Investigation of Catalytic Reactions in Novel Ionic Liquids

A thesis submitted for the degree of Ph.D.

by

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I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of Ph.D is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

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Date : 22/09/03

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Abstract

Solvents play a very important role in organic chemistry. Most reactions must be carried out in solvents, thus for chemists, they have to deal with huge volumes of solvents everyday. Solvents can be highly damaging chemicals for two simple reasons: (1) they are used on a large scale, (2) they are often volatile which makes them difficult to contain. For the reason of environmental protection and reduction of damage to human being, clean technologies have become a major concern throughout both industry and academia. Therefore, search for the replacement of the damaging solvents has became a high priority.

Based on such ideas, we have investigated some catalytic reactions in room temperature ionic liquids 1,3-dialkylimidazolium, which are potentially a new type of variety of solvent system to replace the conventional solvents. We have also studied the applications of ionic liquids in several different fields.

In this respect, the ambient temperature ionic liquid 1,3-dialkylimidazolium systems [BMIM]PF_6 or [BMIM]BF_4 were employed for coupling reactions with nickel (0) complexes as catalyst (Chapter 2); to support the bioreduction with immobilised baker's yeast in the presence of water (Chapter 3); for the studies of diaryl ether-formation reaction catalysed by palladium with ligand in ionic liquid (Chapter 4); and for the indium-catalysed Sakurai reaction in ionic liquid (Chapter 5).

List of abbreviations

Ac	acetate
acac	acetylacetonate
Ar	aryl
BF_4^-	tetrafluoroborate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
$BMIM^+$	1-butyl-3-methylimidazolium
BnCl	benzyl chloride
BnCN	phenylacetonitrile
Bu	butyl
COD	1,5-cyclooctadiene
CTV	cyclotriveratrylene
cP	centipoises
dba	dibenzylidene acetone
DBU	1,8'-diazabicyclo-[5,4,0]-undec-7-ene
DIBAH	di-*iso*-butylaluminum hydride
DMF	*N.N'*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiometric excess
$EMIM^+$	1-ethyl-3-methylimidazolium
Et	ethyl
eq	equation
GC	gas chromatography
L	ligand
LAB	linear alkylbenzenes
MMA	methyl methacrylate
Me	methyl
MTO	methyltrioxorhenium
NADPH	nicotinamide adenine dinucleotide phosphate

nbd	norbornadiene
1-BuPy	1-butylpyridium
1-EtPy	1-ethylpyridium
NMDPP	neomethyldiphenylphosphane
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Np	1-naphthoic acid
OTf^-	triflate
PF_6^-	hexafluorophosphate
Ph	phenyl
Pr	propyl
PTC	phase-transfer catalysis
RE	rare earth
sc	supercritical
THF	tetrahydrofuran
TMSCl	trimethylsilylchloride
$TMSN_3$	azidotrimethylsilane
TsOH	*p*-toluenesulfonic acid
UHP	urea hydrogen peroxide
η	viscosity
ρ	density

Chapter 1.

1. Introduction of ionic liquids

In recent years, significant progress has been made in the application of room temperature ionic liquids in catalytic processes. Ionic liquids are salts consisting of ions, which exist in the liquid state at ambient temperature, *i.e.* they are salts that do not normally need to be melted by means of an external heat source. They are, depending on point of view, often distinguished from the classical definition of molten salts, which is generally thought to refer to a high-melting, highly viscous and very corrosive medium. Ionic liquids are already liquid at low temperature (<100°C) and have relatively low viscosity.

Compared with conventional organic solvents, ionic liquids are often discussed as promising solvents for "clean processes" and "green chemistry" in recent publications [1a–c]. The advantages of ionic liquids can be used in many applications to minimise solvents and catalysts consumption. Ionic liquids have no measurable vapour pressure, therefore there is no loss of solvent through evaporation. Environmental and safety problems arising through the use of volatile organic solvents can be avoided by replacement of a non-volatile ionic liquid as a reaction medium. Ionic liquids can be good candidates for biphasic reactions because of their unique characteristics of combination of a wide range of inorganic and organic materials. The work-up procedures can be simplified for the biphasic reactions and the homogeneous catalysts can be reused many times.

In synthetic chemistry, the conversion rate and chemical specificity are more fundamental and important. It is always an impetus for chemists to design new routes or use new solvents to improve their reactions. Ionic liquids have a great potential to help them in reaching these goals. It was found that using ionic liquid as replacement of conventional organic solvents could accelerate reaction rate and minimise side

reactions in many cases. This is a great contribution to "green chemistry" both in solvent and catalysis.

Ionic liquids are not new, some of which have been known for many decades. $[EtNH_3]NO_3$, for example, which has melting point of 12°C, was first reported in 1914 [2]. The first ionic liquid with chloroaluminate ions (1-ethylpyridinium bromide–aluminium chloride melt salts) has been known since 1951 [3], was the start of the introduction of ionic liquids. However, these systems were not studied further until the late 1970s when the groups of Osteryoung and Wilkes investigated them [4, 5]. For the first time they succeeded in preparing room temperature liquid chloroaluminate melts. Research and development concentrated mainly on electrochemical applications at this time. It was the discovery of 1-ethyl-3-methylimidazolium ($[EMIM]^+$) based chloroaluminate ionic liquid in 1982 that led to the dramatic interest in this active area. The groups of Seddon and Hussey began to use chloroaluminate melts as non-aqueous, polar solvents for the investigation of transition metal complexes in electrochemical aspects [6a–d].

The first publications in which ionic liquids were described as new reaction media and catalysts for organic synthesis appeared at the end of the 1980s. Acidic ionic liquids with chloroaluminate ions proved to be effective as Friedel-Crafts catalysts [7]. Phosphonium halide melts were used successfully in nucleophilic aromatic substitution reactions [8].

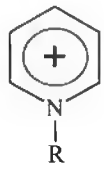
The use of ionic liquids as solvents for homogeneous transition metal catalysts was described for the first time in 1990 by Chauvin *et al.* and by Wilkes *et al.* Chauvin's group dissolved nickel catalysts in weakly acidic chloroaluminate melts and studied the resulting ionic catalyst solutions for dimerisation of propene [9]. Wilkes *et al.* investigated the ethylene polymerisation catalysed by Ziegler-Natta also in weakly acidic chloroaluminate melts [10].

A new type of ionic liquid with enhanced stability against hydrolysis compared with chloroaluminate ionic liquids was reported in 1992 [11]. These systems offer high tolerance to functional groups and opens up a much larger range of applications especially for transition metal catalysis.

Tremendous work has been carried out to understand the physical properties of ionic liquids over the past ten years, and recently more and more attention was drawn to the investigation of reactions in ionic liquids and the synthesis of new ionic liquids [12a-c].

Many ionic liquids are both air and moisture stable, their solubility with water depends on the nature of the anions. For the same 1-butyl-3-methylimidazolium cation, the BF_4^-, $CF_3SO_3^-$, NO_3^-, and Cl^- salts display a complete miscibility with water at 25°C. However, upon cooling down the [BMIM]BF_4/water mixture to 4°C, a water-rich phase separates. On the other hand, the PF_6^-, $(CF_3SO_2)_2N^-$ show a very low miscibility with water. Ionic liquid systems with chloroaluminate anions are extremely hygroscopic and they can react with water to release superacid proton, which can cause unwanted side reaction. Much of the early work focused on moisture sensitive ionic liquids, which restricted the application of ionic liquids in organic synthesis. The discovery of moisture stable ionic liquid brought a new era to the chemistry.

There are four typical types of ionic liquids based on the different cations. The most common salts in use are those with alkylammonium, alkylphosphonium, 1-alkylpyridinium and 1, 3-dialkylimidazolium cations. The combination of cations with various anions represent the main families of ionic liquids (Table 1).

Cation		Anion
		$[BF_4]^-$ $[PF_6]^-$ $[SbF_6]^-$ $[CF_3SO_3]^-$ $[CuCl_2]^-$ $[AlCl_4]^-$ $[AlBr_4]^-$ $[AlI_4]^-$ $[AlCl_3Et]^-$ $[NO_3]^-$ $[NO_2]^-$ $[SO_4]^{2-}$
(a)	(b)	
$[NR_nH_{4-n}]^+$	$[PR_nH_{4-n}]^+$	$[Cu_2Cl_3]^-$ $[Cu_3Cl_4]^-$ $[Al_2Cl_7]^-$ $[Al_3Cl_{10}]^-$
(c)	(d)	

R = alkyl, R' =alkyl

Table 1. Typical cation/anion combination in ionic liquids. (a) 1,3-dialkylimidazolium (b) 1-alkylpyridinium (c) alkylammonium (d) alkylphosphonium cations.

Among the four typical types of ionic liquids, the one based on 1,3-dialkylimidazolium is most widely investigated, and its halogenoaluminate(III) salts are widely studied in electrochemistry and organic synthesis.

1.1 Synthesis of ionic liquids

There are two basic methods for preparation of ionic liquids: (1) Metathesis of a halide salt with a silver, group 1 metal or ammonium salt of the desired anion; (2) Acid-base neutralisation reaction.

The metathesis is the most widely used methodology in preparation of ionic liquids (Figure 1). For example, tetraalkylammonium tetraalkylborides [13a–b], pyridnium

halides [3] and 1,3-dialkylimidazolium salts with various anions [11,14] can be achieved this way.

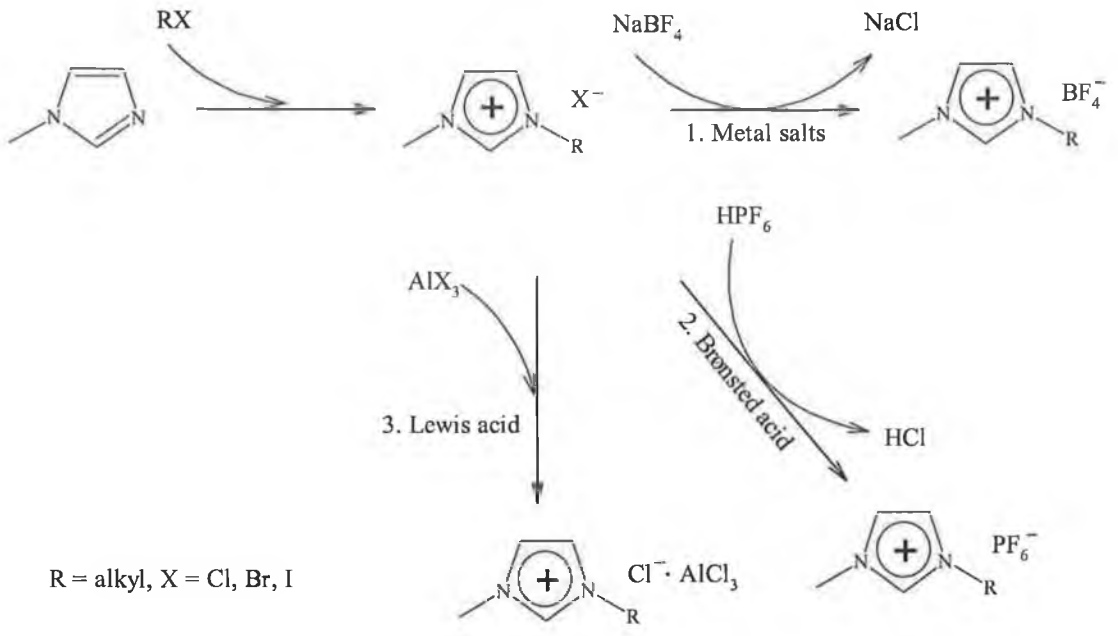


Figure 1. Typical preparation routes for ionic liquids.

This method is also a good way for those preparing new ionic liquids for the first time. However, a small amount of halide ions can be left in ionic liquids, which may react with solute materials.

The second method for preparing ionic liquids is acid-base neutralisation: the alkylammonium salt is treated with an acid to generate the desired anion. Monoalkylammonium nitrate salts are prepared by neutralisation of aqueous solution of amine with nitric acid [15]. Similarly, tetraalkylammonium sulfonates have been prepared by mixing equimolar amounts of the sulfonic acid and the tetraalkylammonium hydroxide [16].

Other methods for the synthesis of ionic liquids are through the quaternization of the appropriate amine and direct combination of a halide salt with a metal halide. A number of 1-alkyl-3-methylimidazolium trifluoromethanesufonate salts are prepared *via* the quaternization, which is by the reaction of methyl triflate with a stoichiometric amount of the 1-alkylimidazole in 1,1,1-trichloroethane [17].

Recently, microwave-assisted preparation of dialkylimidazolium tetrachloroaluminates has been reported [18]. This method developed the synthesis of 1,3-dialkylimidazolium tetrachloroaluminates using a microwave oven under solvent-free conditions. It is relatively much faster, efficient and eco-friendly without using a large excess of alkyl halides as reaction medium to generate ionic liquid *in situ*.

It should be noticed that the synthesis of highly pure, binary ionic liquids is usually achieved by anion exchange over an ion exchanger.

1.2 Physical properties of ionic liquids

1.2.1 Melting point

The melting points of ionic liquids are much lower compared with metal salts. For example, the melting point of sodium chloride is 803°C, but for [BMIM]Cl, the melting point is only 65°C. Investigation showed that in an ionic liquid, the low symmetry, weak intermolecular interactions (such as the forces of hydrogen bonding) and a good distribution of charge in the cation made the melting point lower [19a–c].

The symmetric character of the cation can influence the melting point. For example, $[Me_2Im]^+$ and $[Et_2Im]^+$ salts present higher melting points than the salts with asymmetric cations [17] (Table 2).

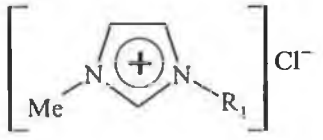
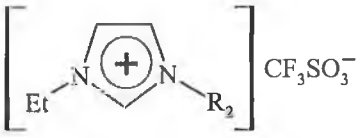
Imidazolium salt		m.p. (°C)
	$R_1 = CH_3$	125
	$R_1 = CH_2CH_3$	87
	$R_1 = CH_2(CH_2)_2CH_3$	65
	$R_2 = CH_2CH_3$	23
	$R_2 = CH_2(CH_2)_2CH_3$	2

Table 2. Influence of different cations on the melting point of imidazolium.

The anion influences the melting point as well. Comparison of the melting points of different salts with the same cation 1-ethyl-3-methylimidazolium (EMIM) concluded that, in most cases, an increasing size of the anion with the same charge leads to a further decrease in the melting point (Table 3).

Cation	**Anion**	m.p. (°C)	Ref.
	Cl^-	87	[5]
	NO_2^-	55	[11]
	NO_3^-	38	[11]
	$AlCl_4^-$	7	[20]
	BF_4^-	6	[21]
	$CF_3SO_3^-$	-9	[17]
	$CF_3CO_2^-$	14	[17]

Table 3. The influence of different anions on the melting point of imidazolium salts.

1.2.2 Lewis acid-base equilibrium of 1,3-dialkylimidazolium chloroaluminate ionic liquids

There is a Lewis acid-base balance manipulated by the ratio of $AlCl_3$ to1,3-dialkylimidazolium halide. The composition of these systems in ionic liquid can be simply described by the following reactions:

$$[Al_2Cl_6] + Cl^- \rightarrow [Al_2Cl_7]^- \quad (1)$$

$$2[AlCl_4]^- \rightleftharpoons [Al_2Cl_7]^- + Cl^- \quad (2)$$

$$2[Al_2Cl_7]^- \rightleftharpoons [Al_3Cl_{10}]^- + [AlCl_4]^- \quad (3)$$

In the equations (1) – (3), the $AlCl_4^-$ is a neutral anion, the Cl^- is a basic anion, the $Al_2Cl_7^-$ and the $Al_3Cl_{10}^-$ are acidic anions.

In an ionic liquid, if imidazolium salt is in excess, the molar ratio of $AlCl_3$ is smaller than 0.5, the ionic liquid which contains $AlCl_4^-$ anion and Cl^- anion is a Lewis base; if the $AlCl_3$ in excess, the molar ratio of $AlCl_3$ is larger than 0.5, the ionic liquid which contains $Al_2Cl_7^-$ anion and $AlCl_4^-$ anion, is a Lewis acid. An ionic liquid prepared from equimolar amounts of $AlCl_3$ and imidazolium salt is a neutral system, the molar ratio is exactly 0.5, the ionic liquid only contains $AlCl_4^-$. The following figure can show the equilibrium clearly (Figure 2).

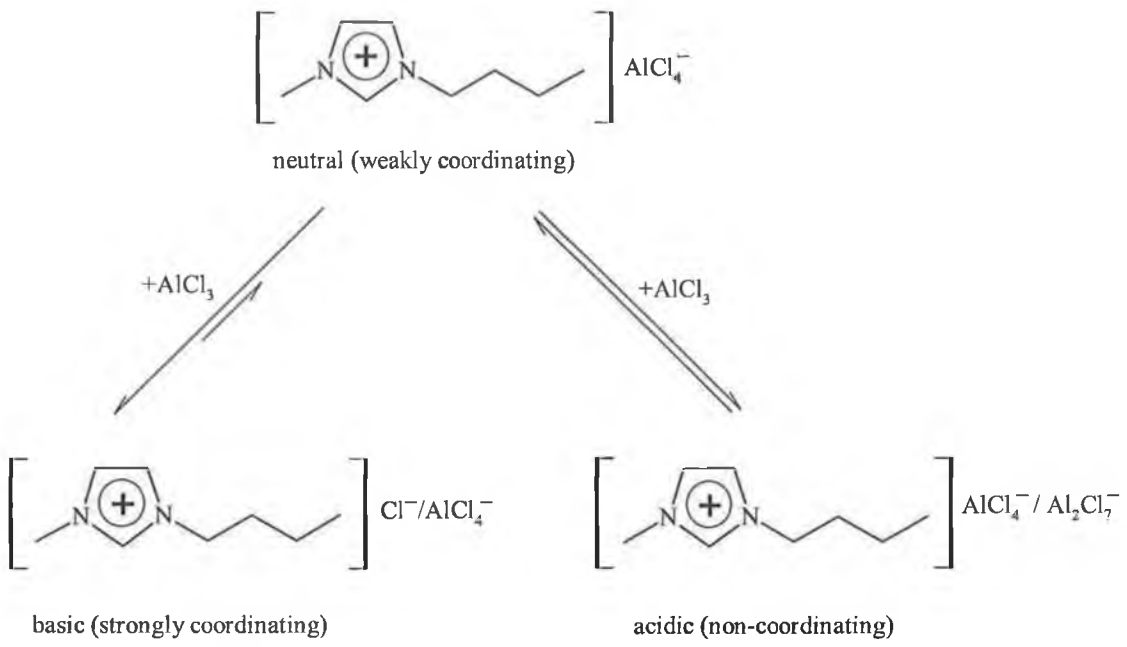


Figure 2. Control of the acidity of [BMIM]Cl by the ratio of $AlCl_3$.

1.2.3 The hydrogen bonding in an ionic liquid

The study of hydrogen bonding of ionic liquids has been based mainly on the model of 1,3-dialkylimidazolium halogenoaluminates. Seddon's group utilised multinuclear NMR spectroscopy and conductivity measurements to show that the [EMIM]Br or [EMIM]I structures consist of layers of anions and cations which are interconnected by an extended network of hydrogen bonds. Each cation is hydrogen bonded to three anions and each anion is hydrogen bonded to three cations. The $H^4\cdots X^-$ and $H^5\cdots X^-$ contacts are considerably longer than the $H^2\cdots X^-$, indicating weaker hydrogen bonds (Figure 3) [22a–b].

However, in [EMIM]Cl ionic liquid, the arrangement is considerably more complicated. Each of the crystallographically distinct chloride ions is hydrogen bonded to three cations, but to different ring protons. One chloride ion is bonded to the H^4 proton of one cation and to the H^2 protons of two other cations, the next is bonded to the H^4 protons of two cations and the H^2 proton of the third cation, the next

is bonded to H^4 proton of one cation and to the H^5 protons of two cations and the final chloride is bonded to the H^2 proton of one cation and to the H^5 protons of two cations.

As AlX_3 ($X = Cl^-$ or Br^-) is added to the appropriate salt the hydrogen-bond network is disrupted and ionic liquids are formed. In basic ionic liquids the extent of hydrogen bonding is still significant. As the liquids are made more acidic the hydrogen-bond acceptor X^- is replaced by $[AlX_4]^-$ and then $[Al_2X_7]^-$, until no hydrogen bonds are present [22a–b].

