulombic attraction between cations and anions. Melting must overcome this attraction.

$$F = K*(q_1*q_2)/r^2$$

Here, F is the Coulombic force; q_1 and q_2 are the charges of particles. The distance between the particles is r, and K is a constant, 8.99×10^9 (Nm^2/C^2).

In many ionic liquids, the charge q is ±1; and the larger the size of the ions, the larger the distance r. Therefore, the size and shape of both the cation and anion can directly impact the melting point. Usually the cation has a low degree of symmetry, which results in a reduced lattice energy, thus lowering melting points.

As Table 1.4 shows, the liquidus range of pyridinium-based ionic liquids depends on the cation-anion combination and can range from -64.5°C up to more than 200 °C. Generally, due to attenuation of the Coulombic attraction, increasing cation/anion size tends to lower the melting points of pyridinium-based ionic liquids.

Table 1.4 Melting Points of Some Pyridinium-based Ionic Liquids

Ionic Liquids	m.p. (^{o}C)	Reference
$[HPy]^+[Cl]^-$	144	Prey, 1941
$[HPy]^+[Br]^-$	200	Robinson and Osteryoung, 1979
$[EtPy]^+[Br]^-$	117~119	Ray and Bhattacharya, 1936
$[BuPy]^+[Cl]^-$	131~132	Robinson and Osteryoung, 1979
$[3\text{-}MeBuPy]^+[Cl]^-$	95	Heinze et al., 2005
$[4\text{-}MeBuPy]^+[Cl]^-$	158~160	Ardizzone et al., 1996
$[4\text{-}MeBuPy]^+[PF_6]^-$	45	Behar et al., 2002
$[3,5\text{-}(CH_3)_2BuPy]^+[Br]^-$	95	Crosthwaite et al., 2005
$[4\text{-}(CH_3)_2NBuPy]^+[Br]^-$	222	Crosthwaite et al., 2005
$[HexPy]^+[(CF_3SO_2)_2N]^-$	0	Crosthwaite et al., 2005
$[3,5\text{-}(CH_3)_2HexPy]^+[(CF_3SO_2)_2N]^-$	10	Crosthwaite et al., 2005
$[3\text{-}Me\text{-}4\text{-}(CH_3)_2NHexPy]^+[Br]^-$	119	Crosthwaite et al., 2005
$[3\text{-}Me\text{-}4\text{-}(CH_3)_2NHexPy]^+[(CF_3SO_2)_2N]^-$	-2	Crosthwaite et al., 2005
$[3\text{-}MePrPy]^+[(CF_3SO_2)_2\ N]^-$	0	Tsukahara et al., 2001
$[2\text{-}ClMePy]^+[I]^-$	204-206	Amin et al., 1979
$[CN(CH_2)_3Py]^+[Cl]^-$	101	Zhao et al., 2004a
$[CN(CH_2)_3Py]^+[PF_6]^-$	95	Zhao et al., 2004a
$[CN(CH_2)_3Py]^+[BF_4]^-$	62	Zhao et al., 2004a
$[CN(CH_2)_3Py]^+[\ CF_3SO_2)_2\ N]^-$	-64.5	Zhao et al., 2004a

In conclusion, anion and cation effects cannot be considered in isolation. Increasing symmetry of ions permits more efficient packing in the crystal cells and increases melting points. Conversely, low symmetry distorts packing and reduces the lattice energy, thereby lowering the melting points. In addition, there are some other factors which should be considered such as hydrogen bonding (Elaiwi et al, 1995), etcetera.

1.2.3 Density

Density is the most straightforwardly determined and unambiguous physical property of ionic liquids and can be easily measured by mass-volume methods. The densities of most ionic liquids at room temperature range from 1.02 g/ml for $[(C_8H_{17})(C_4H_9)_3N]^+$

$[(CF_3SO_2)O]^-$ (Sun et al., 1998) to 1.8 g/ml for $[(CH_3)_3S]^+[Al_2Br_7]^-$ (Matsumoto et al, 2000a; Pernak et al.,2001) The densities of some pyridinium-based ionic liquids at room temperature are summarized in Table 1.5. Generally, the shape and size of both cation and anion can influence the densities of ionic liquids. In most cases, due to the depression of packing among ions (Fuller et al., 1994), the density decreases as the bulkiness of the cation grows. Increasing the mass of the anion, however, results in an increase in the density of ionic liquids.

Table 1.5 Densities of Some Pyridinium-based Ionic Liquids at Room Temperature

Ionic Liquids	Density (g/ml)	Reference
$[HPy]^+I^-$	2.09	Hartl, 1975
$[HPy]^+[C_2H_5OC_2H_4SO_4]^-$	1.28	Kato and Gmehling, 2004
$[EtPy]^+ [(CF_3SO_2)_2N]^-$	1.536	Kato and Gmehling, 2004
$[BuPy]^+ [BF_4]^-$	1.220	Noda et al., 2001
$[BuPy]^+ [(CF_3SO_2)_2N]^-$	1.449	Noda et al., 2001
$[4\text{-}MeBuPy]^+[BF_4]^-$	1.20	Schofer et al., 2001
$[3\text{-}MePrPy]^+ [(CF_3SO_2)_2 N]^-$	1.44	Tsukahara et al., 2001
$[3\text{-}MeBuPy]^+[(CF_3SO_2)_2 N]^-$	1.40	Tsukahara et al., 2001

Table 1.6 Temperature Effect on Densities of Pyridinium-based Ionic Liquids

Temperature (K)	Density (g/ml)		
	$[HPy]^+[C_2H_5OC_2H_4SO_4]^-$	$[EtPy]^+ [(CF_3SO_2)_2N]^-$	$[BuPy]^+ [BF_4]^-$
293.15	1.284	-	1.224
298.15	1.281	1.536	1.220
303.15	1.277	1.531	1.216
308.15	1.273	1.526	1.212
313.15	1.270	1.521	1.208
318.15	1.266	1.516	-
323.15	1.262	1.512	-
328.15	1.259	1.507	-
333.15	1.255	1.502	-
338.15	1.251	-	-
343.15	1.248	-	-
348.15	1.244	-	-

The densities of ionic liquids are significantly influenced by temperature. There are three examples shown in Table 1.6. The first two were reported by Kato and Gmehling in 2004, and the last one proposed by Noda et al. in 2001. In all cases, the densities gradually decreased with increasing the temperature.

Table 1.7 Pressure Effect on the Densities of $[BuPy]^+[BF_4]^-$

298.2 ± 0.1 (K)			323.2 ± 0.1 (K)		
Pressure (Pa)	Density (g/cm^3)	Volume (cm^3/mol)	Pressure (Pa)	Density (g/cm^3)	Volume (cm^3/mol)
0.099±0.001	1.2144±0.0072	183.65±1.09	0.099±0.001	1.1988±0.0071	186.04±1.10
23.54±0.69	1.2224±0.0131	182.44±1.96	-	-	-
36.64±0.69	1.2314±0.0132	181.11±1.94	-	-	-
70.43±0.69	1.2405±0.0133	179.78±1.93	71.46±0.69	1.2286±0.0132	181.53±1.95
103.52±0.69	1.2535±0.0135	177.92±1.91	103.52±0.69	1.2377±0.0133	180.20±1.94
137.99±0.69	1.2610±0.0135	176.86±1.90	137.99±0.69	1.2487±0.0134	178.60±1.92
172.47±0.69	1.2725±0.0137	175.26±1.88	172.47±0.69	1.2562±0.0135	177.53±1.91
202.81±0.69	1.2764±0.0137	174.73±1.88	204.18±0.69	1.2657±0.0136	176.20±1.89

The pressure effect on the densities of 1-*n*-butylpyridinium tetrafluoroborate ionic liquid has also been studied at different temperatures by Gu and Brennecke (2002). As can be seen in Table 1.7, high pressure would increase the densities while lowering the molar volume at the same temperature.

1.2.4 Viscosity

Viscosity is the resistance or thickness of a material to flow, which is a result of the internal friction of the material's molecules. Generally, ionic liquids are more viscous than most commonly used organic solvents. At room temperature, the viscosity range of ionic liquids is from 20.5 cP for $[(CH_3)_3S]^+[HBr_2]^-$ (Ma and Johnson, 1994) to even higher than 574 cP (Sun et al., 1998). The viscosity could be influenced by impurities and also by temperature. Generally, impurities might decrease the viscosities and higher temperatures result in less viscosity. For example, the viscosity of $[BMIM]^+[PF_6]^-$ decreases 27% when the temperature changes from 293K to 298K (Baker et al., 2001). Some literature examing viscosity data of pyridinium-based ionic liquids are summarized in Table 1.8. The viscosities are strongly influenced by the size and shape of the cation. Generally, the viscosity increases as the bulkiness of the cation grows.

Table 1.8 Viscosities of Pyridinium-based Ionic Liquids at 298K

Ionic Liquids	Viscosity(cP)	Reference
$[EtPy]^+ [EtSO_4]^-$	137	Crosthwaite et al., 2005
$[BuPy]^+ [BF_4]^-$	103	Noda et al., 2001
$[BuPy]^+ [(CF_3SO_2)_2N]^-$	57	Noda et al., 2001
$[3\text{-}MeEtPy]^+ [EtSO_4]^-$	150	Crosthwaite et al., 2005
$[3\text{-}MeBuPy]^+ [(CF_3SO_2)_2N]^-$	63	Crosthwaite et al., 2005
$[3\text{-}MeBuPy]^+ [BF_4]^-$	177	Crosthwaite et al., 2005
$[HexPy]^+ [(CF_3SO_2)_2N]^-$	80	Crosthwaite et al., 2005
$[3\text{-}MeHexPy]^+ [(CF_3SO_2)_2N]^-$	85	Crosthwaite et al., 2005
$[3,5\text{-}Me_2HexPy]^+[(CF_3SO_2)_2N]^-$	104	Crosthwaite et al., 2005
$[2\text{-}Et\text{-}3,5\text{-}Me_2HexPy]^+[(CF_3SO_2)_2N]^-$	245	Crosthwaite et al., 2005
$[2\text{-}Pr\text{-}3,5\text{-}Et_2HexPy]^+[(CF_3SO_2)_2N]^-$	206	Crosthwaite et al., 2005
$[4\text{-}(CH_3)_2NHexPy]^+[(CF_3SO_2)_2N]^-$	111	Crosthwaite et al., 2005
$[3\text{-}Me\text{-}4\text{-}(CH_3)_2NHexPy]^+[(CF_3SO_2)_2N]^-$	112	Crosthwaite et al., 2005
$[3\text{-}MeOctPy]^+[(CF_3SO_2)_2N]^-$	112	Crosthwaite et al., 2005

1.2.4 Solubility

Ionic liquids are considered as polar but non-coordinating substances. Hence, most ionic liquids are miscible with water, dichloromethane and ethanol and tend to be immiscible with diethyl ether and toluene. The solubility of ionic liquids depends on the combination of their cation and anion, e.g. changing the cation or anion will change the solubility. For instance, changing Cl^- to $[PF_6]^-$ causes the solubility of the ionic liquid in water to vary from complete miscibility to almost immiscibility. Also, increasing the size of the substituent group on the cation will gradually enhance the immiscibility of ionic liquids in water (Earle and Seddon, 2000). This may be due to large size substituents attenuating the polarity and thereby enhancing the hydrophobicity.

1.2.5 Thermal Stability

Ionic liquids are more thermally stable than traditional organic solvents. They have a negligible vapor pressure due to the reduced Coulombic attraction between ions, which energetically restricts the ion-pair formation required for volatilization. The upper liquidus limit of ionic liquids is the decomposition temperature, which depends on the structure and bonding in ionic liquids. Generally, 150°C is the highest temperature for most ammonium ionic liquids. Many other ionic liquids have liquid ranges more than 300°C compared to the 100°C of water. Particularly, $[EMIM]^+[(CF_3SO_2)_2N]^-$ is stable up to 400°C (Bonhote et al., 1996). Some literature decomposition temperatures of pyridinium-based ionic liquids are listed in Table 1.9. Generally, pyridinium-based ionic liquids could be stable up to 649K for 4-dimethylamino-hexylpyridinium bis(trifluoromethylsulfonyl)imide (Crosthwaite et al., 2005).

Table 1.9 Decomposition Temperature of Pyridinium-based Ionic Liquids

Ionic liquids	T_d (K)	Reference
$[\text{BuPy}]^+[\text{Br}]^-$	467	Crosthwaite et al., 2005
$[\text{BuPy}]^+[\text{BF}_4]^-$	615	Noda et al., 2001
$[\text{BuPy}]^+[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$	677	Noda et al., 2001
$[\text{EtPy}]^+[\text{EtSO}_4]^-$	483	Crosthwaite et al., 2005
$[\text{3-MeEtPy}]^+[\text{EtSO}_4]^-$	486	Crosthwaite et al., 2005
$[\text{3,5-Me}_2\text{EtPy}]^+[\text{EtSO}_4]^-$	482	Crosthwaite et al., 2005
$[\text{3-MeBuPy}]^+[\text{Br}]^-$	472	Crosthwaite et al., 2005
$[\text{3-MeBuPy}]^+[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$	590	Crosthwaite et al., 2005
$[\text{3-MeBuPy}]^+[\text{BF}_4]^-$	506	Crosthwaite et al., 2005
$[\text{3,5-Me}_2\text{BuPy}]^+[\text{BF}_4]^-$	471	Crosthwaite et al., 2005
$[\text{4-Me}_2\text{NBuPy}]^+[\text{Br}]^-$	526	Crosthwaite et al., 2005
$[\text{3-Me-4-Me}_2\text{NBuPy}]^+[\text{Br}]^-$	498	Crosthwaite et al., 2005
$[\text{HexPy}]^+[\text{Br}]^-$	468	Crosthwaite et al., 2005
$[\text{HexPy}]^+[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$	605	Crosthwaite et al., 2005
$[\text{3-MeHexPy}]^+[\text{Br}]^-$	472	Crosthwaite et al., 2005
$[\text{3-MeHexPy}]^+[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$	603	Crosthwaite et al., 2005
$[\text{3,5-Me}_2\text{HexPy}]^+[\text{Br}]^-$	474	Crosthwaite et al., 2005
$[\text{3,5-Me}_2\text{HexPy}]^+[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$	613	Crosthwaite et al., 2005
$[\text{2-Et-3,5-Me}_2\text{HexPy}]^+[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$	601	Crosthwaite et al., 2005
$[\text{2-Pr-3,5-Et}_2\text{HexPy}]^+[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$	598	Crosthwaite et al., 2005
$[\text{4-(CH}_3)_2\text{NHexPy}]^+[\text{Br}]^-$	525	Crosthwaite et al., 2005
$[\text{4-(CH}_3)_2\text{NHexPy}]^+[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$	649	Crosthwaite et al., 2005
$[\text{3-Me-4-(CH}_3)_2\text{NHexPy}]^+[\text{Br}]^-$	505	Crosthwaite et al., 2005
$[\text{3-Me-4-(CH}_3)_2\text{NHexPy}]^+[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$	631	Crosthwaite et al., 2005
$[\text{OctPy}]^+[\text{Br}]^-$	460	Crosthwaite et al., 2005
$[\text{3-MeOctPy}]^+[\text{Br}]^-$	459	Crosthwaite et al., 2005
$[\text{3-MeOctPy}]^+[\text{BF}_4]^-$	547	Crosthwaite et al., 2005
$[\text{3-MeOctPy}]^+[(\text{CF}_3\text{SO}_2)_2\text{N}]^-$	605	Crosthwaite et al., 2005

1.2.6 Polarity

It is well known that the solvent chosen could dramatically affect chemical reactions and solvent effects are considered to be primarily dependent on the solvent polarity. Therefore, polarity is an important property of ionic liquids. The simplest qualitative definition for a polar solvent is one that will dissolve and stabilize dipolar or charged solutes, e.g., 'like dissolves like'. Under this definition, ionic liquids due to their salt nature will be highly polar. The polarities of some pyridinium-based ionic liquids were measured at room temperature and are shown in Table 1.10. The data indicate these ionic liquids are more polar than propan-2-ol but less polar than methanol.

Table 1.10 Polarities of Some Pyridinium-based Ionic Liquids at Room Temperature

Solvents	$E_T(30)$ (kcal/mol)	Reference
Hexane	31	Aki et al., 2001
Diethyl ether	34.5	Aki et al., 2001
1,4-Dioxane	36	Aki et al., 2001
THF	37.4	Aki et al., 2001
Acetone	41.3	Aki et al., 2001
Acetonitrile	45.3	Aki et al., 2001
tert-Butyl alcohol	43.5	Aki et al., 2001
Propan-2-ol	48.5	Aki et al., 2001
$[BuPy]^+[BF_4]^-$	51.44	Park and Kazlauskas, 2001
$[BuPy]^+[(CF_3SO_2)_2N]^-$	51.7	Reichardt, 2005
Ethanol	51.9	Aki et al., 2001
$[PrPy]^+[BF_4]^-$	52.08	Park and Kazlauskas, 2001
$[4\text{-}MePrPy]^+[BF_4]^-$	52.41	Park and Kazlauskas, 2001
Methanol	55	Aki et al., 2001
Water	63.1	Aki et al., 2001

1.2.7 Electrochemical Properties

The preliminary research on ionic liquids was focused on their applications as electrochemical solvents, electrolytes for batteries, and capacitors. One of the first uses of ionic liquids was as a solvent for the room temperature electrodeposition of aluminum (Hurley and Wier, 1951). As desirable solvents in electrochemical processes, ionic liquids possess a series of electrochemical properties, such as high electrical conductivities, wide electrochemical potential windows, excellent solvent transport properties, wide liquidus ranges and good solubility for inorganic, organic and organometallic species.

The electrochemical potential window is the range of voltage over which the solvent is electrochemically inert. In the case of ionic liquids, the 'window' depends on the resistance of the cation to reduction and the resistance of the anion to oxidation. Of course, impurities in ionic liquids have a profound impact on the 'window'. The electrochemical stabilities of ionic liquids in an increasing order are: pyridinium < pyrazolium imidazolium sulfonium ammonium (Wasserscheid and Welton, 2003).

The ionic conductivity is another key criterion for selecting electrochemical solvents. The room temperature conductivities of pyridinium-based ionic liquids are shown in Table 1.11.

Table 1.11 Conductivity of Some Pyridinium-based Ionic Liquids at Room Temperature

Ionic Liquids	Conductivity (ms/cm)	Reference
$[BuPy]^+ [BF_4]^-$	1.9	Noda et al., 2001
$[BuPy]^+ [(CF_3SO_2)_2N]^-$	2.2	Noda et al., 2001

1.2.8 Toxicity

Ionic liquids have been investigated for about 20 years and the information about their chemical, physical, biological, and thermodynamic properties has been reported continuously. Very little data on their toxicity and eco-toxicity, however, has been available until now.

Although ionic liquids can reduce the air pollution, they may cause water pollution due to their high solubility. Therefore, it is important to determine the toxicities of ionic liquids prior to their exposure to the environment. Based on the toxicity database and using quantitative structure-activity relationship (QSAR) model, ionic liquids could be designed particularly for individual industrial processes by tuning the combination of cations and anions to prevent or eliminate pollution of the environment (Rogers and Seddon, 2003). It should be noted that all eco-toxicological assays have to be done in the pure ionic liquids. Otherwise side effects of impurities, which may be produced during synthesis or purification processes, have to be considered (Swatloski et al., 2004).

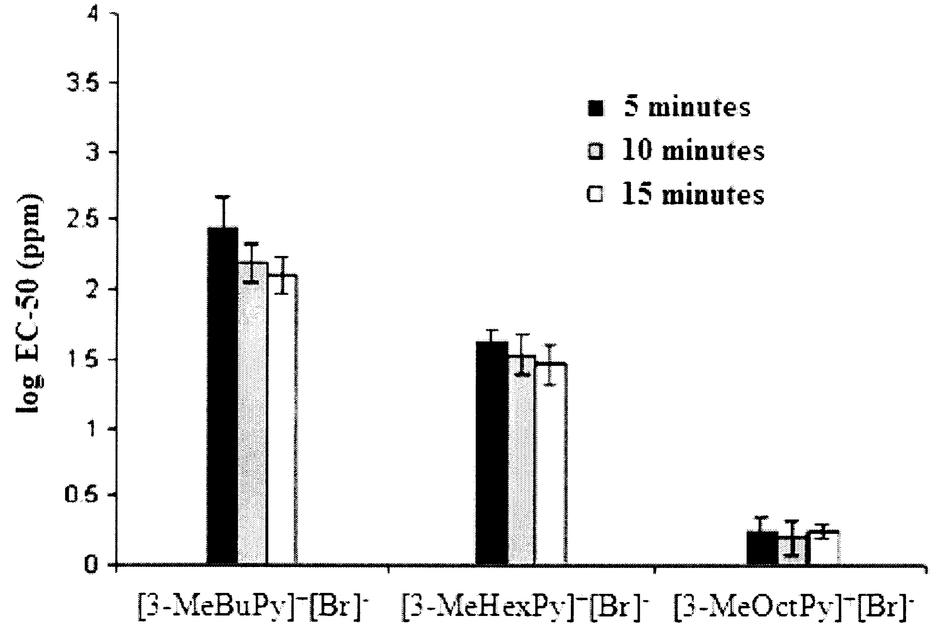


Figure 1.7 EC50 values for three pyridinium-based ionic liquids

In 2005, EC50 values for *Vibrio fischeri* in some pyridinium-based ionic liquids were investigated by Kathryn M. Docherty and Charles F. Kulpa, Jr. (Table 1.12). They found increasing alkyl chain length at N-substitution position of pyridinium-based ionic liquids would increase the toxicity to *V. fischeri* as shown in Figure 1.7 (Lower EC50 or log EC50 values indicate higher toxicity).

Table 1.12 Toxicities of Some Pyridinium-based Ionic Liquids and Organic Solvents

Solvents	EC50 (ppm)
$[3\text{-MeOctPy}]^+[\text{Br}]^-$	1.77 ± 0.20
o-Xylene	9.25
$[3\text{-MeHexPy}]^+[\text{Br}]^-$	29.99 ± 10.83
Phenol	30.76 ± 7.21
Toluene	31.74 ± 15.82
$[3,5\text{-Me}_2\text{BuPy}]^+[(\text{CN})_2\text{N}]^-$	55.71 ± 23.27
Me(CO)*i*Bu	79.60 ± 0.00
$[3\text{-MeBuPy}]^+[(\text{CN})_2\text{N}]^-$	98.00 ± 10.20
Benzene	108.05 ± 85.77
3-MePyridine	110.60 ± 19.60
$[3,5\text{-Me}_2\text{BuPy}]^+[\text{Br}]^-$	119.27 ± 23.88
$[3\text{-MeBuPy}]^+[\text{Br}]^-$	130.48 ± 39.41
$[\text{BuPy}]^+[(\text{CN})_2\text{N}]^-$	409.92 ± 97.68
$[\text{BuPy}]^+[\text{Cl}]^-$	439.97 ± 84.27
$[\text{BuPy}]^+[\text{Br}]^-$	538.40 ± 14.58
Ethylene glycol	621.00
Chloroform	1199.33 ± 1127.51
Dichloromethane	2532.33 ± 1415.38
Ethyl acetate	5822.00
Acetone	19311.14 ± 5295.78
Methanol	101068.50 ± 113703.83

As the data shows, increased methyl substitution on pyridinium ring results in increasing the toxicities to V. *fischeri*. Also, the bulkiness of cation leads to high toxicities. However, as the data is limited, we cannot tell the anion effect on the toxicity. Since building the toxicity database of ionic liquids would help chemists to theoretically predict the possible biological activities of newly designed ionic liquids, it is critical to continue determining the toxicity of more ionic liquids.

1.3 Applications of Pyridinium-based Ionic Liquids

Ionic liquids have recently attracted considerable attention as viable alternatives to conventional organic solvents in not only separation, synthesis, and electrochemical applications, but also for some novel applications such as polymerization, biocatalysis, and nanomaterial processes. All these applications are based on their unique properties which give them the capability to expand traditional laws of chemistry. For example, ionic liquids are highly polar, yet non-coordinating, and are ideal for catalytic reactions; they can be made immiscible with water and/or a number of organic solvents thus facilitating a number of reactions and separation processes. Furthermore, the physical and chemical properties of ionic liquids (such as density, conductivity, viscosity, Lewis acidity and thermostability) could be tuned by varying the combination of the component ions to obtain desired solvent properties.

Much research work has been done for ionic liquids in various fields. As designable solvents, ionic liquids can be made specifically for each individual process. It should be noted there are many advantages to carrying out reactions in ionic liquids: (1) the reactions are easy to perform in ionic liquids, usually no special equipments, conditions and methodologies are required; (2) many reactions can occur faster and more efficiently compared to traditional organic solvents; (3) high product yields and selectivities can be obtained; (4) most ionic liquids can be recycled therefore reducing the process cost.

As an important member in the family of ionic liquids, pyridinium-based ionic liquids have been investigated in various roles, such as solvents, catalysts, precursors and so on. Herein, we summarized the applications of this type of ionic liquids.

1.3.1 Organic Synthesis

1.3.1.1 Aromatic Benzoylation

Benzoylation is an important reaction for the synthesis of benzophenones, which are used as perfumery fixatives. N-butylpyridinium chloroalumate ionic liquid has been explored in the aromatic benzoylation reaction (Rebeiro and Khadilkar, 2000). Their results show various aromatic compounds could be efficiently benzoylated with benzotrichloride in the acidic $[BuPy]^+[Cl]^-$-$AlCl_3$ system, which contained only half of the amount of aluminum chloride compared to the traditional process (Figure 1.8).

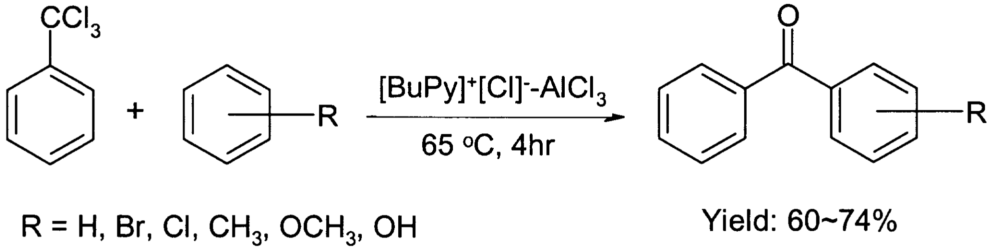


Figure 1.8 Benzoylation in pyridinium-based ionic liquids

1.3.1.2 C-C Cleavage Reaction

The catalytic cracking of polyethylene to light alkanes is one of the most important processes for plastics recycling and conversion into useful feedstocks. Adams et al. successfully performed this reaction in the acidic 1-butylpyridinium chloride–$AlCl_3$ system in 2000. The major products of the reaction are C3–C5 gaseous alkanes (such as isobutene) and no alkenes are observed. Compared to the traditional methods, there are some advantages achieved by using ionic liquids such as (1) high selectivity to low molecular weight products; (2) easy of separation of products from ionic liquids by extraction; (3) ionic liquids are reusable.

1.3.1.3 Cycloaddition

Cycloaddition of carbon dioxide to propylene oxide has been investigated in room temperature ionic liquids, 1-butyl-3-methylimidazolium and 1-butylpyridinium salts, without any additional organic solvents (Peng and Deng, 2001a). However, it was found that $[BMIM]^+[BF_4]^-$ was the most active catalyst with almost 100% conversion and selectivity. The conversion increased with increasing temperature or increasing the amount of ionic liquids in a certain range. Furthermore, the ionic liquids as catalysts for the reaction were recyclable (Figure 1.9).

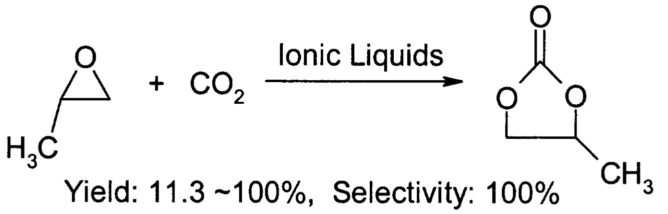


Figure 1.9 Cycloaddition of propylene oxide and carbon dioxide

1.3.1.4 Esterification

Esterifications of alcohols and carboxylic acids performed in 1-butylpyridinium chloride-aluminum chloride have been reported by Deng et al. (2001). Higher conversions (100%) and selectivities (99%) were achieved compared to those carried out in traditional solvents. Moreover, the ionic liquids could be recovered and reused.

Our group has developed a successful method for synthesizing amino acid esters (Zhao, 2002), which are very important intermediates in the chemical and pharmaceutical industry. Satisfactory results were obtained by using pyridinium-based ionic liquids $[EtPy]^+[CF_3COO]^-$ as a catalyst or co-solvent (Figure 1.10).

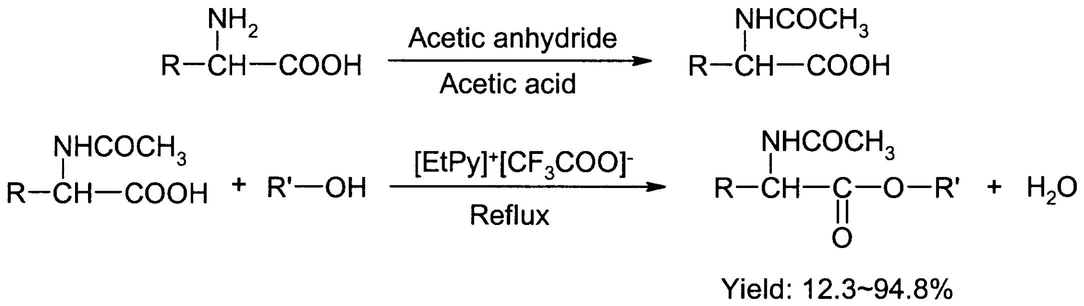


Figure 1.10 Esterification of amino acids

1.3.1.5 Olefin Hydroformylation

Wasserscheid and Waffenschmidt (2000) reported the regioselective, platinum-catalysed hydroformylation of functionalized and non-functionalized olefins in chlorostannate ionic liquids, which were synthesized by mixing 4-methylbutyl-pyridinium chloride $[4\text{-}MeBuPy]^+Cl^-$ with $SnCl_2$ in a molar ratio of 1:1.04. High selectivities (>95%) were found in most cases (Figure 1.11).

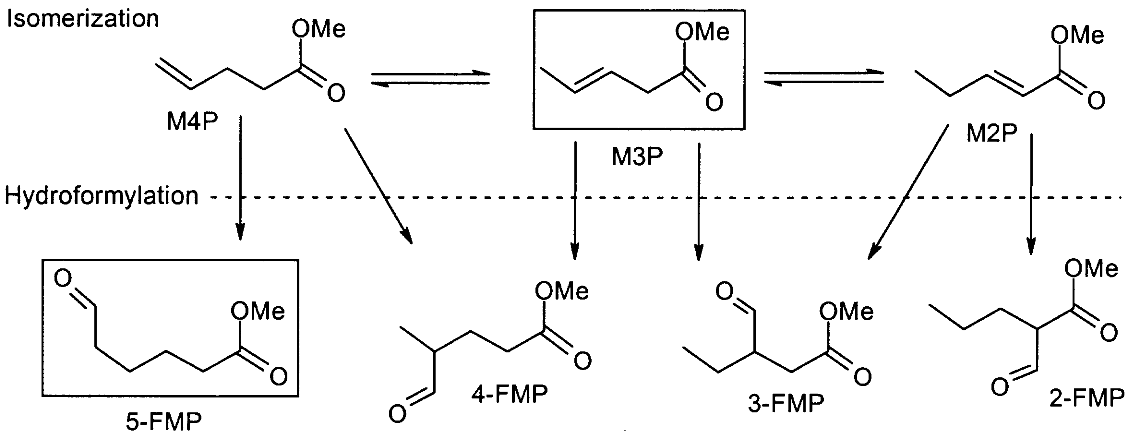


Figure 1.11 Hydroformylation of methyl-3-pentenoate (M3P)

1.3.1.6 Beckmann Rearrangement

The Beckmann rearrangements of ketoximes were catalyzed by phosphorous pentachloride in room temperature pyridinium-based ionic liquids (Peng and Deng, 2001b). High conversion and selectivity were achieved under mild conditions and without any organic solvents. The ionic liquids were recyclable (Figure 1.12).