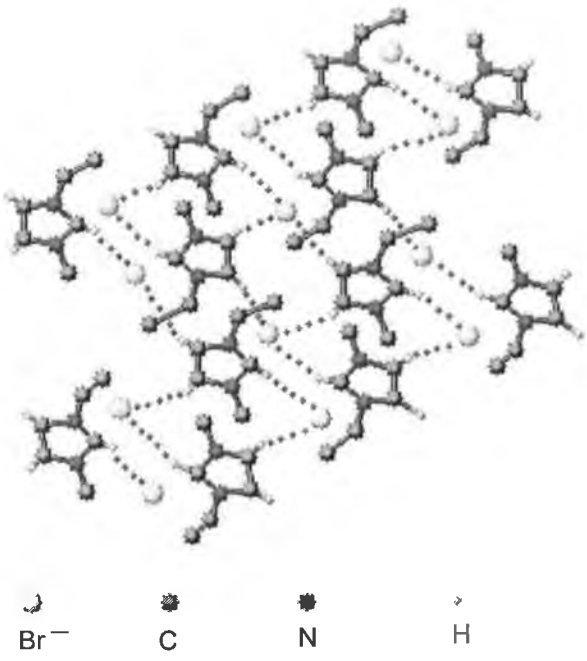


Figure 3. The network of hydrogen bonds in ionic liquid [BMIM]Br.

1.2.4 Density of ionic liquids

Investigation of chloroaluminate melts revealed the density of an ionic liquid depends on the type of cation and anion. A comparison of chloroaluminate melts with different cations gives an almost linear relationship between the density and the length of *N*-alkyl chain on the imidazolium cation [20] (Figure 4).

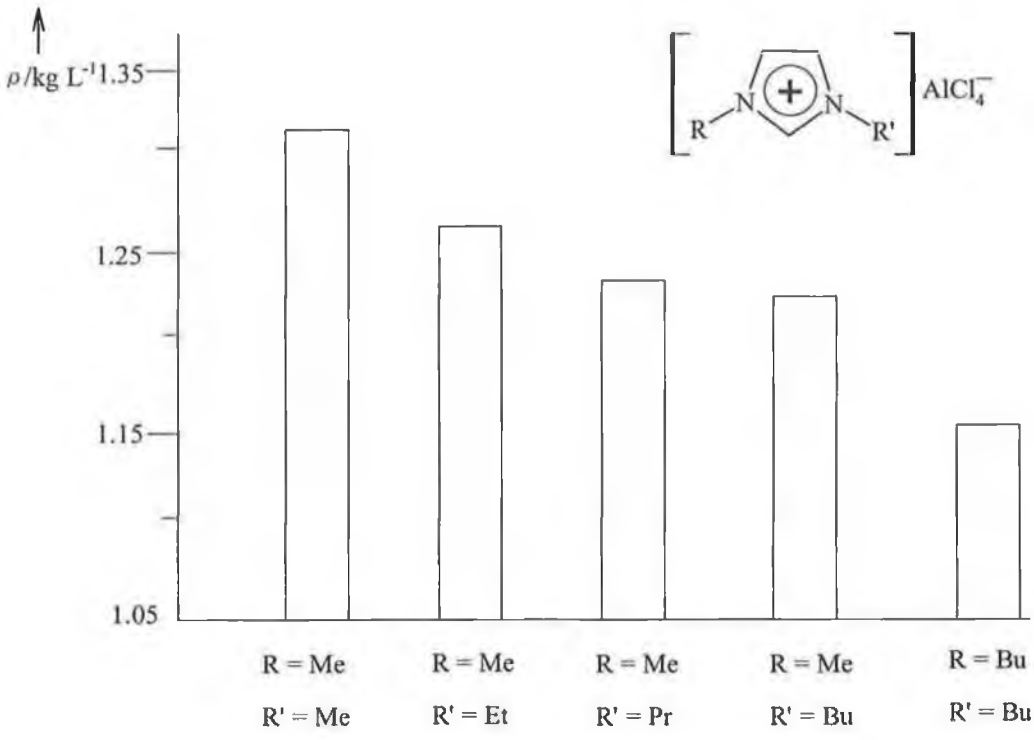


Figure 4. Dependence of the density of 1,3-dialkylimidazolium tetrachloroaluminate melts on the type of both alkyl groups; measurement temperature at 60°C, $x(AlCl_3) = 0.5$.

In general, it is considered the density of comparable ionic liquids decreases as the bulkiness of the organic cation increases.

1.2.5 Viscosity of ionic liquids

The viscosity of ionic liquids is essentially determined by their tendency to form hydrogen bonding and by the strength of their van der Waals interactions.

In studies on the viscosities of chloroaluminate melts of different compositions, we can see the effect of hydrogen bonding. When the composition $x(AlCl_3) < 0.5$, the ionic liquid is Lewis base, the viscosity increased very quickly because of the

formation of hydrogen bonds between the hydrogen atoms of the imidazolium cation and the basic chloride ion [20] (Figure 5). In acidic conditions, $x(AlCl_3) > 0.5$, the anions $AlCl_4^-$ and $Al_2Cl_7^-$ are present, in which the negative charge is much better distributed. This resulted in the formation of weaker hydrogen bonds and a much lower viscosity.

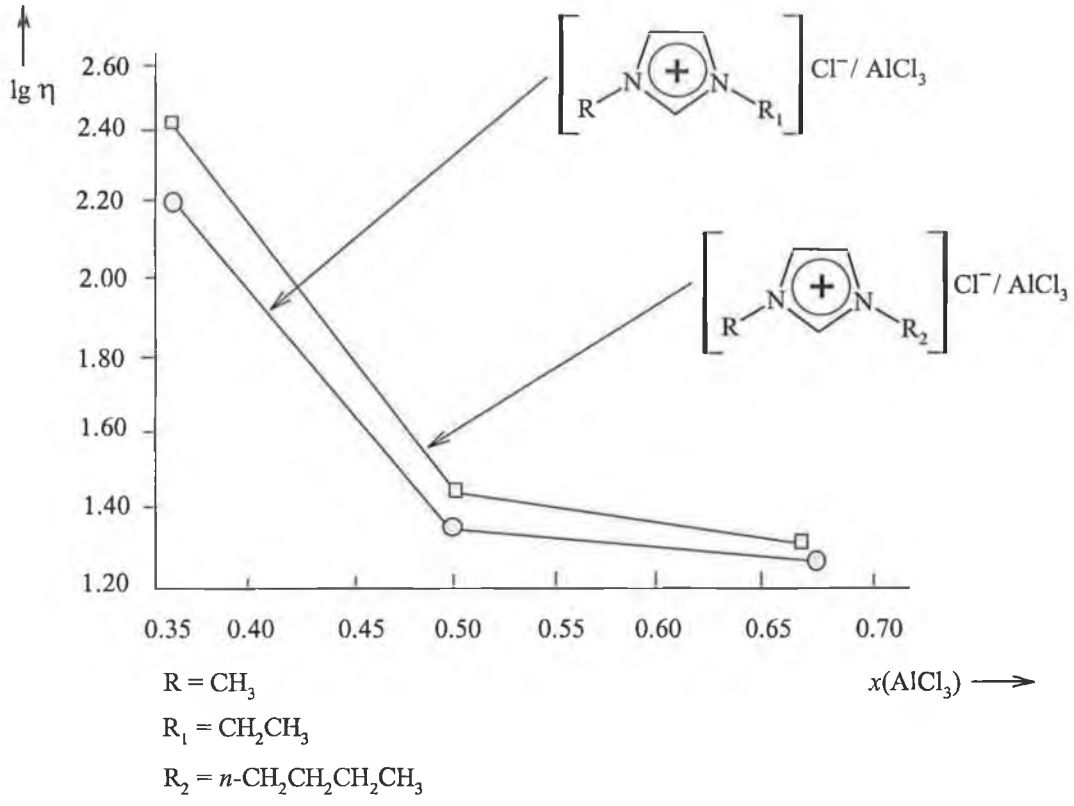


Figure 5. Dependence of the viscosity of two 1,3-dialkylimidazolium tetrachloroaluminate melts on the mole fraction of $AlCl_3$ at 25°C.

The viscosity of 1-*n*-butyl-3-methylimidazolium with different anions showed the interplay between van der Waals interactions and hydrogen bonding. From $CF_3SO_3^-$ ion to the n-$C_4F_9SO_3^-$ ion, and from the CF_3COO^- ion to the n-$C_3F_7COO^-$ ion reveals an obvious increase in viscosity. It is because the van der Waals attraction dominates over the H-bonding which results in a higher viscosity of ionic liquid. From $CF_3SO_3^-$ ion to $(CF_3SO_2)_2N^-$ ion, however, almost complete H-bonding

suppression slightly dominates over the van der Waals attraction increase to give a lower viscosity (Table 4) [18].

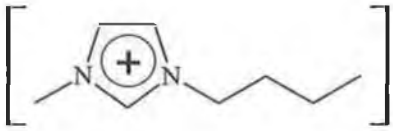
Cation	Anion	η [cP]
	$CF_3SO_3^-$	90
	n-$C_4F_9SO_3^-$	373
	CF_3COO^-	73
	n-$C_3F_7COO^-$	182
	$(CF_3SO_2)_2N^-$	52

Table 4. Dynamic viscosities of various $[BMIM]^+$ salts at 20°C.

The cation structure can also influence the viscosity of ionic liquids. Generally, quaternary ammonium, 1-alkyl-1-methylpyrrolidinium and 1-alkyl-3-methylimidazolium dicyanamides $[N(CN)_2]^-$ give lower viscosity. For example, the viscosity for the $[EMIM][N(CN)_2]$ is 21cP at 25°C with respect to 34cP for $[EMIM](SO_2CF_3)_2N$. For 1,3-dialkylimidazoliun salts, the 1-ethyl-3-methylimidazolium gives the lowest viscosity, in which a side chain with sufficient mobility is combined with a low molecular weight. Longer or fluorinated alkyl chains make the salt more viscous [17].

1.3 Chemical properties

Ionic liquids have a unique property of combination with organic and inorganic compounds, which make them interesting alternative candidates for solvents. The advantages of ionic liquids as solvents are as following:

(1) Non-volatile, the product from ionic liquid can be distilled, and the liquid can be used in extreme situations, such as high vacuum systems and eliminate many containment problems.
(2) Wide liquid range, some ionic liquids can be handled up to 300°C and still remains liquid.
(3) The ability of dissolving a wide range of organometallics, organic and inorganic compounds.
(4) Immiscible with a number of organic solvents, and provide a non-aqueous, polar alternative for two-phase systems.
(5) Composition of poorly coordinating ions, can be highly polar and yet non-coordinating.
(6) Potential to be reused and recycled.

1.3.1 Solubility characteristics of ionic liquids

The anion can influence the solubility of ionic liquids. It can be demonstrated by the example of the water solubility of different melts containing the $[BMIM]^+$ ion. While [BMIM]Br, $[BMIM]CF_3COO$ and $[BMIM]CF_3SO_3$ are highly water-soluble, ionic liquids with the same cation but with a PF_6^- or $(CF_3SO_2)_2N^-$ ion form biphasic mixtures with water. The water content of the ionic liquid $[BMIM](CF_3SO_2)_2N$ at 20°C is only 1.4 weight percent [17].

Several ionic liquids showing a miscibility gap with water have been considered as interesting candidates for separation processes by liquid-liquid extraction. The solubility of different acids and bases in water/$[BMIM]PF_6$ at different pH values of the aqueous phase was investigated [23]. It revealed a higher solubility of neutral substrates in the ionic liquid, while ionic species dissolve preferentially in the aqueous layer and the solubility properties of $[BMIM]PF_6$ versus water show high similarity to organic solvents. The substitution of volatile organic solvents by ionic liquids in extractive separation processes may therefore be an interesting option. Many ionic

liquids are completely miscible with organic solvents if their dielectric constants exceed a characteristic limit. This limit appears to be specific for each cation/anion combination [17].

The solubility of supercritical CO_2 in [BMIM]PF_6 has been investigated recently by Brennecke's group [24]. It showed that $ScCO_2$ is quite soluble in ionic liquids (60 mol% of CO_2 dissolved in the ionic liquid at 80 bar CO_2 pressure), but on the contrary, ionic liquids are not soluble in $scCO_2$. The possibility of extraction was investigated using the interesting sc CO_2 for the extraction of naphthalene from the ionic liquid. They succeeded in recovering the naphthalene quantitatively without any detectable contamination of the extract by the ionic liquid.

The solubility of CO_2 in ionic liquids is very dependent on the water content. Water saturated [BMIM]PF_6 can contain up to 2.3 wt.% water, and has a CO_2 solubility of only 0.13 mol fraction compared with 0.54 mol fraction CO_2 in dried (ca. 0.15 wt.% water) [BMIM]PF_6 at 57 bar 40°C [25].

Recently, continous-flow catalytic system based on the combination of ionic liquids and $scCO_2$ have been reported for hydrogenation [26], hydroformylation [27] and biocatalytic reaction [28].

1.3.2 Polarity of ionic liquids

The polarity of conventional solvents are usually determined by using the longest wavelength absorption band of Reichardt's dye: [2,4,6-triphenylpyridium *N*-4-(2,6-diphenylphenoxide)betaine] [29]. This method has also been used successfully to determine the polarity of a number of ionic liquids. The E_T^N value can be used to show the polarity of ionic liquids. For example, the value of ca. 0.95-1.01 for monoalkylammonium nitrates and thiocyanates is close to that of water (1.00, by definition) [30], and quaternary ammonium sulfonates give lower value of ca. 0.45-0.65 which is more similar to that of polar organic solvents such as DMSO [16].

Recently, the polarity of 1-alkyl-3-methylimidazolium based ionic liquids was investigated by Gordon *et al.* They used reichardt's dye to measure the λ_{max} of a number of ionic liquids and calculated E_T^N value. The results suggested that the 1-alkyl-3-methylimidazolium ionic liquids can be regarded as displaying hydrogen bond donor abilities similar to those of alcohols, while their nucleophilicities are much lower and entirely anion dependent. In this respect they are quite unique materials, since most solvents of such low nucleophilicity are generally regarded as non-polar [31].

Seddon's group also reported that a study of the absorption spectrum of the solvatochromic dye Nile Red in a range of 1-alkyl-3-methylimidazolium based ionic liquids showed similar λ_{max} values to those obtained in short chain alcohols [32].

However, investigation by Armstrong *et al.* gave rise to the question whether the chemical nature of the solvatochromic dye affects the results of the polarity determination of an ionic liquid. They used several 1-butyl-3-methylimidazolium based ionic liquids as stationary phase for gas chromatography to examine the retention times of a large number of substances. Their results showed different polarity of ionic liquids depending on the nature of the tested compounds. For example, [BMIM]PF_6 acts like an non-polar stationary phase when separating non-polar molecules, but for molecules with proton-donor or –acceptor characteristics, it acts very polar [33].

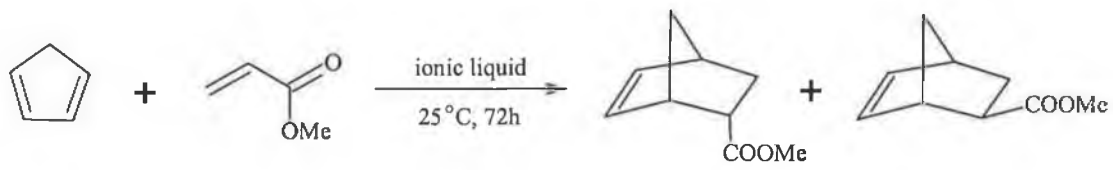
1.4 Organic reactions in ionic liquids

1.4.1 Diels-Alder reactions

Diels-Alder reaction remains one of the most useful carbon-carbon bond-forming reactions in organic synthesis. Recent investigations showed when ionic liquids are used in the reaction significant rate enhancements, high yields and selectivities have been observed. Ionic liquids were employed as both solvent and catalyst for the Diels-

Alder reaction. The first reaction studied was the reaction of cyclopentadiene with methyl acrylate and methyl vinyl ketone in $[EtNH_3]NO_3$ [34]. It was found that rate and stereoselectivity enhancements have been observed in $[EtNH_3]NO_3$ relative to those obtained in conventional organic solvents.

Recently, Welton's group investigated the same reaction in a wide range of ionic liquids [35]. It was found that there was a strong preference for the *endo* product and an acceleration of the reaction in comparison to non-polar organic solvents. Although the rate of reaction and the *endo* selectivity are not higher than those of reaction in water, the ionic liquid is still considered the most successful alternative solvent which can be used (Scheme 1).



1 **2** **3**

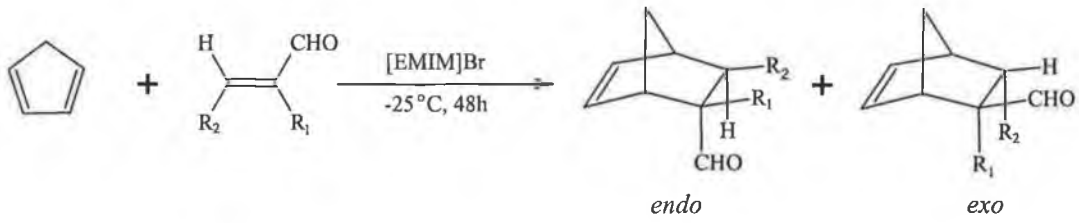
	(a) *endo*	(b) *exo*
$[BMIM]ClO_4$	84	16
$[EMIM]CF_3SO_3$	83	17
$[BMIM]BF_4$	81	19
$[EMIM]NO_3$	77	23
$[EMIM]PF_6$	76	24
$[EtNH_3]NO_3$	87	13
Water	90	10

Scheme 1. Diels-Alder reaction in ionic liquids.

When their results were compared to those in ethylammonium nitrate they achieved lower *endo/exo* ratios. They suggested that could be a consequence of a more highly

ordered structure for the ethylammonium salts, which was held together by N-H hydrogen bonds rather than the weaker C-H hydrogen bonds that dominated by the salts they used.

The Diels-Alder reaction was also investigated by Howarth *et al.* [36]. In this study, the ionic liquid [EMIM]Br was used as heterogeneous and homogeneous Lewis acid to catalyse the reaction between crotonaldehyde or methacrolein and cyclopendiene at low temperature, the *endo* : *exo* selectivities for the crotonaldehyde or cyclopentadiene rections were always greater than 90 : 10 and those for the methacrolein or cyclopentadiene reactions were always greater than 15 : 85. The control reaction between methacrolein or crotonaldehyde and cyclopentadiene without the dialkylimidazolium salt present gave no product after 48h at –25°C. The ionic liquid could be recycled several times to give similar *endo* : *exo* selectivities and yields of products (Scheme 2).



1

4 $R_1 = H, R_2 = Me$

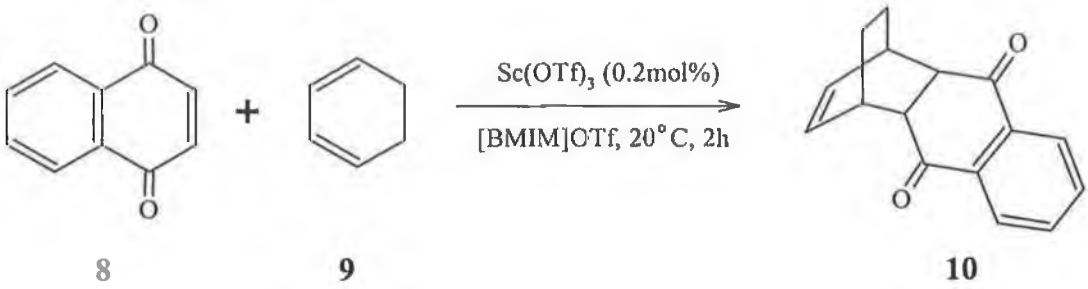
5 $R_1 = Me, R_2 = H$

6 $R_1 = H, R_2 = Me$

7 $R_1 = Me, R_2 = H$

Scheme 2. The Diels-Alder reaction in [EMIM]Br at low temperature.

Recently, scandium triflate catalysed Diels-Alder reactions in ionic liquid have been also reported by Song *et al.*[37]. They demonstrated that these reactions can give highly *endo/exo* selectivety (*endo* : *exo* = 99 : 1) in the presence of 0.2 mol% of $Sc(OTf)_3$ at 20°C (Scheme 3). It was also found that the use of ionic liquid as an additive in CH_2Cl_2 solvent could accelerate the reaction rate.

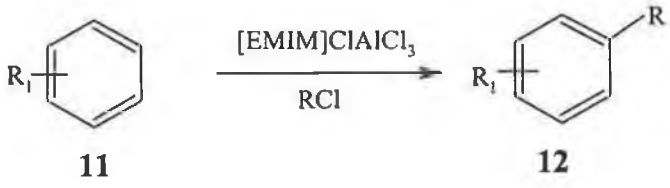


8 9 10

Scheme 3. $Sc(OTf)_3$ catalysed Diels-Alder reaction.

1.4.2 The Friedel-Crafts reactions

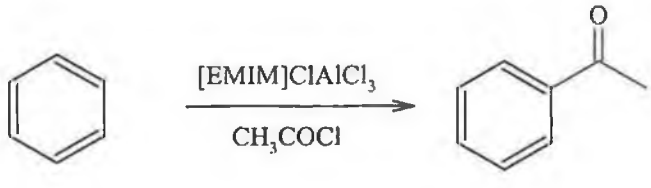
The first Friedel-Crafts acylation in ionic liquid was investigated in 1986 by Wilkes *et al.* [7]. They carried out Friedel-Crafts alkylations and acylations by using primary or secondary halides and various simple benzene derivatives, such as benzene, toluene, and chlorobenzene and using acetyl chlorides and alkyl chlorides in the acidic $[EMIM]ClAlCl_3$ molten salt respectively (Scheme 4).



11 12

R_1 = H, R = (a) Me, (b) Et, (c) *n*-Pr, (d) *n*-Bu, (e) $PhCH_2$, (f) cyclohexyl

R = *n*-Pr, R_1 = (g) CH_3 R = *n*-Pr, R_1 = (h) Cl



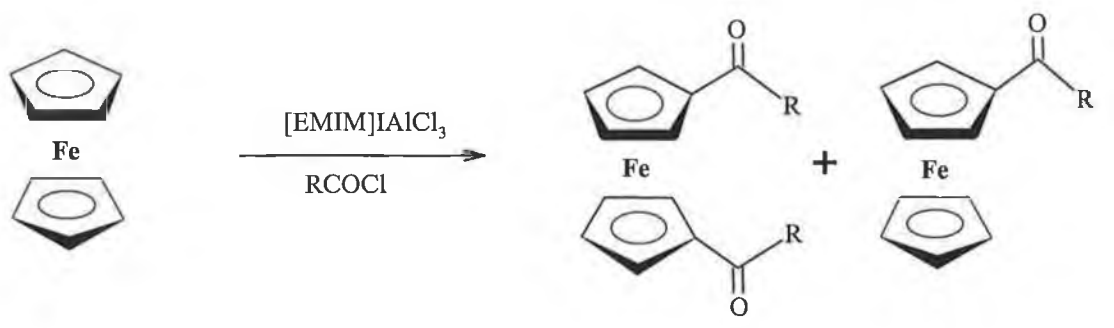
13 14

Scheme 4. Friedel-Crafts alkylations and acylations.

Wilkes *et al.* also showed that the reaction would not happen in a basic condition because of the Lewis acid-base equilibrium in the molten salt ($2AlCl_4^- \rightleftharpoons Al_2Cl_7^- + Cl^-$). When $AlCl_3$ is added in excess, the molten salt is Lewis acid, and it was found that the initial rate of the reaction was dominated by $Al_2Cl_7^-$ species and it was Lewis acid that catalysed the reaction.

Other groups such as Singer *et al.* have investigated the acylations of ferrocene in [EMIM]I·$AlCl_3$ (Scheme 5) [38]. They used several acylating agents and, in general, mixtures of mono- and diacylated ferrocenes were formed.

In Friedel-Crafts reactions, the 1-ethyl-3-methylimidazolium halogenoaluminate ionic liquids act not only as solvents but also catalysts. The main advantages are greatly enhanced reaction rates, high conversion and selectivity.



15 **16** **17**

R = (a) Me, (b) Et, (c) *n*-Pr, (d) *n*-Bu, (e) Ph

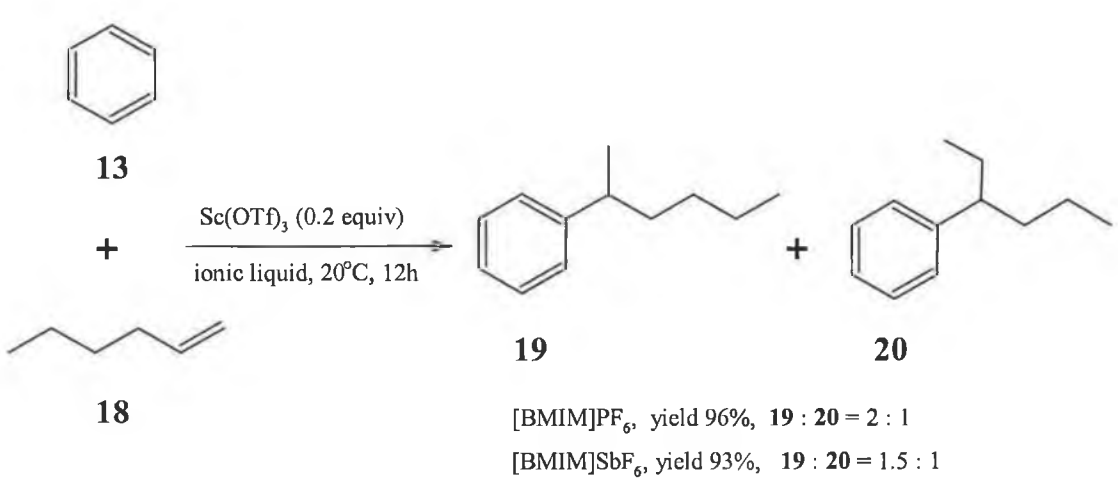
Scheme 5. Friedel-Crafts acylations of ferrocene.

Recently, considerable attention has been focused on the catalytic use of rare earth(III) (RE) salts, especially, RE(III) trifluoromethanesulfonates [$RE(OTf)_3$] as water tolerant and recyclable Lewis acid catalysts in C-C coupling reactions [39a–c]. Song *et al.* used similar catalysts of scandium(III) triflate [$Sc(OTf)_3$] to carry out the

Friedel-Crafts alkylation of aromatic compounds with alkenes in various ionic liquids [40].

In their investigation, they found the Friedel-Crafts reaction catalysed by $Sc(OTf)_3$ could not happen in various organic solvents, such as dichloromethane, acetonitrile and nitromethane. They also found the catalytic activity of $Sc(OTf)_3$ was strongly influenced by the nature of the anion of ionic liquids. For example, when the hydrophobic ionic liquids such as [EMIM]SbF_6, [BMIM]PF_6, [BMIM]SbF_6 were used, the desired alkylated products were obtained quantitatively, although the catalyst $Sc(OTf)_3$ is only slightly soluble and thus exists as a suspended form in these ionic liquids.

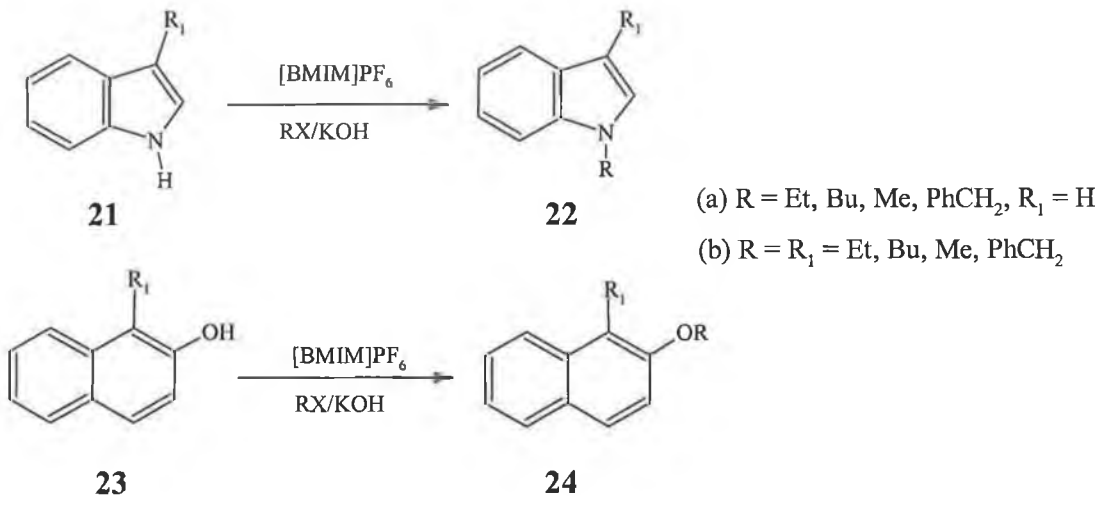
It is noteworthy that the rearrangement of the alkene takes place prior to the ring substitution, which indicates that the carbonium ion is formed first. Polarity of these ionic liquids leads to the stabilization of the polar cationic intermediate. In the hydrophilic ionic liquids, [BMIM]BF_4, [EMIM]OTf and [EMIM]BF_4, the reaction did not occur at all. Otherwise, the advantages of simple procedures, easy recovery and reuse of catalysts, environment friendly and waste-free processes have been mentioned as well (Scheme 6).



Scheme 6. Friedel-Crafts alkylation of benzene with hex-1-ene in ionic liquids.

1.4.3 The alkylations of nucleophiles

The alkylation of nucleophiles has been performed in ionic liquid [BMIM]PF_6 by Seddon *et al.* [41]. Indole and 2-naphthol were *O*- and *N*-alkylated in analogous yields to those carried out in the conventionally used dipolar aprotic solvents such as DMF or DMSO (Scheme 7). The products were isolated by extraction with diethyl ether, and the ionic liquid could be reused after it was degassed.



Scheme 7. *O*-and *N*-alkylation of indole and 2-naphthol.

Chauvin *et al.* have investigated the alkylation reaction of isobutane with 2-butene to give branched *iso*-alkane using [BMIM]Cl·$AlCl_3$ ionic liquids as solvent. The main advantages arising from the use of the ionic liquid are high alkylate quality and simple product separation [42].

The alkylation of benzene with long chain alkenes or halogenated alkanes to produce linear alkylbenzenes (LAB) is also of commercial importance. The traditional catalyst is HF or $AlCl_3$ (catalyst/olefin mole ratio = 5:1–20:1). Acidic ionic liquids have been used as catalysts in the ratio as low as about 0.004 with very high conversion [43].

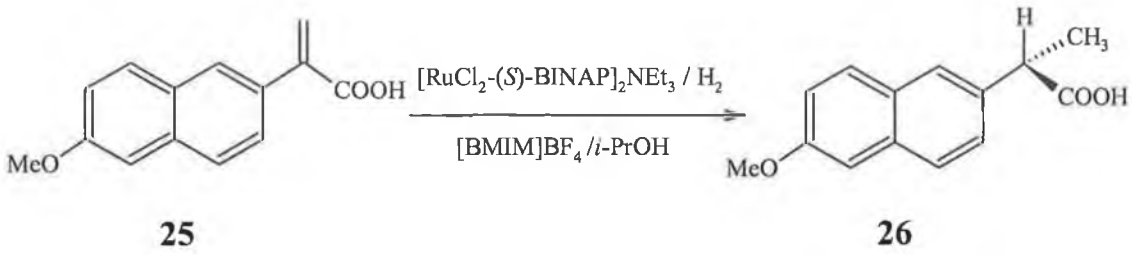
1.4.4 The hydrogenation reactions

Hydrogenation reactions were first widely studied by using the moisture stable imidazolium salts for biphasic catalysis, and the ionic liquid served as solvents for the hydrogenation reactions, which were catalysed by transition-metal complexes. In traditional aqueous-organic solvent system, modification of the ligands to introduce water-solubility is generally necessary but the cost is a great problem.

De Souza used the Wilkinson's complex [$RhClPPh_3$] as a hydrogenation catalyst to hydrogenate cyclohexene reactions in ionic liquids [BMIM]BF_4 and [BMIM]PF_6 [44, 45]. Although it showed no noticeable difference in the turnover rates compared to the conventional solvents, the isolation of product by simple decantation and that the catalyst can be immobilised in the ionic liquid are advantageous.

Chauvin used the Osborn catalyst, [$Rh(nbd)(PPh_3)_2$]PF_6 (nbd = norbornadiene), to hydrogenate pent-1-ene in a variety of ionic liquids, which showed their potential as solvents for the reactions [46]. Although there was a side reaction involving isomer pent-2-ene in [BMIM]SbF_6 and [BMIM]PF_6, it did not significantly lower the rate of hydrogenation. However, the results using a [BMIM]BF_4 ionic liquid were disappointing. This was attributed to the presence of nucleophilicity, ionic liquids do not compete with the unsaturated organic substrate for the coordination to the electrophilic metal centre, which deactivated the catalyst.

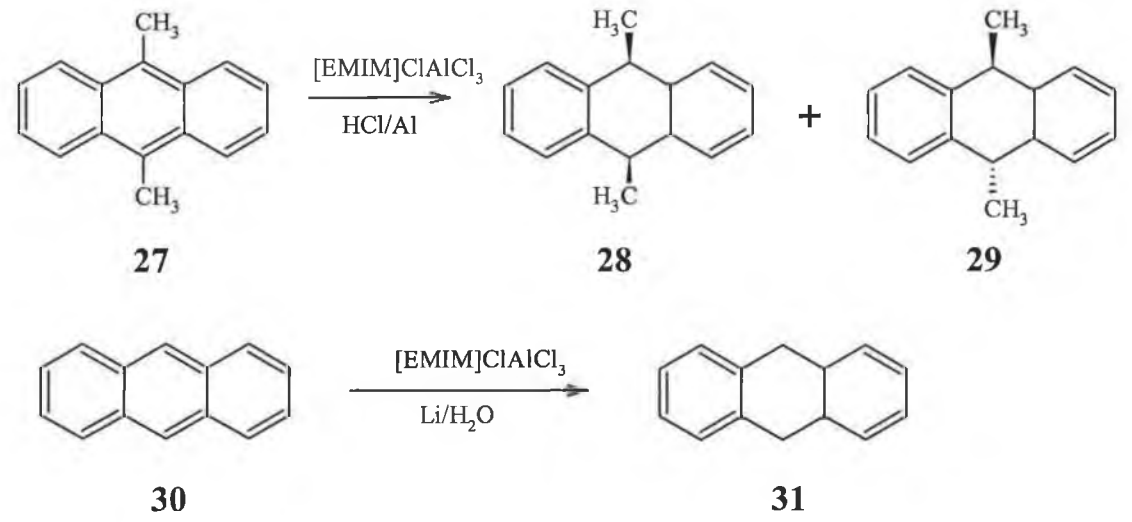
Dupont has investigated the asymmetric hydrogenation of 2-arylacrylic acids, for example, 2-(6-methoxy-2-naphthyl)acrylic acid, by using the chiral [$RuCl_2$-(*S*)-BINAP]$_2$-NEt_3 catalyst (BINAP = 2,2'-bis (diphenylphosphino)-1,1'-binaphthyl) in [BMIM]BF_4 with enantioselectivities of 96% to give the product (*S*)-naproxen [47] (Scheme 8).



25 26

Scheme 8. Preparation of (*S*)-naproxen in ionic liquid [BMIM]BF_4.

Seddon *et al.* has succeeded in hydrogenation of anthracenes and pyrenes in ionic liquid [EMIM]$ClAlCl_3$ [48]. The reaction was carried out with electropositive metals and a proton source. A high selectivity (*cis* : *trans* = 6 : 1) was found when 9,10-dimethylanthracene was treated with Al/HCl in [EMIM]$ClAlCl_3$ ionic liquid (Scheme 9).



27 28 29

30 31

Scheme 9. The hydrogenation of 9,10-dimethylanthracene and anthracene.

Rhodium- and cobalt-catalysed hydrogenation of butadiene and 1-hexene [44, 49], and the Ru-catalysed hydrogenation of aromatic compounds [50] and acrylonitrile-butadiene copolymers [51] have also been reported to be successful in ionic liquids.

Recently, supercritical CO_2 has been employed with ionic liquids to form ionic liquid/scCO_2 biphasic systems. By avoiding the use of organic solvent completely, the systems are environment friendly with high reaction rates [52]. Asymmetric hydrogenation of tiglic acid catalysed by [$Ru(O_2CMe)_2$(*R*)-tolBINAP] in ionic liquid ([BMIM]PF_6 with water) gave 2-methylbutanoic acid with high enantioselectivity (92% ee) and conversion (100%).

It was found that at least for tiglic acid, there is no need to add an alcohol or other organic solvent, nor is there any need to prepare a fluorinated or water-soluble derivative of the catalyst. The products can be extracted from the ionic liquids by supercritical CO_2, with no concomitant extraction of ionic liquid or asymmetric catalyst. Furthermore, the ionic liquid/catalyst solution can be reused several times without significant loss of enantioselectivity or activity.

1.4.5 Polymerisation reactions

It is known that a number of transition metal complexes are good catalysts for polymerisation reactions, but they are poorly soluble in non-polar solvents and the high polar solvents tend to compete for co-ordination sites on the catalyst with the substrate. Therefore, ionic liquids can be a good alternative to transition metal catalysts in polymerisation reactions.

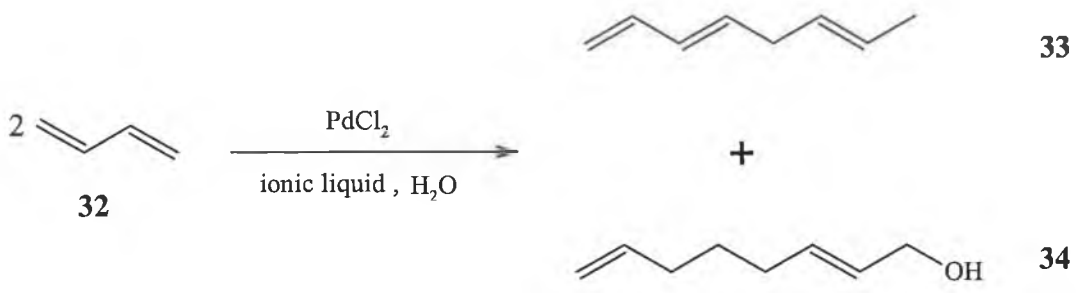
Radical polymerisation of methyl methacrylate (MMA) mediated by copper(I) in [BMIM]PF_6 has been investigated by Seddon's group [53]. It has been demonstrated that the ionic liquid is an excellent solvent for Cu(I)-*N*-propyl-2-pyridylmethanimine mediated living radical polymerisation of MMA. Reactions are relatively fast, as has been observed with other polar/coordinating solvents. The polymer can be recovered essentially copper-free by a simple solvent wash. However, further work is required in order to optimise the process and to realise the potential to recycle the ionic liquid catalyst mixture.

Keim's group recently studied the oligomerisation reaction of ethylene with (η^3-methallyl) [bis(diphenylphosphanyl)methane-monoxide-κ^2-*P,O*]-nickel(II)-hexafluoroantimonate {[(η^3-methallyl)Ni(dppmO)]SbF_6}as catalyst in different solvents. CH_2Cl_2 proved thereby to be the best choice among organic solvents [54]. By using the ionic liquid [BMIM]PF_6 the activity of the cationic Ni complex could be increased by about a factor of seven. The overall selectivity of the biphasic reaction to linear α-olefins was as high as 88% which is even slightly higher than found in the monophasic reaction in CH_2Cl_2.

1.4.6 Dimerizations

Chauvin *et al.* developed a process for the dimerization of propene and butene by using Ziegler-Natta catalysts, nickel(II) chloride and ethyl aluminium dichloride [55]. Propene is converted into isomeric hexenes with high activity at atmospheric pressure and temperatures from –15 to –5°C. The products form an upper phase that can be easily separated by simple decantation. The pale yellow-orange catalyst remaining in the ionic liquid phase can then be reused several times. Under the same conditions, butanes are converted into isooctenes with 97% selectivity, consisting of 3-methylheptene (56%), 3,4-dimethylhexene (38%), and *n*-octene (6%).

The Dupont group carried out the selective linear hydrodimerization of 1,3-butadiene in [BMIM]BF_4, [BMIM]PF_6 and [BMIM]CF_3SO_2 ionic liquids by using classical palladium catalyst precursors (palladium dichloride, acetate and acetylacetonate) with triphenylphosphine, to give the product of 1,3,6-octatriene with 100% selectivity. In addition, the octa-2,7-diene-1-ol was also obtained [56]. The reaction mixture was homogeneous under the reaction conditions (70°C), but the product could be separated easily by cooling the mixture to below 5°C. In addition, the recovered ionic liquid and catalyst could be reused (Scheme 10).



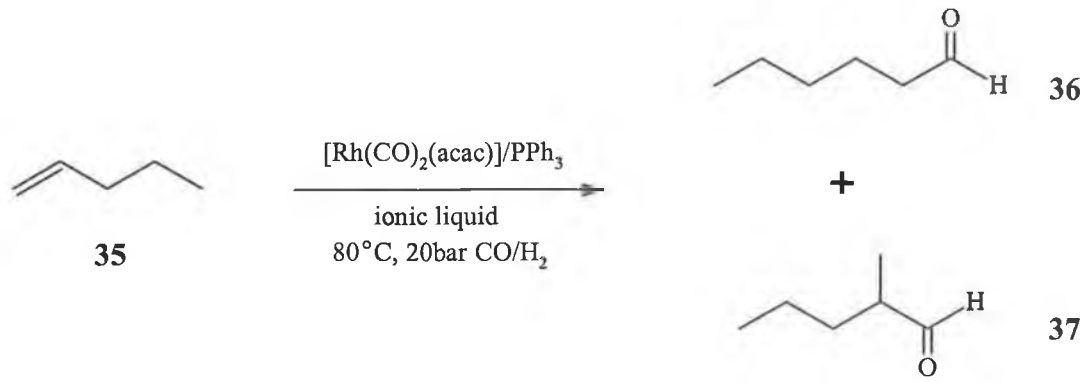
Scheme 10. Dimerization of 1,3-butadiene.