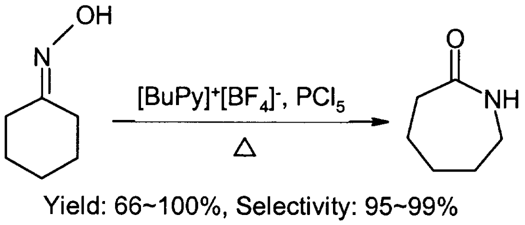


Figure 1.12 Beckmann rearrangements of ketoxime

1.3.1.7 Diels-Alder Reaction

The utility of room temperature chloroaluminate pyridinium-based ionic liquids as solvent and catalyst for Diels-Alder reaction was studied by Carlos W. Lee in 1999. The endo selectivity and rate enhancement were observed (Figure 1.13).

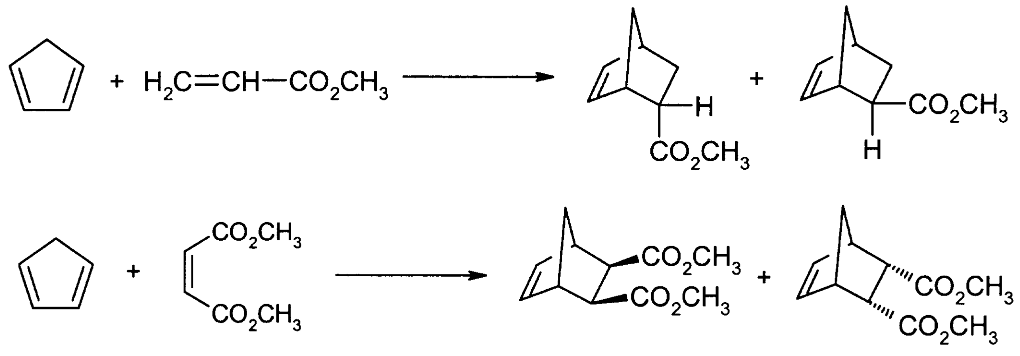


Figure 1.13 Diels-Alder reaction of cyclopentadiene

1.3.1.8 Fischer Indole Synthesis

Fischer indole synthesis is one of the most useful heterocyclic reactions to obtain biologically active products like reserpine, strychnine, yohimbine, indomethacin, as well as some essential amino acids such as tryptamine, photoconductors, and antioxidants. Pyridinium-based ionic liquid, 1-butylpyridinium chloride, has been investigated in this reaction with aluminum chloride by Rebeiro and Khadilkar in 2001. Chloroaluminate pyridinium-based ionic liquids were employed as solvent and catalyst. Good yields have been achieved under relatively mild conditions (Figure 1.14).

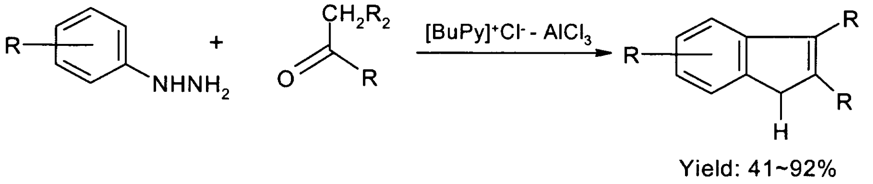


Figure 1.14 Fischer indole synthesis of ketones

1.3.1.9 Friedel-Crafts Alkylation

The long-chain alkylation of methylnaphthalene is a very important process due to long-chain alkylmethylnaphthalenes being the core intermediates for synthesizing alkylmethylnaphthalene sulfonate (AMNS). It has a great potential for enhanced oil recovery with low costs and high efficiency. Friedel-Crafts alkylation of α -methylnaphthalene with long-chain alkenes has been investigated in chloroaluminate room temperature ionic liquids and organic polycation ionic liquid - methylenedipyridinium chloroaluminate (MeDiPyCl–$AlCl_3$) (Zhao et al., 2005). It is found that the $[BuPy]^+Br^-$–$AlCl_3$ ionic liquid exhibits outstanding catalytic properties. Under the optimum reaction conditions, high conversion (90%) and selectivity (100%) were obtained. Furthermore, the ionic liquids could be recycled and reused without loss of their catalytic activity (Figure 1.15).

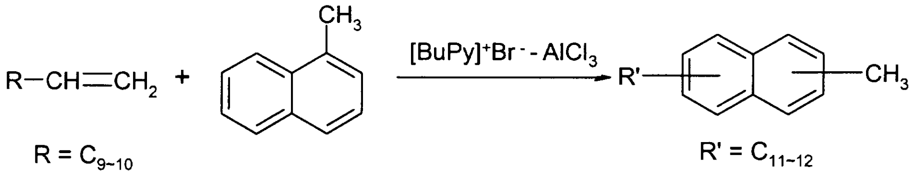
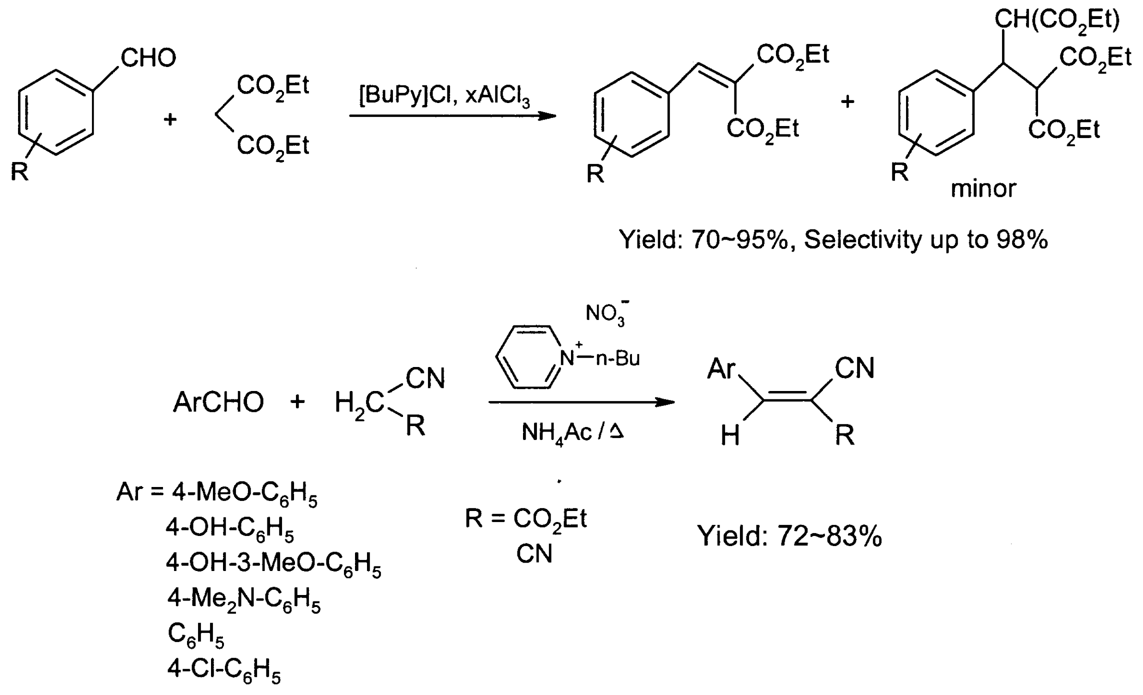


Figure 1.15 Friedel-Crafts alkylation reaction of α-methylnaphthalene

1.3.1.10 Knoevenagel Condensation

Knoevenagel condensation is one of the most useful methods for alkene synthesis. In 2002, Harjani et al. first investigated n-butyl pyridinium aluminum chloride in this reaction. Furthermore, Li et al. (2003) also successfully carried out this reaction in n-butyl pyridinium nitrate, which performed as a reusable reaction medium (Figure 1.16).



Yield: 70~95%, Selectivity up to 98%

Yield: 72~83%

Figure 1.16 Knoevenagel condensation

1.3.1.11 Stille Coupling Reaction

The Stille Coupling is a C-C bond forming reaction. Generally, it is a palladium catalyzed reaction between orango-stannanes and organic halides and allows synthesizing different products from the most combinations of halides and stannanes. The main drawback is the usage of tin compounds, which are toxic and have low polarity. Zhao, Dongbin et al. (2004a) have investigated the nitrile-functionalized pyridinium-based ionic liquids in the reaction of iodobenzene and phenyltributylstannane (Figure 1.17). Based on the transmission electron microscopy (TEM) images, palladium nanoparticles have been formed in ionic liquids and identified as the active catalysts for the Stille reaction. The palladium-ionic liquids, however, could not be recycled and reused efficiently.

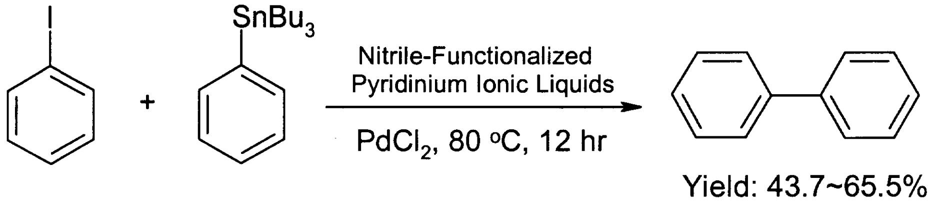


Figure 1.17 Stille coupling reactions in pyridinium-based ionic liquids

1.3.1.12 Suzuki Cross-Coupling Reaction

The Suzuki C-C coupling reaction is another versatile method for generating new carbon-carbon bonds. However, there are some problems in the traditional reactions such as poor solubility of reagents, decomposition of catalyst, and difficulty of product separation. In order to improve the reaction, palladium catalyzed Suzuki reactions have been studied in the nitrile-functionalized pyridinium-based ionic liquids by Zhao, Dongbin et al. (2004a). The $PdCl_2$-ionic liquids complexes show good catalytic activity, but could not be recycled and reused efficiently, which is evident from the fact that the yield of the fifth run is less than 15%. (Figure 1.18)

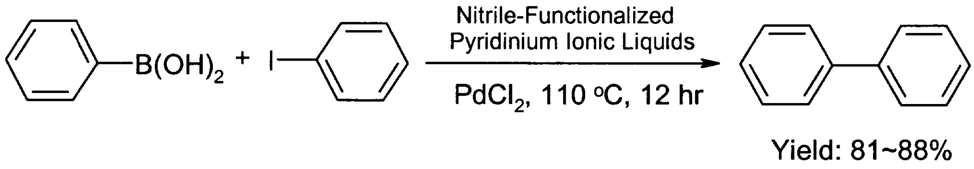
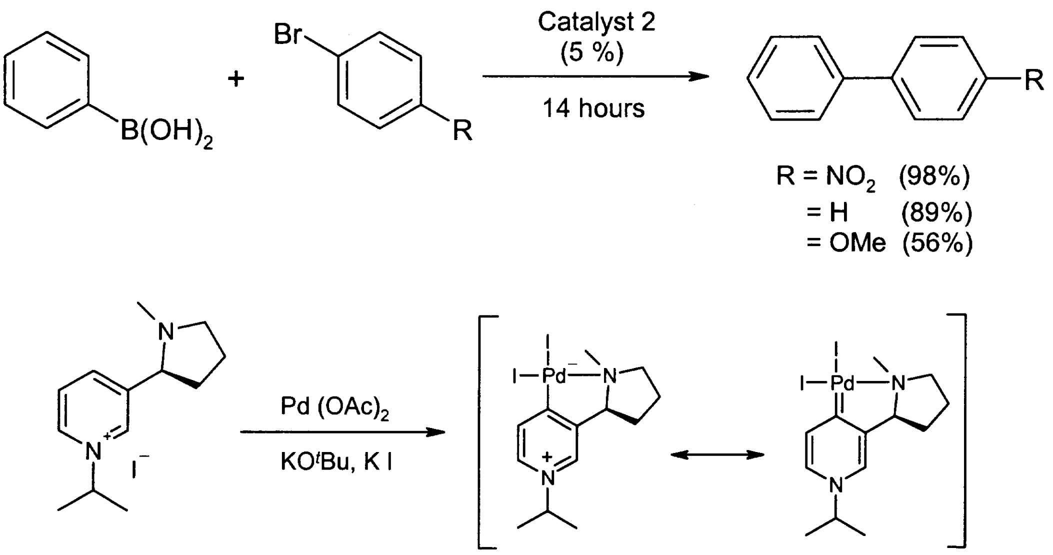


Figure 1.18 Suzuki coupling reactions of phenylboronic acid and iodobenzene

In 2005, Albrecht and Stoeckli-Evans proposed that as a ligand precursor, pyridinium-based ionic liquids **1** reacts with $[Pd(OAc)_2]$ in the presence of a base such as KO*t*Bu to form the pyridylidene complex **2**, which catalyzed the Suzuki coupling reactions of phenylboronic acids and aryl halides (Figure 1.19). It should be noted that pyridinium-based ionic liquids acted not only as solvents in this reaction but as reagents.



1 2

Figure 1.19 Suzuki coupling reaction of phenylboronic acid and aryl bromide

1.3.2 Polymerization

1.3.2.1 Olefin Dimerization

Linear dimerization of 1-butene has been successfully performed in buffered chloroaluminate ionic liquid solvents (Ellis et al., 1999). Satisfactory results have been achieved in [4-MeBuPy]$^+$Cl$^-$/AlCl$_3$ (0.45/0.55) buffered with excess LiCl. The reported buffering procedures facilitated the reactions with catalyst (cod)Ni(hfacac), permitting the reaction to take place in biphasic reaction mode with easy catalyst separation and efficient catalyst recycling. Compared with that of conventional organic solvents such as toluene, significant enhancement of catalytic activity was observed. The same reaction has also been explored in different chloroaluminate ionic liquids by Wasserscheid and Eichmann in 2001 (Figure 1.20).

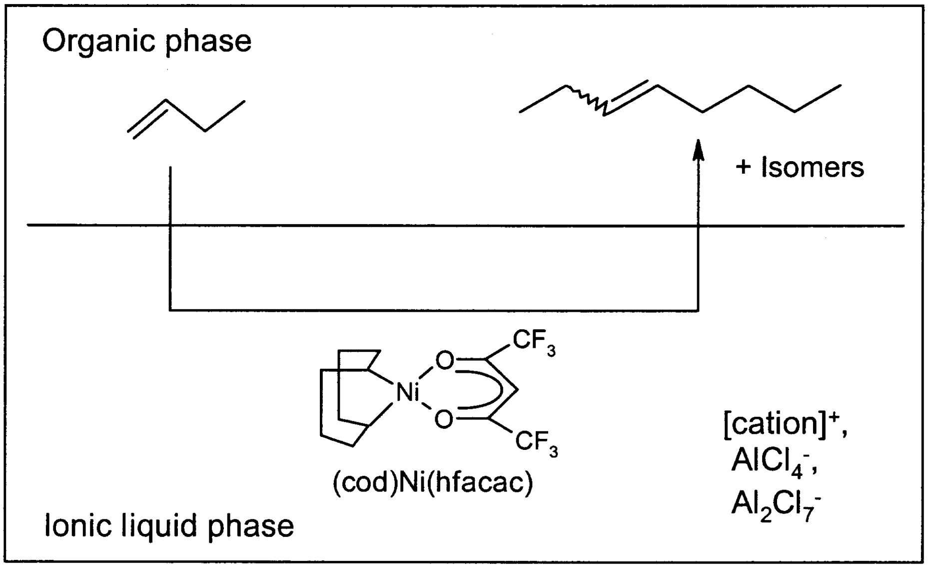


Figure 1.20 Linear dimerization of 1-butene in biphasic model

1.3.2.2 Electrochemical Polymerization

Arnautov (1997) first investigated the possibility of ionic liquids for the electrochemical synthesis of polyphenylene (PP). A new ionic liquid was made by mixing butylpyridinium chloride with alkoxy aluminum chloride $AlCl_2(OC_2H_5)$ instead of with the more traditional aluminum chloride. The use of it for the electrochemical PP synthesis was successful.

1.3.3 Biocatalysis

1.3.3.1 Enzymatic Resolution of Amino Acid Ester

The application of pyridinium-based ionic liquids in biocatalysis with alcalase was first studied by Zhao and Malhotra (2002b). The results are compared with those performed in the organic solvent – acetonitrile. The ionic liquid, N-ethyl-pyridinium-based trifluoroacetate, shows better results on both yield and enantioselectivity (Figure 1.21).

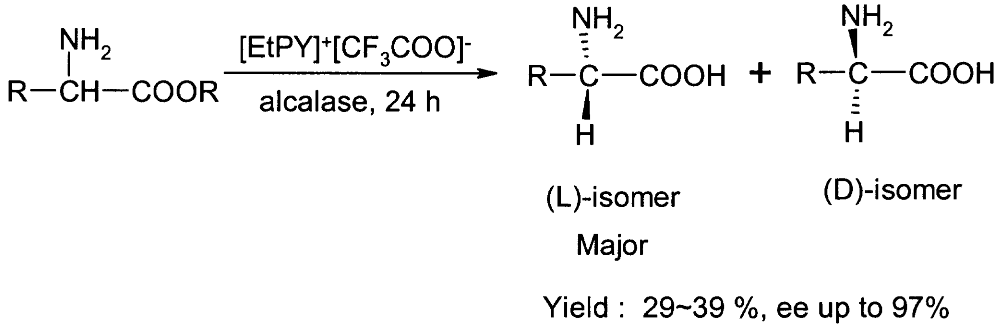


Figure 1.21 Enantioselective resolution of N-acetyl amino acids

1.3.3.2 Transesterification

The kinetic resolution of 1-phenylethanol catalyzed by lipase in ionic liquids has been investigated by Schöfer et al. (2001). High conversion (46%) and enantioselectivity (>98%) have been obtained in pure 4-methylbutylpyridinium tetrafluoroborate (Figure 1.22). They mentioned the unreacted starting materials and products could be removed by vacuum distillation. Then the ionic liquids could be recycled and reused for the next reaction cycle.

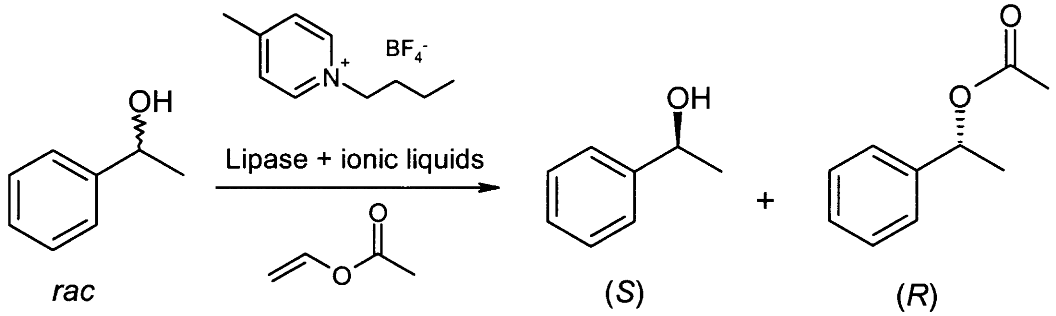


Figure 1.22 Enzymatic resolution of 1-phenylethanol in ionic liquids

1.3.4 Electrochemical Applications

Ionic liquids were primarily developed by electrochemists more than 50 years ago. Since they possess a number of electrochemical properties such as large window of electrochemical stability, high conductivity and high thermal stability, ionic liquids are proven to be excellent candidates for electrochemical process. For example, room temperature ionic liquids have been successfully employed as electrolytes for lithium rechargeable batteries. Most recently, ionic liquids are utilized with ionic polymer membranes and form transducers, actuators and sensors which have long term air stability (Bennett, 2005).

In conclusion, all applications described above show that ionic liquids have been investigated as a new class of solvents in an increasing number of applications. Many exciting applications have been reported. However, in this field of research, there are many ideas and applications which still need further investigated. We sincerely wish some day this new solvent - ionic liquid, could be employed in the chemical and pharmaceutical industries.

1.4 Objectives

In recent years, imidazolium-based ionic liquids have been investigated in organic synthesis and found to be highly suitable media for many organic reactions. Though the pyridinium-based ionic liquids have also been known for some time, reports on the potential of this class of ionic liquids have not been explored to the same extent. Most of them are N-butyl pyridinium-based ionic liquids (Welton, 1999; Zhao et al., 2002; Zhao and Malhotra, 2002a; Wasserscheid and Welton, 2003). This leaves curiosity to further investigate the application of other pyridinium-based ionic liquids as potential media for organic reactions.

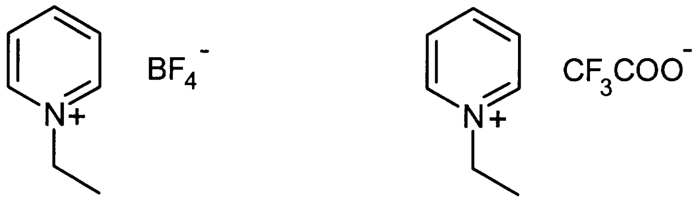
Previously, it has been shown (Zhao, 2002) that N-ethyl-pyridinium-based ionic liquids are good reaction media for biocatalysis. Based on these results, we initiated an investigation of the application of N-ethyl-pyridinium-based ionic liquids as solvents for various organic reactions. Two different ionic liquids have been studied, namely: 1-ethyl-pyridinium trifluoroacetate ($[EtPy]^+[CF_3COO]^-$) and 1-ethyl-pyridinium tetrafluoroborate ($[EtPy]^+[BF_4]^-$). The objective of this dissertation research is to develop an improved method for synthesizing pyridinium-based ionic liquids. These ionic liquids have been used for systematic investigation of five different reactions: (i) Diels-Alder reaction; (ii) Friedel-Crafts alkylation; (iii) Friedel-Crafts acylation; (iv) asymmetric Friedel-Crafts reaction; (v) asymmetric reduction of ketones.

CHAPTER 2

PYRIDINIUM-BASED IONIC LIQUIDS

2.1 Background Information

In past decade, there has been a dramatic increase in the research of a novel class of solvents - ionic liquids. However, the most reported use of these solvents in organic synthesis has been that of imidazolium-based ionic liquids. Lesser attention has been paid to the ionic liquids derived from pyridine. Although pyridinium-based ionic liquids are reported in literature, synthesis of these ionic liquids is yet to be explored. Therefore, in order to extend and supplement the research on this type of ionic liquids, we synthesize two kinds of pyridinium-based ionic liquids and investigate them in various organic reactions. In our studied organic reactions, two ionic liquids (Figure 2.1) namely, 1-ethyl-pyridinium tetrafluoroborate ([EtPy]$^+$[BF$_4$]$^-$) and 1-ethyl-pyridinium trifluoro-acetate ([EtPy]$^+$[CF$_3$COO]$^-$) were employed.



[EtPy]$^+$ [BF$_4$]$^-$　　[EtPy]$^+$ [CF$_3$COO]$^-$

Figure 2.1 Pyridinium-based ionic liquids studied

2.2 Synthesis and Purification of Ionic Liquids

2.2.1 Materials and Methods

N-ethyl-pyridinium bromide was purchased from Alfa Aesar, a Johnson Matthey Company. Trifluoroacetic acid, silver (I) oxide and Tetrafluoroboric acid were purchased from Sigma Aldrich.

Generally, there are two basic methods for synthesizing ionic liquids: 1) Metathesis of a halide salt with, for example, a silver, alkali or ammonium salt containing the desired anion. 2) Acid-base neutralization reaction. In this study, the first method was employed for synthesizing pyridinium-based ionic liquids. 1-ethyl-pyridinium trifluoroacetate ($[EtPy]^+[CF_3COO]^-$) and 1-ethyl-pyridinium tetrafluoroborate ($[EtPy]^+[BF_4]^-$) were prepared following the literature method (Holbrey and Seddon, 1999; Zhao et al., 2003), but some improvements have been made in our study.

IR, UV-visible Spectroscopy and NMR techniques have been employed to analyze the ionic liquids.

2.2.2 Synthesis of 1-Ethylpyridinium Trifluoroacetate $[EtPy]^+[CF_3COO]^-$

Trifluoroacetic acid (13.3 ml, 0.1726 mol) was slowly added to stirred slurry of silver (I) oxide (20.0g, 0.0863 mol) and distilled water (50 ml) in 400ml beaker at about 45°C. To avoid photodegradation of the silver (I) oxide, the reaction mixture was fully covered with aluminum foil. The mixture was stirred continuously until the indication of the formation of a solution was extant. A solution of N-ethyl-pyridinium bromide (32.46 g, 0.1726 mol) and distilled water (60 ml) was added to the reaction mixture. As the reaction took place and ionic liquids formed, yellow precipitate of silver (I) bromide started to be observed. The mixture was stirred at room temperature for a certain time until no more precipitate formed. When the stirring was stopped, the precipitate would remain at the bottom of the beaker and a clear water layer at the top. Because N-ethyl pyridinium bromide is hygroscopic, silver (I) trifluoroacetate is generally in excess in the reaction mixture. Therefore, we added a 1M solution of N-ethyl pyridinium bromide drop wisely and stirred the mixture to make the fresh milky precipitate to fall down to the bottom. We repeated this step until no further precipitate was produced. To confirm that there was no excess N-ethyl-pyridinium bromide in the mixture, we added one drop of 1M silver (I) trifloroacetate solution to the mixture. If no milky precipitate occurred, we added one drop of 1M N-ethyl-pyridinium bromide and then stirred for 10 minutes. The solubility of AgBr (5.35×10^{-13} M^2 at 25°C) guarantees the residue of starting materials in the reaction mixture as low as possible, and therefore can be ignored. We filtered off the yellow precipitate of silver (I) bromide and then removed the solvent by rotary evaporation under reduced pressure at about 65 °C. The resulting ionic liquid is a light yellow liquid (27.5ml, 93%).

$$2CF_3COOH + Ag_2O \longrightarrow 2CF_3COOAg + H_2O$$

$$[EtPy]^+[Br]^- + CF_3COOAg \longrightarrow [EtPy]^+[CF_3COO]^- + AgBr \downarrow$$

Figure 2.2 Synthesis of $[EtPy]^+[CF_3COO]^-$ by a two-step reaction

2.2.3 Synthesis of 1-Ethylpyridinium Tetrafluoroborate $[EtPy]^+[BF_4]^-$

Tetrafluoroboric acid (30.0 ml, 0.230 mol, 48% solution in water) was slowly added to stirred slurry of silver (I) oxide (26.66g, 0.115 mol) and distilled water (50 ml) in a 400ml beaker at about 45°C. To avoid photodegradation of silver (I) oxide, the reaction mixture was fully covered with aluminum foil. The mixture was stirred continuously until the reaction was completed, as indicated by the formation of a solution. A solution of N-ethyl-pyridinium bromide (43.2 g, 0.230 mol) and distilled water (60 ml) was added to the reaction mixture. As the reaction took place and ionic liquids formed, yellow precipitate of silver (I) bromide became detectable. The mixture was stirred at room temperature for a certain time until no more precipitate formed. Once the stirring was stopped, the precipitate would remain at the bottom of the beaker and the clear water layer remained at the top. Because N-ethyl pyridinium bromide is hygroscopic, silver (I) tetrafluoroborate is generally in excess in the reaction mixture. Therefore, we added 1M solution of N-ethyl pyridinium bromide drop wisely, and stirred to make the fresh milky precipitate to fall down to the bottom. We repeated this step until no more precipitate produced. To ensure that there was no excess N-ethyl pyridinium bromide in the mixture, we added one drop of 1M silver (I) tetrafloroborate solution. If no milky precipitate occurred, we added one drop of 1M N-ethyl pyridinium bromide and stirred for 10 minutes. The solubility of AgBr (5.35×10^{-13} M^2 at 25°C) guarantees that the residue of starting materials in the reaction mixture as little as possible and can be ignored. The yellow precipitate of silver (I) bromide was filtered off, and then the solvent was removed by rotary evaporation under reduced pressure at about 65 °C. The resulting ionic liquid is a colorless liquid (31.1ml, 91%).

$$2HBF_4 + Ag_2O \longrightarrow 2AgBF_4 + H_2O$$

$$[EtPy]^+[Br]^- + AgBF_4 \longrightarrow [EtPy]^+[BF_4]^- + AgBr\downarrow$$

Figure 2.3 Synthesis of $[EtPy]^+[BF_4]^-$ by a two-step reaction

2.2.4 Purification of Ionic Liquids

Any color and/or other impurities, such as unreacted starting materials or residual halide present in the synthesized ionic liquids could be removed by passing ionic liquids through a charcoal column with distilled water (Swartling et al., 2000).

In our synthesis of ionic liquids, we followed Swartling's method and the distilled water was removed by rotary evaporation under reduced pressure at 65 °C. The resulting ionic liquids are put into oven for 24 hours to remove the moisture and ready to use.

2.3 Results and Discussion

2.3.1 Density of Ionic Liquids

The densities of two ionic liquids $[EtPy]^+[BF_4]^-$ and $[EtPy]^+[CF_3COO]^-$ were measured by mass-volume method and shown in Table 2.1.

Table 2.1 Densities of Ionic Liquids Studied (1atm, 20°C)

Ionic Liquid	Experimental(g/ml)	Literature(g/ml)	Reference
$[EtPy]^+[BF_4]^-$	1.311	1.302	Zhao, 2002
$[EtPy]^+[CF_3COO]^-$	1.290	1.273	Zhao, 2002

The data shows our experimental data are slightly higher than those reported earlier. It may be because the improvements promoted the synthetic reactions to proceed completely.

2.3.2 UV-Visible Spectra of Ionic Liquids

UV-visible spectroscopy has been employed to analyze the ionic liquids $[EtPy]^+[CF_3COO]^-$ and $[EtPy]^+[BF_4]^-$. The spectra are shown in Figure 2.4 and 2.5. The main absorption is due to the pyridinium ion at 259.94 nm. Pure ionic liquids show strong absorption below 280 nm, so we dilute the ionic liquids to 0.0002mol/l and compare them to the corresponding reactants at the same concentration.