The Dimersol process developed in France by the Institute Français du Pétrol (IFP), is an industrial scale single-phase no-solvent system for the dimerization of propene and butene catalysed by nickel complexes giving more valuable branched hexenes and octenes [57]. The process is widely used in industrial plants worldwide.

1.4.7 Hydroformylation reactions

For many hydroformylation reactions, the big problems are the separation of catalysts and the loss of catalysts. The use of water-organic solute systems has not proven to be successful, resulting in low reaction rates. The application of ionic liquids as homogenous catalysis for the biphasic system has been seen to be superior to water.

Chauvin *et al.* used $Rh(acac)(CO)_2$ with PPh_3 to catalyse the hydroformylation of 1-pentene in $[BMIM]BF_4$, $[BMIM]PF_6$ and $[BMIM]SbF_6$ ionic liquids [55]. The reactions showed high catalytic activity and the catalyst could be recyclable, but some loss of catalysts still remained. To avoid this, sulphonated triphenylphosphine ligands were used, however, but only led to reductions of reaction rate (Scheme11).

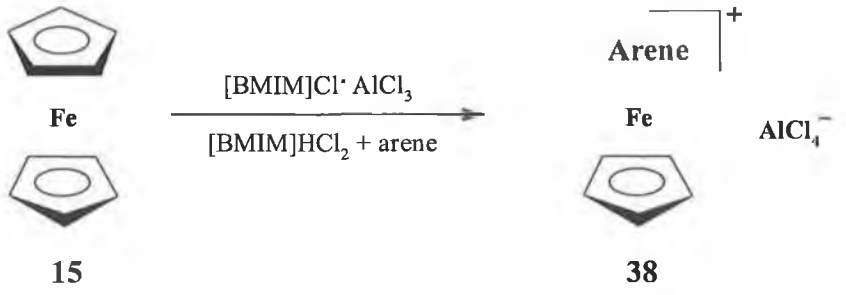


Scheme 11. Hydroformylation of 1-pentene with $[Rh(CO)_2(acac)]/PPh_3$.

Other groups have showed that Rh catalysts can be used for the hydroformylation of 1-hexene in tetraalkylphosphonium tosylate salts [58] and the reaction of methyl-3-pentanoate in $[BMIM]PF_6$ [59]. The separation by decanting the liquid of organic product at room temperature was easy and the loss of catalyst can be minimized.

1.4.8 Organometallic reaction

Arene exchange reactions of ferrocene are well known to be catalysed by aluminium(III) chloride. Welton *et al.* have used the acidic ionic liquid $[BMIM]Cl{\cdot}AlCl_3$ as a good candidate for the preparation of a number of arene(cyclopentadienyl)iron(II) complexes, for example, $[Fe(C_5H_5)(arene)]^+$, from ferrocene [60, 61]. The ionic liquid acts as both a solvent and Lewis acid source. However, the products could only be formed on addition of a proton source because the ionic liquid used was aprotic (Scheme 12).



15 38

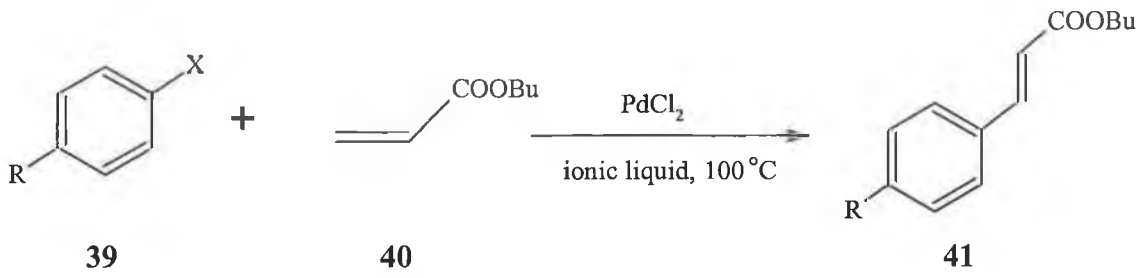
Arene = (a) benzene, (b) toluene, (c) biphenyl, (d) 4-bromobiphenyl, (e) naphthalene

Scheme 12. Arene exchange reactions of ferrocenes.

1.4.9 Heck reactions

The Heck reaction is a useful tool in organic synthesis for the creation of C-C bond. It was first discovered by Heck and Mizoriki in the late 1960s, the reaction is the arylation of alkenes catalysed by palladium(II) complexes [62a–b].

The reaction has been carried out in the tetraalkylammonium and tetraalkylphosphonium salts by Kaufmann *et al.* [63]. The palladium(II) chloride and acetate were immobilized in the ionic liquids and then reduced to palladium(0) complexes by multiple ligands to catalyse the C-C coupling reaction. The vinylation of bromobenzene with *n*-butyl acrylate was successfully carried out in phosphonium salts at 100°C in the presence of triethylamine, to give *trans*-cinnamic *n*-butyl ester in good yields (Scheme 13).



39 **40** **41**

(a) R = H, X = Br (b) R = OCH_3, X = Br (c) R = NO_2, X = Cl

Scheme 13. Heck reaction in ionic liquid.

The authors describe a stabilizing effect of the ionic liquid on the palladium catalyst. In almost all reactions no precipitation of elemental palladium was observed even at complete conversion of the aromatic halide. The reaction products were isolated by distillation from the non-volatile ionic liquid.

A recent investigation of Heck reaction in ionic liquid by Hermann and Böhm show clear advantages over commonly used organic solvents (such as DMF) especially for the conversion of the industrially interesting chloroarenes [64]. With almost all tested catalyst systems an additional activation and stabilization was observed. The molten salt $[NBu_4]Br$ (m.p.103°C) proved to be a particularly suitable reaction medium among the ionic liquid systems under investigation. In the reaction of bromobenzene with styrene using bis(1,3-dimethylimidazolin-2-ylidene)diiodopalladium(II) as catalyst the yield of stilbene could be increased from 20% (DMF) to over 99% ($[NBu_4]Br$) under otherwise identical conditions. The products can be easily removed from the solution by distillation and the catalyst can be reused up to thirteen times without significant drop in activity.

Other examples of Heck reaction in ionic liquid were investigated by Seddon's group [65]. They described the option of a work-up procedure in the three-phase system $[BMIM]PF_6$/water/hexane. While the used catalyst $[(BMIM)_2PdCl_4]$ remains in the ionic liquid, the products dissolve in the organic layer. The salt formed as a by-

product of reaction ($[Hbase]^+X^-$) is extracted into the aqueous phase. Interestingly, the authors observed significant differences in reactivity between the application of either imidazolium salts or pyridium salts in the Heck reaction.

Recently, the Heck reaction of aryl halides with acrylates and styrene in [BMIM]Br and $[BMIM]BF_4$ catalysed by palladium-carbene complexes *in situ* has been reported [66]. A significantly enhanced reactivity of the Heck reaction in [BMIM]Br rather than in $[BMIM]BF_4$ was described. The difference was explained with the fact that only in the bromide melt the formation of palladium-carbenes was observed.

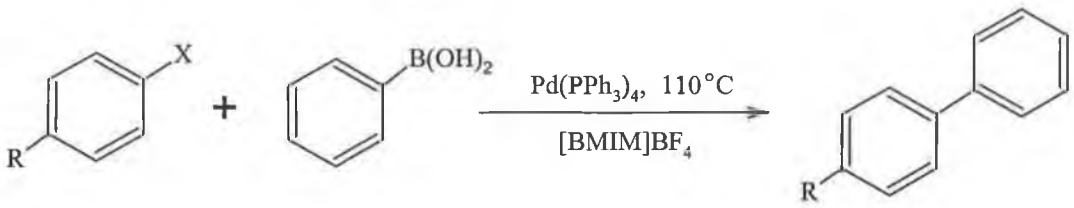
More recently, palladium-catalysed regioselective arylation of an electron-rich olefin by aryl halides has also been accomplished in ionic liquid, using aryl iodides and bromides as arylating agents instead of the commonly used, but commercially unavailable and expensive, aryl triflates [67]. The reaction proceeds with high efficiency and remarkable regioselectivity, leading almost exclusively to substitution by various aryl groups at the olefinic carbon α to the heteroatom of butyl vinyl ether.

Howarth *et al.* also investigated the Heck reaction in ionic liquid $[BMIM]PF_6$ using $Pd(OAc)_2$ with PPh_3 as catalyst. It was found that there was not much improvement on yields comparing with conventional organic solvent DMF, but the loss of expensive catalyst can be avoided and the catalyst can be reused for several times without decreasing activity [68].

1.4.10 The Suzuki cross-coupling reaction

The Suzuki cross-coupling reaction is an extremely versatile method for the generation of new C-C bonds and it is employed most successfully in the synthesis of biaryls. Conventional reaction, however, suffers from a number of drawbacks such as catalyst loss into the product, catalyst decomposition and poor reagent solubility.

Recently, the Suzuki cross-coupling reaction has been investigated by Welton's group [69]. By using palladium triphenylphosphine complexes as catalyst in ionic liquid [BMIM]BF_4 at 110°C, the reaction of bromobenzene with phenylboronic acid afforded biphenyl in 93% yield (Scheme 14).



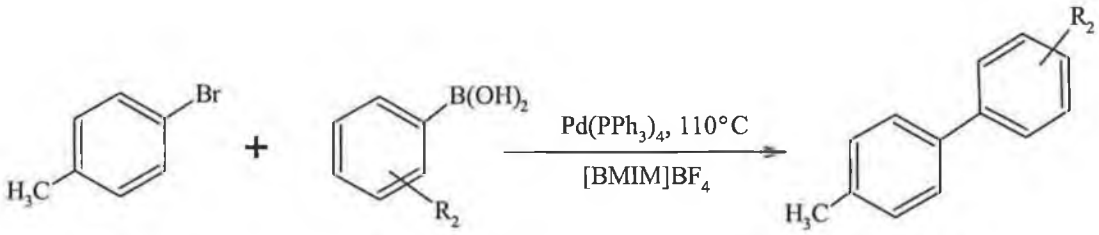
42 **43** **44**

X = Br, R = (a) Cl, (b) $COCH_3$, (c) CH_3, (d) OCH_3

R = H, X = (e) I, (f) Br, (g) Cl

Scheme 14. Suzuki cross-coupling reaction in ionic liquid [BMIM]BF_4.

The effect of the arylboronic acid partner on the Suzuki reaction in ionic liquid [BMIM]BF_4 was investigated as well. The results of the functionalised arylboronic acids seem to parallel those obtained with the same functional groups on the arylhalide. This suggests that both the nature of the arylhalide and the arylboronic acid affects the reaction, apparently in an analogous manner (Scheme 15).



45 **46** **47**

R_2 = (a) 4-CH_3, (b) 2-CH_3, (c) 4-OMe, (d) 4-COMe

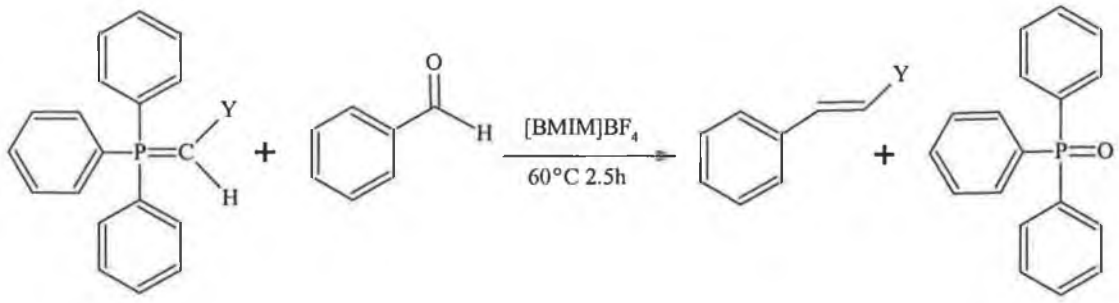
Scheme 15. The Suzuki reaction of different substituted arylboronic acids with arylhalide.

The Suzuki cross-coupling reactions in ionic liquid showed the following advantages: (1) significant increase in reactivity at reduced catalyst concentration, especially with respect to non-activated arylbromides; (2) homo-coupled products can be eliminated, affording isolated products in high purity avoiding laborious purification procedures (3) the reaction can be performed under air without loss of yield or catalyst decomposition (4) the procedures developed permit respective catalytic runs without loss of catalyst activity.

1.4.11 Wittig reaction

The Wittig reaction is amongst the most popular methods for C=C bond formation, giving in most cases good to excellent stereocontrol. In classical methods, the separation of alkene from the by-product (Ph_3PO), which is usually done by crystallisation or chromatography is still a problem. But in ionic liquid, however, it becomes simple and easy.

Recently, the Wittig reaction has been performed in ionic liquid [BMIM]BF_4 by Le Boulaire *et al.* [70]. The reactions of various aromatic and aliphatic aldehydes with phosphorus ylide have been carried out in [BMIM]BF_4 in good to excellent yields, and the ionic liquid can be reused without any problem (Scheme 16).



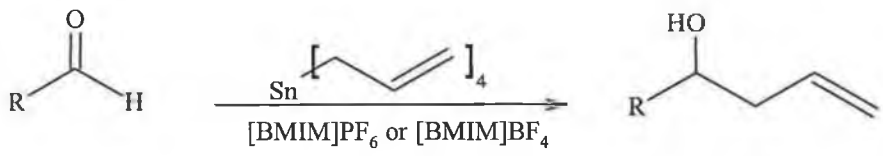
48 **49** **50** **51**

Y = (a) COMe, (b) COOMe, (c) CN

Scheme 16. Wittig reaction in ionic liquid [BMIM]BF_4.

1.4.12 Allylation reactions

The allylation reaction is a useful organic transformation, of which the most common method is the use of metal-allyl complexes to afford the desired allylic product. Recently, the allylation of aldehydes to produce homoallylic alcohols has been carried out successfully using tetraallylstannane by Gordon *et al.* [71] (Scheme 17). The reaction was carried out in [BMIM]PF_6 and [BMIM]BF_4, and there was little difference in the yields. The yields varied from 66-93% depending on the nature of aldehyde employed. The recycled ionic liquid has been used for the same reaction and no decrease in the yield was found.



52 **53**

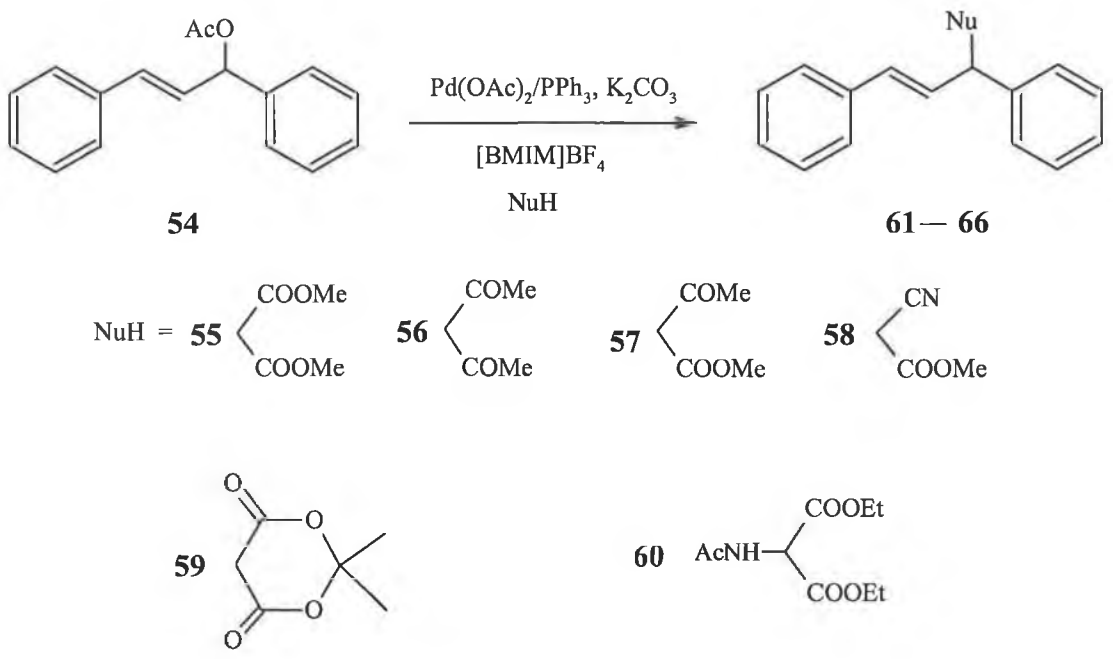
R = (a) Ph, (b) p-ClC_6H_4, (c) *p*-MeC_6H_4, (d) *p*-$MeOC_6H_4$, (e) Pr, (f) C_5H_{12},
(g) *trans*-PhC = CMe, (h) (*s*)-$Me_2C = CH(CH_2)_2CHMeCH$—

Scheme 17. Allylation reaction of aldehydes in ionic liquids.

More recently, indium-mediated allylation of aldehydes and ketone with allyl bromides in ionic liquids has been reported by the same author [72]. The homoallylic alcohol products were obtained in high yields when the reactions carried out at room temperature using stoichiometric quantities of indium. For example, 92% yield was obtained for 1-phenylbut-3-en-1-ol in [BMIM]BF_4. They also found that the addition of 5mol% $Sc(OTf)_3$ resulted in large increase in both reaction rate and selectivity when the tetraallyltin was used for the allylation of 2-methoxyhexanone and benzoin methyl ether.

Another group also investigated the allylation of carbonyl compounds with allyl bromide in ionic liquids using a number of metal as additives. It was found metal Zn, Sn, In mediated the allylation at room temperature gave excellent yields of homoallylic alcohols. They also examined the reaction of benzaldehyde with a number of asymmetrical allylic bromides and found the regioselectivity is similar to those observed in aqueous media [73].

Palladium catalysed allylic alkylation was recently investigated by Xiao *et al.* [74]. The reaction was carried out using $Pd(OAc)_2/PPh_3$ as catalyst in the present of K_2CO_3 in $[BMIM]BF_4$, and the reaction of 3-acetoxy-1,3-diphenylprop-1-ene with dimethyl malonate was investigated first (Scheme 18).



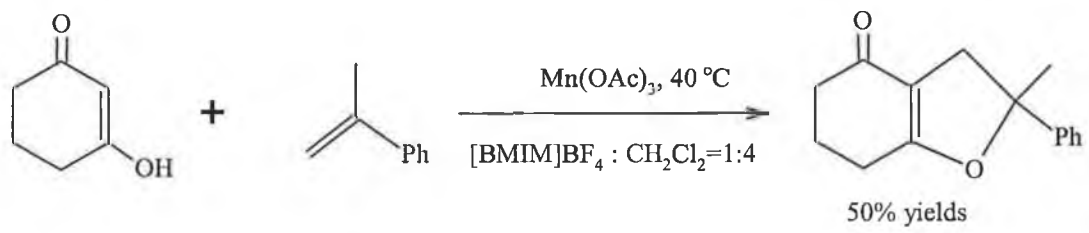
Scheme 18. The allylic akylation of 3-acetoxy-1,3-diphenylprop-1-ene with Dimethyl malonate.

The initial rate was slightly lower due to the slow dissolution of the substrates, ligand and base to make the concentration of active Pd° species lower at the beginning of the reaction. The reaction rate decreased markedly when the molar ratio of PPh_3 :

$Pd(OAc)_2$ was less than 4 : 1. The ionic liquid could be reused several times without losing activity, however, the extraction of products caused the leak of palladium species out of the ionic liquid. Replacing PPh_3 with the hydrophilic phosphine [P(*m*-$C_6H_4SO_3Na)_3$] led to effective recycling of the catalyst.

1.4.13 Manganese(III) acetate mediated radical reaction

Manganese(III) acetate is known to oxidise a variety of carbonyl compounds to form radicals. These radicals can undergo cyclisation or intermolecular addition reactions to form radical adducts, which may be oxidised by a second equivalent of manganese(III) acetate (Scheme 19a).



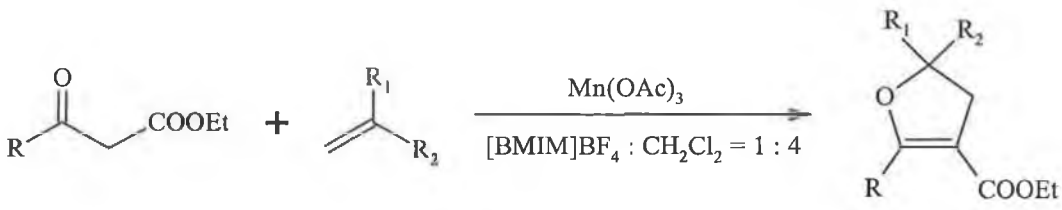
67 **68** **69**

Scheme 19a. Manganese(III) acetate mediated radical reaction in the presence of ionic liquid.