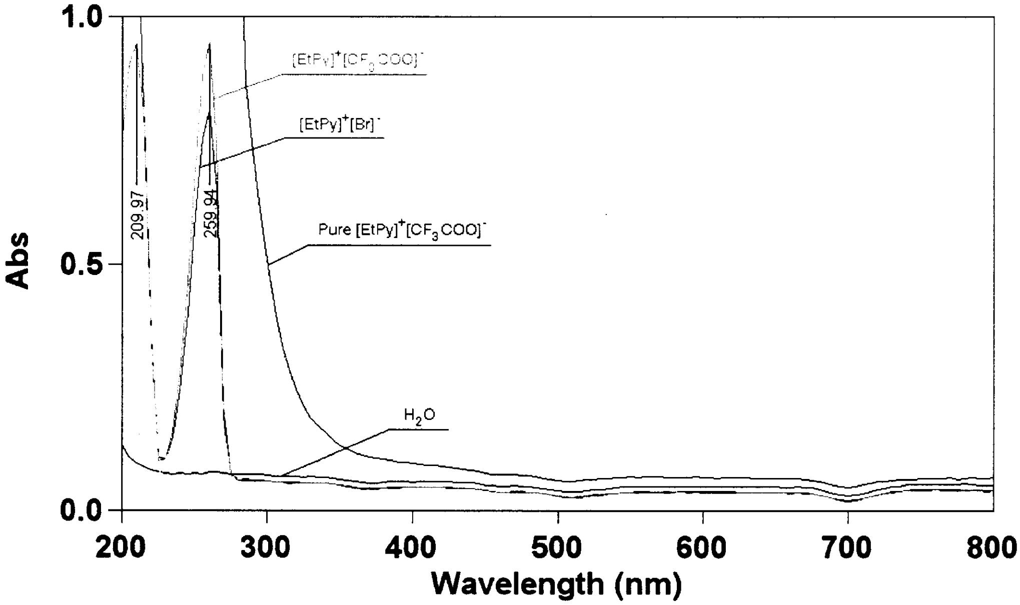


Figure 2.4 UV-Visible Spectra of $[EtPy]^+[CF_3COO]^-$

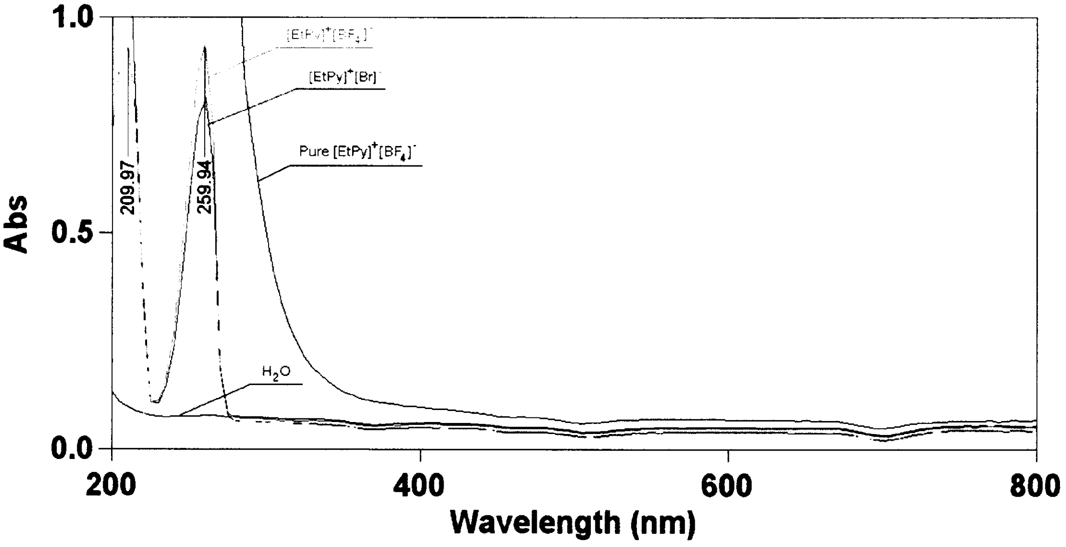


Figure 2.5 UV-Visible Spectra of $[EtPy]^+[BF_4]^-$

It should be mentioned that at the same concentration, the peak at 259.94 nm of $[EtPy]^+[CF_3COO]^-/[EtPy]^+[BF_4]^-$ is slightly higher than $[EtPy]^+[Br]^-$. The reason for this may be twofold: 1) $[EtPy]^+[Br]^-$ is hygroscopic which tends to lower the concentration in experiment process; 2) the impact effect of different anions.

A comparison of Figure 2.4 and Figure 2.5 shows the peak at 209.97 nm may be attributed to the anions in ionic liquids. However, the real reason for the first peak is still unknown.

Even though they have different anions, when we compared the two ionic liquids $[EtPy]^+[BF_4]^-$ and $[EtPy]^+[CF_3COO]^-$, we found they had similar absorption strength at the same position.

2.3.3 IR Spectra of Ionic Liquids

IR spectroscopy technique also has been employed to analyze the ionic liquids. The spectra are shown in Figure 2.6 and Figure 2.7. Note: Nujol was employed as the suspension solvent to "dilute" the pure ionic liquids.

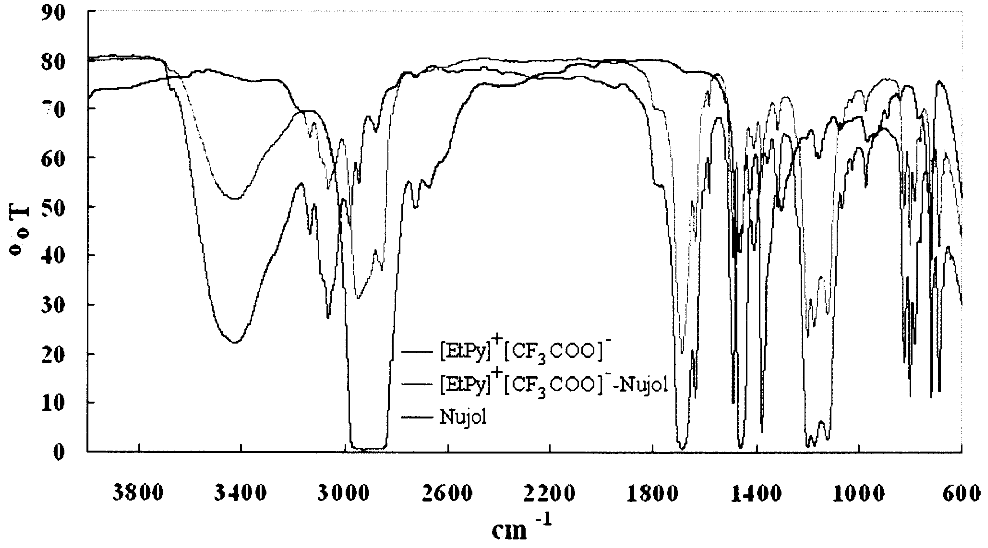


Figure 2.6 IR Spectrum of $[EtPy]^+[CF_3COO]^-$

Table 2.2 Main IR Bands of $[EtPy]^+[CF_3COO]^-$

Peak freq. (cm^{-1})	Band assgnt [a]
3434	H_2O (O-H), str
3136,3065	Ar (C-H), str/b
2985, 2947,2882	Aliphatic (C-H), str
1671,1635,1585	Ar (C-C), str
1490	Ar, str/deform
1415	Me (C-H), b, asym
1358	Me (C-H), b, sym
1320	Ring, b, i, sym
1124,1066	C-H, b, i
974	Ring, b, o
827, 801	Ring, b, i, asym
782	Me (C-H), b
720	Ring, b, o, asym
687	CH_2, b

[a] Abbreviations: str, stretching; b, bending; deform, deformation; i, in plane; o, out of plane; sym, symmetrical; asym, asymmetrical.

C-H stretching vibrations were observed in the region 3200-2000 cm^{-1}. The peaks at > 3000 cm^{-1} can be attributed to the ring C-H stretch, while those at < 3000 cm^{-1} can be attributed to aliphatic C-H stretches. Other bands are listed in Table 2.2 and Table 2.3 (Tait and Osteryoung, 1984).

The anion $[CF_3COO]^-$ is a strong complex anion and participates in strong hydrogen bonding. So the IR spectrum of $[EtPy]^+[CF_3COO]^-$ (Figure 2.6) shows a hydrogen bonding bands in the region 3300-3650 cm^{-1}. However, anion $[BF_4]^-$ is weakly complex and is not expected to participate in strong hydrogen bonding. This has been confirmed by weak hydrogen bonding bands in the region 3500-3650 cm^{-1} in the IR spectrum of $[EtPy]^+[BF_4]^-$ (Figure 2.7).

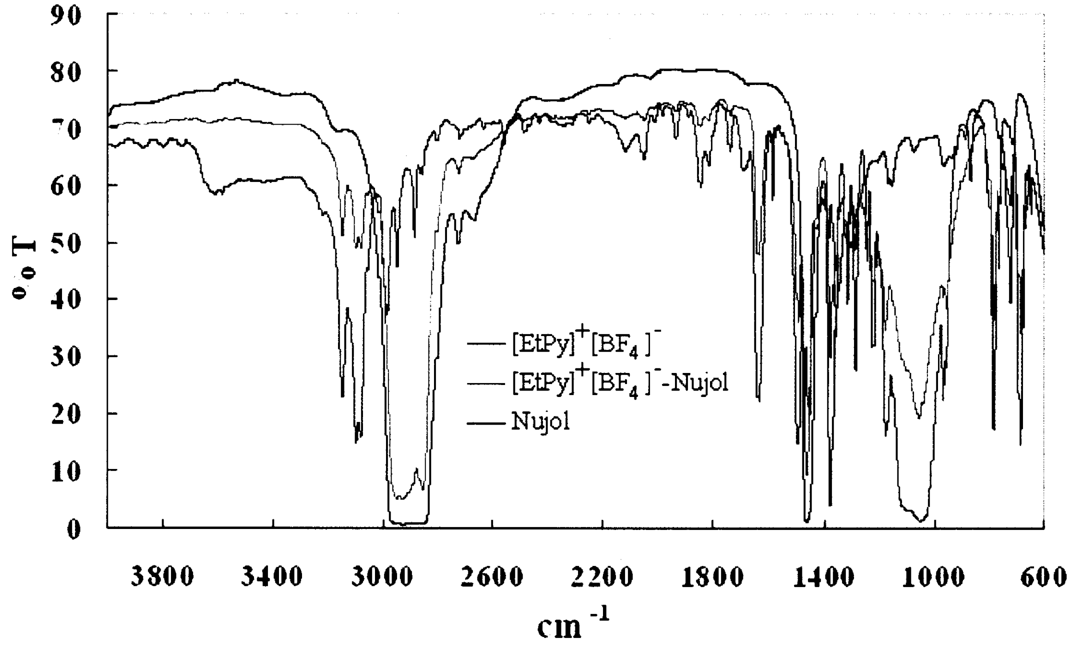


Figure 2.7 IR Spectrum of $[EtPy]^+[BF_4]^-$

Table 2.3 Main IR Bands of $[EtPy]^+[BF_4]^-$

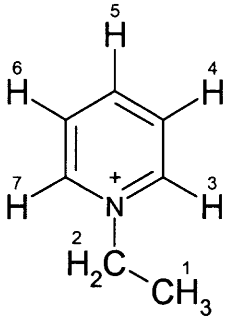
Peak freq. (cm^{-1})	Band assgnt [a]
3609, 3584	H_2O (O-H), str
3145,3099,3082	Ar (C-H), str/b
2986, 2949,2887	Aliphatic (C-H), str
1693, 1638, 1586	Ar (C-C), str
1497	Ar, str/deform
1386	Me (C-H), b, asym
1356	Me (C-H), b, sym
1318, 1287, 1244, 1223	Ring, b, i, sym
1177	Ring, b, i, asym
1051	C-H, b, i
969, 959	Ring, b, o
869, 767	Ring, b, o, asym
787	Me (C-H), b
689	CH_2, b

[a] Abbreviations: str, stretching; b, bending; deform, deformation; i, in plane; o, out of plane; sym, symmetrical; asym, asymmetrical.

2.3.4 NMR Spectra of Ionic Liquids

Both ^{1}H NMR and ^{13}C NMR (300 MHz) were employed to analyze the ionic liquids at room temperature. Note: deuterated water (D_2O) acted as the solvent in this study and its chemical shift was set to 4.73 ppm as a reference in ^{1}H NMR. Methanol was used as the reference in ^{13}C NMR and its chemical shift was set to 49.10 ppm.

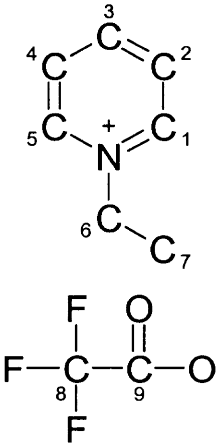
Table 2.4 ^{1}H NMR Chemical Shifts of Ionic Liquids



H Position	Chemical Shift (ppm)		
	$[EtPy]^+Br^-$	$[EtPy]^+[BF_4]^-$	$[EtPy]^+[CF_3COO]^-$
1 (3H)	1.94 (triplet)	1.90 (triplet)	1.24 (triplet)
2 (2H)	5.06 (quartet)	4.92 (quartet)	4.27 (quartet)
3 (1H)	9.38 (doublet)	9.11 (doublet)	8.48 (doublet)
4 (1H)	8.45 (triplet)	8.31 (triplet)	7.68 (triplet)
5 (1H)	8.93 (triplet)	8.80 (triplet)	8.15 (triplet)
6 (1H)	8.45 (triplet)	8.31 (triplet)	7.68 (triplet)
7 (1H)	9.38 (doublet)	9.11 (doublet)	8.48 (doublet)

As can be seen in Figure 2.8, the anions of ionic liquids have an important effect on the ^{1}H NMR spectra. Different anions could influence the electron density and distribution on the pyridinium cation, and thus could change the chemical shifts. Trifluoroacetate anion shows the strongest shielding effect on the chemical shifts of the protons. Therefore, the spectrum of $[EtPy]^+[CF_3COO]^-$.moved to the upfield. All chemical shifts are shown in Table 2.4 and Table 2.5. The ^{13}C NMR spectra of those three ionic liquids are similar to each other (Figure 2.9). The splitting in C_8 is due to Fluorine.

Table 2.5 ^{13}C NMR Chemical Shifts of Ionic Liquids



C Position	Chemical Shift (ppm)		
	[EtPy]$^+$Br$^-$	[EtPy]$^+$[BF$_4$]$^-$	[EtPy]$^+$[CF$_3$COO]$^-$
1	144.24	144.15	144.24
2	128.38	128.45	128.67
3	145.63	145.63	145.85
4	128.38	128.45	128.67
5	144.24	144.15	144.24
6	57.27	57.52	57.68
7	16.46	15.76	15.95
8	-	-	116.41
9	-	-	161.81

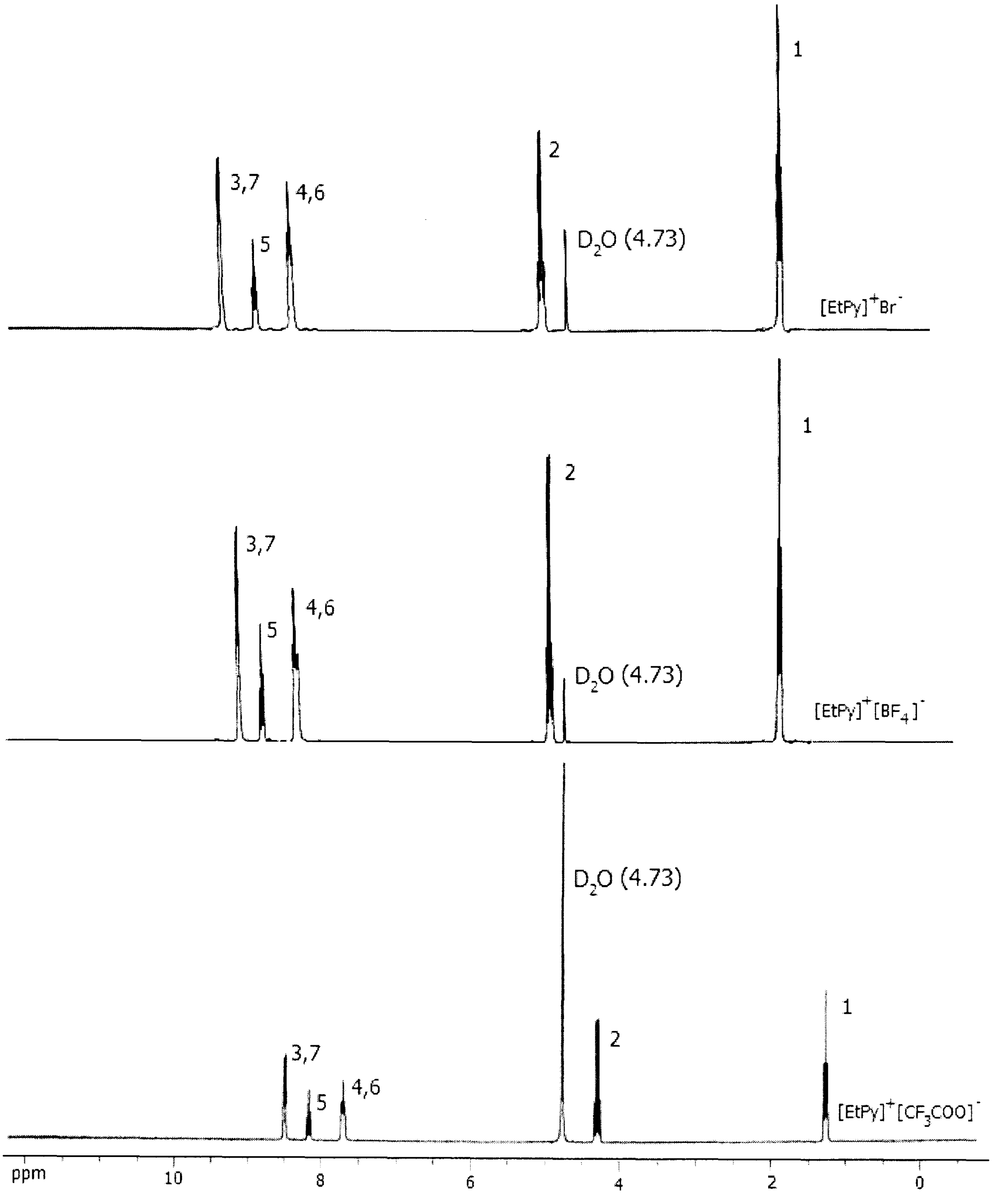


Figure 2.8 ^{1}H NMR spectra of ionic liquids

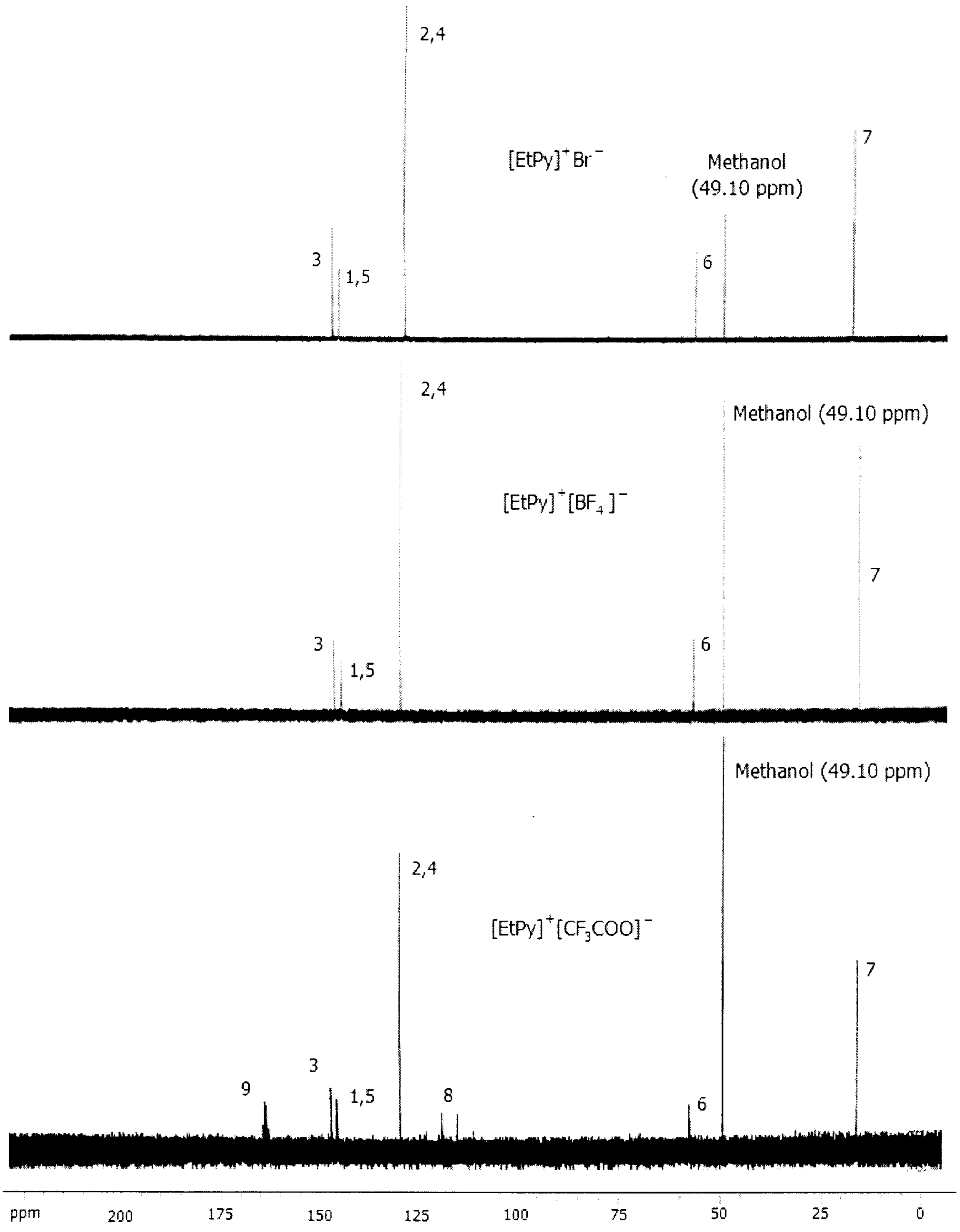


Figure 2.9 ^{13}C NMR spectra of ionic liquids

CHAPTER 3

DIELS-ALDER REACTION

3.1 Background Information

Diels-Alder reaction which is a widely used reaction in organic synthesis (Carey and Sundberg, 2000), and in the chemical industry (Griffiths and Previdoli, 1993) is one of the most important tools for carbon-carbon bond formation. In 1928, two German Chemists, Otto Diels and Kurt Alder, discovered that butadiene reacts vigorously with maleic anhydride to give cis-1, 2, 3, 6-tetrahydrophthalic anhydride (Figure 3.1). The discoverers won the Nobel Prize in 1950 "for their discovery and development of diene synthesis".

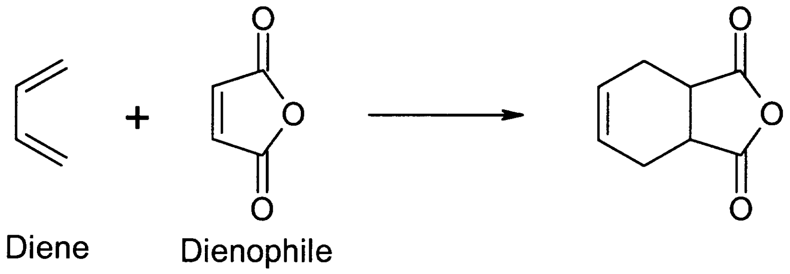
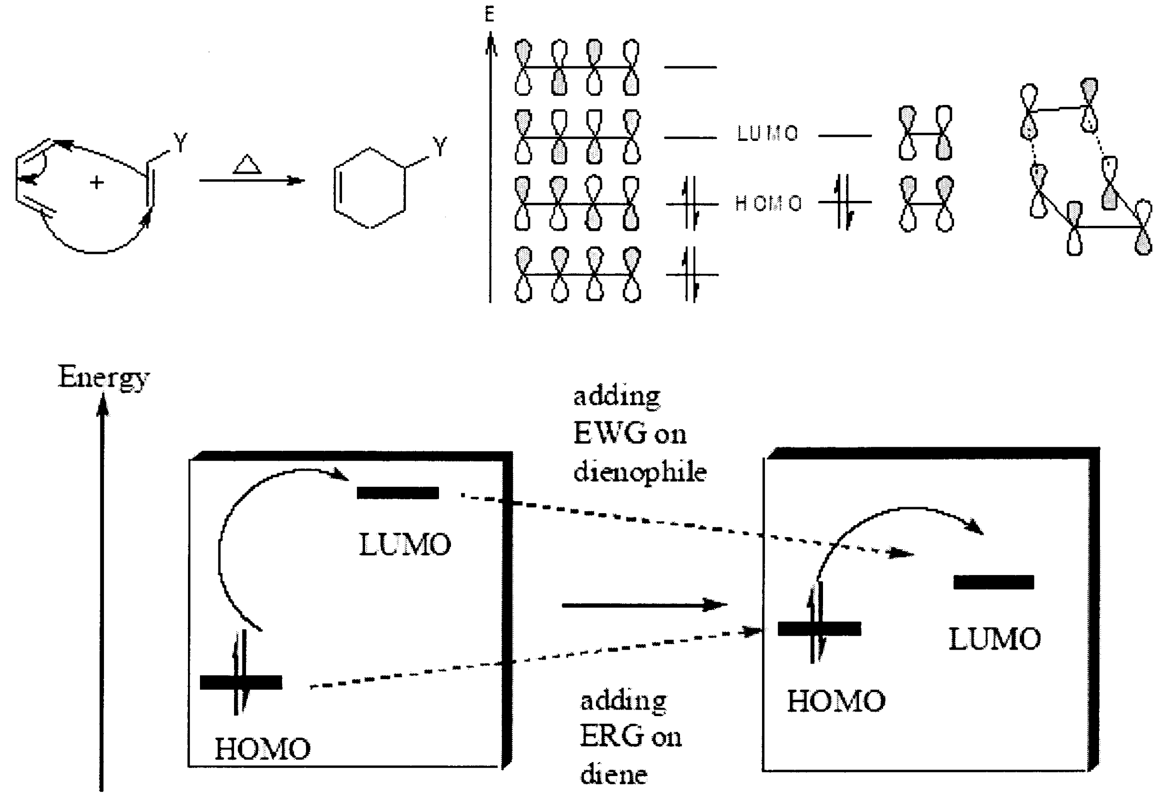


Figure 3.1 First discovered Diels-Alder reaction

Diels-Alder reaction is [4+2]-cycloaddition of a conjugated diene and a dienophile (an electrocyclic reaction that involves the 4 π electrons of the diene and 2 π electrons of the dienophile to form an unsaturated six-member ring). One new π bond and two new σ bonds are formed when the dienophile attacks the diene. The driving force of the reaction is the formation of new σ-bonds, which are thermodynamically more stable than the π bonds. The normal Diels-Alder reaction is favored by electron-withdrawing groups (EWG) on the dienophile and by electron-donating groups (EDG) on the diene. It is because that ERG are "pushing" up the HOMO of diene and EWG are "pushing" down the LUMO of dienophile. Therefore, the energy gap becomes smaller. The consequence of this effect is a dramatic increase in the rate of the cycloaddition. The general mechanism is shown below (Figure 3.2).



Substitution effect on HOMO-LUMO gap

Figure 3.2 General mechanism of simplest Diels-Alder reaction

It is well known that the reactivity and selectivity of Diels-Alder reactions are strongly influenced by the Lewis acidity of the medium. Therefore, the reaction has been investigated using water (Rideout and Breslow, 1980; Breslow et al., 1983), surfactants

(Diego-Castro and Hailes, 1998), lithium amides (Handy et al., 1995), borane-THF complex (Furuta et al., 1988), etcetera. Rate enhancement has been seen in different solvents and catalysts systems as well. Considering the practical importance and wide spectra of applications of Diels-Alder reaction in organic synthesis and the chemical industry, the development of 'green' methods for the purpose of improving rate and selectivity of this reaction has lately received increased attention.

As high polar solvents, ionic liquids have the potential to influence the outcome of Diels-Alder reaction. There have been reports on the usage of ionic liquids for Diels-Alder reactions (Figure 3.3). However, most of these studies have focused only on solvents derived from imidazole. For the pyridinium-based ionic liquids, only N-butyl-pyridinium chloride has been studied and $AlCl_3$ was still needed in the reactions. Herein, we wish to report the first study on the application of N-ethyl-pyridinium-based ionic liquids as a solvent for the Diels-Alder reaction.

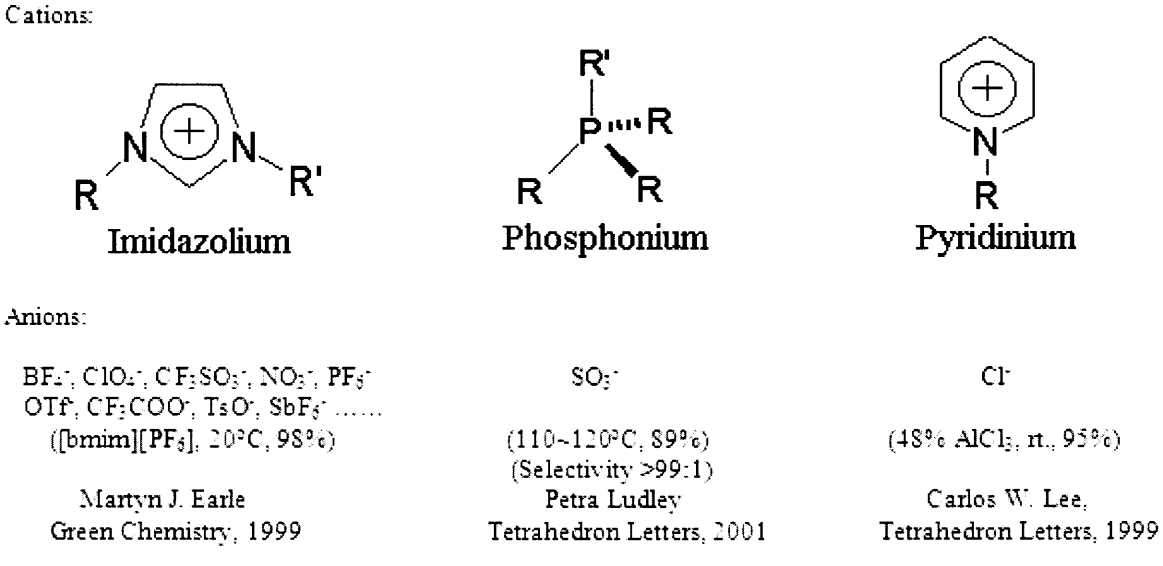


Figure 3.3 Literature examples of Diels-Alder reaction in ionic liquids

3.2 Materials and Methods

3.2.1 Materials

Isoprene, acrylonitrile, acrylic acid, and methacrylic acid were purchased from Sigma Aldrich. Pyridinium-based ionic liquids were prepared in our lab following the procedure in Section 2.2.

3.2.2 General Procedures

Isoprene (60 mmol) was added slowly to a mixture of a dienophile (40 mmol) and an ionic liquid (46 mmol) under argon at room temperature. The biphasic reaction mixture was allowed to stir (400 rpm) at room temperature for the desired time period. After the reaction was over, the mixture was diluted with 3 mL of water and 3 mL of petroleum ether and then was shaken vigorously. The organic layer was separated from the ionic liquid. Any leftover organic material was extracted with ethyl ether and the ionic liquid was dried at 65 °C under vacuum to remove moisture, and purified following the method in Section 2.2.4. It was then reused. The combined organic extracts were first washed with saturated sodium bicarbonate (5 mL), followed by water (5 mL), and finally brine (5 mL). Evaporation under reduced pressure and drying over Na_2SO_4 yielded the products, which passed through flash column chromatography (acetone/petroleum ether 1:25) to give the purified materials (Figure 3.4).