These C-C coupling reactions are synthetically attractive because manganese(III) acetate is inexpensive and, in contrast to related tributyltin hydride reactions, this oxidative method of radical generation leads to functionalised products. However the poor solubility of manganese acetate in organic solvents limited its application.

Recently, the radical cyclisation reaction of 1,3-dicarbonyl compounds and alkenes mediated by manganese(III) acetate in the ionic liquids $[BMIM]BF_4$ and $[BMIM]PF_6$ has been carried out [75] (Scheme 19b). The yields are often more than 50% and the catalysts can be easily recovered by addition of further organic solvent to the reaction

mixture. After filtration, the manganese acetate was reacted with potassium permanganate to re-oxidize the catalyst from manganese(II) to manganese(III). The manganese(III) acetate can be easily recycled depending on the nature of ionic liquid. For example, [BMIM]PF_6 makes it difficult to remove manganese by products. However, [BMIM]BF_4, can be recovered on work-up (≥95% yield) and reused without any detrimental effort on the product yields.



70 **71** **72**

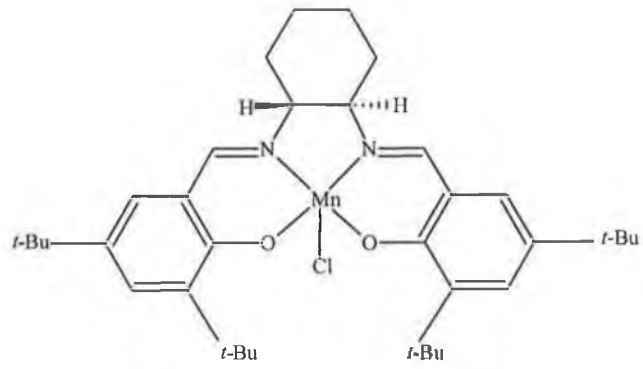
(a) R = R_1 = Me, R_2 = Ph, yield 87% (b) R = Me, R_1 = R_2 =Ph, yield 60%

(c) R = R_2 = Ph, R_1 = Me, yield 50% (d) R = Me, R_1 = H, R_2= C_6H_{13}, yield 38%

Scheme 19b. $Mn(OAc)_3$ catalysed radical reactions of β-keto esters with alkenes.

1.4.14 Oxidation reactions in ionic liquids

Recently, the selective oxidation reaction using Jacobsen's chiral (salen)Mn(III) epoxidation catalyst, [*N,N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] manganese(III) chloride (Figure 6), was investigated by Song and Roh [76].

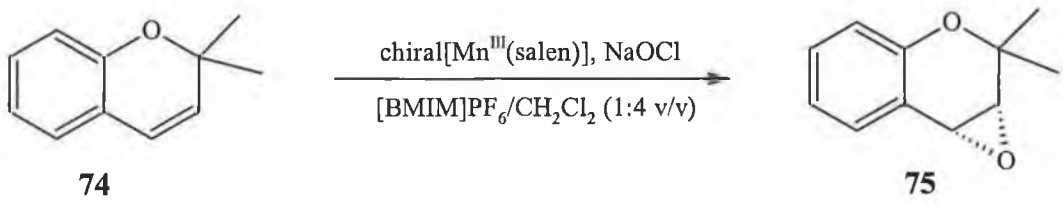


(*R*,*R*)-1

73

Figure 6. Jacobsen's catalyst (*R, R*)-1.

They carried out the asymmetric epoxidations in the presence of 4% mol of (*R, R*)-1 with 2,2- dimethylchromene, 6-cyano-2,2-dimethylchromene, indene, *cis*-β-methylstyrene, and 1-phenylcyclohexene as substrates in [BMIM]PF_6 /CH_2Cl_2 (1:4 v/v) using NaOCl as the oxidant at 0°C . The reaction revealed a clear enhancement of the catalyst activity by the addition of the ionic liquid to the organic solvent. In the presence of ionic liquid an 86% conversion of 2,2-dimethylchromene was observed after 2h. Without the ionic liquid the same conversion was obtained only after 6h. In both cases the enantiomeric excess was as high as 96% (Scheme 20).

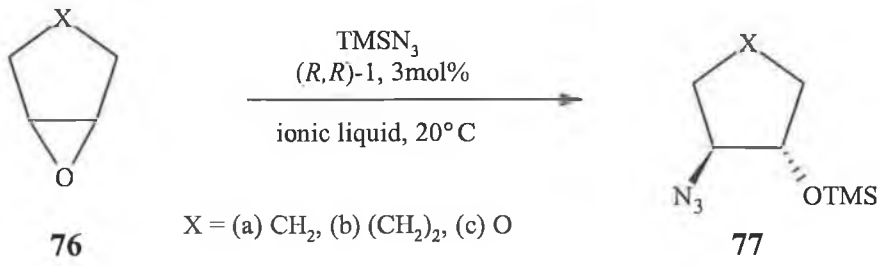


74 **75**

Scheme 20. Asymmetric epoxidation of alkene in the presence of ionic liquid.

They also carried out the asymmetric ring open reaction of epoxides using Cr(salen) catalyst in different ionic liquids [77] (Scheme 21). They found both reactivity and enantioselectivity were strongly influenced by the nature of the anion of the ionic liquids. When the hydrophobic ionic liquid [BMIM]PF_6 was used, the desired azido

silyl ether was obtained with the same degree of yield and enantiomeric excess (94% ee) as those obtained under homogeneous conditions reported by Jacobsen *et al.* [78].

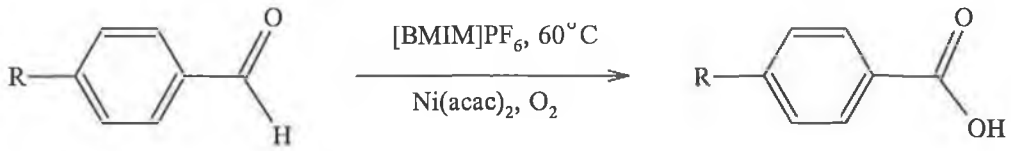


76 **77**

Scheme 21. Enantioselective ring opening of *meso* epoxides in ionic liquids.

Using the other hydrophobic ionic liquid [BMIM]SbF_6, the reaction was run with similar conversion, although in slightly lower ee. In sharp contrast to those results, in the hydrophilic ionic liquids, [BMIM]BF_4 or [BMIM]OTf, the reaction hardly occurred. In the case of using the BF_4 salt, only 5% yield of product was obtained in nearly racemic form (3% ee). More dramatically, in the OTf salt the reaction did not proceed at all.

The oxidation of aromatic aldehydes in ionic liquid [BMIM]PF_6 was investigated by Howarth recently [79]. Several aromatic aldehydes have been oxidised using the catalyst [Ni(acac)$_2$] and dioxygen at atmospheric pressure to give moderate to good yields. It was the first time to use the nickel(II) acetylacetonate and dioxygen in ionic liquid, which are often used in perfluorinated solvents and the catalyst can be reused several times without leaching of it (Scheme 22).



78 **79**

R = (a) H, (b) Me, (c) Cl, (d) Br, (e) OMe, (f) OH, (g) CHO

Scheme 22. Oxidation of aromatic aldehydes in ionic liquid.

Methyltrioxorhenium (MTO) catalysed epoxidation in ionic liquids was carried out by Abu-Omar *et al.* recently [80]. The MTO catalyst is an environment-friendly oxidation system, as the only by-product of the MTO-peroxide system is water. The creation of two active oxygen-transfer complexes, a monoperoxo- and a diperoxorhenium species, during the catalytic cycle has been well established, as have the mechanisms of oxygen transfer (Figure 7). Urea hydrogen peroxide (UHP) has been shown to be a water-free peroxide source for MTO-catalysed epoxidation. The only disadvantage is that the UHP is insoluble in organic solvents, such as chloroform, methylene chloride, and acetonitrile. Hence, the MTO-UHP system in organic media is heterogenous. In ionic liquid $[BMIM]BF_4$, both MTO and UHP are soluble to form homogeneous peroxorhenium species. The yields of products are comparable to previously published data and the work-up procedures are easier as well.

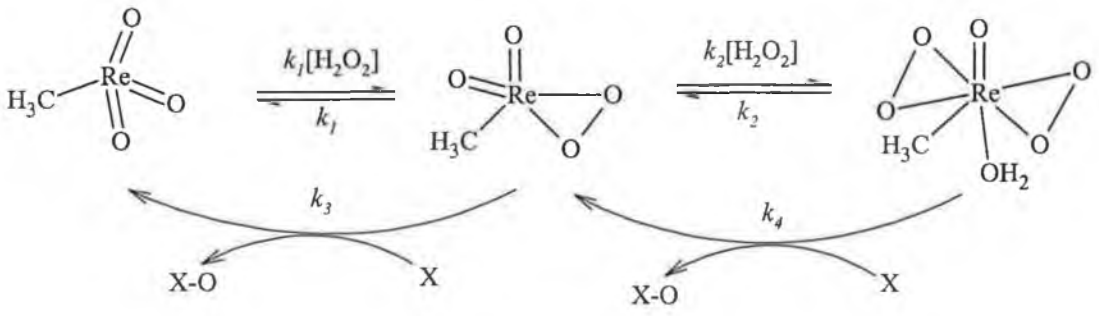
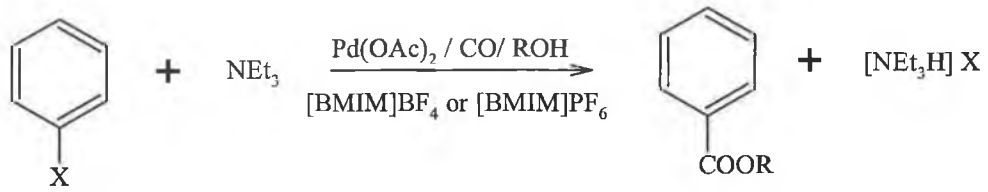


Figure 7. The mechanisms of MTO-peroxide system.

1.4.15 Palladium-catalysed alkoxycarbonylations

Palladium catalysed carbonylation of aryl halides is a highly effective method for the synthesis of various carbonyl compounds such as carboxylic acids, ester, amides, aldehydes and ketones. The separation of the products and the catalyst still is problematic in normal homogeneous catalytic reactions. In order to overcome this problem, palladium(0)-catalysed single and double carbonylation of aryl halides in $[BMIM]BF_4$ and $[BMIM]PF_6$ has been investigated [81] (Scheme 23).

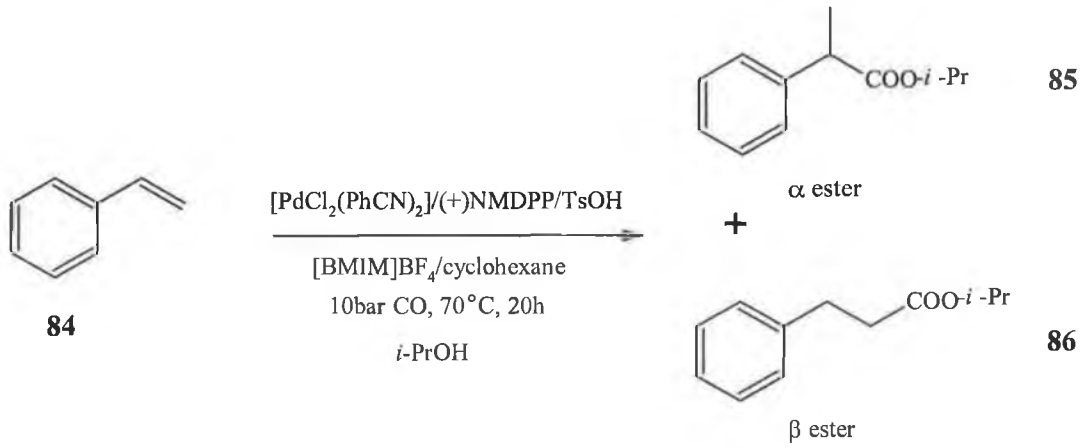


80 **81** **82** **83**

Scheme 23. Palladium-catalysed carbonylation of aryl halides.

The results showed that the ionic liquids could significantly enhance the reaction rate of carbonylation and the catalyst could be recycled. The products can be obtained easily by distillation or extraction.

Another example of palladium-catalysed alkoxycarbonylation of styrene and styrene derivatives was carried out by Monteiro *et al.*[82]. In the biphasic system $[BMIM]BF_4$ and cyclohexane, styrene, isopropyl alcohol and CO were mixed to form 2-isopropylphenylpropionate. With (+)-neomethyldiphenylphosphane [(+)-NMDPP] as ligand, the product was obtained in high yield (*iso*-propyl 2-phenylpropionate, yield 89%) and very good regioselectivity ($\alpha : \beta = 99.5 : 0.5$). Despite the chiral phosphane ligands, the observed asymmetric induction was, however, very low (ee < 5%). The ionic liquid allowed simplified product isolation due to the biphasic reaction procedure (Scheme 24).

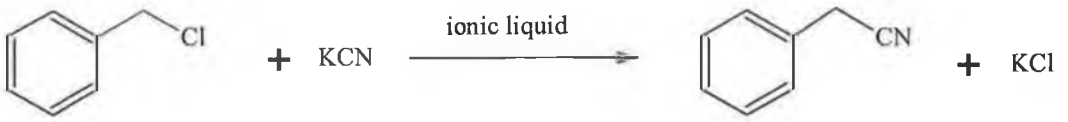


Scheme 24. Palladium catalysed alkoxylcarbonylation.

1.4.16 Nucleophilic displacement reaction

Nucleophilic displacement reactions are often carried out under phase-transfer catalysis (PTC) to facilitate the reaction between the organic reactants and the inorganic salts that provide the nucleophiles. The phase-transfer catalyst, often a tetraalkylammonium salt, acts as a shuttle for the reactant anion between a polar phase that contains the salt reactant and a non-polar phase that contains the organic reactant. This technique not only overcomes the problem of contacting the reactants, but also provides activation of the nucleophilic anion, since it is much less tightly bound to a tetraalkylammonium cation than it would be to a metal cation. In conventional PTC typical organic solvents are environmentally undesirable species such as methylene chloride or *o*-dichlorobenzene, and catalyst separation and recovery are significant challenges. Ionic liquids with bulky organic cations, are suited for the type of reactions for which PTC is effective.

Recently, the use of ionic liquids as catalytic green solvents for nucleophilic displacement reaction was investigated [83]. The cyanide displacement of benzyl chloride to yield phenylacetonitrile was chosen as a model reaction (Scheme 25).



87 **88**

Scheme 25. Cyanide displacement on benzyl chloride.

A recyclable and catalytic ionic liquid solvent system for nucleophilic substitution reactions has been developed, demonstrating the viability of ionic liquids as a solvent for reactions between organic compounds and inorganic salts (Figure 8).

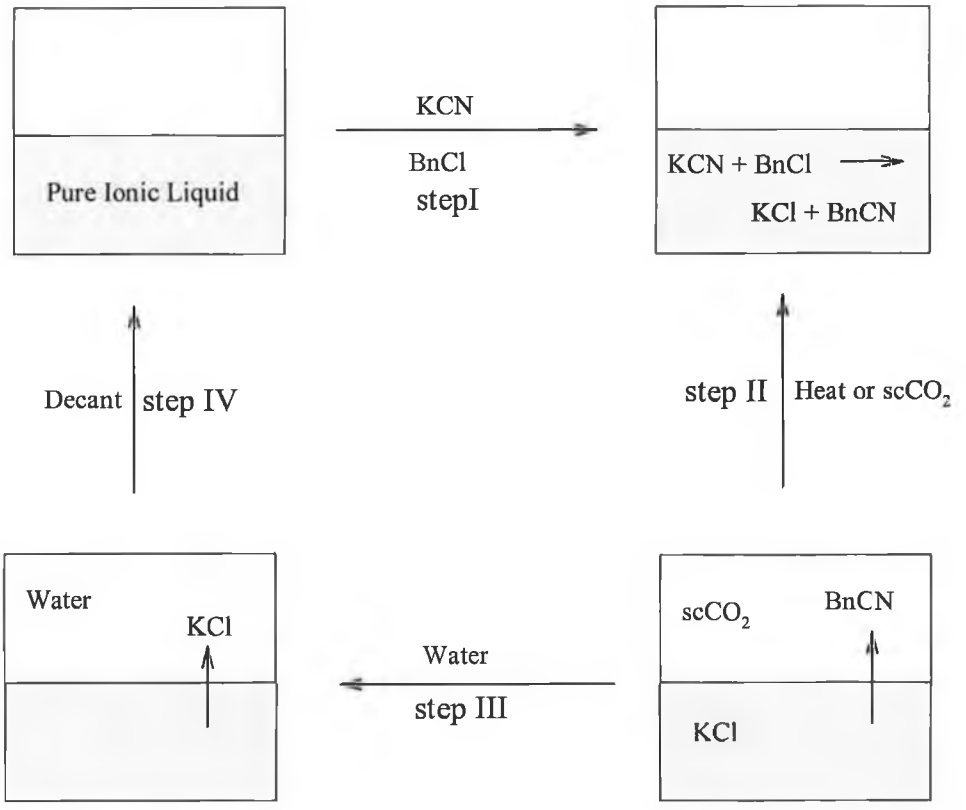
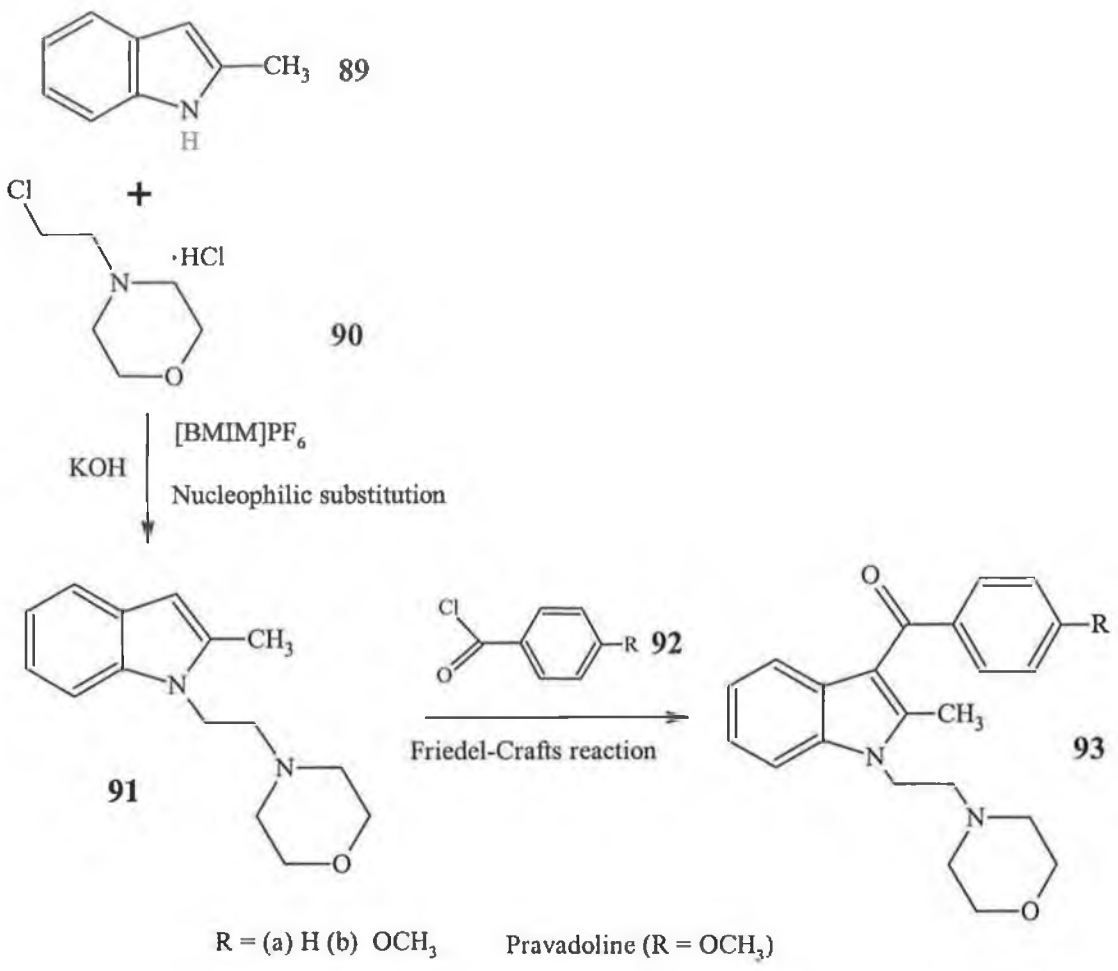


Figure 8. A recyclable ionic liquid solvent for nucleophilic substitution reaction.

In step I, the reactants are added to the ionic liquid and the reaction is allowed to proceed. Step II involves the removal of the organic reactant *via* vaporization or supercritical fluid extraction. Washing up with water, as in step III, will remove the salt product and after decantation, step IV, the purified ionic liquid is obtained and available for another reaction cycle.

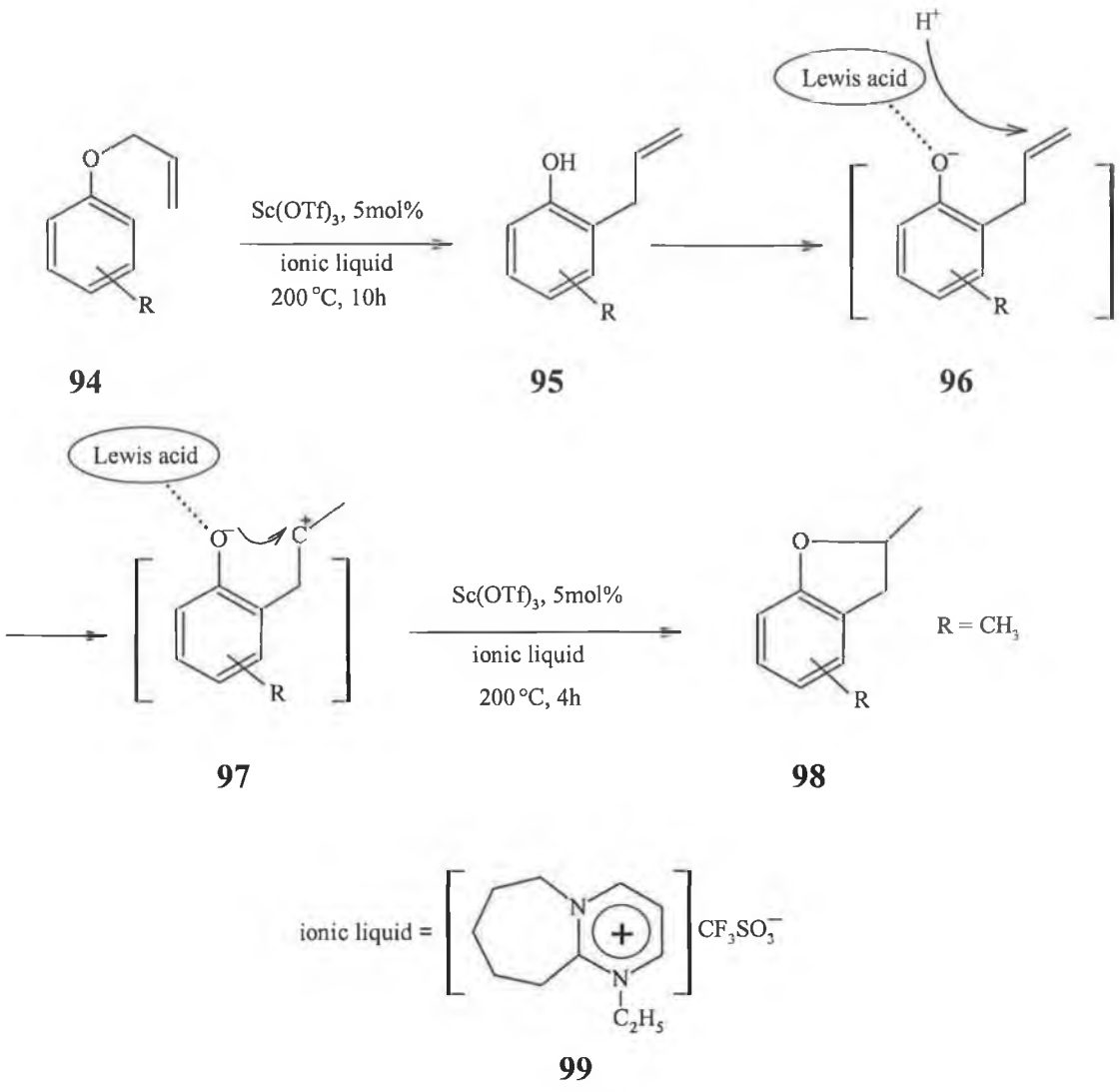
1.4.17 Sequential reactions

Sedden's group has demonstrated sequential regioselective nucleophilic displacement reaction and Friedel-Crafts reaction to afford the pharmaceutical Pravadoline in the same ionic liquid [BMIM]PF_6 (Scheme 26). The Friedel-Crafts reaction was found to work without the need for Lewis acids and without all the associated waste aluminum problems of a conventional Friedel-Crafts reaction. It is thought to be the first high yield (94%) green route to a pharmaceutical in an ionic liquid avoiding the problem of large quantities of waste found in traditional industrial pharmaceutical processes [84].



Scheme 26. Pharmaceutical preparation in ionic liquid.

Another Lewis acid-catalysed sequential reaction involving a Claisen rearrangement followed by a cyclisation reaction in ionic liquid has also been reported [85] (Scheme 27). It was found that the ionic liquid, 8-ethyl-1,8-diazabicyclo-[5,4,0]-7-undecenium trifluoromethanesulfonate ([EtDBU]OTf), is a good alternative reaction medium for sequential reactions which can be reused and stable at high temperature.

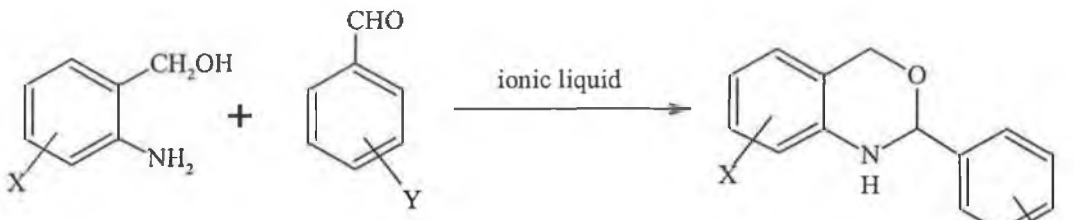


Scheme 27. Sequential reactions in ionic liquid.

1.4.18 Preparation of heterocyclic compounds

One pot synthetic methods are one of the most important organic reactions in the synthesis of heterocycles. In general, these reactions are carried out in polar organic solvents such as THF, DMF or DMSO, and after quenching with water, the products are extracted with organic solvents. Therefore, these processes generate considerable quantities of waste containing solvent media and catalyst. A series of ionic liquids such as 8-ethyl-1,8-diazabicyclo-[5,4,0]-7-undecenium trifluoromethanesulfonate and

8-methyl-1,8-diazabicyclo-[5,4,0]-7-undecenium trifluoromethanesulfonate have been developed and used as replacement for the more expensive organic solvents in the one pot synthesis of heterocycles to give the products in excellent yields (84%–96%)[86] (Scheme 28). These ionic liquids are safe to use and are fully recyclable with no process emissions.



100 **101** **102**

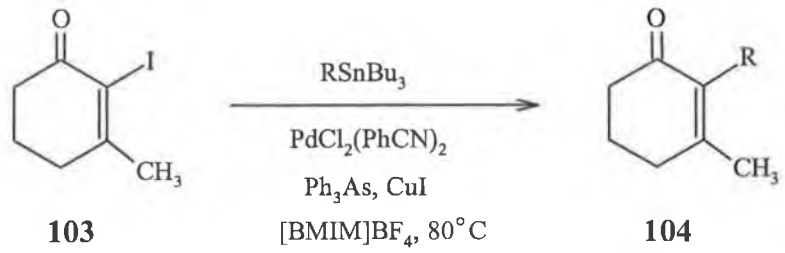
X = H, Cl Y = 4-F, 4-CF_3

Scheme 28. Preparation of heterocyclic compounds in ionic liquids.

1.4.19 The Stille coupling reaction

The Stille coupling reaction has been one of the most widely used steps in the preparation of a wide variety of materials including polyenes, diaryls, and aromatic carbonyl compounds. The main advantages of the reaction stem from the air and moisture stable coupling partner and the compatibility of the coupling condition with a wide array of functional groups. However, the one major limitation is the toxicity of the organic reagents and by-products. Moreover, like all transition metal catalysed cross-coupling reactions, the catalyst itself has the problems of expense and the need of expensive and/or toxic ligands.

A series of Stille coupling reactions in the ionic liquid [BMIM]BF_4 has been successfully demonstrated [87] (Scheme 29). The reaction of α-iodoenone and vinyltributyltin afforded results comparable to those obtained using NMP as the solvent. For example, the isolated yield of 2-allyl-3-methyl-cyclohexen-2-one is 82% from [BMIM]BF_4 after 2h comparing with 95% from NMP after 30 min.



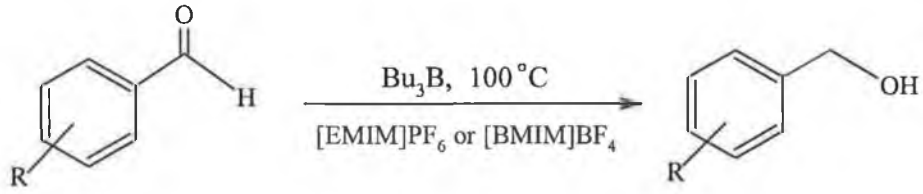
103 **104**

R = vinyl, phenyl, tolyl

Scheme 29. The Stille coupling reaction in ionic liquid.

1.4.20 Reduction of aldehydes with organoborane reagent

The reduction of aromatic and aliphatic aldehydes was carried out by Kabalka and Malladi recently [88]. The reduction of aldehydes by organoborane reagents is an important organic transformation. Generally, boron hydrides are utilised as reducing agents due to their facile reactivity. Trialkylboranes, most notably the pinanyl derivatives, have also been found to be especially useful reducing reagents. However, reductions involving simple trialkylboranes generally require reaction temperatures in excess of approximately 150°C. Ionic liquids, such as [BMIM]BF_4, [EMIM]PF_6 can be employed in trialkylborane reductions of aromatic and aliphatic aldehydes with enhanced rate at low temperature (Scheme 30).



105 **106**

R = (a) H, (b) Br, (c) F, (d) CH_3, (e) OCH_3

Scheme 30. Reduction of aldehydes using trialkylboranes in ionic liquids.

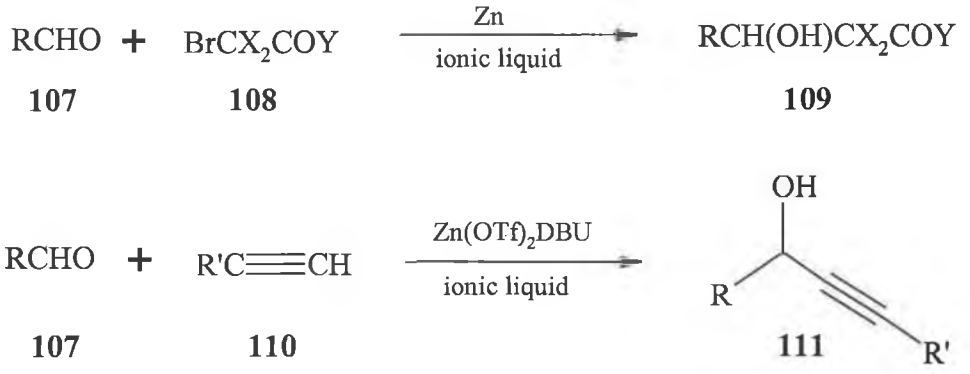
It was found that both aromatic and aliphatic aldehydes are reduced by tributylborane in ionic liquids. The presence of a *para*-substituted electron-donating group appears to hinder the reaction. For example, *p*-methoxybenzaldehyde was reduced by tributylborane to give *p*-methoxybenzyl alcohol (yield 40%). The products are easily removed from the ionic liquids *via* extraction and no decrease in reduction yields when the ionic liquid was reused.

1.4.21 Electrophilic nitration of aromatics

Electrophilic nitration of aromatics is a fundamental reaction of great industrial importance and the products are generally key intermediates. Although the mechanistic and synthetic aspects of nitration chemistry have been very thoroughly studied over the years, there is continuing concern over environmental aspects, disposal problems and regeneration of the used acids. Recently, a series of ionic liquids based on $[EMIM]^+$ and $[HNEt\text{-}i\text{-}Pr_2]^+$ cations have been utilised as solvent for aromatic nitration [89]. It was found that ionic liquids [EMIM]OTf, $[EMIM]CF_3COO$ and $[HNEt\text{-}i\text{-}Pr_2]CF_3COO$ were quite promising. For example, nitration of toluene using NH_4NO_3 with trifluoroacetic anhydride in $[EMIM]CF_3COO$ gave yield 65% of isomers after extraction with ether and CH_2Cl_2 (GC analysis : *o*-nitrotoluene 49.5%, *m*-nitrotoluene 2.0% and *p*-nitrotoluene 48.5%) comparing with the yield 59% in $[EMIM]NO_3$. The nitration in ionic liquids is a useful alternative to classical nitration routes due to easier product isolation and the recovery of the ionic liquid, and because it avoids problems associated with neutralisation of large quantities of strong acid.

1.4.22 Synthesis and reaction of zinc reagents (Reformatsky reaction)

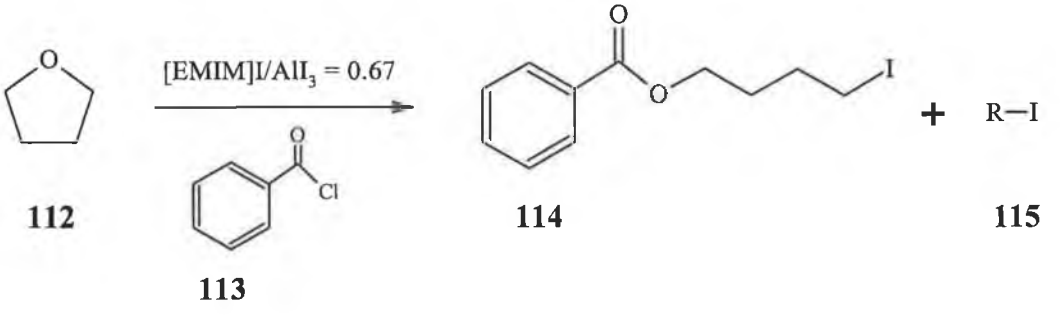
It is known that the preparation of Reformatsky reagents derived from ethyl bromodifluoroacetate in tetrahydrofuran is mediated by zinc. The same reaction has been carried out in ionic liquids with yields at least as good as those with conventional solvents [90] (Scheme 31). Synthesis and reaction of alkyl zinc reagents has also been investigated.



Scheme 31. The synthesis and reaction of zinc reagent in ionic liquids.

1.4.23 Acylative cleavage of cyclic and acyclic ethers

Although several methods for cleaving ethers are available, a general reliable method to selectively cleave ether linkages in complex and otherwise fragile molecules has not been reported. Recently, Singer *et al.* have demonstrated the acylative cleavage of a series of cyclic and acyclic ethers in ionic liquid [EMIM]X·AlX_3 [91] (Scheme 32). The ionic liquids are employed as solvent and Lewis acid in these reactions. It was found that the cyclic ether tetrahydrofuran affords an excellent yield of (4'-iodobutyl)benzoate (95%) when the ionic liquid [EMIM]I·AlI_3 is used strictly acidic, but suffers a decrease in yield (61%) of difunctionalised product when the mildly acidic halogenoaluminate is used as solvent.

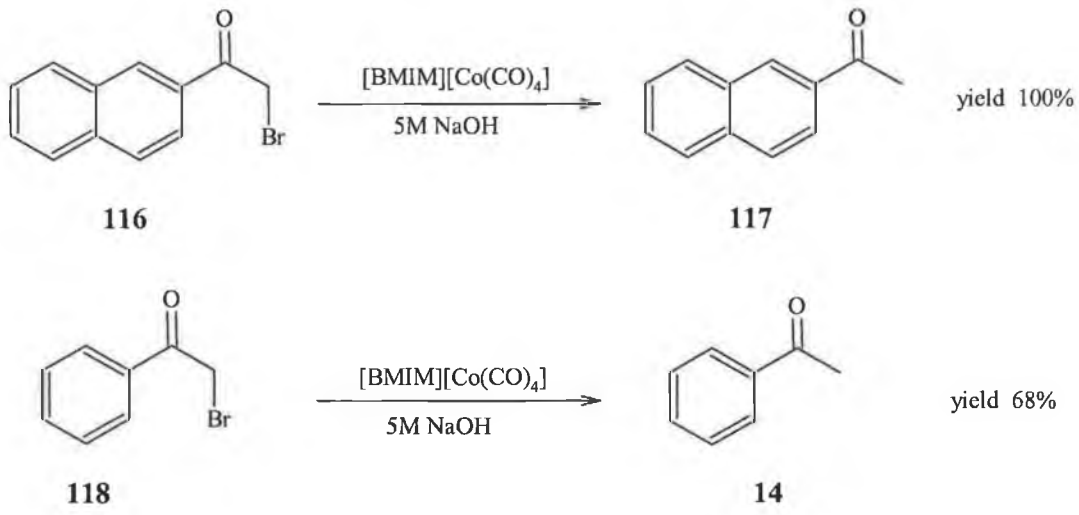


Scheme 32. Acylative ether cleavage in ionic liquid [EMIM]I·AlI_3.

Interestingly, the other cyclic ethers investigated in this study, 1,5-dimethyltetrahydrofuran and tetrahydropyran display inverse behaviour in that they afford good yield of cleavage products only when the mildly acidic halogenoaluminate is used as solvent. Diethyl ether, a primary ether, gave relatively poor yields (22%) of ethylbenzoate under all conditions attempted in this study.

1.4.24 The dehalogenation reaction

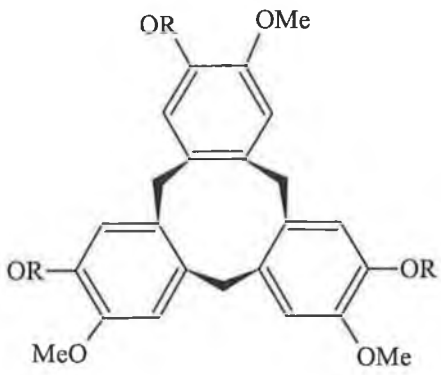
Recently, a new type ionic liquid based on 1-butyl-3-methylimidazolium as cation and $[Co(CO)_4]^-$ as anion was prepared by Welton's group [92]. They used a metathesis reaction of the white solids $Na[Co(CO)_4]$ and [BMIM]Cl in propanone to afford a blue-green ionic liquid $[BMIM][Co(CO)_4]$. As we know, transition metal complexes are widely used in organic synthesis and catalysts, the new type ionic liquid with transition metal carbonyl $[Co(CO)_4]^-$ as anion would be a suitable medium for the reaction of transition metal complexes. Some characteristics of $[BMIM][Co(CO)_4]$ were investigated as well, for example, the electric window is above +4V. The dehalogenation reaction of 2-bromo-2'-acetonaphthone and 2-bromoacetophenone to their corresponding ketones was investigated (Scheme 33).



Scheme 33.The dehalogenation reaction in $[BMIM][Co(CO)_4]$.

1.4.25 Synthesis of cyclotriveratrylene (CTV) and *tri*-(*O*-allyl)CTV

Cyclic CTVs (Figure 9) have been known for over several decades but now they are receiving considerable attention as supramolecular host compounds for various species from low molar mass organic solvents through to C_{60}. CTVs are traditionally synthesized under harsh dehydrating conditions and require the use of large quantities of organic solvent in the reaction work-up.



119

CTV : R = Me

tri-(*O*-allyl)CTV : R =

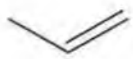


Figure 9. CTV and *tri*-(*O*-allyl)CTV.