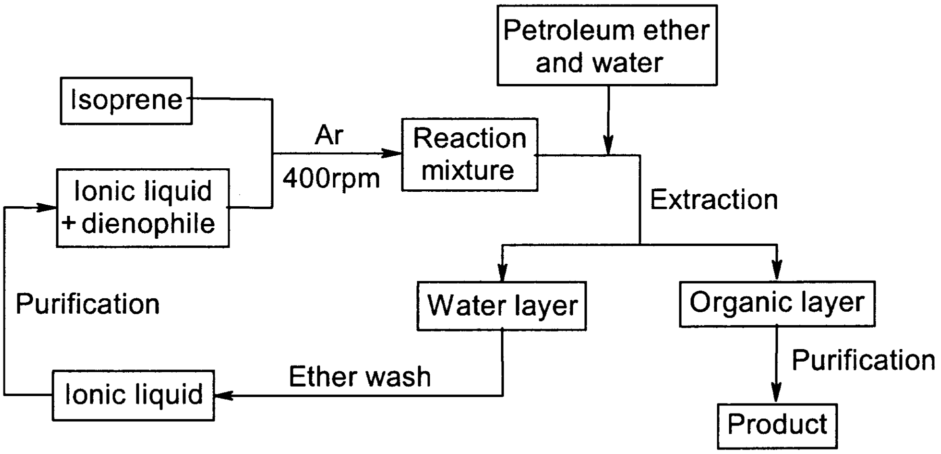


Figure 3.4 Flow chart of Diels-Alder reaction in ionic liquids

3.2.3 Analysis Methods

All reactions were carried out under argon atmosphere. The reaction samples and products were analyzed using a Varian CP-3800 Gas Chromatograph equipped with SPB^{TM}-5 column, 30m × 0.25mm × 0.25μm. The yields of major products were determined by the area ratio of each chromatograph peak as compared with the standard compounds. The ratio of isomers was confirmed by ^{1}H NMR (500 MHz, in $CDCl_3$).

4-Methylcyclohex-3-ene-1-carbonitrile

^{1}H-NMR (500 MHz, $CDCl_3$), δ = 1.30-1.40 (m, 1H), 1.56-1.64 (m, 1H), 1.63 (s, 3H), 1.86-2.06 (m, 2H), 2.18-2.40 (m, 2H), 2.69-2.79 (m, 1H), 5.30 (m, 1H).

3-Methylcyclohex-3-ene-1-carbonitrile

^{1}H-NMR (500 MHz, $CDCl_3$), δ = 1.18-1.27 (m, 1H), 1.47-1.56 (m, 1H), 1.69 (s, 3H), 1.73-1.86 (m, 2H), 2.06-2.18 (m, 2H), 2.79-2.86 (m, 1H), 5.40 (m, 1H).

4-Methylcyclohex-3-ene-1-carboxylic acid

^{1}H-NMR (500 MHz, $CDCl_3$), δ =1.65 (s, 3H), 1.66-1.79 (m, 2H), 1.97-2.06 (m, 2H), 2.20-2.30 (m, 2H), 2.49-2.58 (m, 1H), 5.32-5.44 (m, 1H), 11.96 (s, 1H).

3-Methylcyclohex-3-ene-1-carboxylic acid

^{1}H-NMR (500 MHz, $CDCl_3$), δ = 1.67 (s, 3H), 1.57-1.75 (m, 2H), 1.95-2.16 (m, 2H), 2.58-2.65 (m, 2H), 2.68-2.78 (m, 1H), 4.68-4.72 (m, 1H), 11.96 (s, 1H).

1,4-Dimethylcyclohex-3-ene-1-carboxylic acid

^{1}H-NMR (500 MHz, $CDCl_3$), δ =1.25 (s, 3H), 1.57-1.63 (m, 2H), 1.66 (s, 3H), 2.48-2.56 (m, 4H), 5.69 (m, 1H), 11.41 (s, 1H).

1,3-Dimethylcyclohex-3-ene-1-carboxylic acid

^{1}H-NMR (500 MHz, $CDCl_3$), δ =1.22 (s, 3H), 1.53-1.57 (m, 2H), 1.67 (s, 3H), 2.04-2.12 (m, 2H), 2.41-2.48 (d, 2H), 5.35 (m, 1H), 11.41 (s, 1H).

3.3 Results and Discussion

3.3.1 Effect of Solvent and Reaction Time

The utility of two ionic liquids (scheme 1) namely, 1-ethyl-pyridinium tetrafluoroborate ($[EtPy]^+[BF_4]^-$) and 1-ethyl-pyridinium trifluoroacetate ($[EtPy]^+[CF_3COO]^-$) was investigated in reactions of isoprene **1** with acrylonitrile **2**, acrylic acid **3** and methacrylic acid **4** (Figure 3.5).

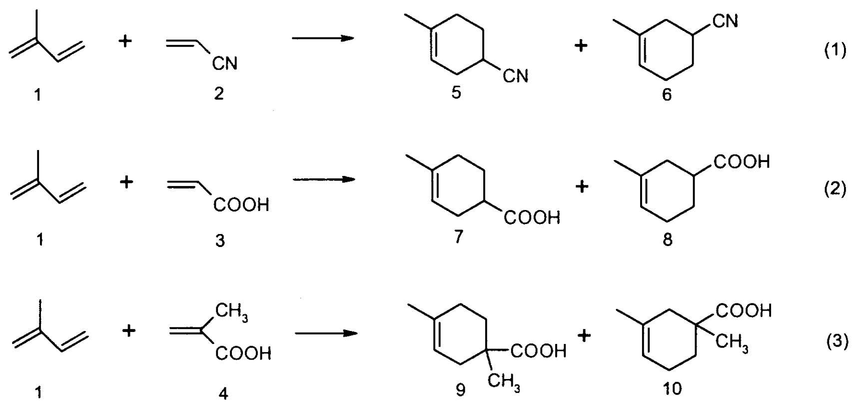


Figure 3.5 Reactions of isoprene with different dienophiles

Table 3.1 Diels-Alder reactions of Isoprene **1** with Dienophiles at 20 °C

Entry	Solvent	Dienophile	Time (h)	Yield[a] (%)	Selectivity[a] ("para like": "meta like")
1	CH_2Cl_2	Acrylonitrile, **2**	72	12	64:36
2[c]	Phosphonium tosylates	Acrylonitrile, **2**	24	38	69:31[b]
3	$[EtPy]^+[CF_3COO]^-$	Acrylonitrile, **2**	2 (24)	90 (97)	89:11[b] (75:25)
4	$[EtPy]^+[CF_3COO]^-$	Acrylonitrile, **2**	72	99	75:25
5	$[EtPy]^+[BF_4]^-$	Acrylonitrile, **2**	2 (24)	42 (64)	84:16[b] (66:34)
6	$[EtPy]^+[BF_4]^-$	Acrylonitrile, **2**	72	83	58:42
7	CH_2Cl_2	Acrylic acid, **3**	72	27	70:30
8[d]	Borane-THF + CH_2Cl_2	Acrylic acid, **3**	30	75	-
9	$[EtPy]^+[CF_3COO]^-$	Acrylic acid, **3**	2 (24)	97 (98)	95:5[b] (85:15)
10	$[EtPy]^+[CF_3COO]^-$	Acrylic acid, **3**	72	98	80:20
11	$[EtPy]^+[BF_4]^-$	Acrylic acid, **3**	2 (24)	32 (50)	82:18[b] (65:35)
12	$[EtPy]^+[BF_4]^-$	Acrylic acid, **3**	72	55	62:38
13	CH_2Cl_2	Methacrylic acid, **4**	72	5	58:42
14[e]	Borane-THF + CH_2Cl_2	Methacrylic acid, **4**	68	66	-
15	$[EtPy]^+[CF_3COO]^-$	Methacrylic acid, **4**	2 (24)	55 (64)	62:38 (54:46)
16	$[EtPy]^+[CF_3COO]^-$	Methacrylic acid, **4**	72	67	1:1[b]
17	$[EtPy]^+[BF_4]^-$	Methacrylic acid, **4**	24	18	66:34
18	$[EtPy]^+[BF_4]^-$	Methacrylic acid, **4**	72	22	55:45[b]

[a] Determined by GC; [b] Ratio determined by 1H NMR; [c] 80°C (Ludley and Karodia, 2001); [d] 0 °C (Furuta et al., 1988); [e] 20°C (Furuta et al., 1988).

In a typical reaction, the diene **1** and dienophile **2, 3, 4** were added to the ionic liquid directly, and the mixture was stirred (400 rpm) at the desired reaction temperature for the specified time period. The molar ratio of isoprene: dienophile: ionic liquid is 1.5:1:1. All reactions are heterogeneous in nature. At the end of the reaction, organic layer could be easily decanted from the ionic liquid, and any organic residues removed by extraction with ethyl ether. The purified ionic liquid was further investigated in experiments for recycling and reuses. As shown in Figure 3.5 (Equations 1-3), both 'para like' (**5, 7, 9**) and 'meta like' (**6, 8, 10**) products were obtained in each case. However, in all cases the major products are 'para like'. Table 3.1 shows the results of reaction of isoprene with various dienophiles at room temperature.

As the data shows, the reaction rate and yields of Diels-Alder reaction are dependent on the solvent. An initial study of reactions carried out in CH_2Cl_2 as solvent gave low product yields (entry 1, 7, 13), thus indicating the need for a polar medium for the reaction. The observations and results of our earlier studies (Zhao, 2002), prompted us to investigate this reaction in pyridinium-based ionic liquids. In a comparison of the results with literature data of reactions using Borane-THF complex (entry 8, 14), improved yields were obtained using ionic liquids in relatively short reaction period. Also, much better yields were obtained using our reaction protocol, compared to the other ionic liquids for the same system reported in the literature (entry 2). When $[EtPy]^+[BF_4]^-$ was used as solvent medium the reaction occurred slowly, but at a relatively faster rate than seen in CH_2Cl_2. The same reactions when carried out in $[EtPy]^+[CF_3COO]^-$, occurred rapidly with much higher product yields. Interestingly, moreover, as the reaction continued beyond 2 hours there was a decrease in 'para/meta like' product ratio, while overall yield of the combined products increased. This was true in the case of all reactions irrespective of the ionic liquid used. This may be indicative of the need of a specific reaction time in order to approach equilibrium. It should also be noted that as an electron donating group, the methyl group makes the methacrylic acid relatively less reactive than acrylic acid. As a result, overall yields are lower than those seen in the case of the reaction with acrylic acid.

Table 3.2 Time Effect on Diels-Alder Reactions of Isoprene **1** with Acrylic Acid **2**

Entry	Solvent	Time (min)	Yield (%)	Selectivity ("para like": "meta like")
1	CH_2Cl_2	20	4	78:22
2		40	8	74:26
3		60	12	71:29
4		80	15	70: 30
5		100	17	70: 30
6		120	19	70: 30
7	$[EtPy]^+[CF_3COO]^-$	20	47	96:4
8		40	70	96:4
9		60	83	96:4
10		80	90	96:4
11		100	94	95:5
12		120	97	95:5
13	$[EtPy]^+[BF_4]^-$	20	12	87:13
14		40	20	86:14
15		60	25	84:16
16		80	28	84:16
17		100	30	83:17
18		120	32	82:18

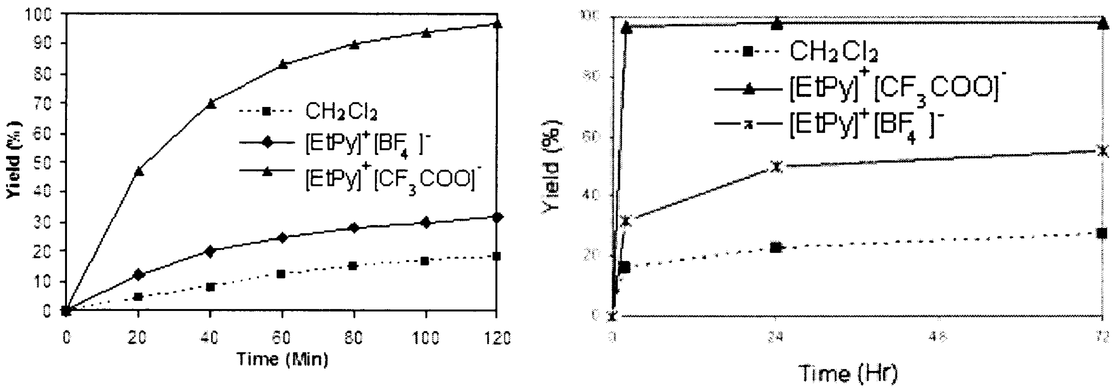


Figure 3.6 Diels-Alder reactions of isoprene with acrylic acid at 20 °C

Table 3.2 and Figure 3.6 show the effect of various solvents on the rate of reaction between isoprene and acrylic acid at 20 °C. Initially, in each solvent, the reaction occurs rapidly and exhibits little change with prolonged time period. Ionic liquid $[EtPy]^+[BF_4]^-$ has an effect in enhancing the rate of reaction. However, $[EtPy]^+[CF_3COO]^-$ seems to be ideal and has the greatest effect on increasing the reaction rate.

The reaction order for the Diels-Alder reaction of isoprene and acrylic acid in $[EtPy]^+[CF_3COO]^-$ has also been explored. In this reaction, the rate law is:

$\text{Rate} = k\,[\text{isoprene}]^a[\text{acrylic acid}]^b[\text{other factors}]^c$

Here k is the rate constant. As these reactions were carried out under the same conditions (with the exception of changing the amount of reactants), the last item in the rate law equation could be considered as a constant. We ran three reactions to determine a and b.

Isoprene: Acrylic acid (The molar ratio) → the overall yield (after 20 minutes)

(1) 1.5 : 1.0 → 47%

(2) 1.0 : 1.0 → 36%

(3) 1.0 : 1.5 → 40%

We assume that the concentrations of reactants remained constant during 20 minutes and the dosage change of the reactants would not impact the total volume of the reaction mixture. Using the data above we substituted the rate and concentrations for each reactions:

$\text{Rate 1} = k\,[1.5/v]^a[1.0/v]^b[\text{other factors}]^c = (0.47/v)/20\text{min}$

$\text{Rate 2} = k\,[1.0/v]^a[1.0/v]^b[\text{other factors}]^c = (0.36/v)/20\text{min}$

$\text{Rate 3} = k\,[1.0/v]^a[1.5/v]^b[\text{other factors}]^c = (0.40/v)/20\text{min}$

Divided the rate 1 equation by rate 2 equation $\rightarrow a = 0.66 \approx 1$;

Divided the rate 2 equation by rate 3 equation → $b = 0.26 \approx 0$.

Therefore, the Diels-Alder reaction of isoprene and acrylic acid in $[EtPy]^+[CF_3COO]^-$ is first order reaction and the experimentally determined rate law for this reaction is

Rate = k[Isoprene]

3.3.2 Effect of Reaction Temperature

We also investigated the effect of temperature on Diels-Alder reaction in ionic liquid $[EtPy]^+[CF_3COO]^-$. These reactions were also carried out at 0 °C and 45 °C. Results are shown in Table 3.3. With a decrease in temperature to 0 °C, the selectivity increased slightly, but the overall yield decreased. On the other hand at 45 °C the rate of reaction was accelerated, while selectivity dropped significantly. There may be two reasons for these results: (1) the amount of by-products increases at higher temperature; (2) increased temperature provides more energy for the reaction to proceed easier on both sides, thus decreasing the selectivity. It is also important to note that at 0 °C and 20 °C, the reactions mixtures were in two phases. On increasing the reaction temperature to 45 °C, the reaction mixture became a homogenous solution.

Table 3.3 Diels-Alder Reactions in $[EtPy]^+[CF_3COO]^-$ at 0 °C and 45 °C

Entry	Dienophile	Time (h)	Temp. (°C)	Yield (%)	Selectivity to main product (%)
1	Acrylic acid	2(24)	0	91(98)	98(90)
2	Acrylic acid	2(24)	45	98(98)	74(56)
3	Acrylonitrile	2(24)	0	81(94)	98(84)
4	Acrylonitrile	2(24)	45	98(98)	67(50)
5	Methacrylic acid	2(24)	0	40(61)	72(60)
6	Methacrylic acid	2(24)	45	62(69)	50(50)

3.3.3 Recycle and Reuse of $[EtPy]^+[CF_3COO]^-$

Finally, we investigated the reusability and efficiency of ionic liquid $[EtPy]^+[CF_3COO]^-$. After the first reaction, the ionic liquid was separated from the organic layer. Any leftover organic material was extracted with ethyl ether and the ionic liquid dried at 65 °C under reduced pressure (Figure 3.7).

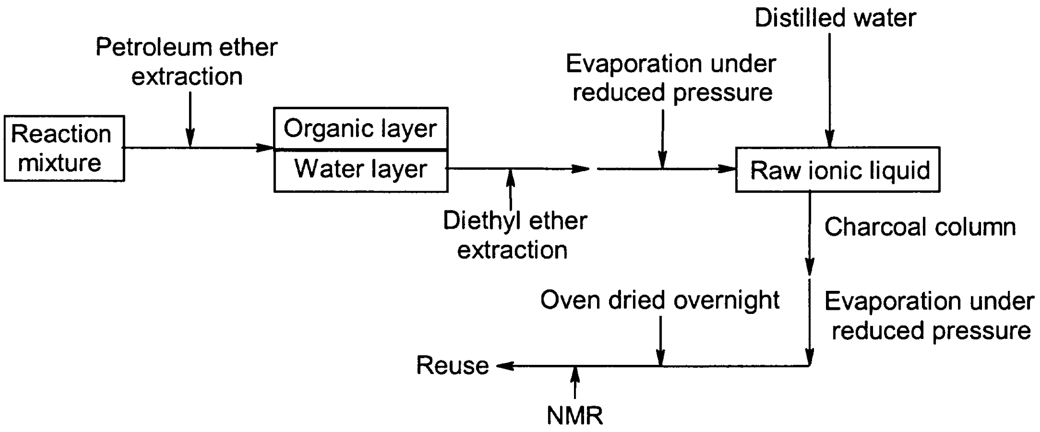


Figure 3.7 Flow chart of recycling process of $[EtPy]^+[CF_3COO]^-$

Successive runs were performed with the recovered ionic liquid $[EtPy]^+[CF_3COO]^-$ for reaction between isoprene and acrylonitrile (Figure 3.5, Equation 1), at 20 °C for 24 hours. As the results in Table 3.4 show, the ionic liquid could be recovered quantitatively and without much loss of activity. This is evident from the fact that the overall product yield of the Diels-Alder reaction is not affected even after six runs with the recovered ionic liquid.

Table 3.4 Recovery and Reuse of $[EtPy]^+[CF_3COO]^-$ in Reaction of Isoprene and Acrylonitrile at 20 °C

Recycling #	Recovered Ionic Liquid Yield (w%)	Overall product Yield (%)
1	96	97
2	97	97
3	95	95
4	96	96
5	97	94
6	96	92

3.4 Proposed Mechanism

The mechanism of Diels-Alder reaction has been subject to much debate. Although a number of successful examples of exploring ionic liquids as solvents to this reaction have been reported, the molecular origin of how ionic liquids influence the well-known Diels-Alder reaction is a matter of controversy. The goal is to provide physical insight into the molecular origin of catalysis and stereoselectivity caused by ionic liquids in order to design new catalytic methods for other cycloaddition reactions. Currently, there are three main ideas on how ionic liquids induce their catalytic effect: (1) high internal pressure, (2) Lewis acid catalysis, (3) a combination of both.

In the 1980's, some researchers reported that polar solvents with salts can increase the association of diene (HOMO) and dienophile (LUMO), e.g., eliminate the HOMO-LUMO gap and therefore enhance the reaction rate (Rideout and Breslow, 1980; Breslow et al., 1983). It was also found that there are three main possible reaction pathways on which the mechanism occurs (Figure 3.8): (1) the concerted synchronous mechanism (The two new bonds are formed simultaneously. In the transition state, these two forming bonds have the same lengths.); (2) non-concerted asynchronous mechanism (The reaction undergoes multistage process. The transition state is a di-radical, one bond being formed, and the other not.); (3) concerted asynchronous mechanism (It is a mixture of first two possible, one bond being more properly formed and thus shorter than the other.). One of these ideas is supported by a kinetic study done by Dewar and Pierini in 1984. Their experiment suggests that the reaction is **concerted** and **synchronous**.

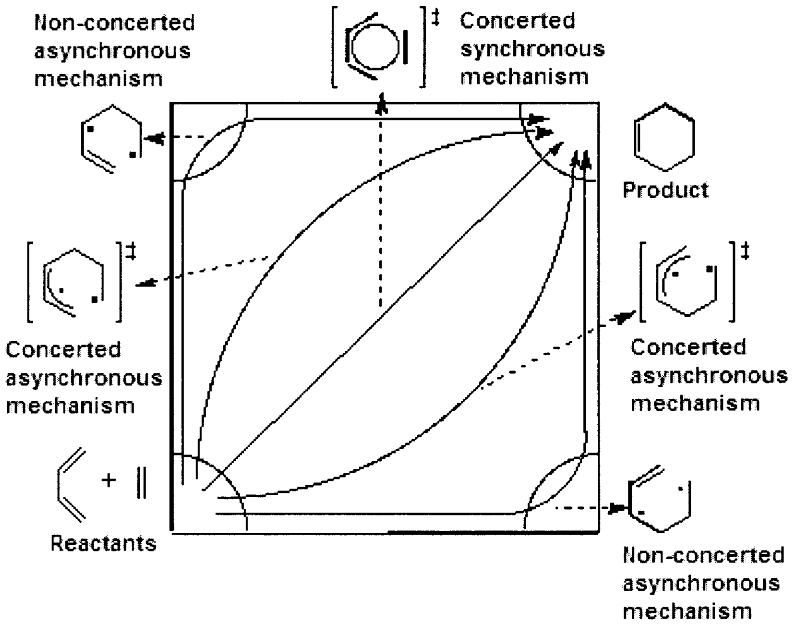


Figure 3.8 More O'Ferral-Jencks diagram of Diels-Alder mechanism

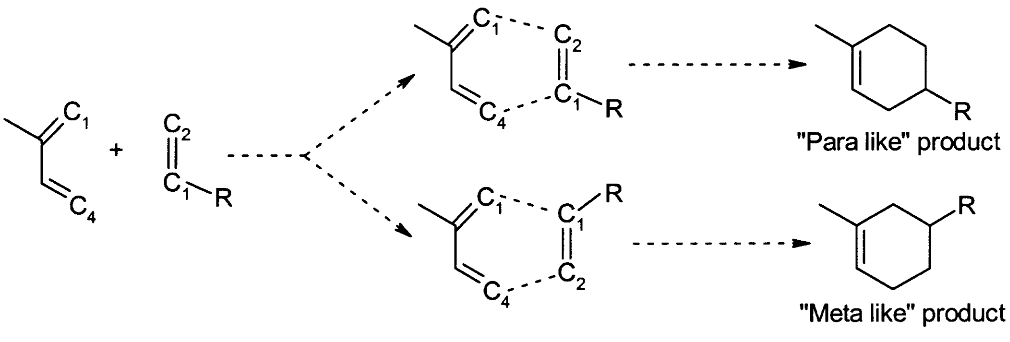


Figure 3.9 The mechanism of Diels-Alder reactions

Based on literature review and our experimental data, we proposed the mechanism of Diels-Alder reactions (Figure 3.9). There are three possible reasons why Diels-Alder reaction can be carried out in ionic liquid. (1) N-ethyl-pyridinium-based ionic liquids are polar solvents, which can stabilize the transition state of Diels-Alder reaction, therefore facilitating the reaction. (2) Both pyridinium-based ionic liquids are Lewis acids, which show catalytic activity in the reaction. (3) Ionic liquids are room temperature molten salts, which can facilitate the Diels-Alder reaction with strong hydrophobic effect (Rideout and Breslow, 1980; Breslow et al., 1983). The experimental data shows that $[EtPy]^+[CF_3COO]^-$ dramatically increases the reaction rate, which is due to its strong Lewis acidity.

3.5 Summary

Our study has shown for the first time that pyridinium-based ionic liquids can be used effectively as solvents in the Diels–Alder reaction. The reaction rate and yield of Diels-Alder reaction are dependent on the solvent used. $[EtPy]^+[CF_3COO]^-$ gives better results in comparison to $[EtPy]^+[BF_4]^-$ and CH_2Cl_2. $[EtPy]^+[CF_3COO]^-$ can be recycled efficiently and reused in the studied Diels-Alder reactions.

CHAPTER 4

FRIEDEL-CRAFTS REACTION

Friedel-Crafts reaction is one of the most useful synthetic methods in organic chemistry. Therefore, research in this field is permanently ongoing and of high interest (Bandini et al., 2004; Olah, 1973). The Friedel-Crafts reaction could be either alkylation or acylation. The reaction is carried out *via* formation of a carbocation in the presence of Lewis acid. The most commonly used catalyst is aluminum chloride. Other Lewis acids such as BF_3, $ZnCl_2$, $TiCl_4$, SbF_5 and $SnCl_4$ can also promote this reaction. Alkylation places an alkyl group on a benzene ring, while acylation introduces an acyl group into a benzene ring by either an acyl halide or an acid anhydride.

As the most commonly used catalyst for Friedel-Craft alkylation, $AlCl_3$ has low solubility in many organic solvents. However, people found it can dissolve in molten salts. The first example of F-C alkylation in molten salts (e.g. $AlCl_3$-NaCl) was reported in the 1950's (Baddeley and Williamson, 1956). It was found that the reaction rate and yield were improved. However, there is a problem: NaCl has a high melting point, which leads to high reaction temperature correspondingly. Therefore, side reactions and decomposition could happen more frequently than in the cases with a lower reaction temperature. Room temperature ionic liquids, however, can solve this problem.

4.1 Friedel-Crafts Alkylation

4.1.1 Background Information

Friedel-Crafts alkylation of benzene with alkyl halides in the presence of aluminum chloride was discovered by Charles Friedel and James M. Crafts in 1877. Alkyl halides by themselves are insufficiently electrophilic to react with benzene. A Lewis acid catalyst, such as aluminum chloride, could enhance the electrophilicity of an alkylating agent by complexing the halide and forming a carbocation. Subsequently, the electrophilic C^+ attacks the benzene ring. This step destroys the aromatic ring and creates a cyclohexadienyl cation intermediate. Finally, the deprotonation of the intermediate generates the products. A general mechanism of alkylation is shown in Figure 4.1 (Carey and Sundberg, 2000).

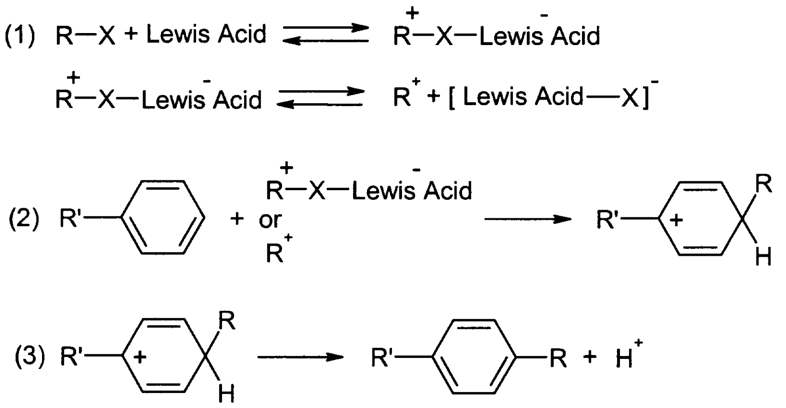


Figure 4.1 General mechanism of Friedel-Crafts alkylation

The overall transformation of Friedel-Crafts alkylation introduces an alkyl group on an aromatic ring. However, the process has disadvantages, such as the formation of aluminate waste, troublesome product recovery and purification, and the inability to reuse catalysts. There have been some reports on synthesis and improved reaction characteristics of the Friedel-Crafts reactions in ionic liquids (Zhao et al., 2005; Zhao et al., 2004b; Formentin and Garcia, 2002; Qiao and Deng, 2001; Boon et al., 1986; Decastro et al., 2000). However, all these studies have focused only on the ionic liquids derived from imidazole (Figure 4.2). Pyridinium-based ionic liquids have similar solvation properties as imidazolium-based ionic liquids. However, their application has not been explored for Friedel-Crafts reaction.

Cation:

Catalyst:

$AlCl_3$, $FeCl_3$, $BiCl_3$, Bi_2O_3, $Bi(OTf)_3$ ......

[BMIM]Cl-$AlCl_3$, 0°C, 99% (96%)

Qiao, K and Deng, Y.

J. Mol. Catal. A, 2001.

Anions:

BF_4^-, PF_6^-, SbF_6^-,
OTf^-, TsO^-, Cl^-......

Figure 4.2 Literature example of Friedel-Crafts alkylation in ionic liquids

4.1.2 Materials and Methods

4.1.2.1 Materials

Anhydrous aluminum chloride, iron (III) chloride, benzene, 1-bromopropane, 1-chlorobutane, benzyl chloride were purchased from Sigma Aldrich. Pyridinium-based ionic liquids were prepared in our lab following the procedure in Section 2.2.

4.1.2.2 General Procedures

Each reaction was carried out under N_2 atmosphere in oven-dried glassware. Ionic liquids were dried overnight in oven at 70°C. In a typical reaction, the catalyst, anhydrous $AlCl_3$ or $FeCl_3$ (16 mmol), was slowly added to a pyridinium-based ionic liquid (8 mmol) and the mixture was stirred at 45°C until the catalyst dissolved completely. Benzene **1** (16 mmol) and alkyl halides **2** or **3** or **4** (8 mmol) were directly added to the mixture. This resulted in the formation of two phases: organic layer (upper) and ionic liquid layer (lower). The reaction mixture was stirred (250 rpm) at the desired reaction temperature for four hours. Subsequently, the mixture was diluted with 3 ml of water and 3 ml of petroleum ether and shaken vigorously. The organic layer was separated from the lower layer. Any leftover organic material was extracted with ethyl ether and the ionic liquid was dried at 65 °C under reduced pressure to remove water. And after purification (Section 2.2.4), it was ready to be reused. The combined organic extracts were washed with water (3 mL) followed by brine (3 mL). The evaporation of the solvent under reduced pressure gave the products, which were dried over Na_2SO_4 (Figure 4.3).

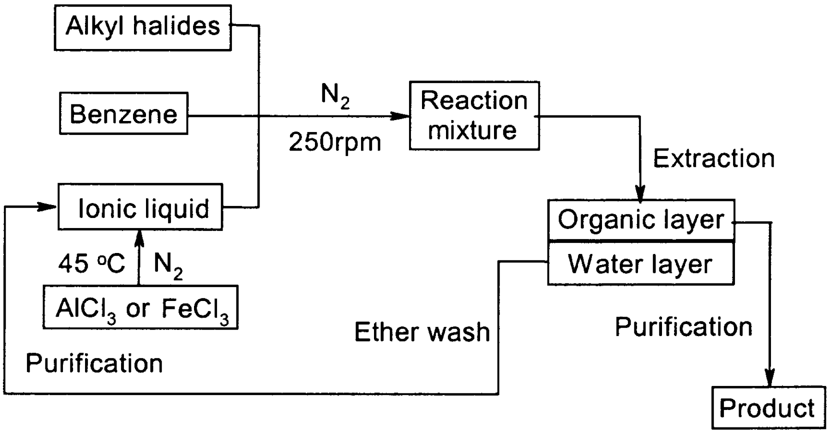


Figure 4.3 Flow chart of Friedel-Crafts alkylation in ionic liquids

4.1.2.3 Analysis Methods

All analyses were carried out by Varian CP-3800 Gas Chromatograph equipped with SPB^{TM}-5 column, 30m × 0.25mm × 0.25μm. The conversion and selectivity were determined by the area ratios of each chromatograph peak compared with the standards.

4.1.3 Results and Discussion

The utility of ionic liquids $[EtPy]^+[CF_3COO]^-$ and $[EtPy]^+[BF_4]^-$ was investigated in alkylation of benzene **1** with 1-bromopropane **2**, 1-chlorobutane **3** and benzyl chloride **4** (Figure 4.4).

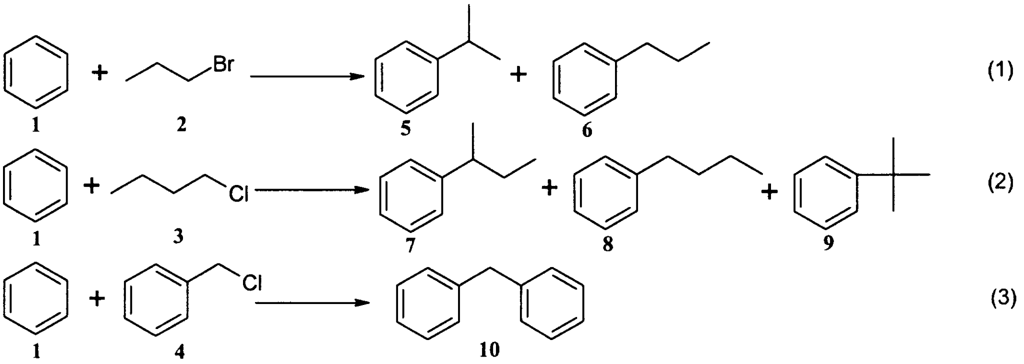


Figure 4.4 Friedel-Crafts alkylation reactions with benzene

4.1.3.1 Alkylation of Benzene with 1-Bromopropane

As shown in Figure 4.4 Equation 1, both *iso*-product (**5**) and *n*- product (**6**) were obtained in the alkylation of benzene and 1-bromopropane. The reaction proceeds *via* the formation of a carbocation intermediate, whose primary propyl cation may undergo a hydride shift to form a more stable cation – isopropyl cation. Therefore, the major product in each case is *iso*-propylbenzene. Table 4.1 shows the results of reaction of benzene with 1-bromopropane in different metal chloride-ionic liquid systems at room temperature and at 50°C.

Table 4.1 The Friedel-Crafts Alkylation of Benzene **1** with 1-Bromopropane **2**[a]

Entry	Catalyst-Solvent	Conv.(%) rt (50°C)	Selectivity to major product (%)
1	$[EtPy]^+[BF_4]^-$	17 (43)	65 (72)
2	$[EtPy]^+[CF_3COO]^-$	29 (51)	71 (76)
3	$AlCl_3$-$[EtPy]^+[BF_4]^-$	60 (81)	75 (84)
4	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	72 (91)	78 (93)
5	$FeCl_3$-$[EtPy]^+[BF_4]^-$	56 (80)	74 (81)
6	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	71 (90)	77 (89)

[a] Molar ration of benzene: 1-bromopropane: catalyst: IL = 2: 1: 2: 1.

As the data shows, the yields of Friedel-Crafts alkylation are dependent on the catalyst-solvent composition. An important outcome of our initial studies was that the reaction occurred in ionic liquids even in the absence of a catalyst (entries 1 and 2). This is due to the Lewis acidity of ionic liquids. However, the low conversions indicated the need for a catalyst to enhance this reaction. A comparison of the results of aluminum chloride (considered environmental hazardous) with iron chloride, shows the same catalytic activity. This demonstrated that the $FeCl_3$-IL system could efficiently replace $AlCl_3$-IL in the Friedel-Crafts alkylations. Also, a comparative study at two different temperatures (room temperature and 50°C) showed that higher product conversion and selectivity are obtained with increased temperature. This could be because increased temperature prefers thermodynamically stable 2^o cation i.e., *iso*-propyl carbocation compared to 1^o cation. However, further increasing the temperature to 75°C resulted in decreased yield and selectivity of the desired product, and some unidentified byproducts were formed. In all cases, the results with $[EtPy]^+[CF_3COO]^-$ are better than those with

$[EtPy]^+[BF_4]^-$ even though they have the same cation, which indicates the anions of ionic liquids are critical for the reactions. $FeCl_3$-$[EtPy]^+[CF_3COO]^-$ gave the best performance in the Friedel-Crafts alkylation and it is much more friendly to the environment compared with aluminum chloride.

In order to investigate the catalytic activity of $FeCl_3$-IL system, reactions with various amounts of $FeCl_3$ were studied with different ionic liquids compositions in the Friedel-Crafts reactions of benzene and bromopropane at room temperature for four hours. We kept the molar ratio of benzene: bromopropane: ionic liquid is 2:1:1 as a constant and changed the quantity of $FeCl_3$. The $FeCl_3$-IL systems were studied separately in two different pyridinium-based ionic liquids. The results are summarized in Figure 4.5.

Bezene:1-Bromo-propane:IL:$FeCl_3$ (molar ratio)	$[EtPy]^+$ $[BF_4]^-$	$[EtPy]^+$ $[CF_3COO]^-$
	Conv. (%)	
2:1:1:0	17	29
2:1:1:0.5	22	37
2:1:1:1	35	60
2:1:1:2	56	71
2:1:1:3	58	71

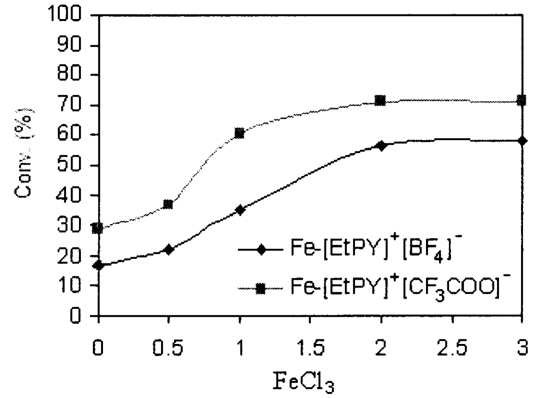


Figure 4.5 Alkylation of benzene and 1-bromopropane with different amounts of $FeCl_3$

Figure 4.5 shows that better results are obtained with larger amount of $FeCl_3$. However, when the quantity of $FeCl_3$ is more than 2 equivalent of ionic liquid, the catalytic activity does not change any more. Similar descriptions have also been reported by others (Boon et al., 1986; Decastro et al., 2000). Therefore, reactions of benzene with other alky halides were studied with 2 equiv. $FeCl_3$.

4.1.3.2 Alkylation of Benzene with 1-Chlorobutane

Results of alkylation of benzene with 1-Chlorobutane in different metal chloride-ionic liquid systems are shown in Table 4.2. As Equation 2 in Figure 4.4 shows, '*sec*-' (7), '*n*-' (8) and '*tert*-' (9) products were obtained in this reaction. We would expect *tert*-butylbenzene, thermodynamically the most stable of the three, to be the major product. However, interestingly *sec*-butylbenzene is the major product.

Table 4.2 The Friedel-Crafts Alkylation of Benzene **1** with 1-Chlorobutane **3**

Entry	Catalyst-Solvent	Conv.(%) rt (50°C)	Selectivity to major product (%)
1	$[EtPy]^+[BF_4]^-$	21 (45)	66 (75)
2	$[EtPy]^+[CF_3COO]^-$	34 (55)	76 (80)
3	$AlCl_3$-$[EtPy]^+[BF_4]^-$	68 (87)	76 (88)
4	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	77 (96)	81 (93)
5	$FeCl_3$-$[EtPy]^+[BF_4]^-$	67 (88)	74 (87)
6	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	77 (94)	83 (94)

As Table 4.2 shows, slightly better conversions and product selectivities are obtained compared to the reaction of benzene with 1-bromopropane (Table 4.1). This could be because Cl^- is more electronegative than Br^- resulting in enhanced electrophilicity of the intermediate carbocation thereby promoting the reactions. Comparable results are obtained in $AlCl_3$-IL and $FeCl_3$-IL systems. In the reactions with 1-Chlorobutane, higher conversions are observed at 50°C. Also, $[EtPy]^+[CF_3COO]^-$ turns out to be a better medium than $[EtPy]^+[BF_4]^-$, which also indicates the anions of ionic liquids are important for the reactions. One interesting thing, we note, is when we raise the temperature, the selectivity to *sec*-butylbenzene also increases, which seems to be in contrast with the general mechanism of the reactions. So far, unfortunately, we do not know the reasons, and further investigation is underway.

4.1.3.3 Alkylation of Benzene with Benzyl Chloride

Table 4.3 shows the results of alkylation of benzene with benzyl chloride at different temperatures, catalysts and solvent conditions. In this reaction, the product conversion decreased significantly compared to previous cases. The decreased reactivity could be due to bulkier size of the benzyl chloride.

Table 4.3 The Friedel-Crafts Alkylation of Benzene **1** with Benzyl chloride **4**

Entry	Catalyst-Solvent	Conv.(%) rt (50°C)
1	$[EtPy]^+[BF_4]^-$	<1 (6)
2	$[EtPy]^+[CF_3COO]^-$	<1 (12)
3	$AlCl_3$-$[EtPy]^+[BF_4]^-$	21 (47)
4	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	35 (59)
5	$FeCl_3$-$[EtPy]^+[BF_4]^-$	20 (44)
6	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	33 (56)

Here again, the metal chloride-ionic liquid system still shows better results than the pure IL. Also, in all cases, results with $[EtPy]^+[CF_3COO]^-$ are better than those with $[EtPy]^+[BF_4]^-$. Both $FeCl_3$-IL and $AlCl_3$-IL systems show comparable efficiency.

4.1.3.4 Recycle and Reuse of Ionic Liquids

We investigated the reusability and efficiency of ionic liquids with or without catalysts. The recycling process involved washing the used ionic liquids with diethyl ether. Any organic residue left in the ionic liquid layer could be separated by the ether wash. The ionic liquid layer was then separated and dried under reduced pressure at 65°C (Figure 4.6).

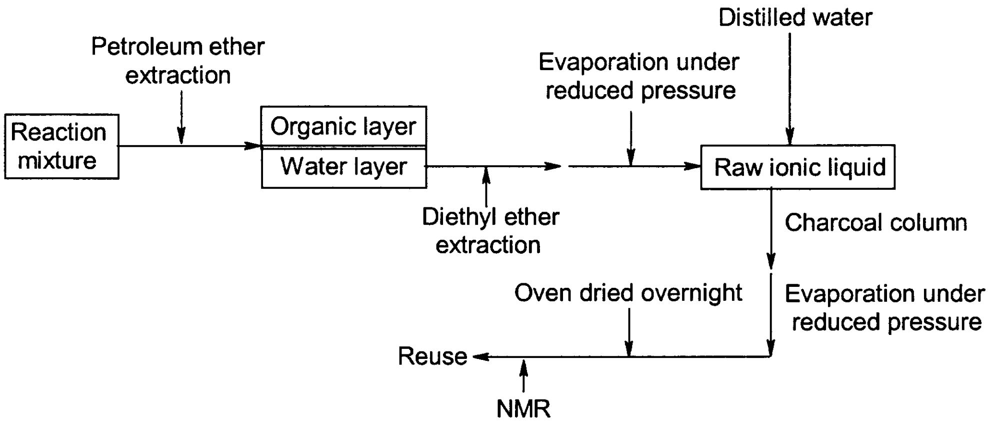


Figure 4.6 Flow chart of recycling process of ionic liquids

Successive runs were performed with the recovered ionic liquid $[EtPy]^+[BF_4]^-$ or $[EtPy]^+[CF_3COO]^-$ for the alkylation between benzene and 1-chlorobutane (Figure 4.4, Equation 2) at 50°C for four hours.

Table 4.4 Recycling of Ionic Liquids in the Alkylation of Benzene and 1-Chlorobutane

Recycling #	$[EtPy]^+[BF_4]^-$		$[EtPy]^+[CF_3COO]^-$	
	Recovered (w%)	Conv. (%)	Recovered (w%)	Conv. (%)
0	-	45 (75)	-	55 (80)
1	94	43 (73)	93	53 (75)
2	92	44 (74)	92	51 (78)
3	93	41 (72)	93	50 (76)

As the results in Table 4.4 show, both ionic liquids could be recovered quantitatively and almost without loss of activity and selectivity. This is evident from the fact that the conversion of the Friedel-Crafts alkylations was not affected even after the third run with the recovered ionic liquid. However, yields of the ionic liquid recovery from the used iron chloride-ionic liquid system (Figure 4.7) were relatively low.

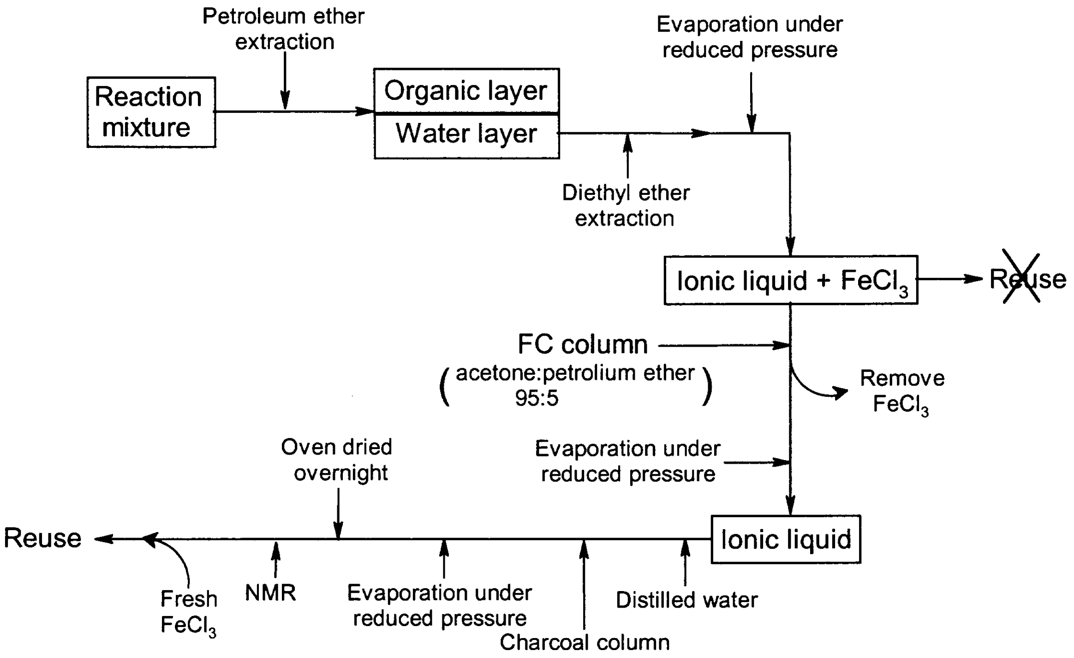


Figure 4.7 Flow chart of recycling process of iron chloride-ionic liquid system

Table 4.5 Recycling of ILs-$FeCl_3$ in the Alkylation of Benzene and 1-Chlorobutane

Recycling #	$FeCl_3$-$[EtPy]^+[BF_4]^-$		$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	
	Recovered (w%)	Conv. (%)	Recovered (w%)	Conv. (%)
0	-	88 (87)	-	94 (94)
1	88	75 (84)	90	82 (92)
2	85	67 (83)	86	76 (90)
3	89	65 (81)	87	75 (91)

As can be seen in Table 4.5, although the ionic liquids in $FeCl_3$-IL system can be recovered efficiently, the conversion dropped dramatically even with fresh $FeCl_3$. This may be due to some impurities in recovered ionic liquids. On the other hand, product selectivity remained nearly the same.

4.1.4 Proposed Mechanism

Our experimental data shows that pyridinium-based room temperature ionic liquids ($[EtPy]^+[BF_4]^-$ and $[EtPy]^+[CF_3COO]^-$) are good solvents for the Friedel-Crafts alkylation reaction. Based on the classical mechanism of alkylation (Figure 4.1), we propose the following mechanism in IL-MCl_3 (M = Al or Fe) catalysis system (Figure 4.8).

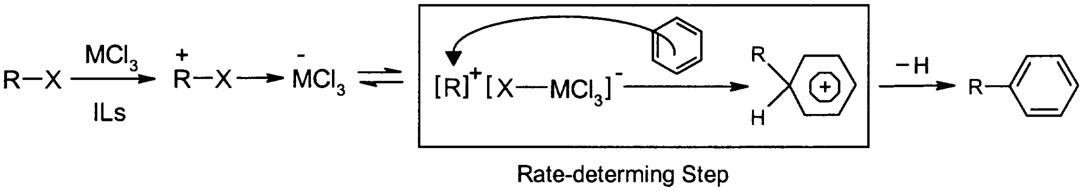


Figure 4.8 Proposed mechanism of Friedel-Crafts alkylation

We found that the rate of this reaction is significantly enhanced in ionic liquids compared to organic solvents (Ross and Xiao, 2002). This enhanced rate of the reactions might be caused by lowering the activation energy of the rate-determine step. Mainly, there are five possible reasons why Friedel-Crafts alkylation can be carried out in ionic liquids. (1) Ionic liquids are high polar solvents. (2) They are Lewis acids. (3) They exhibit an hydrophobic effect. (4) $AlCl_3$/$FeCl_3$ can be dissolved in ionic liquids. (5) They are room temperature molten salts.

In 1986, Boon et al. found that Friedel-Crafts reaction is dependent on the concentration of Lewis acid. For $AlCl_3$ catalysis system, it depends on the concentration of the $[Al_2Cl_7]^-$ ion, which is acting as the Lewis acid in the reaction. Therefore, excess $AlCl_3$ (2 equiv.) in ionic liquids will increase the concentration of $[Al_2Cl_7]^-$ in the $AlCl_3$-rich environment. Furthermore, the product could be easily extracted by petroleum ether, indicating that the product did not combine with the catalyst. This further indicates ionic liquids could be the potential alternatives of conventional organic solvents in Friedel-Crafts reaction.

4.1.5 Summary

The pyridinium-based ionic liquids are suitable media for Friedel-Crafts alkylation of benzene. The reactions proceed not only at a better rate but also at relatively lower temperature, yielding a high product conversion. The $[EtPy]^+[CF_3COO]^-$-$FeCl_3$ was found to be the best catalysis system which can efficiently substitute the aluminum catalysis system. High selectivity is obtained at 50°C. However, $[EtPy]^+[CF_3COO]^-$-$FeCl_3$ cannot be recycled and reused as efficiently as $[EtPy]^+[CF_3COO]^-$.

4.2 Friedel-Crafts Acylation Reactions

4.2.1 Background Information

The Friedel-Crafts acylation of aromatic compounds is an important method for the synthesis of aromatic ketones (Olah, 1973). This method has been widely used in the synthesis of pharmaceuticals, fine chemicals and polymers (Kozhevnikov, 2003; Metivier, 2001; Wan et al., 2001; Spagnol et al., 1996). It is a very effective way of attaching a hydrocarbon-based group to an aromatic ring. An example is the acylation of benzene with acetyl chloride to form the acetophenone, which is an important and useful intermediate for further transformations. Although the overall transformation is Ar-H to Ar-COR (a ketone), it is easily converted into other functional groups. For example, the carbon-oxygen double bond can be reduced to give a secondary alcohol, which is an important starting material in chemical and pharmaceutical industries.

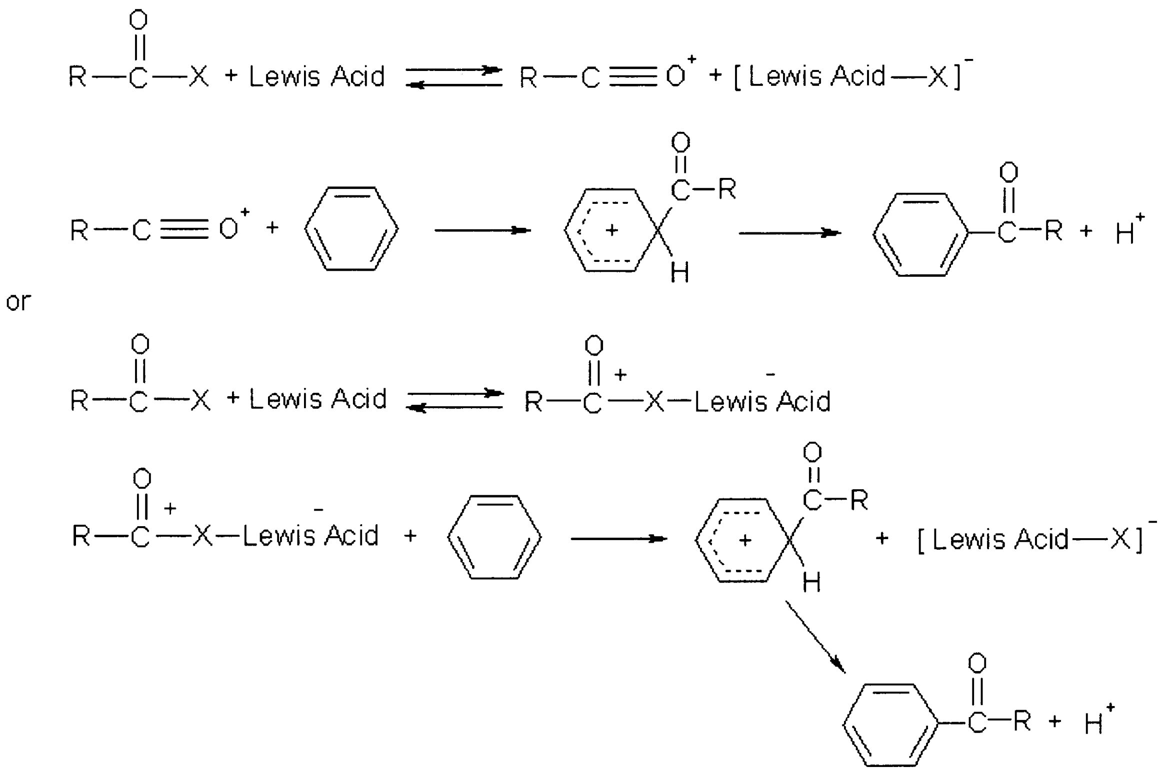


Figure 4.9 General mechanism of Friedel-Crafts acylation

The acylation reaction involves the substitution by an acyl group, RCO- , which is derived from a carboxylic acid derivative, usually an acyl halide or anhydride. The carbonyl group in such acid derivatives is sufficiently basic that formation of a complex occurs with strong Lewis acids. A general mechanism is shown in Figure 4.9 (Carey and Sundberg, 2000). The acylating reagent reacts with the Lewis acid to form a discrete positively charged acylium (or oxocarbonium) ion, which acts as the electrophile, or the active electrophile could be a complex formed by the acylating reagent and Lewis acid catalyst. Then the electrons of the aromatic **C=C** act as a nucleophile, attacking the electrophile. This step destroys the aromaticity giving the reforms in the **C=C** and the aromatic system and regenerating the active catalyst. It places an acyl group on a benzene ring. Generally, Lewis acids such as BF_3, $ZnCl_2$, $TiCl_4$, SbF_5, etcetera, could promote this reaction; however, $AlCl_3$ still is most common used catalyst. Although, this reaction is widely applied in industry, there are some disadvantages such as long reaction time, troublesome product recovery and purification, catalysts which cannot be reused, and the formation of environmentally hazardous and corrosive aluminate waste. In contrast, very few examples are reported in the literature where $FeCl_3$, an environmentally favorable catalyst is applied for this reaction (Dufang, 1991; Yamamoto et al., 1993).

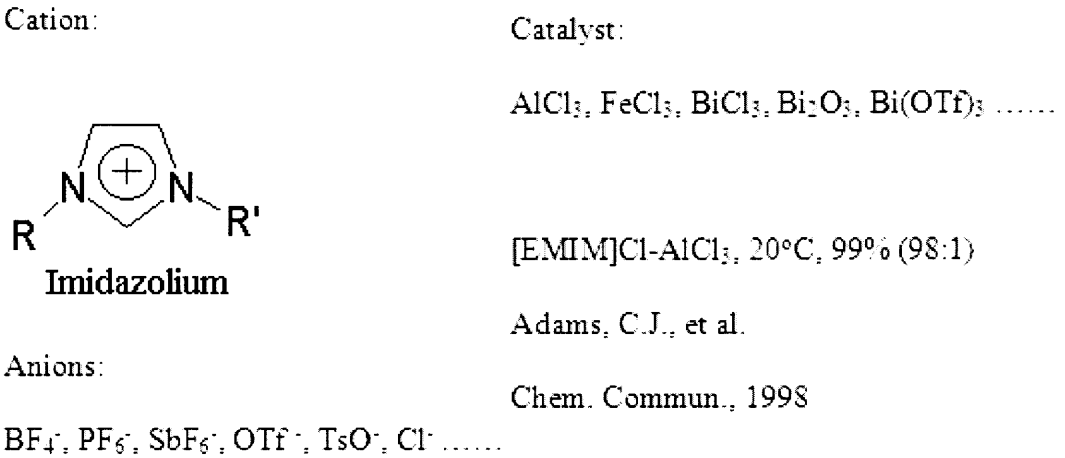


Figure 4.10 Literature example of Friedel-Crafts acylation in ionic liquids

There are examples reporting clean synthesis and improved reaction characteristics of the Friedel-Crafts acylation reactions in ionic liquids (Csihony et al., 2001; Gmouh et al., 2003; Yeung et al., 2002; Ross and Xiao, 2002; Valkenberg et al., 2001; Earle et al., 1998; Csihony et al., 2002). The conversion and selectivity of the reaction in these studies vary with the catalysts, substrates and reaction conditions. Also, all of these studies have focused only on the imidazolium-based ionic liquids (Figure 4.10). Encouraged by earlier successful investigations with pyridinium-based ionic liquids (Zhao, 2002), we embarked on the study of Friedel-Crafts acylation in these solvents. Herein, we wish to report the results of this first study on the Friedel-Crafts acylation using pyridinium-based ionic liquids as solvents.

4.2.2 Materials and Methods

4.2.2.1 Materials

Anhydrous aluminum chloride, iron (III) chloride, acetic anhydride, benzene, toluene, and bromobenzene were purchased from Sigma Aldrich. Pyridinium-based ionic liquids were prepared in our lab following the procedure in Section 2.2.

4.2.2.2 General Procedures

In a typical reaction, the reaction was carried out under N_2 atmosphere in oven-dried glassware. Ionic liquids were dried overnight in the oven at 70°C. The catalyst, anhydrous $AlCl_3$ or $FeCl_3$ (16 mmol), was slowly added to a pyridinium-based ionic liquid (8 mmol). The mixture was stirred at 45°C until the catalyst was completely dissolved. Acetic anhydride **1** (8 mmol) was added to the mixture and stirred for 15 minutes then aromatics **2** or **3** or **4** (16 mmol) were added. Two phases were formed and the reaction mixture was allowed to stir (250 rpm) at the desired reaction temperature for four hours. After the reaction was over, the mixture was diluted with 3 mL water and 3 mL petroleum ether and shaken vigorously. The organic layer was separated from ionic liquid. Any leftover organic material was extracted with ethyl ether and the ionic liquid was dried at 65 °C under reduced pressure to remove water. It was then reused after purification. The combined organic extracts were washed with water (3 mL) followed by brine (3 mL). Evaporation under reduced pressure yielded the product and then it was dried over Na_2SO_4 (Figure 4.11).

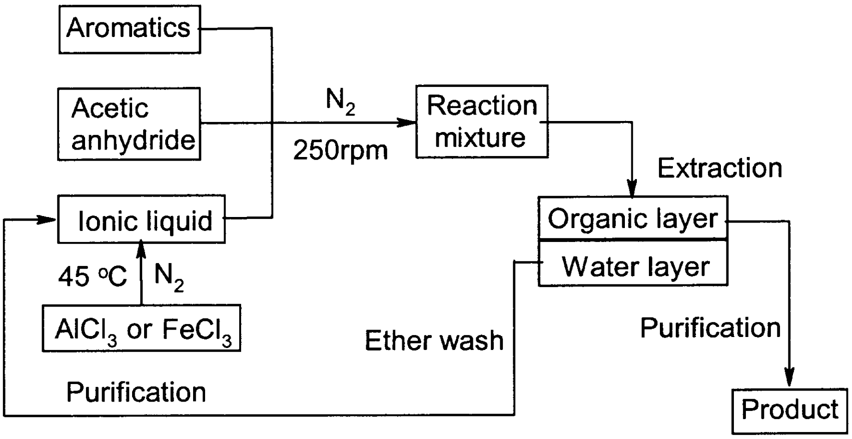


Figure 4.11 Flow chart of Friedel-Crafts acylation in ionic liquids

4.2.2.3 Analysis Methods

All analyses were carried out by using Varian CP-3800 Gas Chromatograph equipped with SPB^{TM}-5 column, 30m × 0.25mm × 0.25μm. The conversion (based on the consumption of acetic anhydride) and the yield of major products were determined by the area ratio of each chromatograph peak as compared with the standard compounds.

4.2.3 Results and Discussion

The utility of ionic liquids $[EtPy]^+[CF_3COO]^-$ and $[EtPy]^+[BF_4]^-$ was investigated in acylation reactions of acetic anhydride **1** with benzene **2**, toluene **3** and bromobenzene **4** (Figure 4.12).

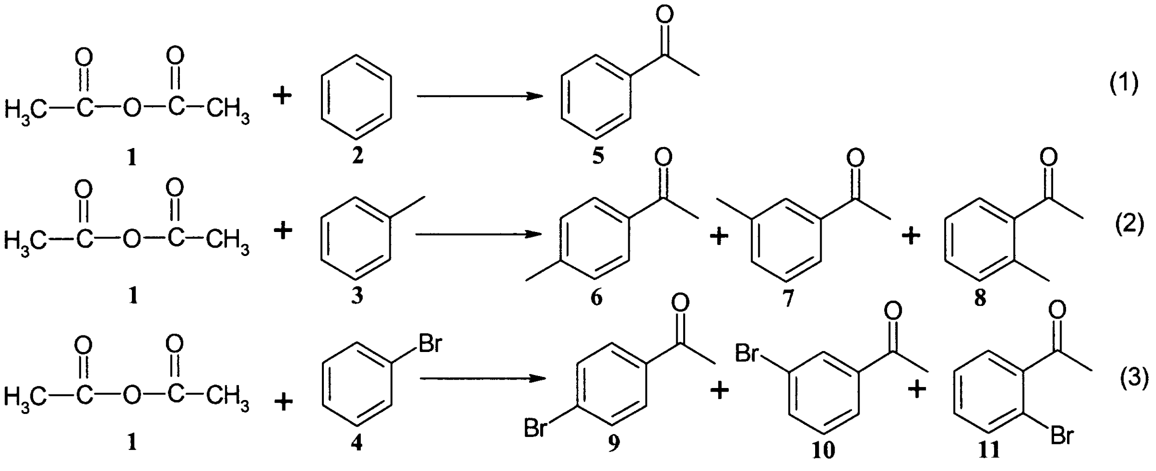


Figure 4.12 Friedel-Crafts acylation reaction with acetic anhydride

In a typical reaction, a specified amount of catalyst (anhydrous $FeCl_3$ or $AlCl_3$) was slowly added to ionic liquid and the mixture was continuously stirred at 45°C until the catalyst was completely dissolved. Acetic anhydride **1** and aromatic compound **2**, **3** or **4** were added directly to the metal chloride-ionic liquid mixture. As a result two phases (ionic liquid and organic) were formed, and the mixture was stirred (250 rpm) at a desired reaction temperature for four hours. The molar ratio of aromatic: acetic anhydride: ionic liquid was maintained at 2:1:1.