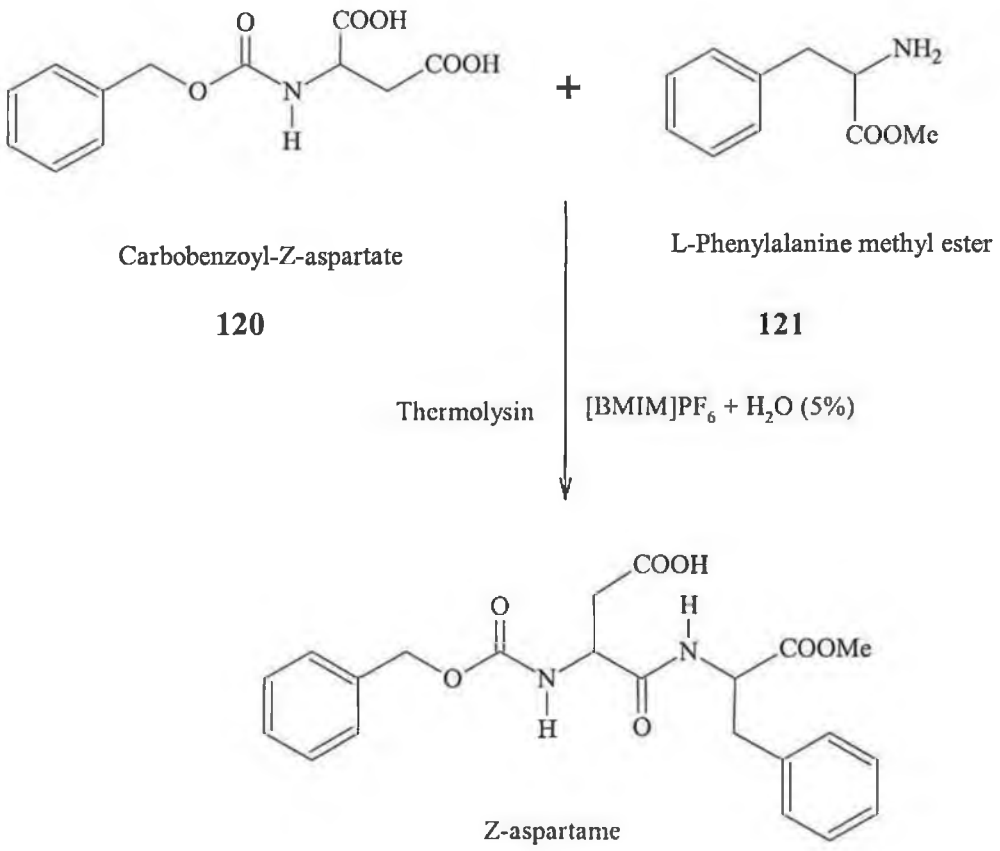
Recently, the ionic liquid tributylhexylammonium bis(trifluoromethylsulfonyl)amide has been reported as a safe, non-volatile reaction medium for the synthesis of CTV [93]. The methodology developed obviates the need for the use of large quantities of organic solvent and strong dehydration acids yet provides a pure crystalline product in high yields. Unlike most traditional synthetic routes to CTV, extensive recrystallisation or chromatographic steps are avoided and the ionic liquid medium is readily recovered.

1.4.26 Enzyme catalysis in ionic liquids

Today, a large number of biotransformations making use of whole cells or isolated enzyme are employed in industry, for example, the kinetic resolution of chiral amines using lipases in BASF [94]. Nevertheless, there are still problems with substrate

solubility, yield or (enantio-) selectivity. Some progress has been made by addition of organic solvent or high salt concentrations or use of microemulsions or supercritical fluids. Recent research has shown that it is possible to carry out enzyme-catalysed reaction and other types of biotransformations in ionic liquids.

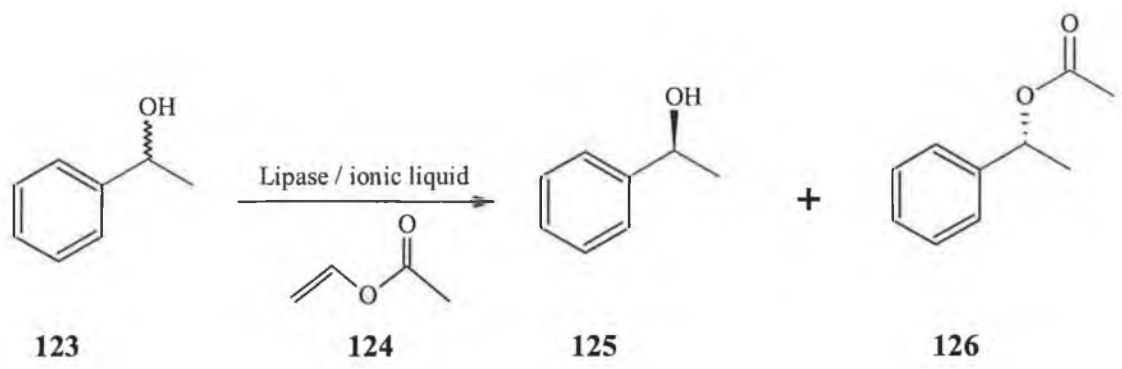
The first example of an enzymatic synthesis in an ionic liquid was demonstrated by the synthesis of Z-aspartame, a precursor to the artificial sweetener aspartame, by the reaction of two amino acid derivatives, carbobenzoxy-L-aspartate and L-phenylalanine methyl ester, catalysed by thermolysin, a proteolytic enzyme [95] (Scheme 34).



Scheme 34. Enzyme catalysed synthesis of Z-aspartame in ionic liquid.

The reaction was carried out using [BMIM] PF_6 containing 5% by volume of water. The yield was 95%, which is similar to that reported for enzymatic aspartame synthesis in organic solvents with low water content, with a competitive reaction rate. In addition, the enzyme, which normally requires immobilisation, exhibited excellent stability in the ionic liquid.

Recently, the application of lipases for an enantioselective reaction in pure ionic liquids based on 1-butyl-3-methylimidazolium such as [BMIM]PF_6, [BMIM]CF_3SO_3 and [BMIM]$(CF_3SO_2)_2N$ were reported [96] (Scheme 35).



Scheme 35. Kinetic resolution of 1-phenylethanol catalysed by enzyme in ionic Liquid.

As a model system, the kinetic resolution of *rac*-1-phenylethanol by transesterification with vinyl acetate was investigated. Lipase shows good activity and, in some cases, improved enantioselectivity in the reaction. In addition, the ionic liquids are not volatile. Therefore it is possible to remove the products by distillation and repeat the catalytic cycle after addition of fresh substrate. The enzyme suspended in ionic liquid could be reused three times with less than 10% loss of activity per cycle and the enantioselectivity was not influenced.

Transesterifications of alcohols in the presence of vinyl acetate in [EMIM]BF_4 and [BMIM]PF_6 using *C. antarctica* lipase B (CALB, immobilised) and *Pseudomonas*

cepacia lipase (PCL, native) as enzyme catalysts has been also reported [97]. Comparing to conventional organic solvents, such as toluene and THF, ionic liquids reveal a great potential as alternative media for biocatalysis and biotransformation as they proceed with markedly enhanced selectivity of the lipase, up to 25 times more enantioselectivity is observed in ionic liquids than in the normal organic solvents.

The biotransformation of highly polar substrates such as carbohydrates is difficult to carry out in common organic solvents because of their sparing solubility. The first example of such a biotransformation in an ionic liquid system has been reported [98]. It shows that *Rhodococcus* R312, a whole-cell biocatalyst that facilitates the transformation of nitriles to amides, could be used for the conversion of 1,3-dicyanobenzene to 3-cyanobenzamide and 3-cyanobenzoic acid in the biphasic water-[BMIM]PF_6 system. But the enzyme is not active in [BMIM]PF_6, and the ionic liquid acts only as a reservoir for the substrates. The *Rhodococcus* R312 remain in the aqueous phase, which is where the reaction takes place and the ionic liquid is used to dissolve concentrations of substrate above the aqueous solubility limit, which then partition into the aqueous phase. The results indicated improved catalytic stability compared with the use of organic solvents, and there is some evidence that the ionic liquid may alter the selectivity of the transformation.

Chapter 2.

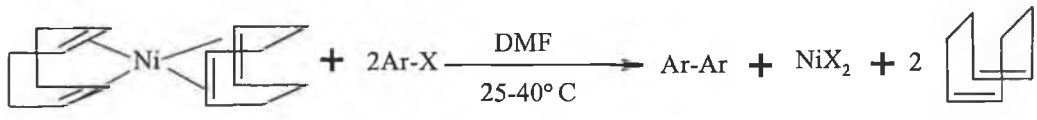
2. The coupling reactions of arylhalides in ionic liquid

2.1 The methods of synthesis of biaryl compounds

Symmetrical biaryl compounds are synthesised by the homocoupling reactions of aryl halides. Generally the reactions can be achieved by three ways: (1) the Ullmann reaction [99a–b]; (2) the two-step procedure of the metal complexes promoted reaction [100a–b]; (3) the one-step procedure of nickel(0) complexes reaction.

The Ullmann reaction uses copper metal as catalyst and needs special conditions, such as high temperature (often higher than 200°C) and aryliodides are mostly used, which limit its application. The second way involves the reaction of intermediate arylmagnesium halides or aryllithium reagents, but substrates with functional groups are often stable to arylmagnesium or aryllithium intermediates, a serious restriction.

The third way was first discovered by Semmelhack *et al.*[101], using nickel(0) complexes such as bis(1,5-cyclooctadiene)nickel(0) $[Ni(COD)_2]$ or tetrakis(triphenylphosphine)- nickel(0) $[Ni(PPh_3)_4]$ in DMF to afford biaryls (Scheme 36).

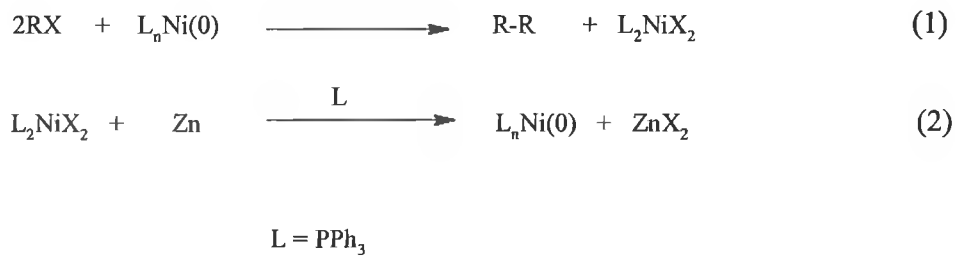


$$2Ar\text{-}X \xrightarrow[DMF]{Ni(PPh_3)_4} Ar\text{-}Ar + NiX_2$$

Scheme 36. The coupling reaction of arylhalides with nickel(0) complexes.

As compared with the classic Ullmann reaction, this method proceed under mild conditions and tolerate a large variety of functional groups. However, these sensitive reagents were conventionally prepared by inconvenient techniques involving trialkyl- or dialkylalkoxyaluminium species as reducing agents under vacuum line or dry-box conditions [102a–b].

Kende *et al.* have developed the Semmelhack's method, in which the reactive nickel(0) reagent was prepared *in situ* from easily accessible, air-stable dichlorobis(triphenylphosphine)nickel(II) by reduction with Zn dust in the presence of triphenylphosphine, generating $Ni(PPh_3)_3$ *in situ*, and then the solution of zerovalent nickel complex for specific organic transformation [103] (Scheme 37).



Scheme 37. The preparation of nickel(0) complex by the reduction of Zn dust.

A suitable organic solvent for the coupling reaction is a polar solvent such as DMF or NMP. No reaction of aryl halides and bis(1,5-cyclooctadiene)nickel occurs at moderate temperature in less polar solvents such as tetrahydrofuran (THF) or toluene. Dimethylsulfoxide (DMSO) and hexamethylphosphoric triamide are not useful due to rapid decomposition of the nickel reagent in these solvents [101].

The reactivity of the aryl halides is approximately in the order I > Br > Cl. Generally, both electron-attracting and electron-donating substituents allow efficient coupling with no significant difference in rate, but nitro groups strongly inhibit coupling reaction [101].

It provides a simple way for the *in situ* generation and utilization of nickel(0) complex for halide coupling in organic synthesis.

2.2 The mechanism of the reaction of nickel(0) complexes with aromatic halides

Nickel species is a relatively unique metal among the transition metals in that a variety of complexes are easily prepared containing nickel in the zerovalent state. The NiL_n (L = PPh_3, PEt_3 *etc.*) species generally undergo oxidative addition of arylhalides under quite mild conditions. This reaction represents direct formation of a σ-bonded organometal species, like a Grignard reagent. But the difference is the much lower polarization of the carbon-nickel bond and the potential compatibility of the reaction with common polar functional groups such as alcohols, carbonyl groups, *etc.*

The mechanism of coupling reaction of arylhalides with Ni(0) complexes is a very interesting area, and it involves a strong electron-transfer component in the reaction, which has been investigated by Tsou and Kochi thoroughly [104]. The investigation of the coupling reaction of arylhalides with nickel(0) complexes was carried out by using a triethylphosphine derivative in non-polar solvents such as benzene, toluene and hexane. It was found that the reaction afforded *trans*-arylnickel(II) halides A, together with paramagnetic nickel(I) halides B as side product.

$$Ni^{0}L_4 + ArX \rightarrow \underset{A}{ArNi^{II}XL_2} + \underset{B}{XNi^{I}L_3} + etc. \qquad (L = PEt_3)$$

The relative yields, A/B, are strongly dependent on the halide (I < Br < Cl), as well as the nuclear substituents and the solvent polarity. The second-order rate constants (k_2) for various *meta*- and *para*-substituted iodobenzenes are linearly related to those of the corresponding bromo- and chloro-arenes. The mechanisms can be expressed as follows (Figure 10):

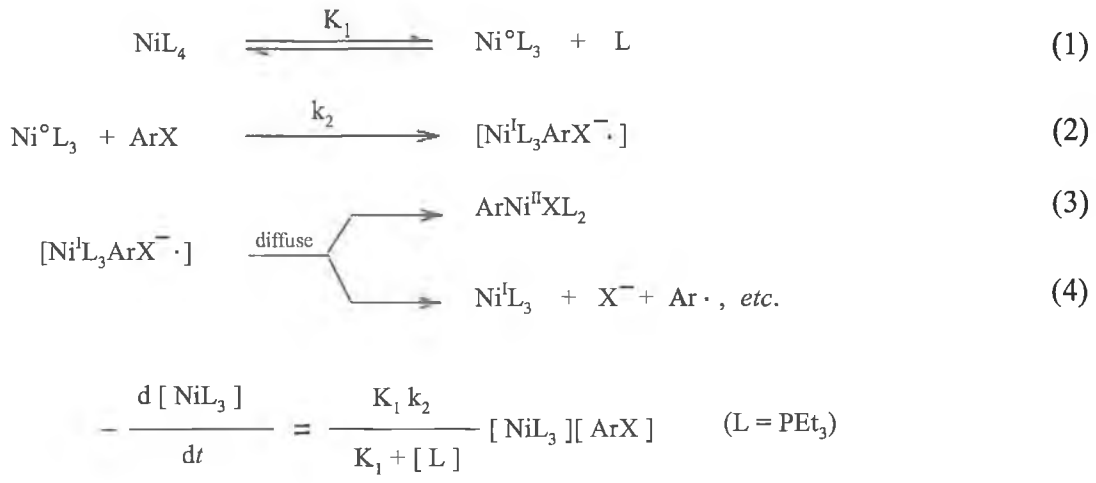


Figure 10. The general mechanism for the reaction of nickel(0) and aryl halides.

According to Figure 10, the equilibrium formation of the coordinatively unsaturated $Ni(PEt_3)_3$ in eq (1) is followed by the slow rate-limiting electron transfer in eq (2) to afford an ion pair indicated in brackets. Cage collapse affords oxidative adduct in eq (3), which is competitive with diffusion in eq (4). The stability and lifetime of the caged ion pair then determine the product distribution.

The geometry of the ion pair is most likely to be that in which the nickel lies below the plane of the aromatic ring and displaced toward the halide. The transition state for insertion stemming from the collapse of such an ion pair is depicted in Figure 11.

Figure 11. Contribution to the reaction state for oxidative addition of aryl halides to $Ni(PEt_3)_3$ by collapse of the ion pair.

However, the absence of a direct correlation between the reactivities of various aryl halides and the distribution between nickel (I, II) products demands that the rate-limiting activation process precedes and is separate from the product-forming steps. Evidence for the paramagnetic ion pair [Ni(I)ArX^{-}·] as the common intermediate which is partitioned between A and B is presented, and discussed in the light of electrochemical measurements of the one-electron oxidation of nickel(0) complexes and the reduction of aryl halides [104].

According to figure 10, the rate-limiting electron transfer from nickel(0) donor to the aryl halide acceptor produces an ion pair which are subject to two competitive modes of decay, *viz.*, (1) collapse to oxidative adduct and (2) fragmentation of the ArX^{-}· moiety, followed by diffusion of aryl radicals out of the solvent cage. The importance of electrostatic effects in the collapse of the ion pair to oxidative adduct is shown by the high sensitivity of A to the presence of charged nuclear substituents such as Me_3N^+ and COO^- groups. The aryl halogen bond strength is the most important factor in the spontaneous fragmentation of the anion radical of the aromatic halide as determined from lifetimes obtained from electrochemical studies [104].

Finally, the co-ordinatively unsaturated $Ni(PEt_3)_3$ is the kinetically active species and responsible for the inverse phosphine dependence on the rate of reaction. It is included in the pre-equilibrium formation of a π complex $[(Et_3P)_3NiArX]$ as a possible precursor for electron transfer.

Further investigation found that biaryl formation involved a radical-chain process in which paramagnetic nickel(I) and arylnickel(III) species are reactive intermediates. The propagation steps include the oxidative addition of ArX to nickel(I) to produce the reactive arylnickel(III) species, which undergoes aryl transfer with *trans*-$ArNiX(PEt_3)_2$ to afford a diarylnickel(III) intermediate, followed by reductive elimination of biaryl and the regeneration of nickel(I).

$$\mathrm{Ar\cdot + ArNi^{II}X \rightarrow \underset{\substack{|\\ Ar}}{ArNi^{III}X} \rightarrow Ar\text{-}Ar + Ni^{I}X} \qquad (1)$$

$$\mathrm{Ni^{I}X + ArX \rightarrow ArNi^{III}X_2} \qquad (2)$$

$$\mathrm{ArNi^{III}X_2 + ArNi^{II}X \rightarrow Ni^{II}X_2 + \underset{\substack{|\\ Ar}}{ArNi^{III}X} \rightarrow Ar\text{-}Ar + Ni^{I}X,}\ \textit{etc.} \qquad (3)$$

This series of chain reactions provide an efficient mechanism for the cross coupling of *trans*-$ArNiX(PEt_3)_2$ and ArX selectively to Ar-Ar, except for a competition from a halogen exchange process which, in effect, scrambles aryl groups between *trans*-$ArNiX(PEt_3)_2$ and an arylnickel(III) species. The initiation of the catalytic cycle is associated with electron transfer from *trans*-$ArNiX(PEt_3)_2$ to ArX, and it can be manipulated by a rational choice of initiators and inhibitors. In the course of biaryl formation, the triethylphosphine ligand reacts with excess ArX to produce arylphosphonium salts, $ArPEt_3^+$, by a second catalytic process induced by the nickel (I) intermediate.

The phosphine levels in the reaction are critical to initiation and inhibition of both these catalytic or chain processes, the two systems are interdependent in that arylphosphonium formation removes triethylphosphine, which is an inhibitor in the biaryl formation. Conversely, in the course of biaryl formation, phosphine is released to fuel the formation of arylphosphonium salts.

Another similar reaction mechanism has been proposed for the Ni(0)-mediated coupling reaction of aryl halides in polar aprotic solvents in the presence of excess Zn [105] (Figure 12). The catalytic cycle shown in Figure 12 can serve as a working model for a mechanism involves the reduction of Ni(II) to Ni(0) by Zn. This is followed by the oxidative addition of ArX to the Ni(0) species. This Ni(II) species then undergoes a one-electron reduction to $ArNi(I)L_3$ ($L = PPh_3$). ArX oxidatively adds to this species to give a diarylNi(III) complex which undergoes rapid reductive

elimination, resulting in the formation of the biaryl product and the generation of $Ni(I)XL_3$. There are two productive reaction pathways available to this Ni species. $Ni(I)XL_3$ can be reduced by Zn to regenerate $Ni(0)L_3$, which can then repeat the catalytic cycle. Alternatively, ArX can undergo direct oxidative addition to $Ni(I)XL_3$ followed by reduction by Zn to form the $ArNi(I)L_3$ species once again.