4.2.3.1 Acylation of Benzene with Acetic Anhydride

As shown in Figure 4.12 Equation 1, acetophenone was obtained as the major product in acylation of benzene **2** with acetic anhydride **1** in different metal chloride-ionic liquid systems at various temperatures. The results are listed in Table 4.6.

Table 4.6 The Friedel-Crafts Acylation of Acetic Anhydride **1** with Benzene **2**[a]

Entry	Catalyst-Solvent	Conv.(%) rt / 50°C / 75°C	Selectivity to major product (%) rt / 50°C / 75°C
1	$[EtPy]^+[BF_4]^-$	51 / 72 / 78	100 / 97 / 69
2	$[EtPy]^+[CF_3COO]^-$	60 / 77 / 81	100 / 99 / 71
3	$AlCl_3$-$[EtPy]^+[BF_4]^-$	77 / 92 / 94	100 / 96 / 70
4	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	84 / 98 / 99	100 / 99 / 74
5	$FeCl_3$-$[EtPy]^+[BF_4]^-$	73 / 90 / 93	100 / 94 / 73
6	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	82 / 97 / 97	100 / 97 / 75

[a] molar ration of benzene: acetic anhydride: catalyst: IL = 2: 1: 2: 1.

The first important observation here is that a significant amount product formation was seen in ionic liquid medium (entry 1, 2), even in the absence of any catalyst. This renders truly green characteristics to the reaction procedure. Further, as the data shows, the reaction yields are dependent on the catalyst-solvent composition. When the same reaction was carried out in the presence of a catalyst in ionic liquid, the product yields improved. Both $FeCl_3$ and $AlCl_3$ promoted the reaction, giving nearly the same product yield. This suggests that the $FeCl_3$-IL system could efficiently substitute $AlCl_3$-IL system for the Friedel-Crafts acylations. Also, a comparative study at different temperatures (rt, 50°C and 75°C) showed that the product conversions were higher when the reaction temperature was increased to 50°C. However, further increasing the temperature to 75°C resulted in decreased yield of the desired product, and the formation of unidentified byproducts. In all cases, the results with $[EtPy]^+[CF_3COO]^-$ are better than those with $[EtPy]^+[BF_4]^-$ even though they have the same cation. This indicates the anions of ionic liquids are critical for acylation reactions.

In order to find a suitable catalyst amount in the $FeCl_3$-IL system, this reaction was studied with different $FeCl_3$ molar ratios at room temperature for four hours in both ionic liquids. However, the molar ratio of benzene: acetic anhydride: ionic liquid was maintained at 2:1:1. The results are shown in Figure 4.13.

Bezene:Acetic anhydride:IL:$FeCl_3$ (molar ratio)	$[EtPy]^+$ $[BF_4]^-$	$[EtPy]^+$ $[CF_3COO]^-$
	Acetophenone Yield (%)	
2:1:1:0	51	60
2:1:1:0.5	55	69
2:1:1:1	63	78
2:1:1:2	73	82
2:1:1:3	75	83

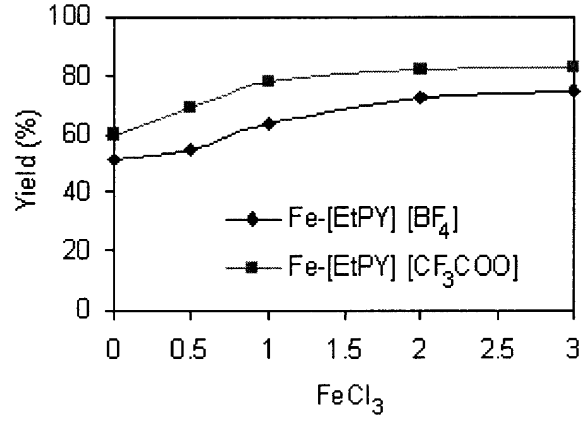


Figure 4.13 The acylation of benzene and acetic anhydride with different amounts of $FeCl_3$

As the data shows, the catalytic activity increases when the amount of $FeCl_3$ is increased to 2 molar equivalents. However, further increasing the molar ratio of $FeCl_3$ to 3 equivalents did not have any significant change in product yields. This optimized $FeCl_3$ amount in ionic liquid, i.e., 2 equivalents, is similar to other studies reported in the literature (Gmouh et al., 2003; Earle et al., 1998). Therefore, further investigations were carried out with these optimized conditions.

4.2.3.2 Acylation of Toluene with Acetic Anhydride

The acylation of toluene (Figure 4.12, eq. 2) resulted in three products, i.e., *para-* (**6**), *meta-* (**7**) and *ortho-*(**8**). The major product of this reaction was the *para*-compound. Results of this reaction in different metal chloride-ionic liquid systems at room temperature and at 50°C are shown in Table 4.7.

Table 4.7 The Friedel-Crafts Acylation of Acetic Anhydride **1** with Toluene **3**

Entry	Catalyst-Solvent	Conv.(%) rt (50°C)	Selectivity to major product (%)
1	$[EtPy]^+[BF_4]^-$	55 (75)	57 (66)
2	$[EtPy]^+[CF_3COO]^-$	62 (80)	61 (72)
3	$AlCl_3$-$[EtPy]^+[BF_4]^-$	77 (89)	63 (70)
4	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	86 (98)	65 (77)
5	$FeCl_3$-$[EtPy]^+[BF_4]^-$	74 (89)	63 (71)
6	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	85 (96)	67 (80)

As Table 4.7 shows, higher conversions were observed with toluene compared to that with benzene at room temperature (Table 4.6). This could be due to the inductive effect of the CH_3- moiety, which increases the reactivity of the phenyl ring in toluene. However, significant amount of *ortho*-product is also formed, which results in reduced overall selectivity. A comparative study at two different temperatures (rt and 50°C) showed that higher product conversions are obtained with increased temperatures. Similar to previous reaction, these results also show that the catalytic activity of $FeCl_3$-IL is comparable with $AlCl_3$-IL system. The ionic liquid $[EtPy]^+[CF_3COO]^-$ has relatively more influence on acylation reaction compared to $[EtPy]^+[BF_4]^-$. Again, it is suggested that the anions of ionic liquid have some influence as well. Therefore, further systematic studies with different anions are required for better understanding of the anion effect.

4.2.3.3 Acylation of Bromobenzene with Acetic Anhydride

As shown in Equation 3 of Figure 4.12, acylation of bromobenzene with acetic anhydride gave three products. In this reaction, *para*-isomer i.e. (*p*-bromobenzene) methyl ketone **9**, was the major product. Similar to previous examples, the reaction was tested in both ionic liquids at two different temperatures. The results are listed in Table 4.8.

Table 4.8 The Friedel-Crafts Acylation of Acetic Anhydride **1** with Bromobenzene **4**

Entry	Catalyst-Solvent	Conv.(%) rt (50°C)	Selectivity to major product (%)
1	$[EtPy]^+[BF_4]^-$	54 (71)	61 (74)
2	$[EtPy]^+[CF_3COO]^-$	63 (77)	69 (82)
3	$AlCl_3$-$[EtPy]^+[BF_4]^-$	76 (86)	73 (86)
4	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	84 (95)	83 (92)
5	$FeCl_3$-$[EtPy]^+[BF_4]^-$	73 (88)	76 (87)
6	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	82 (93)	85 (93)

The data suggests that an electron-withdrawing group Br- renders bromobenzene less reactive than benzene and toluene. As a result, the conversion is slightly lower than the previous reactions. However, the selectivity is relatively higher than for toluene. This could be because that *ortho*- and *para*- directing and deactivating effect of -Br seem more predominant on the *para*- position. Also, in this case, steric effect favors the *para*-product. Though, improved conversions are seen with the metal chloride-ionic liquid system, it is noteworthy that a reaction could also proceed in ionic liquid alone. In all cases, the results with $[EtPy]^+[CF_3COO]^-$ are better than those with $[EtPy]^+[BF_4]^-$, and $FeCl_3$-IL show efficiency similar to the $AlCl_3$-IL system.

4.2.3.4 Recycle and Reuse of Ionic Liquids

The IL-catalyst system was recycled to investigate the reusability and efficiency of ionic liquids, with or without catalyst. The recycling process involved washing the used ionic liquids with diethyl ether to remove any leftover organic residues. Two layers formed (ionic liquid and organics). The resulted ionic liquids were separated and the ionic liquid dried under reduced pressure at 65°C to get the recovered ionic liquids (Figure 4.14).

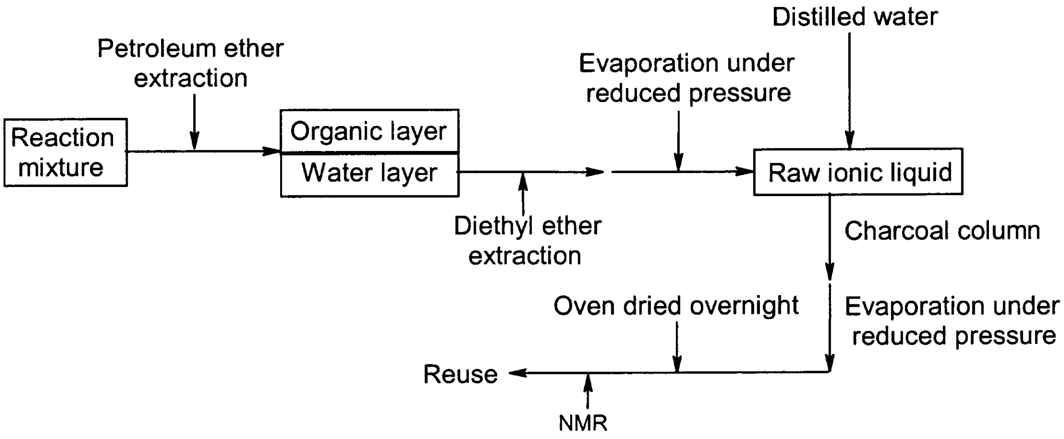


Figure 4.14 Flow chart of recycling process of ionic liquids

Successive runs were tested for acylation between benzene and acetic anhydride (Figure 4.12, Equation 1) at 50°C for four hours. The results are shown in Table 4.9. Both ionic liquids could be recovered quantitatively with negligible loss of activity. Moreover, the acylation was not affected even after third run with the recovered ionic liquid. A similar study was also carried out with recovered $FeCl_3$-IL system (Figure 4.15) for the acylation of benzene with acetic anhydride. The results are shown in Table 4.10.

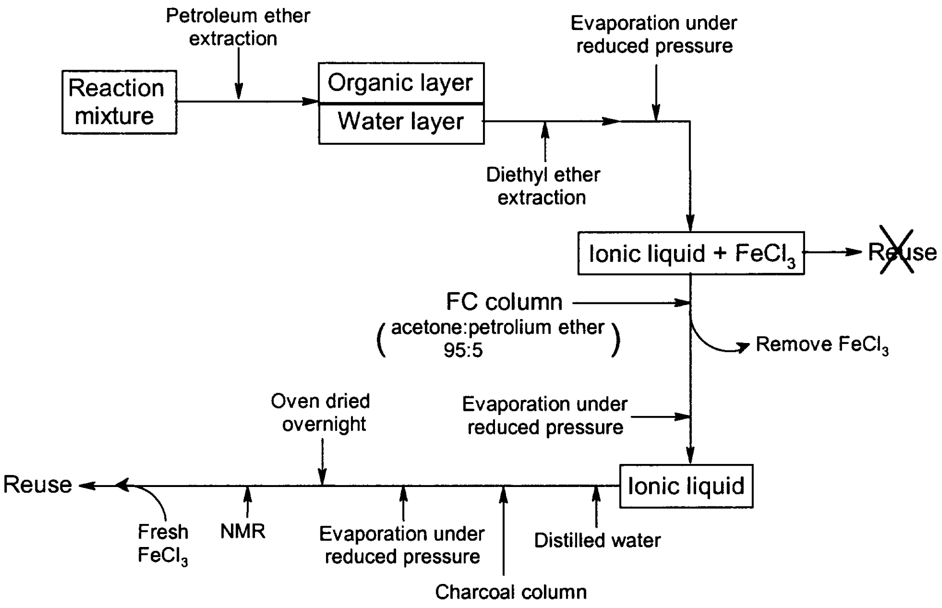


Figure 4.15 Flow chart of recycling process of iron chloride-ionic liquid system

Table 4.9 Recycling of Ionic Liquids in the Acylation of Benzene and Acetic anhydride

Recycling #	$[EtPy]^+[BF_4]^-$		$[EtPy]^+[CF_3COO]^-$	
	Recovered (w%)	Conv. (%)	Recovered (w%)	Conv. (%)
0	-	72 (97)	-	77 (99)
1	93	70 (97)	96	76 (98)
2	93	70 (95)	94	74 (97)
3	94	68 (96)	95	74 (98)

Table 4.10 Recycling of ILs-$FeCl_3$ in the Acylation of Benzene and Acetic Anhydride

Recycling #	$FeCl_3$-$[EtPy]^+[BF_4]^-$		$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	
	Recovered (w%)	Conv. (%)	Recovered (w%)	Conv. (%)
0	-	90 (94)	-	97 (97)
1	90	88 (91)	88	96 (94)
2	87	84 (89)	91	91 (91)
3	89	83 (88)	88	88 (92)

In this case, even though ionic liquids in $FeCl_3$-IL system could be recovered efficiently, the yield of acylation product (Acetophenone) decreased gradually. This may be due to some impurities in recovered ionic liquids.

4.2.4 Proposed Mechanism

It is well known that $AlCl_3$ is low soluble in many organic solvents but dissolves in molten salts. The first example of F-C acylation in molten salts (e.g. $AlCl_3$-NaCl) was reported by Raudnitz and Laube in 1929. They found the reaction rate and yield were improved. Similarly, they met the same problems as in Friedel-Crafts alkylation, e.g. NaCl has a high melting point, leading to correspondingly high reaction temperatures. Therefore, side reaction and decomposition could happen more often than the cases at lower reaction temperatures. However, ionic liquids, especially room temperature ionic liquids, can solve this problem.

$[EtPy]^+[BF_4]^-$ and $[EtPy]^+[CF_3COO]^-$ are suitable as solvents for the Friedel-Crafts acylation of aromatic compounds. Based on the classical mechanism of acylation (Figure 4.9), we propose the following mechanism in IL-MCl_3 (M = Al or Fe) catalysis system (Figure 4.16).

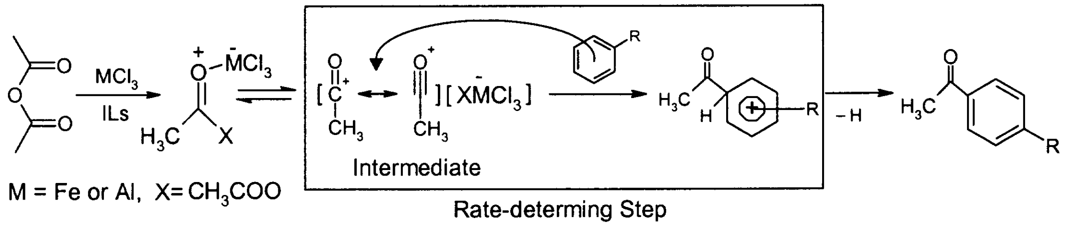


Figure 4.16 Proposed mechanism of Friedel-Crafts acylation

We found that the rate of this reaction is significantly enhanced in ionic liquids compared to organic solvents (Ross and Xiao, 2002; Sreekumar and Padmakumar, 1997). This enhanced rate of the reactions is due to lowered activation energy of the rate determining step. However, using ionic liquids instead of organic solvents does not change the mechanism of the Friedel-Crafts acetylation reaction. Furthermore, the product could be easily extracted with petroleum ether, indicating that the product did not combine with the catalyst.

Similar to the alkylation, there are five possible reasons why Friedel-Crafts acylation can be carried out in ionic liquids: (1) ionic liquids are high polar solvents; (2) they are Lewis acids; (3) hydrophobic effect; (4) $AlCl_3$/$FeCl_3$ can be dissolved in ionic liquids; and (5) they are room temperature molten salts.

4.2.5 Summary

The pyridinium-based ionic liquids are suitable media for Friedel-Crafts acylation reactions. High conversions were obtained at relatively lower temperatures, as compared with the literature studies (Ross and Xiao, 2002; Valkenberg et al., 2001; Sreekumar and Padmakumar, 1997) which were carried out at high temperatures and obtained similar results. The combination of $[EtPy]^+[CF_3COO]^-$-$FeCl_3$ is found to be an excellent catalysis system, which could efficiently substitute the aluminum catalysis system. High selectivity is obtained at 50°C. However, $[EtPy]^+[CF_3COO]^-$-$FeCl_3$ cannot be recycled and reused as efficiently as pure IL.

CHAPTER 5

ASYMMETRIC FRIEDEL-CRAFTS REACTION OF AROMATIC AMINES

5.1 Background Information

In past three decades, asymmetric synthesis has emerged as one of the most rapidly developing research areas in organic chemistry. A great deal of interest in this area has been focused on catalytic asymmetric synthesis, a critical tool for pharmaceutical and fine chemical industries and academia. The importance of this field is evident from the fact that in 2001, the Nobel Prize in Chemistry was given to three researchers who made pioneering contributions in this area.

As a novel class of solvents, ionic liquids have been successfully applied in various organic reactions. However, most of these studies have mainly focused on non-asymmetric reactions. Asymmetric synthesis in ionic liquids is still at a preliminary stage. The first example in asymmetric synthesis was proposed by Chauvin in 1995, and most of the related studies were published after the year 2000. As summarized by Baudequin et al. in 2003 and shown in Figure 5.1, there could be three different ways to achieve asymmetric synthesis in ionic liquids. (1) With chiral starting materials, ionic liquids act as solvents, which can take place of the environmentally unfriendly organic solvents. (2) With achiral starting materials, chiral ionic liquids act not only as solvents but also as chiral catalyst or chiral inducer. (3) Similar to the 2nd strategy with achiral starting materials, ionic liquids only act as solvents (and chiral ligands would be needed in this case).

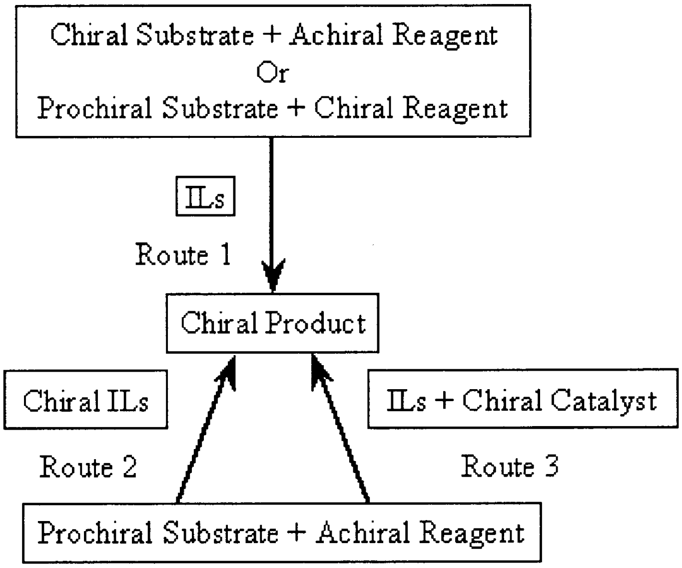


Figure 5.1 Three strategies for asymmetric synthesis in ionic liquids

The polar and non-coordinating properties of ionic liquids suggest the considerable potential of these solvents on the reactivities and selectivities of asymmetric reactions. Therefore, it is reasonable to expect that ionic liquids could also play a significant role in asymmetric synthesis. Our earlier studies show that N-ethyl-pyridinium-based ionic liquids show positive results in non-asymmetric transformations such as Diels-Alder reaction and Friedel-Crafts alkylation & acylation. This prompted our curiosity to investigate the application of pyridinium-based ionic liquids as solvents in the asymmetric conversion. In this study, we investigated 1-ethylpyridinium trifluoroacetate $[\mathrm{EtPy}]^+[\mathrm{CF_3COO}]^-$ and 1-ethylpyridinium tetrafluoroborate $[\mathrm{EtPy}]^+[\mathrm{BF_4}]^-$ as solvents in asymmetric Friedel-Crafts reaction of aromatic amines.

The asymmetric Friedel-Crafts reaction of aromatic amines with α–dicarbonyl compounds is an important reaction in organic chemistry (Olah et al., 1991). This reaction provides a simple procedure for synthesizing optically active aminomandelic acid derivatives, which have been found to have broad applications such as starting materials, intermediates, and/or resolving agents in the preparation of many chiral pharmaceutical and agricultural products (Nakamura et al., 1993). It has been reported that Friedel-Crafts reaction of glyoxylate with N, N-Dimethylanilines could be promoted by tert-butyl bisoxazoline-copper (II) complex (Gathergood et al., 2000) or BINOL-titanium (IV) complex (Yuan et al., 2004). High yields and enantioselectivities have been achieved in organic solvents. However, the effect of ionic liquids so far has not been reported. Therefore, we investigated our N-ethyl-pyridinium-based ionic liquids in this reaction.

5.2 Materials and Methods

5.2.1 Materials

3-Bromo-N,N-dimethylaniline and 3-Methoxy-N,N-dimethylaniline were purchased from Lancaster Synthesis, Inc. (now a part of Alfa Aesar, a Johnson Matthey Company). 3-Chloro-N,N-dimethylaniline was purchased from Alfa Aesar, a Johnson Matthey Company. Ethyl glyoxylate (50% in toluene), N,N-dimethylaniline, 3-methyl-N,N-dimethylaniline, Titanium(IV) isopropoxide, Copper(II) trifluoromethanesulfonate, (*R*)-1, 1'-Bi-2-naphthol ((*R*)-BINOL) and (*R*)-6, 6'-Dibromo-1,1'-bi-2-naphthol ((*R*)-BINOL-Br) were purchased from Sigma Aldrich. Pyridinium-based ionic liquids were prepared in our lab following the procedure shown in Section 2.2.

5.2.2 General Procedures

The reaction was carried out under N_2 atmosphere in the oven-dried glassware. Ionic liquids were dried overnight in an oven at 70°C. Chiral ligands (0.05 mmol, 10 mol %)

and catalyst (0.05mmol, 10 mol %) were added to 1 ml pyridinium-based ionic liquid. The mixture was stirred until the solid was completely dissolved. In this step, a gentle heat would be needed at about 45~60°C. Then the system was cooled down to the specific temperature.

In the meantime, ethyl glyoxylate was prepared by the distillation of commercially available ethyl glyoxylate-toluene solution. It should be noted that toluene came out first at around 110°C; while ethyl glyoxylate (about 98%GC) was left as residue. Freshly distilled ethyl glyoxylate (1 mmol) and amine (0.5 mmol) were added to the reaction system. After a specific reaction time, 3 ml of water and 3 ml of diethyl ether were added to quench the reaction. It should be noted that after adding water, $Ti(O^iPr)_4$ became a white suspension, which could be filtered off easily. However, this phenomenon did not happen for $Cu(OTf)_2$. The water layer was evaporated under reduced pressure and the ionic liquids could be recycled and purified (Section 2.2.4). It was then reused. The organic layer was concentrated under reduced pressure and the product was purified by flash chromatography on silica gel using hexanes-ethyl acetate (70: 30) as an eluent.

5.2.3 Analysis Methods

All analyses were carried out by HP CP-3800 HPLC equipped with a chiralcel OD-H column (hexanes/2-propanol = 90: 10). The enantiomeric excess (ee) was determined by the area ratios of each chromatographic peak. ^1H NMR was employed to confirm the products (500 MHz, in $CDCl_3$).

(*R*)-2-[4-(Dimethylamino)phenyl]-2-hydroxyacetic acid ethyl ester (**3a**)

A white solid, m. p. = 104°C. Enantiomeric excess was determined by HPLC (flow rate = 1.0 ml/min), t_r (minor) 11.7 min, t_r (major) 12.6 min. ^{1}H-NMR (500 MHz, $CDCl_3$), δ = 1.22 (t, $-CH_2C\underline{H_3}$), 3.00 (s, $-N(C\underline{H_3})_2$), 3.47 (d, $-O\underline{H}$), 4.20 (q, $-C\underline{H_2}CH_3$), 5.10 (d, $-C\underline{H}$), 6.71 (m, 2H-Ar), 7.22-7.26 (m, 2H-Ar).

(*R*)-2-[2-chloro-4-(Dimethylamino)phenyl]-2-hydroxyacetic acid ethyl ester (**3b**)

A Colorless oil. Enantiomeric excess was determined by HPLC (flow rate = 1.0 ml/min): tr (minor) 13.2 min, t_r (major) 16.8 min. ^{1}H-NMR (500 MHz, $CDCl_3$), δ = 1.22 (t, $-CH_2C\underline{H_3}$), 2.99 (s, $-N(C\underline{H_3})_2$), 3.60 (d, $-O\underline{H}$), 4.24 (q, $-C\underline{H_2}CH_3$), 5.43 (d, $-C\underline{H}$), 6.67 (dd, 1H-Ar), 6.91 (d, 1H-Ar), 7.22 (d, 1H-Ar).

(*R*)-2-[2-bromo-4-(Dimethylamino)phenyl]-2-hydroxyacetic acid ethyl ester (**3c**)

A colorless oil. Enantiomeric excess was determined by HPLC (flow rate = 1.0 ml/min): t_r (minor) 11.3 min, t_r (major) 16.5 min. ^{1}H-NMR (500 MHz, $CDCl_3$), δ = 1.20 (t, $-CH_2C\underline{H_3}$), 2.92 (s, $-N(C\underline{H_3})_2$), 3.58 (d, $-O\underline{H}$), 4.22 (q, $-C\underline{H_2}CH_3$), 5.40 (d, $-C\underline{H}$), 6.66 (dd, 1H-Ar), 6.94 (d, 1H-Ar), 7.18 (d, 1H-Ar).

(*R*)-2-[2-methyl-4-(Dimethylamino)phenyl]-2-hydroxyacetic acid ethyl ester (**3d**)

A light yellow oil. Enantiomeric excess was determined by HPLC (flow rate = 1.0 ml/min): t_r (minor) 11.1 min, t_r (major) 16.0 min. ^{1}H-NMR (500 MHz, $CDCl_3$), δ = 1.24 (t, $-CH_2C\underline{H_3}$), 2.43 (s, $-ArC\underline{H_3}$), 2.96 (s, $-N(C\underline{H_3})_2$), 3.43 (d, $-O\underline{H}$), 4.21 (q, $-C\underline{H_2}CH_3$), 5.29 (d, $-C\underline{H}$), 6.55-6.61 (m, 2H-Ar), 7.13 (d, 1H-Ar, which is farther from N).

(*R*)-2-[2-methoxy-4-(Dimethylamino)phenyl]-2-hydroxyacetic acid ethyl ester (**3e**)

A colorless oil. Enantiomeric excess was determined by HPLC (flow rate = 1.0 ml/min): t_r (minor) 17.4 min, t_r (major) 20.5 min. ^{1}H-NMR (500 MHz, $CDCl_3$), δ = 1.21 (t, -$CH_2C\underline{H_3}$), 2.96 (s, -$N(C\underline{H_3})_2$), 3.61 (d, -$O\underline{H}$), 3.84 (s, -$OC\underline{H_3}$), 4.21 (q, -$C\underline{H_2}CH_3$), 5.19 (d, -$C\underline{H}$), 6.26 (dd, 1H-Ar), 6.31 (d, 1H-Ar), 7.10 (d, 1H-Ar).

5.3 Results and Discussion

The Friedel-Crafts reactions of aromatic amine **1** with ethyl glyoxylate **2** catalyzed by chiral BINOL-metal complex in pyridinium-based ionic liquids ($[EtPy]^+[BF_4]^-$ and $[EtPy]^+[CF_3COO]^-$) as solvents were investigated (Figure 5.2).

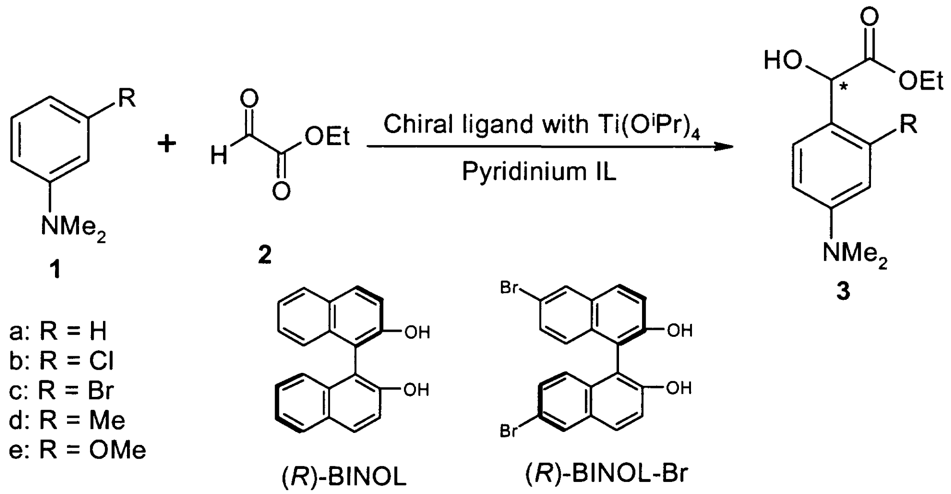


Figure 5.2 Asymmetric Friedel-Crafts reaction of aromatic amines

The effects of reaction time, temperature, the composition of catalyst-ionic liquids and various substituents in reactants were investigated. Also, the effect of reusability of recycled ionic liquids on reaction outcomes was studied.

5.3.1 Effect of Catalyst and Solvent

Initially, the acylation of N, N-dimethylaniline **1a** and ethyl glyoxylate **2** with two different chiral ligands and two different Lewis acids (Titanium (IV) isopropoxide and Copper(II) trifluoromethanesulfonate) in pyridinium-based ionic liquids at room temperature for 24 hours was investigated (Figure 5.2). We kept the molar ratio of **1a**: **2**: the complex 1:2:0.2 as a constant. The results are summarized in Table 5.1.

Table 5.1 Friedel-Crafts Acylation of N, N-dimethylaniline with Ethyl Glyoxylate

Entry	Ligand	Catalyst	Solvent	Yield (%)	ee (%)
1*	(*R*)-BINOL	$Ti(O^iPr)_4$	Toluene	99	77
2*	(*R*)-BINOL		CH_2Cl_2	99	70.6
3*	(*R*)-BINOL		THF	99	48
4	(*R*)-BINOL		$[EtPy]^+[CF_3COO]^-$	84	77
5	(*R*)-BINOL		$[EtPy]^+[BF_4]^-$	73	48
6*	(*R*)-BINOL-Br		Toluene	99	90.6
7	(*R*)-BINOL-Br		$[EtPy]^+[CF_3COO]^-$	86	88
8	(*R*)-BINOL-Br		$[EtPy]^+[BF_4]^-$	74	59
9	(*R*)-BINOL	$Cu(OTf)_2$	$[EtPy]^+[CF_3COO]^-$	86	74
10	(*R*)-BINOL		$[EtPy]^+[BF_4]^-$	68	38
11	(*R*)-BINOL-Br		$[EtPy]^+[CF_3COO]^-$	87	87
12	(*R*)-BINOL-Br		$[EtPy]^+[BF_4]^-$	70	53

* Yuan et al., 2004

As the data shows, the yield and enantioselectivity are dependent on the ligand-catalyst-solvent system used. In this reaction, they both decreased in ionic liquids compared to organic solvents. This is because the reactant N, N-dimethylaniline is an N-donator which has a lone pair elections. It may coordinate to the N-ethylpyridinium cation, therefore decreasing the yield. Chiral ligand (*R*)-BINOL and (*R*)-BINOL-Br gave comparable yields. However, (*R*)-BINOL-Br has higher ee, which could be because the inductive effect of electron-withdrawing group -Br at 6, 6'-positions of BINOL, i.e., -Br at 6, 6'-positions of BINOL increases the Lewis acidity, thus facilitating the reactions

(Ishii et al., 2000). A comparison of two metal catalysts shows that, even though they both provide similar product yield, $Ti(O^{i}Pr)_4$ has better enantioselective properties. Furthermore, $Ti(O^{i}Pr)_4$ was more easily removed from the reaction mixture, as it precipitated by adding water to the system. Therefore, $Ti(O^{i}Pr)_4$ was chosen to be the catalyst for further studies. Reactions when carried out in $[EtPy]^+[BF_4]^-$, gave lower product yield and ee. This is because the Lewis acidity of $[EtPy]^+[CF_3COO]^-$ is higher than $[EtPy]^+[BF_4]^-$.

5.3.2 Effect of Reaction Time

The influence of reaction time for the Friedel-Crafts reaction of N, N-dimethylaniline **1a** with ethyl glyoxylate **2** catalyzed by different chiral ligand-$Ti(O^{i}Pr)_4$ complex at room temperature has been investigated. The results are summarized in Table 5.2.

Table 5.2 Time Effect for F-C acylation of N, N-dimethylaniline with Ethyl Glyoxylate

Time (hr)	Chiral Ligand-Solvent [Yield (%) / ee (%)]			
	(*R*)-BINOL $[EtPy]^+[CF_3COO]^-$	(*R*)-BINOL-Br $[EtPy]^+[CF_3COO]^-$	(*R*)-BINOL $[EtPy]^+[BF_4]^-$	(*R*)-BINOL-Br $[EtPy]^+[BF_4]^-$
4	36 / 81	39 / 89	35 / 51	37 / 61
8	55 / 81	57 / 88	50 / 49	54 / 61
16	77 / 78	81 / 88	68 / 49	69 / 59
20	81 / 77	85 / 88	71 / 49	73 / 59
24	84 / 77	86 / 88	73 / 48	74 / 59
30	85 / 77	86 / 87	74 / 48	74 / 58

As can be seen in Table 5.2, the enantioselectivity was almost not affected. While the yield increased initially within the first 24 hours, no significant changes were observed upon prolonging the time thereafter. The change in yield along with the reaction time in various chiral ligand-solvent systems is plotted in Figure 5.3. Also, in all cases, the results with $[EtPy]^+[CF_3COO]^-$ are better than those with $[EtPy]^+[BF_4]^-$. The combination of (*R*)-BINOL-Br-Ti complex with $[EtPy]^+[CF_3COO]^-$ has the most effective in increasing the rate of reaction.

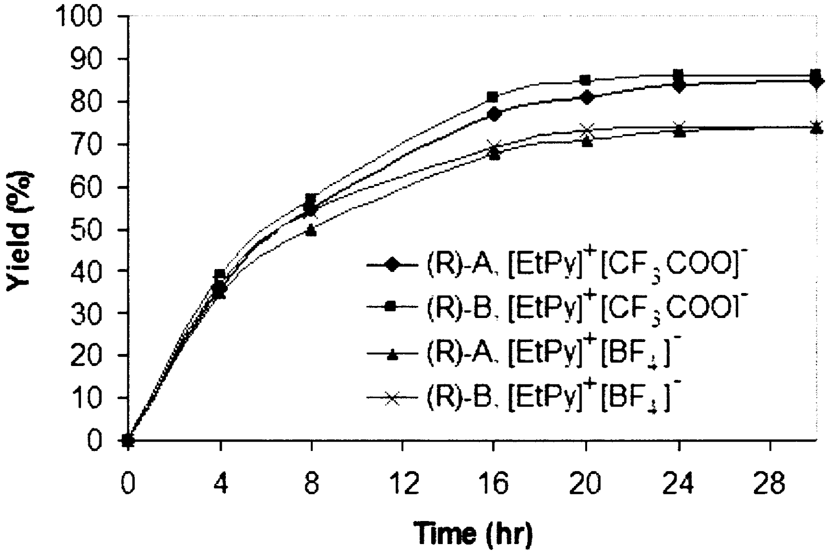


Figure 5.3 Time effect of F-C reaction of N, N-dimethylaniline with ethyl glyoxylate

5.3.3 Effect of Substituents

Various aromatic amines have been investigated in Friedel-Crafts acylation with ethyl glyoxylate. All reactions were catalyzed by chiral ligand-$Ti(O^iPr)_4$ complex in $[EtPy]^+[CF_3COO]^-$ at room temperature for 24 hours.

As can be seen in Table 5.3, as electron-withdrawing groups (EWG), Cl- and Br- deactivate the benzene ring the yield were thereby decreased. The ee increased, which may be due to the steric factor. As an electron-donating group, Me- group can activate the benzene ring and promote the reaction to occur. Therefore, the yields (entry 4 and 9) are increased in comparison to the results of N,N-dimethylaniline (entry 1 and 6). However, the ee decreased, which might be due to the steric hindrance. Entry 5 and 10 show that the yield and ee of MeO- group have decreased dramatically, even though MeO- is an electron-donating group. This is because the product contains a hydroxyl group and a methoxyl group, which might combine with the catalyst to form a six member ring, thus inhibiting the reaction. In all cases, chiral ligand (*R*)-BINOL-Br has higher ee compared with (*R*)-BINOL, which is due to the inductive effect of bromine.

Table 5.3 Friedel-Crafts Reaction of Various Aromatic Amines

Entry	Amine	Ligand	Yield (%)	ee (%)
1	1a (-H)	(*R*)-BINOL	84	77
2	1b (-Cl)	(*R*)-BINOL	79	81
3	1c (-Br)	(*R*)-BINOL	72	73
4	1d (-Me)	(*R*)-BINOL	86	68
5	1e (-OMe)	(*R*)-BINOL	54	63
6	1a (-H)	(*R*)-BINOL-Br	86	88
7	1b (-Cl)	(*R*)-BINOL-Br	80	91
8	1c (-Br)	(*R*)-BINOL-Br	74	85
9	1d (-Me)	(*R*)-BINOL-Br	89	81
10	1e (-OMe)	(*R*)-BINOL-Br	55	74

5.3.4 Effect of Reaction Temperature

The Friedel-Crafts reaction of various aromatic amine with ethyl glyoxylate catalyzed by different chiral ligand-Ti(O^{i}Pr)$_4$ complex at 0 °C and -20 °C were investigated. Results are shown in Table 5.4.

Entry 1 shows extremely low yield and ee, which is because [EtPy]$^+$[BF$_4$]$^-$ becomes frozen at around 0^{o}C, which attenuates the catalytic and enantioselective effects. Therefore, we only investigated the reactions in [EtPy]$^+$[CF$_3$COO]$^-$.

In all cases, with a decrease in temperature, the overall yield decreased, which is due to the decreased temperature lowering the reaction energies. However the enantioselectivities increased. Meta-substitution effect shows the same rule as the results at room temperature.

Table 5.4 The Friedel-Crafts Reactions at Different Temperature

Entry	Amine	Temp. (°C)	Time (hr)	Solvent	Yield (%) / ee (%)	
					BINOL	BIONL-Br
1	1a (-H)	0	36	$[EtPy]^+[BF_4]^-$	47 / 10	50 / 16
2	1a (-H)	0	36	$[EtPy]^+[CF_3COO]^-$	81 / 85	82 / 91
3	1c (-Cl)	0	36		74 / 83	76 / 94
4	1d (-Br)	0	36		67 / 80	68 / 87
5	1b (-Me)	0	36		83 / 79	85 / 85
6	1e (-OMe)	0	36		49 / 70	50 / 77
7	1a (-H)	-20	48		77 / 89	77 / 92
8	1b (-Cl)	-20	48		70 / 87	71 / 96
9	1c (-Br)	-20	48		60 / 83	62 / 89
10	1d (-Me)	-20	48		78 / 84	80 / 87
11	1e (-OMe)	-20	48		44 / 73	46 / 79

5.3.5 Recycle and Reuse of Ionic Liquids

The reusability of ionic liquid for the Friedel-Crafts reaction of N, N-dimethylaniline **1a** with ethyl glyoxylate **2** catalyzed by the complex of (*R*)-BINOL-Br- $Ti(O^iPr)_4$ were investigated. The recycling process involved washing the used ionic liquids with diethyl ether. Any organic residue left in the ionic liquid layer could be separated by the ether wash. The ionic liquid layer was decanted and evaporated under reduced pressure at 65°C, then purified following the method in Section 2.2.4 (Figure 5.4). Successive runs were performed with the recovered ionic liquid $[EtPy]^+[BF_4]^-$ or $[EtPy]^+[CF_3COO]^-$ at room temperature for 24 hours.

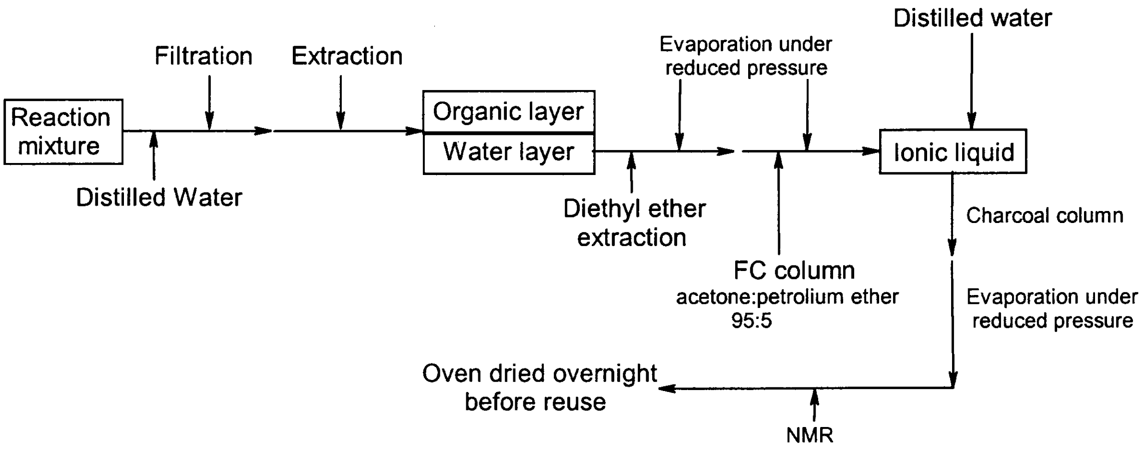


Figure 5.4 Flow chart of recycling process of ionic liquids

Table 5.5 Recycling and Reuse of Ionic Liquids

Recycling #	$[EtPy]^+[BF_4]^-$		$[EtPy]^+[CF_3COO]^-$	
	Recovered(w%)	Yield/ee(%)	Recovered(w%)	Yield/ee(%)
0	-	74 / 59	-	86 / 88
1	92	72 / 58	93	84 / 87
2	94	73 / 58	93	83 / 87
3	91	72 / 57	92	82 / 87
4	93	71 / 56	94	83 / 86
5	92	69 / 55	92	82 / 85

As Table 5.5 shows, both ionic liquids could be recovered efficiently and utilized almost without loss of activity and selectivity. This is evident from the fact that the yield and ee of the Friedel-Crafts acylations are not much affected even after the 5th run with the recovered ionic liquid.

5.4 Proposed Mechanism

On the basis of Mikami's (1993) and Corey's (1997) work, Yuan et al. (2004) proposed a detailed transition state working model for the asymmetric Friedel-Crafts reaction of aromatic amines with ethyl glyoxylate (Figure 5.5). The BINOL-Ti complex and the formyl group in ethyl glyoxylate form a six-member ring transition state by hydrogen bonding. As an electrophile, the carbon in formyl group will be attacked by the most nucleophilic site (*para*- position) of N, N-dimethylaniline. The attack would be easier to occur from *re* face (bottom) than from *si* face (top) due to the steric hindrance caused by the naphthol group. Therefore, product with (*R*-) configuration is predominant. Based on all of these studies, a detailed catalytic cycle for asymmetric Friedel-Crafts reaction of aromatic amines in pyridinium-based ionic liquids is proposed and shown in Figure 5.6.

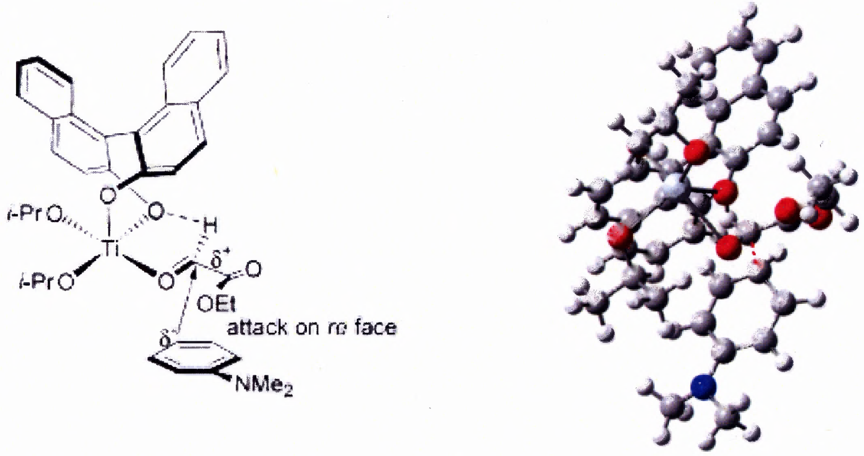


Figure 5.5 The transition state model of asymmetric Friedel-Crafts reaction

In our study, the catalytic activity and enantioselectivity were found to be influenced by the substituents of BINOL derivatives. The experimental data shows that the (*R*)-6, 6'-Br-BINOL-Ti complex was a more effective catalyst than the BINOL-Ti complex. This is because -Br, as an electron-withdrawing group, could draw away the electrons of BINOL-Br-Ti complex, thus increasing the Lewis acidity of the catalysis system. This would make the carbon of formyl group more electrophilic, thereby facilitating the reactions.

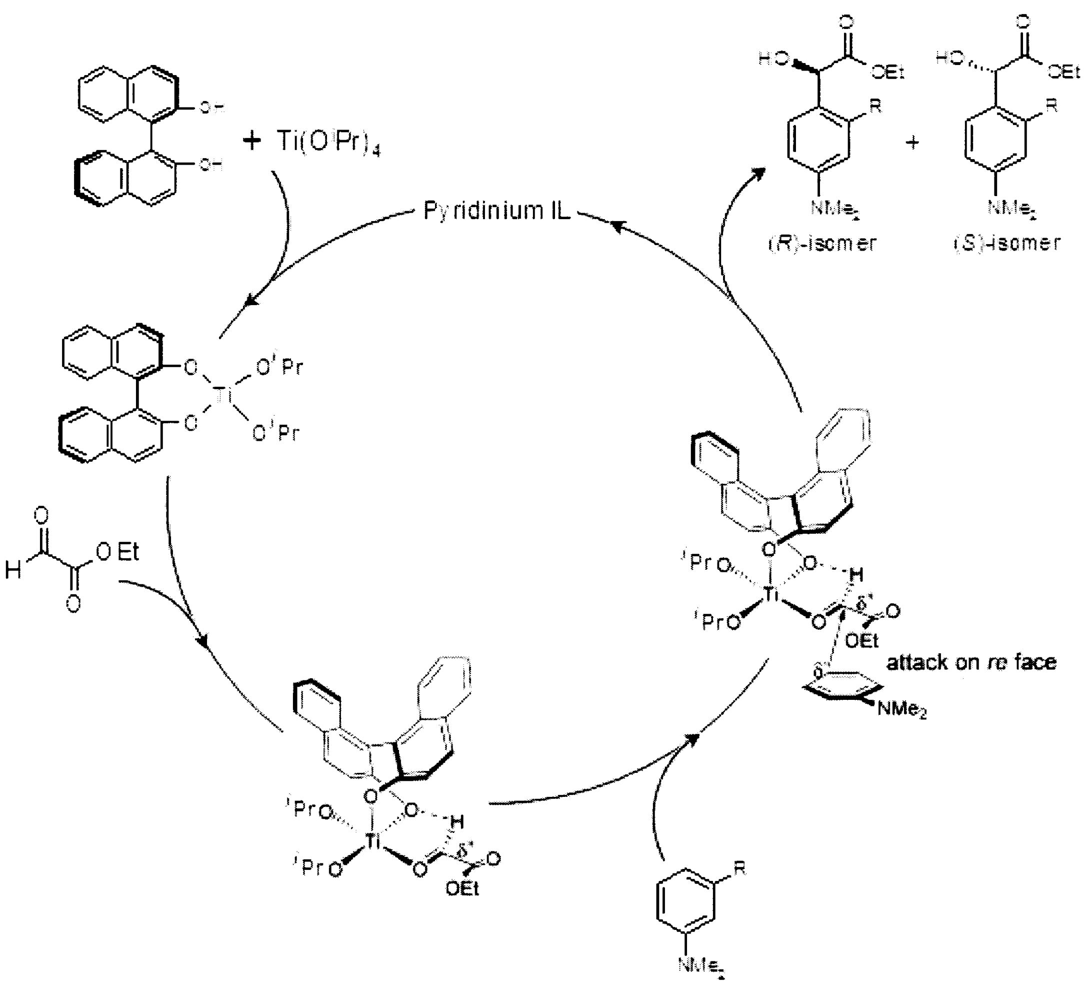


Figure 5.6 Catalytic cycle of asymmetric Friedel-Crafts reaction studied

5.5 Summary

Pyridinium-based ionic liquids are viable solvents for asymmetric Friedel-Crafts reaction of aromatic compounds with ethyl glyoxylate in the presence of BINOL-metal complex as chiral catalysts. The reaction yield and ee are dependent on the combined effects of ionic liquids, catalysts, chiral ligands, substituents, temperature and reaction time. High yields and excellent enantioselectivities were achieved under relatively mild conditions. $[EtPy]^+[CF_3COO]^-$ was found to be a suitable solvent which can efficiently substitute for the traditional organic solvents. Furthermore, both ionic liquids could be recycled and reused efficiently as opposed to traditional organic solvents.

CHAPTER 6

ASYMMETRIC REDUCTION OF AROMATIC KETONES

6.1 Background Information

Enantioselective reduction of prochiral carbonyl compounds is one of the most important asymmetric reactions (Seyden-Penne, 1997). Generally, aldehydes and ketones can be reduced to the corresponding alcohols by various reductants such as alkali metal aluminum hydrides, alkali metal borohydrides, and metal cyanoborohydride, etc. As for the asymmetric reduction of prochiral ketones to chiral secondary alcohols, those metal hydrides are modified with chiral alkoxyl or amino ligands - R^*OH or RR^*NH. It provides an efficient method to synthesize optically active alcohols that have been found to be applied as starting materials or chiral introducing agent for preparing many chiral pharmaceutical and chemical products.

Lithium aluminum hydride (LAH) is a powerful reducing agent with excellent solubility in ethereal solvents. As a hydrogen donor, it is widely employed for reductions of aldehydes, ketones, esters, amides and nitriles. The first attempted modification of lithium aluminum hydride with (+)-camphor was done by Bothner-By in 1951, and the modified system showed excellent reactivity and selectivity in asymmetric reductions. Since then, a wide variety of chiral ligands have been investigated to modify lithium aluminum hydride. Most of those chiral modifiers are readily available and naturally occurring substances such as alkaloids (Cervinka, 1965; Cervinka and Belovsky, 1967), sugars (Landor et al., 1966; Landor et al., 1967; Cervinka and Fabryova, 1967), alcohols (Noyori et al., 1979; Noyori, 1981), amines (Mukaiyama et al., 1977; Asami and

Mukaiyama, 1979), and amino alcohols (Yamaguchi, 1972; Yamaguchi and Mosher, 1973; Jacquet and Vigneron, 1974; Vigneron and Jacquet, 1976; Terashima, 1980), etcetera.

In our previous studies, N-pyridinium-based ionic liquids show excellent results in asymmetric Friedel-Crafts reaction of aromatic amines. Therefore, we embarked upon study utilizing the same ionic liquids, i.e. $[EtPy]^+[CF_3COO]^-$ and $[EtPy]^+[BF_4]^-$ for the asymmetric reduction of aromatic ketones. Based on Noyori's successful work on the reduction of ketones by the complex of $LiAlH_4$ containing chiral 1, 1'-Bi-2-naphthol (BINOL) and an alcohol in 1979, we employed the BINOL–LAH complex as the catalyst to investigate enantioselective reductions of aryl alkyl ketones.

6.2 Materials and Methods

6.2.1 Materials

Lithium aluminum hydride, (*R*)-1,1'-Bi-2-naphthol, (*R*)-6,6'-Dibromo-1,1'-bi-2-naphthol, acetophenone, propiophenone, butyrophenone, isobutyrophenone, valerophenone, 2,2-dimethylpropiophenone, isovalerophenone were purchased from Sigma Aldrich. Pyridinium-based ionic liquids were prepared in our lab following the procedure in Section 2.2.

6.2.2 General Procedures

Since $LiAlH_4$ can react violently with water (methanol, ethanol etc.), it must be handled away from moisture. The reaction equations are shown in Figure 6.1.

In this study, all reactions were carried out under N_2 atmosphere in oven-dried glassware. Ionic liquids were dried overnight in an oven at 70°C. Chiral ligand (*R*)-1,1'-Bi-2-naphthol or its derivative (*R*)-6,6'-Dibromo-1,1'-bi-2-naphthol (2 mmol, 1 equiv.) was added to 2 ml pyridinium-based ionic liquid. The mixture was stirred until the solid was dissolved. A gentle heat (around 45~60°C) might be needed in this step. Then the catalyst, lithium aluminum hydride (2 mmol, 1 equiv.), was slowly added to the mixture, which would produce a very small amount of suspension (if a large amount of precipitate occurs, the experiment has to be repeated). Furthermore, in this step, we noticed some bubbles were generated. After being stirred (250 rpm) for 30 minutes at the specified reaction temperature, the reactant, aromatic ketone (2 mmol, 1 equiv.), was dropped in. The reaction mixture was stirred (250 rpm) at this temperature for the desired time period. Finally, 2 N HCl (5 ml) was added to quell the reaction and the mixture was warmed to room temperature. The organic compound was extracted by diethyl ether (5 ml) and washed first with saturated sodium bicarbonate (5 ml) followed by brine (5 ml). Evaporation under reduced pressure yielded the concentrated organic mixture, which was further purified by flash chromatography (acetone/hexanes 1:7) to give the purified materials. The water layer was evaporated under reduced pressure, and the ionic liquids could be recycled and purified following the methods in Section 2.2.4. However, we find that, in this case, $[EtPy]^+[CF_3COO]^-$ changed color from colorless/light yellow to yellow, then to brown.

$$\mathrm{LiAlH_4} + 4\,\mathrm{H_2O} \longrightarrow \mathrm{LiOH} + \mathrm{Al(OH)_3} + 4\,\mathrm{H_2}\uparrow$$

$$\mathrm{LiAlH_4} + 4\,\mathrm{ROH} \longrightarrow \mathrm{LiOR} + \mathrm{Al(OR)_3} + 4\,\mathrm{H_2}\uparrow$$

Figure 6.1 $LiAlH_4$ reacts with water or alcohols

6.2.3 Analysis Methods

All analyses were carried out by HP CP-3800 HPLC equipped with a chiralcel OD-H column (hexanes/2-propanol = 75: 25). The ee was determined by the area ratios of each chromatograph peak. ^{1}H NMR was employed to confirm the products (500 MHz, in $CDCl_3$).

(*R*)-1-Phenylethan-1-ol (**a**)

A colorless liquid. Enantiomeric excess was determined by HPLC (flow rate = 0.6 ml/min), t_r (minor) 8.25 min, t_r (major) 8.68 min. ^{1}H-NMR (500 MHz, $CDCl_3$), δ = 1.48 (d, $-C\underline{H}_3$), 2.41 (s, $-O\underline{H}$), 4.82-4.87 (m, $-C\underline{H}$), 7.21-7.35 (m, 5H-Ar).

(*R*)-1-Phenylpropan-1-ol (**b**)

A colorless liquid. Enantiomeric excess was determined by HPLC (flow rate = 0.6 ml/min; hexanes: 2-propanol = 75:25), t_r (minor) 7.95 min, t_r (major) 8.43 min. ^{1}H-NMR (500 MHz, $CDCl_3$), δ = 0.91 (t, $-C\underline{H}_3$), 1.65-1.90 (m, $-C\underline{H}_2$), 2.13 (d, $-O\underline{H}$), 4.55-4.61 (m, $-C\underline{H}$), 7.18-7.31 (m, 5H-Ar).

(*R*)-1-Phenylbutan-1-ol (**c**)

A white solid. m.p. = 47°C. Enantiomeric excess was determined by HPLC (flow rate = 0.6 ml/min), t_r (minor) 7.27 min, t_r (major) 7.87 min. ^{1}H-NMR (500 MHz, $CDCl_3$), δ = 0.92 (t, $-C\underline{H}_3$), 1.31-1.37 (m, $-C\underline{H}_2CH_3$), 1.54-1.81 (m, $-C\underline{H}_2CH_2CH_3$), 3.22 (s, $-O\underline{H}$), 4.59-4.64 (m, $-C\underline{H}$), 7.17-7.29 (m, 5H-Ar).

(*R*)- 1-Phenyl-2-methylpropan-1-ol (**d**)

A colorless liquid. Enantiomeric excess was determined by HPLC (flow rate = 0.6 ml/min), t_r (minor) 6.73 min, t_r (major) 7.45 min. ^{1}H-NMR (500 MHz, $CDCl_3$), $\delta = 0.77$ (d, $-C\underline{H_3}$), 0.98 (d, $-C\underline{H_3}$), 1.87-2.01 (m, $-C\underline{H}(CH_3)_2$), 2.08 (s, $-O\underline{H}$), 4.27-4.30 (m, $-C\underline{H}OH$), 7.22-7.32 (m, 5H-Ar).

(*R*)-1-Phenylpentan-1-ol (**e**)

A colorless liquid. Enantiomeric excess was determined by HPLC (flow rate = 0.6 ml/min), t_r (minor) 7.00 min, t_r (major) 7.68 min. ^{1}H-NMR (500 MHz, $CDCl_3$), $\delta = 0.95$ (t, $-C\underline{H_3}$), 1.42-1.85 (m, $-(C\underline{H_2})_3CH_3$), 2.01 (s, $-O\underline{H}$), 4.63-4.67 (m, $-C\underline{H}OH$), 7.20-7.31 (m, 5H-Ar).

(*R*)-1-Phenyl-3-methylbutan-1-ol (**f**)

A colorless liquid. Enantiomeric excess was determined by HPLC (flow rate = 0.6 ml/min), t_r (minor) 6.48 min, t_r (major) 7.33 min. ^{1}H-NMR (500 MHz, $CDCl_3$), $\delta = 0.95$ (d, $-(C\underline{H_3})_2$), 1.36-1.61 (m, $-C\underline{H_2}$), 1.79-1.90 (m, $-C\underline{H}(CH_3)_2$), 3.06 (d, $-O\underline{H}$), 4.21 (t, $-C\underline{H}OH$), 7.20-7.29 (m, 5H-Ar).

(*R*)-1-Phenyl-2,2-dimethylpropan-1-ol (**g**)

A colorless liquid. Enantiomeric excess was determined by HPLC (flow rate = 0.6 ml/min), t_r (minor) 6.25 min, t_r (major) 7.23 min. ^{1}H-NMR (500 MHz, $CDCl_3$), $\delta = 0.82$ (s, $-(C\underline{H_3})_3$), 1.67 (d, $-O\underline{H}$), 4.20-4.24 (m, $-C\underline{H}OH$), 7.25-7.36 (m, 5H-Ar).

6.3 Results and Discussion

The enantioselective reduction of aromatic ketones catalyzed by the complex of (*R*)-1, 1'-Bi-2-naphthol ((*R*)-BINOL) or its derivative (*R*)-6, 6'-Dibromo-1, 1'-bi-2-naphthol ((*R*)-BINOL-Br) and lithium aluminum hydride was investigated in pyridinium-based ionic liquids ($[EtPy]^+[BF_4]^-$ and $[EtPy]^+[CF_3COO]^-$) (Figure 6.2).

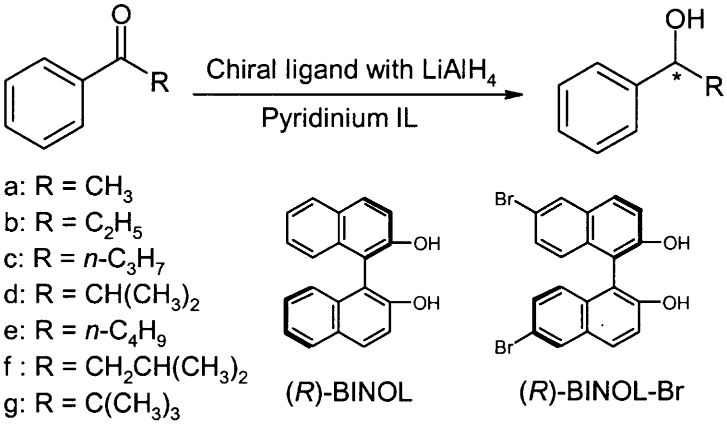


Figure 6.2 Asymmetric reduction of aromatic ketones

In this study, ionic liquids were employed as solvents and (*R*)-BINOL or (*R*)-BINOL-Br acted as the chiral promoter. We followed the 3rd strategy in Figure 5.1. The effects of solvent, reaction time, temperature, the amount of catalyst and various substituents in reactants were investigated. Recycle-ability and reuse of ionic liquids were studied as well.

6.3.1 Effect of Catalyst Dosage

On the basis of Noyori's work, we investigated the asymmetric reduction of acetophenone catalyzed by various quantities of the chiral BINOL-LAH-EtOH complex in pyridinium-based ionic liquids at room temperature for 24 hours (Figure 6.2 a). We kept the molar ratio of chiral ligand: $LiAlH_4$: ethanol = 1:1:1 as a constant. Concerned that ethanol may react with $LiAlH_4$, the reactions were performed under the same conditions but without alcohol. The results are summarized in Table 6.1.

Table 6.1 Asymmetric Reduction of Acetophenone with Various Amount of Catalyst

Solvents	Dosage of catalyst (equiv.)[a]	with Ethanol	without Ethanol
		Yield / ee (%)	Yield / ee (%)
THF[b]	2.0	95~100 / 64	-
$[EtPy]^+[CF_3COO]^-$	0.5	78 / 58.1	91 / 63.2
	1.0	96 / 65.8	99 / 67.7
	1.5	99 / 66.3	99 / 67.8
	2.0[b]	99 / 67.5	99 / 68.0
	2.5	99 / 67.9	99 / 68.1
	3.0	99 / 68.6	99 / 68.1
$[EtPy]^+[BF_4]^-$	0.5	76 / 53.5	86 / 59.4
	1.0	97 / 62.9	99 / 66.1
	1.5	99 / 63.7	99 / 66.2
	2.0[b]	99 / 64.6	99 / 66.3
	2.5	99 / 66.4	99 / 66.3
	3.0	99 / 66.4	99 / 66.3

[a] 1 equivalent is counted on the basis of acetophenone (2mmol);
[b] Reported by Noyori et al., 1979.

As the data shows, if with ethanol, 2 equivalents of the catalysis complex or more were needed. However, the required amount of the catalyst was deducted in the reactions without ethanol. Therefore, in our further studies, we kept using chiral BINOL-LAH (1 equivalent) to catalyze the reactions without alcohol.

The results with $[EtPy]^+[CF_3COO]^-$ are better than those with $[EtPy]^+[BF_4]^-$. Similar to the previous reactions, this may be due to the different Lewis acidities, i.e., $[EtPy]^+[CF_3COO]^-$ is more acidic than $[EtPy]^+[BF_4]^-$. Also, as room temperature molten salts, $[EtPy]^+[CF_3COO]^-$ and $[EtPy]^+[BF_4]^-$ can make the reactive species more accessible than can organic solvents.

6.3.2 Effect of Reaction Time

Kinetics studies have been performed in the asymmetric reduction of acetophenone at room temperature up to 24 hours. We kept the molar ratio of chiral ligand (*R*)-BINOL: $LiAlH_4$ = 1:1 as a constant. The results are listed in Table 2.

Table 6.2 Reaction Time Effect of Asymmetric Reduction of Acetophenone

Ionic Liquid	Reaction Time (hr)	Yield (%)	ee (%)
$[EtPy]^+[CF_3COO]^-$	1	73	71.1
	2	96	69.7
	4	99	68.5
	8	99	68.0
	12	99	68.0
	24	99	67.7
$[EtPy]^+[BF_4]^-$	1	76	67.7
	2	97	67.2
	4	99	67.0
	8	99	66.4
	12	99	66.2
	24	99	66.1

As can be seen in Table 6.2, the enantioselectivities decreased with reaction time, while the yields increased. This may be because a specific time is needed to reach reaction equilibrium. However, after four hours, this decrease became so slight that it can be ignored. At the meantime, the maximum yields were obtained. After 8 hours, the enantioselectivities almost did not change further with a more prolonged time period. Considering the time-saving and lack of significant differences among results, we still choose 4 hours as the reaction time for the further studies. In all cases, even the enantioselectivities with $[EtPy]^+[CF_3COO]^-$ are better than those with $[EtPy]^+[BF_4]^-$ due to its stronger Lewis acidity, and the product yield is slightly lower than in those with $[EtPy]^+[BF_4]^-$ at the beginning. This may be because $[EtPy]^+[CF_3COO]^-$ might react with $LiAlH_4$ because it has carbonate group in the trifluoroacetate anion, which may cause a slight delay of the reductions.

6.3.3 Effect of Substituents and Reaction Temperature

The asymmetric reductions of various aryl alkyl ketones in ionic liquids have been investigated at various temperatures, e.g., room temperature, 0°C, and -30°C (Table 6.3). It should be noted that, at around 0°C, the reaction mixture was frozen caused by $[EtPy]^+[BF_4]^-$ in the reduction of acetophenone, which yielded 73% (±)-1-phenylethanol and 30.18% ee. Therefore, we only carried out the reductions in $[EtPy]^+[CF_3COO]^-$ at low temperatures. -30°C is the lowest temperature that the reaction mixture can stay in liquid status. Below this point, the reaction system would be frozen.

As the data in Table 6.3 shows, with a decrease of temperature to -30°C, the enantioselectivities increased. But the overall yields decreased even with prolonged reaction period. This is because lower temperatures eliminate the reaction energy thus reducing the overall yield. However, ee increased because the activation energies for forming both enantiomers did not change.

Comparing the results of various ketones at the same temperature, we found the size and shape of alkyl group have a significant influence on the reductions. Due to the steric hindrance, larger size and more branches of alkyl group would block the reaction thus reducing the yield and ee (especially at low temperatures). Following the order of ketones a ~ g, the enantioselectivity slightly decreased at each temperature case. Besides of the steric effect, this may also be influenced by the reaction phase effects. From ketones a ~ g, the homogeneous reaction system gradually turns to the heterogeneous mixture, therefore disturbing the reactions. Since the reaction mixture was stirred vigorously (250 rpm), the difference among the results is minor. It should be noted that from entry 6 to 7, the enantioselectivity has a relatively significant drop. This should be caused by the steric hindrance of a tertiary butyl group, which is right next to the carbonyl group, and therefore shields the reactive site of ketones.

Table 6.3 Asymmetric Reduction of Ketones Catalyzed by BINOL-LAH

Entry	Ketone	Yield / ee (%)		
		RT (4hr)	0°C (24hr)	-30°C (24hr)
1	$C_6H_5COCH_3$	99 / 68.5	91 / 75.1	85 / 83.5
2	$C_6H_5COCH_2CH_3$	99 / 69.2	93 / 79.7	86 / 84.9
3	$C_6H_5CO(CH_2)_2CH_3$	98 / 69.7	91 / 79.3	83 / 84.0
4	$C_6H_5COCH(CH_3)_2$	97 / 68.7	85 / 78.3	79 / 82.0
5	$C_6H_5CO(CH_2)_3CH_3$	96 / 68.5	87 / 78.6	80 / 84.0
6	$C_6H_5COCH_2CH(CH_3)_2$	97 / 67.6	82 / 74.0	76 / 77.7
7	$C_6H_5COC(CH_3)_3$	95 / 58.9	79 / 64.2	71 / 70.3

Based on our results of asymmetric Friedel-Crafts reaction of aromatic amine, we are curious whether (*R*)-6, 6'-Dibromo-1,1'-bi-2-naphthol ((*R*)-BINOL-Br) can promote the reductions as well as did BINOL. Therefore, we investigated the reductive reactions under the same conditions but catalyzed by BINOL-Br-LAH instead of BINOL-LAH.

As can be seen in Table 6.4, BINOL-Br-LAH showed better enantioselectivity than BINOL-LAH at each temperature. Similar to the previous asymmetric Friedel-

Crafts reaction, -Br, as an electron withdrawing group, could drag away the electrons of BINOL-Br-LAH complex, which might activate the reactive site on ketones thus promoting the reductions.

Table 6.4 Asymmetric Reduction of Ketones Catalyzed by BINOL-Br-LAH

Entry	Ketones	Yield / ee (%)		
		RT (4hr)	0°C (24hr)	-30°C (24hr)
1	$C_6H_5COCH_3$	99 / 69.7	91 / 78.9	86 / 87.6
2	$C_6H_5COCH_2CH_3$	99 / 73.3	91 / 82.9	90 / 81.6
3	$C_6H_5CO(CH_2)_2CH_3$	99 / 73.6	83 / 89.9	82 / 89.6
4	$C_6H_5COCH(CH_3)_2$	97 / 70.2	85 / 79.8	80 / 86.7
5	$C_6H_5CO(CH_2)_3CH_3$	96 / 72.9	86 / 81.7	78 / 88.6
6	$C_6H_5COCH_2CH(CH_3)_2$	96 / 71.2	80 / 78.5	75 / 80.9
7	$C_6H_5COC(CH_3)_3$	93 / 62.1	75 / 68.2	68 / 73.5

6.3.4 Recycle and Reuse of Ionic Liquids

We investigated the reusability of ionic liquids for the asymmetric reduction of acetophenone catalyzed by the complex of (*R*)-BINOL-LAH. The recycling process involved washing the used ionic liquids with diethyl ether. Any organic residue left in the ionic liquid layer could be removed by the ether wash. The ionic liquid layer was decanted and evaporated under reduced pressure at 65°C, then purified following the method in Section 2.2.4 (Figure 6.3). Successive runs were performed with the recovered ionic liquid $[EtPy]^+[BF_4]^-$ or $[EtPy]^+[CF_3COO]^-$ at room temperature for four hours.

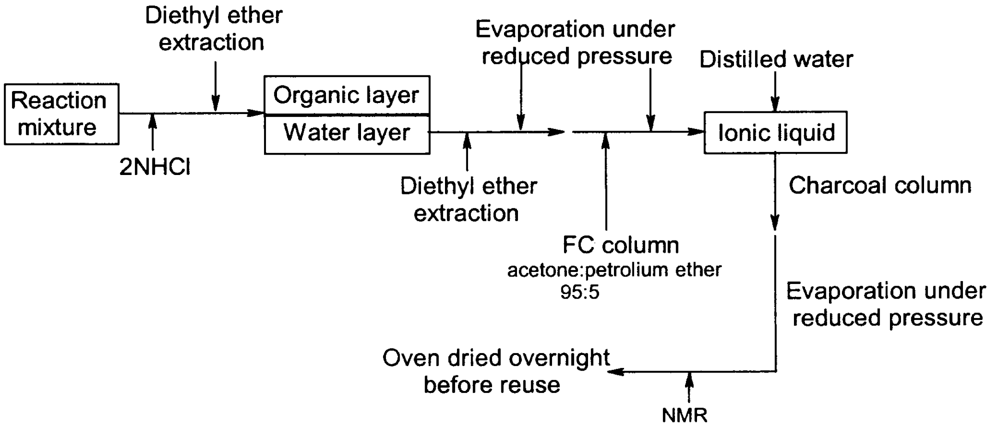


Figure 6.3 Flow chart of recycling process of ionic liquids

Table 6.5 Recycling and Reuse of Ionic Liquids

Recycling #	$[EtPy]^+[BF_4]^-$		$[EtPy]^+[CF_3COO]^-$	
	Recovered(w%)	Yield/ee(%)	Recovered(w%)	Yield/ee(%)
0	-	99 / 67	-	99 / 68
1	93	97 / 64	87	98 / 51
2	92	98 / 65	76	99 / 43
3	90	98 / 63	68	99 / 37

The results show ionic liquid $[EtPy]^+[BF_4]^-$ could be recovered efficiently and almost without loss of activity and selectivity. This is evident from the fact that the yield and ee were not affected much even after the 3th run. In this reaction, however, $[EtPy]^+[CF_3COO]^-$ could not be recovered as efficiently as the previous cases. It may be because lithium aluminum hydride, as a powerful reductant, might react with carbonyl group of trifluoroacetate anion. The evidence is that a color change of $[EtPy]^+[CF_3COO]^-$ has been observed during experiments, which changed from colorless/light yellow to yellow, then to brown.

In $[EtPy]^+[CF_3COO]^-$, enantiomeric excess dropped dramatically. This is due to solvent properties which changed along with the transformation. However, the reduction yields have not been affected.

6.4 Proposed Mechanism

Based on Noyori's work (1979), we proposed a detailed transition state working model for the asymmetric reduction of aryl alkyl ketones (Figure 6.4). As mentioned in Section 6.2.2, after adding $LiAlH_4$ to the mixture of BINOL and ionic liquid, the BINOL-LAH complex formed accompanied with gas (H_2) generating. The BINOL-LAH complex and the carbonyl group in ketones form a six-membered, chelating ring transition state. There are two possible transition states in this study, which is dependent on the different reactive site recognition. As can be seen in Figure 6.4, transition state (*R*)-T.S. with axial alkyl and equatorial phenyl groups is favored over (*S*)-T.S., which has the opposite conformations, i.e., phenyl group at axial position and alkyl group at equatorial position. Because (*S*)-T.S. suffers severe steric repulsion between the benzene ring and the binaphthyl group, thus distorting the molecule orbitals, and therefore increasing the activation energy of (S)-enantiomer. As a result, (*R*-) configuration products are major products in accordance with the experimental data.

The structures of transition states also make it easy to be understood that the bulky and branched alkyl group of ketones could eliminate the energy gap between *R* and *S* configuration products, therefore decreasing the enantioselectivities.

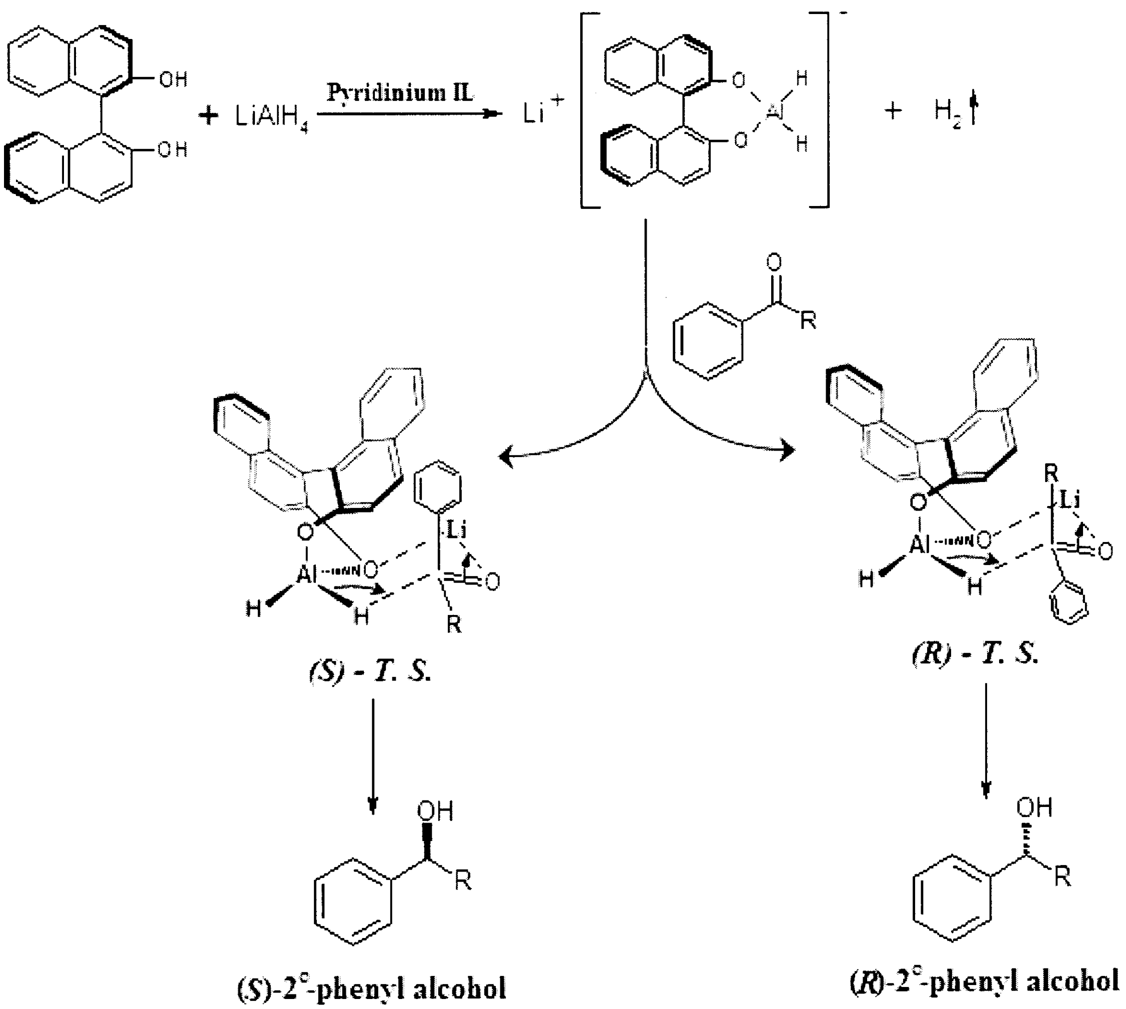


Figure 6.4 The proposed mechanism of asymmetric reduction of aromatic ketones

6.5 Summary

Both pyridinium-based ionic liquids are feasible media for asymmetric reduction of aromatic ketones with chiral BINOL/BINOL-Br modified lithium aluminum hydride. They can efficiently substitute the traditional organic solvents (e.g. THF). The reactions proceed at relatively fast rate and achieve high yield and ee. In our study, the catalytic activity and enantioselectivity were found to be influenced by the substituents of BINOL derivatives. The experimental data shows that the (*R*)-6, 6'-Br-BINOL-LAH complex was a more effective catalysis system than the (*R*)-BINOL-LAH complex. However, this reaction still has a problem: $[EtPy]^+[CF_3COO]^-$ could not be recycled quantitatively and the enantioselectivity dropped down when reused.

CHAPTER 7

CONCLUSIONS

In this study, two pyridinium-based ionic liquids, N-ethyl pyridinium tetrafluoroborate $[EtPy]^+[BF_4]^-$ and N-ethyl pyridinium trifluoroacetate $[EtPy]^+[CF_3COO]^-$ were prepared and the synthesis procedure improved by introducing a titration step. These pyridinium-based ionic liquids were tested as solvents for C-C and C-H bond forming reactions. These reactions are:

1) Diels-Alder Reactions

It is the first study using N-ethyl-pyridinium cation based ionic liquids in Diels-Alder reactions. The reactions between isoprene and representative dienophiles showed highly enhanced reaction rate with $[EtPy]^+[CF_3COO]^-$, and to lesser extent in $[EtPy]^+[BF_4]^-$. This could be due to three reasons: (i) high polarity; (ii) strong Lewis acidity; and (iii) strong hydrophobic effect of ionic liquids. Furthermore, $[EtPy]^+[CF_3COO]^-$ could be recycled and reused efficiently.

2) Friedel-Crafts Alkylation and Acylation

The reaction strategy and conditions were studied in detail for both alkylation and acylation reactions. We found that $FeCl_3$ could efficiently replace $AlCl_3$ as catalyst in both these ionic liquids. Thus providing an environmentally acceptable catalyst ($FeCl_3$) substitutes more commonly used but hazardous $AlCl_3$. The improved results seen in these ionic liquids could be due to: (1) high polarity; (2) strong Lewis acidity; (3) strong hydrophobic effect; and (4) high solvating property of these solvents. The ionic liquids-$FeCl_3$ mixture could not be easily recycled and reused. Even adding fresh $FeCl_3$ into the already used mixture did not give good results. However, we could recycle ionic liquids alone and effectively use it with fresh $FeCl_3$.

3) Asymmetric Friedel-Crafts Reactions

It is the first investigation on the application of N-ethyl-pyridinium-based ionic liquids for this reaction. Both ionic liquids can be recycled and reused efficiently. However, the reaction yields were lower than those with organic solvents. This could be due to the interaction between cations and reactants. Further investigation with other anions would be needed for better understanding.

4) Asymmetric Reduction of Aromatic Ketones

It is the first study on the application of N-ethyl-pyridinium cation containing ionic liquids as solvents in asymmetric reduction of aromatic ketones. The enantioselectivity observed is lower than seen in organic solvents. However, the amount of catalytic complex required was reduced compared to those with organic solvents. For the representative examples studied $[EtPy]^+[CF_3COO]^-$ could not be easily recycled. The yield of recovered ionic liquid and the % ee of the reduced ketone product dropped significantly. While $[EtPy]^+[BF_4]^-$ could be recycled and reused efficiently.

These studies show that N-ethyl-pyridinium cation based ionic liquids are feasible solvents for C-C and C-H bond forming reactions investigated here. As this cation is non-toxic (Zhang and Malhotra, 2005), more reactions should be studied in these ionic liquids for development of methodologies useful in the chemical and pharmaceutical industries.

APPENDIX A

SOME CONCEPTS

CHIRALITY is the ability of a chemical substance to exist in two mirror-image forms which cannot be superimposed upon each other; each of them rotates polarized light in opposite directions.

CONCERTED reaction is a reaction that takes place in a single kinetic step.

EC50 value is a statistically or graphically estimated concentration of a substance (or a toxicant) resulting in 50% effect reduction of a given population of organisms under defined conditions. Decreasing EC50 values indicate higher toxicity.

ECOTOXICOLOGY is a specialized area within toxicology and is the study of the fate of toxic substances and their effects on an ecosystem; ecotoxicology builds on the science of toxicology and the principles of toxicological testing, although its emphasis is more on the population, community, and ecosystem.

ELECTROCHEMICAL WINDOW is the range within which cations and anions are inert toward electrochemical oxidation and reduction.

ENANTIOMER is either one of a pair of compounds that are mirror images on each other but are not identical.

ENANTIOMERIC EXCESS (ee/e.e.) is the proportion of the major enantiomer less that of the minor enantiomer and commonly expressed as a percentage. The five main ways of determining e.e.'s are:

- Polarimetry
- Isotope dilution

- Gas chromatographic methods
- Liquid chromatographic methods
- NMR resolution with
    - chiral derivatives
    - chiral solvating agents
    - chiral shift reagents

GREEN CHEMISTRY is the use of chemistry for pollution prevention or, more specifically, is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances.

LC50 is lethal concentration. The value is the statistically derived estimate of a concentration of a substance resulting in death of 50% individuals by a predetermined time; decreasing LC50 values indicate higher toxicity.

LD50 is lethal dose. The amount of a substance that is lethal to 50 per cent of the experimental animals exposed to it. LD 50 is usually expressed as the weight of the substance per unit of animal body weight (in order to account for weight difference among animals).

POLAR SOLVENT is a solvent that will dissolve and stabilize dipolar or charged solutes.

SYNCHRONOUS reaction is a reaction in which the various changes in bonding have progressed to similar extents in the transition state.

TOXICOLOGY is the study of adverse effects of xeno-biotics on living systems.

APPENDIX B

REACTION PICTURES

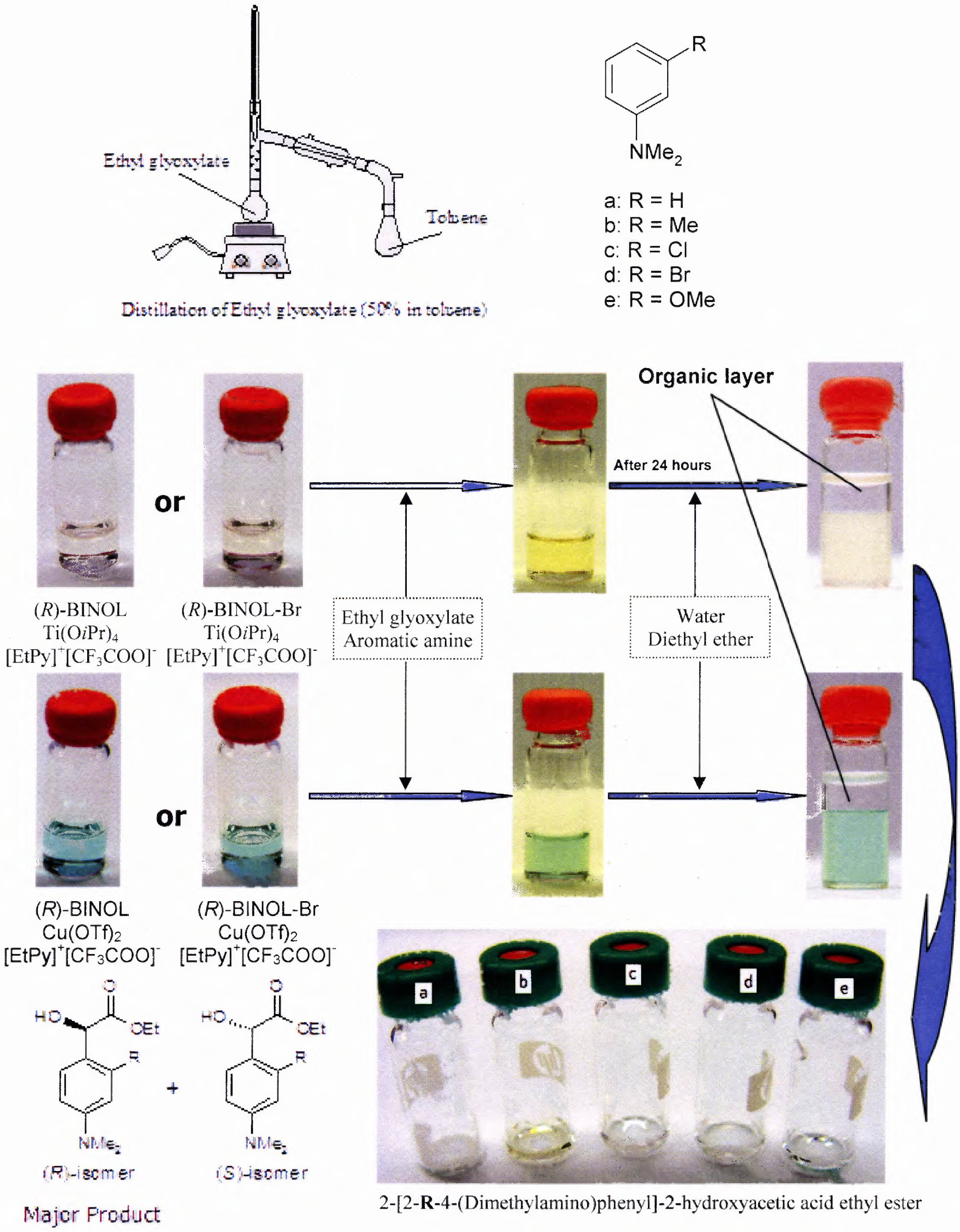


Figure B.1 The asymmetric Friedel-Crafts reaction

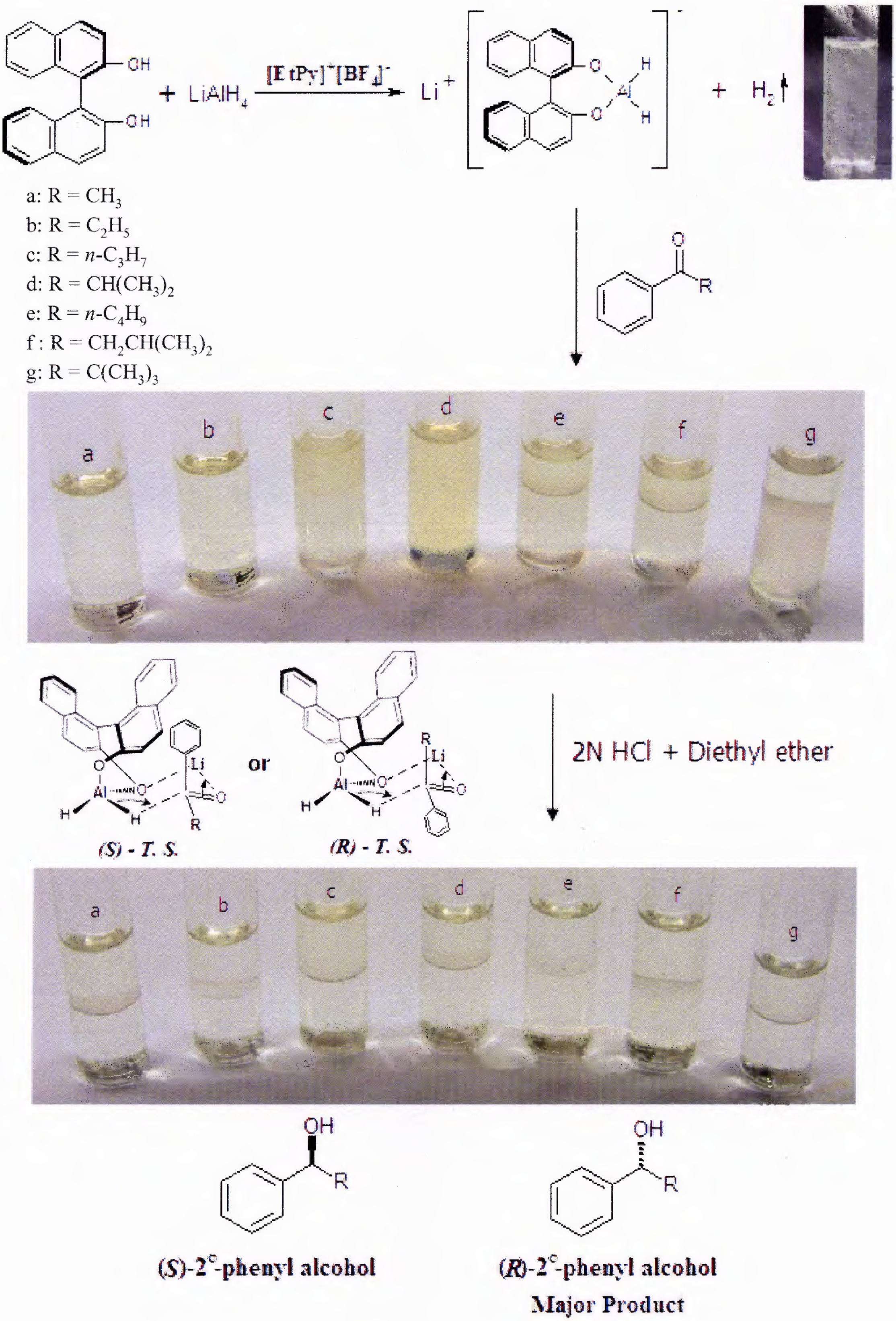


Figure B.2 The asymmetric reduction of aromatic ketones

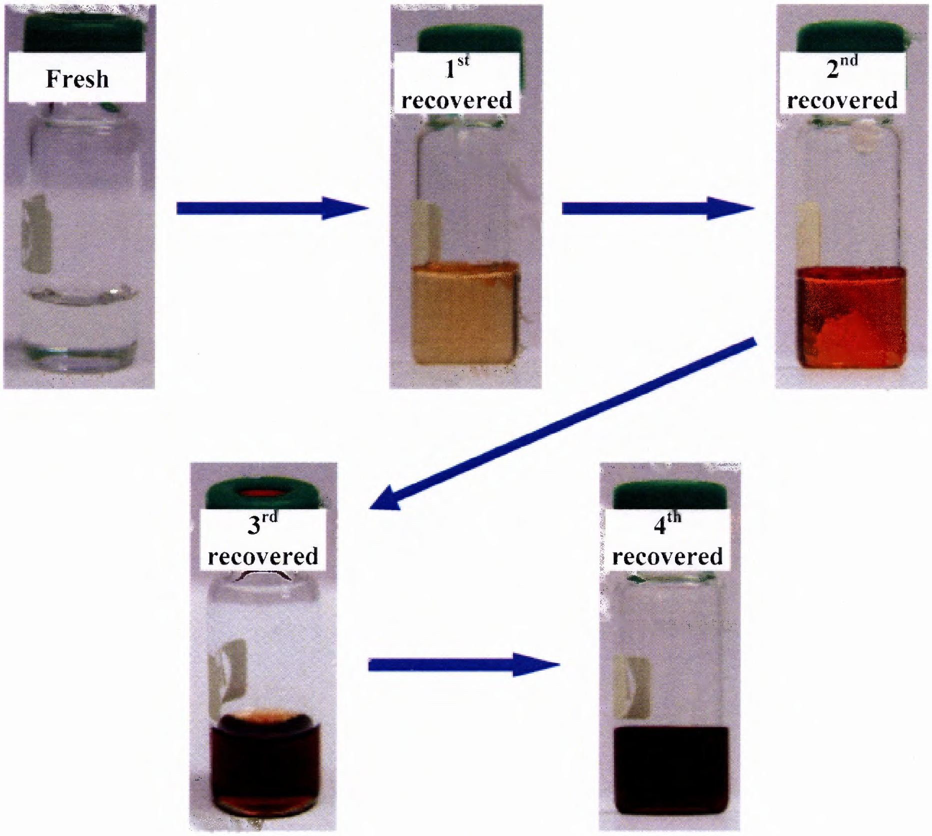


Figure B.3 Recylce and reuse of $[EtPy]^+[CF_3COO]^-$ in the asymmetric reduction of acetophenone

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