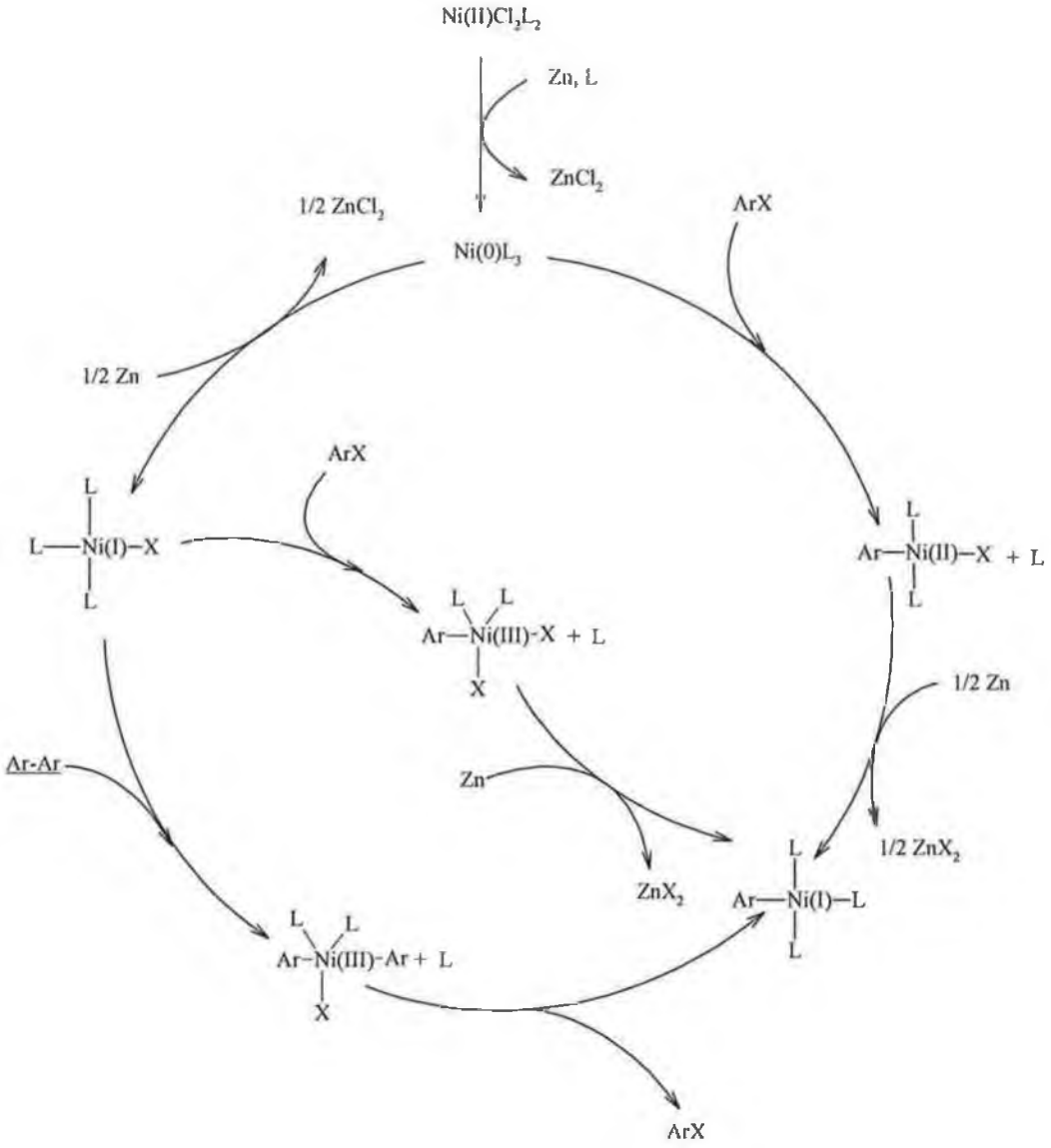


Figure 12. Cyclic mechanism of Ni catalysed-coupling reaction.

Although figure 12 shows the most probable sequence of steps, the rate-determining step is ambiguous. The rate of oxidative addition of aryl halides to Ni(0) species is considered to be a fast reaction in other coupling reaction [106]. The rate-determining step in the homocoupling reaction of aryl halides under similar reaction conditions in the presence of excess Zn is the reduction of the arylnickel(II) species to the arylnickel(I) species [106].

However, at high conversions of ArX, the rate-determining step becomes oxidative addition of ArX to the Ni(I) species. Thus, the rate constants for these reactions are within first order of magnitude of each other. When the reduction occurs by electrochemical means, rather than *via* Zn, the rate-determining step at low concentrations of ArBr is oxidative addition of ArBr to the ArNi(I) species and at higher concentrations of ArBr is the reductive elimination of biaryl from the Ni species.

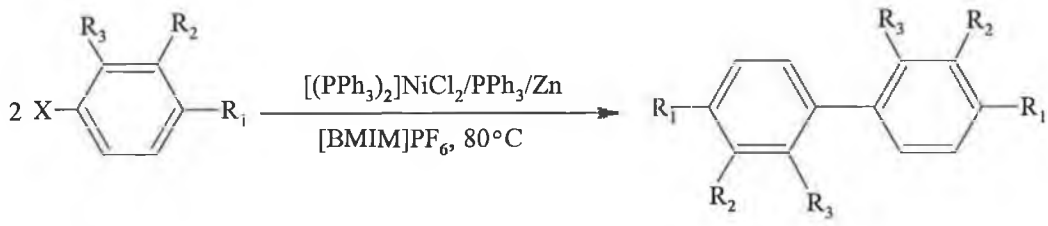
2.3 The coupling reactions in ionic liquid [BMIM]PF_6

So far, all of the coupling reactions have been carried out in conventional ways, usually aprotic organic solvents are used, such as DMF. The reaction was performed under N_2 for 24hr at 50°C. After reaction, the solvent and catalyst could not be recycled.

The ionic liquid is an excellent solvent which can dissolve a wide range of organic and inorganic material, in general, are highly polar yet non-coordinating, are immiscible with wide range of organic solvents and are not volatile. As mentioned before, ionic liquids can be a good media for the reaction catalysed by metal transition complexes and could be a suitable candidate for the coupling reaction.

2.4 Results and discussions

The coupling reaction catalysed by bis(triphenylphosphine)nickel(II) dichloride complexes with triphenylphosphine as ligand in the presence of Zn dust was carried out using [BMIM]PF_6 as solvent at 80°C for 48h. Followed by extraction of the products with diethyl ether. A number of arylhalides were employed in the reaction and the results are shown in Table 5 (Scheme 38).



130 – 137 **138 – 145**

Scheme 38. The coupling reaction of arylhalides with various substitutents.

It was found that in general the aryl bromides substituted at the *ortho* or *para* position by an electron withdrawing substituent give lower yields of biaryl than the simple substrate bromobenzene **130**, while the substrate **133** gives the lowest yield of all (Table 5). The yields of biaryls with electron-donating substituents were relatively higher. In theory, the electron-withdrawing substituent could help the homocoupling reaction, but in fact, the efficient catalyst nickel(0) complex was both activating carbon-bromide and carbon-substituent bonds to result the reaction towards forming by-products, which was observed [107]. This could be the main reason lowered the yields of homocoupling reaction in ionic liquid.

On the other hand, for the electron-donating substituted arylhalides, the nickel(0) complex catalyst was more effective to the carbon-bromide bond rather than carbon-substituent bond resulting lower by-products, so the yield was relatively higher [108].

In case of **133,** it is unlikely that this low yield was due to aryl iodide instead of an aryl bromide used, as aromatic iodide often give high yields for the reaction in DMF, except when there is acyl substitution at the *para* or *ortho* position. The low yield is therefore due to the influence of bigger steric hindrance of the ester group in the *ortho* position and the viscosity of ionic liquid [BMIM]PF_6 promoting the stability of hindrance for the formation of diaryl (Table 5). It is also known that aryl bromides show dramatic variations in yields of the biaryl as a result of substitution in the aromatic ring [109].

It was also found that ionic liquid could enhance the yields of coupling reaction of aryl halides to different degrees. A comparison of the yields of the coupling reaction carried out both in DMF and ionic liquid [BMIM]PF_6 (Table 5) showed that ionic liquid could significantly increase the yields in most cases, except entry 4 and entry 7. For entry 4, it might be that the steric hindrance is bigger in ionic liquid than in DMF. For entry 7, it might be that the influence of the electron-withdrawing group, make the benzene ring more deactivating, therefore gives lower yield.

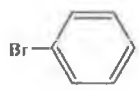
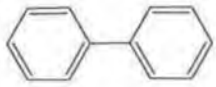
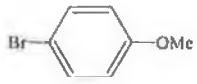
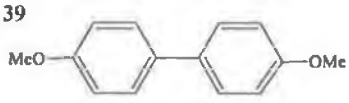
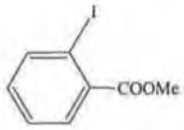
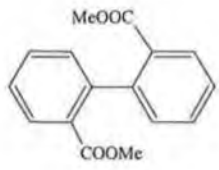
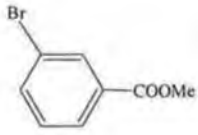
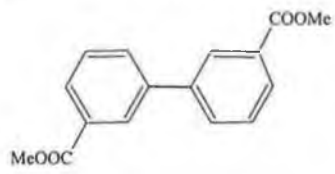
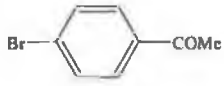
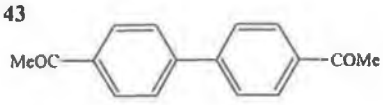
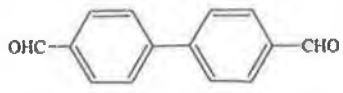
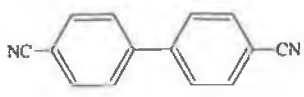
Entry	Substrate	Product	Yield (%)	
			Ionic liquid	DMF
1	**130** 	**138** 	85	78
2	**131** 	**139** 	55	40
3	**132** 	**140** 	76	60
4	**133** 	**141** 	40	58
5	**134** 	**142** 	71	68
6	**135** 	**143** 	60	57
7	**136** 	**144** 	44	48
8	**137** 	**145** 	75	71

Table 5. The coupling reaction of aryl halides in ionic liquid [BMIM]PF_6.

It is worth noting that the ionic liquid and the catalyst can be reused. When the reaction was carried out in normal solvent DMF, after reaction, the mixture was

poured into water and the products were extracted by diethyl ether, which caused the loss of solvent and catalyst, was expensive commercially and could be damaging to the environment.

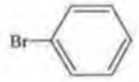
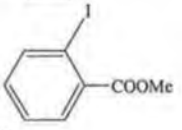
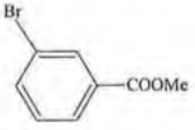
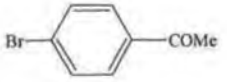
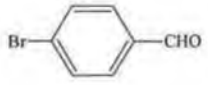
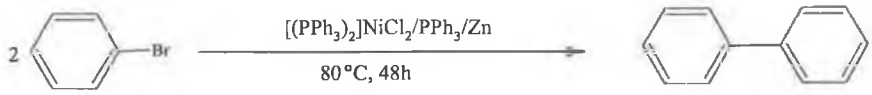
Entry	Substrate	Yield (%)	
		Normal	Recycled
1		85	82
2		55	50
3		76	72
4		40	38
5		71	70
6		60	55
7		44	43
8		75	72

Table 6. The comparison of yields between normal and recycled ionic liquid.

The ionic liquid can be recycled by simple separation after reaction, and then dried under vacuum at 60°C for 48h and deoxygenated. The used catalyst can be separated by simple filtration, and can be reused at least one more time without requiring the

addition of further catalyst. The comparative yields obtained by using recycled ionic liquid are summed up in (Table 6). It was found there was a slightly reduction in yields between normal ionic liquid and the recycled ionic liquid.



Entry	Solvent	Catalyst	Yield (%)
1	DMF	no	0
2	DMF	0.5mol	78
3	[BMIM]PF_6	no	0
4	[BMIM]PF_6	0.25mol	50
5	[BMIM]PF_6	1.0mol	75
6	[BMIM]PF_6	0.5mol	85
7	[BMIM]PF_6	0.5mol (recycled)	80
8	[BMIM]PF_6 (recycled)	0.5mol (recycled)	75
9	[BMIM]BF_4	0.5mol	78
10	[BMIM]BF_4	1.0mol	78
11	[BMIM]BF_4	0.5mol (recycled)	73
12	[BMIM]BF_4(recycled)	0.5mol (recycled)	65

Table 7. The coupling reaction of aryl halides in different conditions.

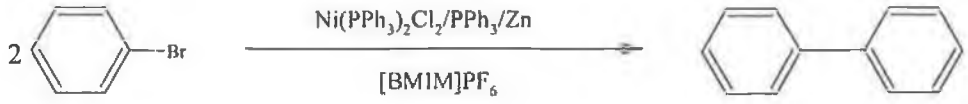
In order to investigate other factors which influence on yields, a simple aryl halide bromobenzene **130** was employed to carry out the coupling reaction in different conditions. It was found that no reaction would occur without catalyst both in DMF and ionic liquid (Table 7, entry 1 and entry 3). The recycled catalyst could reduce the

yield in small degree (entry 7) and 10% decrease was found when the reaction was carried out using both recycled ionic liquid and catalyst (entry 8). The reason for the decrease in yield using recycled ionic liquid might be that some impure materials were still remained in ionic liquid and it affected solubility of catalyst in ionic liquid. More interestingly, the amounts of catalyst could affect the yields as well. When the catalyst was half the amount of substrate, the yield was best, because too much catalyst would be harmful to the reaction (entry 6).

It is noteworthy that a little difference in the yields obtained using the two different ionic liquid [BMIM]PF_6 and [BMIM]BF_4 (entry 5 and entry 10).

More interestingly, the ligand PPh_3 influences the yield as well. Table 8 shows the results of the coupling reaction of bromobenzene **130** under different conditions. It was found that the molar ratio PhBr : Zn : PPh_3 : $[Ni(PPh_3)_2Cl_2]$ = 1 : 1 : 1.5 : 0.5 gave the best yield (entry 3, yield 85%). It revealed that a relative excess of ligand PPh_3 could enhance the reaction, because the Zn salt also need the ligand to coordinate during the reaction, but large excess PPh_3 could retard the homocoupling reaction [107]. No reaction occurred in the absence of PPh_3.

In conclusion, the coupling reaction of arylhalids can be demonstrated in ionic liquid [BMIM]PF_6. The enhancement of yields was observed comparing those carried out in DMF. Although currently there are no significant advantages over the reactions carried out in conventional solvents. But the simplified work-up procedure, recyclable catalyst and ionic liquid would be preferable. Further work will investigate the influences of various ligands for the homocoupling reaction in ionic liquids.



Entry	Molar ratio				Yield (%)
	PhBr	Zn	PPh_3	$[Ni(PPh_3)_2Cl_2$	
1	1	1	0.5	0.5	75
2	1	1	1.0	0.5	83
3	1	1	1.5	0.5	85
4	1	1	2.0	0.5	75
5	1	1	0.25	0.5	74
6	1	1	0.25	1.0	74
7	1	1	no	0.5	0
8	1	1	1.5	1.0	80

Table 8. The coupling reaction of bromobenzene under various molar ratio.

2.5 Experimental section

All melting point determinations were carried out on a Griffin melting point apparatus and uncorrected. All infra-red spectra were recorded on a Perkin Elmer System 2000 FTIR spectrometer.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance NMR spectrometer, operating at 400 MHz and 100 MHz in Aldrich deuterated chloroform with tetramethylsiline as an internal standard respectively at the Dublin City University. (d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet).

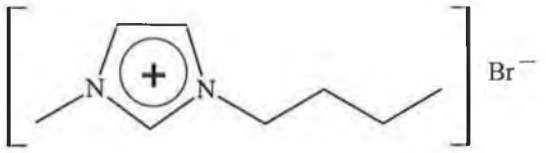
Riedel-de Haën silica gel 60 F254 TLC plates (0.2 mm layer thickness) were used for thin layer, and were examined with UV illumination at λ 254 nm. Riedel-de Haën silica gel S were used for flash chromatography according to the method of Still *et al.*[110].

All reagents and chemicals were obtained from Aldrich Chemical Company (UK) or Lancaster Synthesis Ltd.(UK) and use as received unless otherwise noted.

2.5.1 The synthesis of ionic liquids [BMIM]PF_6 and [BMIM]BF_4

Synthesis of 1-butyl-3-methylimidazolium bromide **127**

A stirred solution of 1,1,1-trichloroethane (200ml) and 1-methylimidazole (33.2g, 0.4mol) in a three-neck round-bottom flask with a reflux condenser and a dropping funnel which was filled with bromobutane (54.8g, 0.4mol). Bromobutane was dropped into the flask slowly over 1 h, and the mixture was stirred and heated at 67°C for 6 h. the molten salt was decanted from the hot solution in a separatory funnel, washed with 1,1,1-trichloroethane (3×50ml), and then placed under vacuum at 70°C overnight to remove the solvent to give **127** (58g, 66.2%).



127

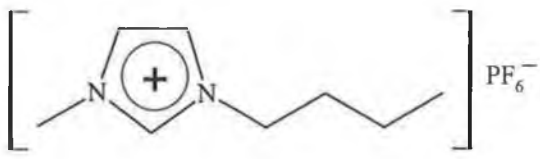
IR : ν_{max} (neat) 3149, 3081, 2966, 2868, 1628, 1576, 1461, 1167, 843, 758 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 9.89 (s, 1H, CH), 7.56 (s, 1H, CH), 7.46 (s, 1H, CH), 4.20 (t, J = 7.60Hz, 2H, CH_2), 3.97 (s, 3H, CH_3), 1.76 (qn, J = 7.60Hz, 2H, CH_2), 1.19–1.29 (m, J = 7.60Hz, 2H, CH_2), 0.80 (t, J = 7.60Hz, 3H, CH_3) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 137.2, 124.2, 122.6, 50.0, 37.0, 32.4, 19.7, 13.8 ppm.

Synthesis of 1-butyl-3-methylimidazolium hexafluorophosphate **128**

To a solution of 1-butyl-3-methylimidazolium bromide (58g, 0.26mol) in water (250ml) in a 500ml conical flask, hexafluorophosphoric acid (66g, 60% HPF_6, 0.27mol) was added slowly in an ice bath, the mixture was stirred vigorously for further 12h. The upper layer of water was separated, and the ionic liquid was washed with water until it was no more acidic. The ionic liquid was then placed under vacuum at 60°C for 48h to remove excess water to give **128** (62.7g, 86%).



128

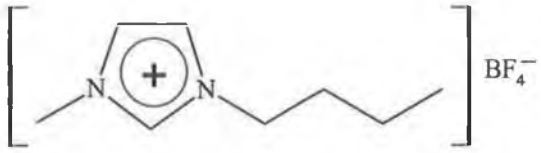
IR : ν_{max} (neat) 3170, 3125, 2966, 2940, 2876, 1573, 1468, 841 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 8.36 (s, 1H, CH), 7.32 (s, 1H, CH), 7.29 (s, 1H, CH), 4.10 (t, J = 7.60Hz, CH_2, 2H), 3.84 (s, 3H, CH_3), 1.79 (qn, J = 7.60Hz, CH_2, 2H,), 1.24–1.33 (m, J = 7.60Hz, CH_2, 2H), 0.86 (t, J = 7.60Hz, 3H, CH_3) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 135.9, 123.9, 122.7, 49.9, 36.2, 31.9, 19.8, 13.5 ppm.

Synthesis of 1-butyl-3-methylimidazolium tetrafluoroborate **129**

To a solution of 1-butyl-3-methylimidazolium bromide (58g, 0.26mol) in acetone (250ml) in 500ml round flask, sodium tetrafluoroborate (30g, 0.27mol) was added. After 24h stirring, the mixture was filtered through a plug of celite (l = 3cm) and the volatile acetone was removed under vacuum to give **129** (52.9g, 90%).



129

IR : ν_{max} (neat) 3166, 3121, 2967, 2941, 2883, 1575, 1472, 1061 cm^{-1}.

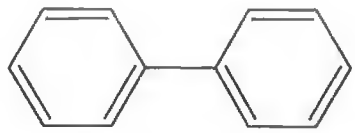
^{1}H-NMR (400MHz) ($CDCl_3$): δ 9.05 (s, 1H, CH), 7.75 (s, 1H, CH), 7.65 (s, 1H, CH), 4.16 (t, J = 7.80Hz, 2H, CH_2), 3.85 (s, 3H, CH_3), 1.68–1.75 (m, 2H, CH_2), 1.21–1.30 (m, 2H, CH_2), 0.85 (t, J = 7.80Hz, 3H, CH_3) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 142.2, 129.4, 128.0, 54.8, 41.2, 37.4, 24.6, 18.9 ppm.

2.5.2 The synthesis of biaryls in ionic liquid

Biphenyl **138**

Into a three-neck 250ml round-bottom flask, $(PPh_3)_2NiCl_2$ (3.625g, 5mmol), PPh_3 (2.62g, 10mmol), Zn (0.66g, 10mmol) and 25ml dry, O_2-free [BMIM]PF_6 were placed. The flask was evacuated and filled with N_2, placed in an oil bath at 80°C while the reactants were stirred rapidly for 24h, during which time the colour changed from the initial dark blue to dark green and then to light green-yellow. After 24h, bromobenzene **130** (1.57g, 10mmol) was added and the mixture was stirred under N_2 at 80°C for 48h. When cooled down to room temperature, the mixture was extracted with diethyl ether (5×20ml), which were combined together and then removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **138** (0.66g, 85%).



138

m.p. : 68 – 70°C, Lit. : 71°C [111]

R_f : 0.67 (hexane : ethyl acetate = 15 : 1)

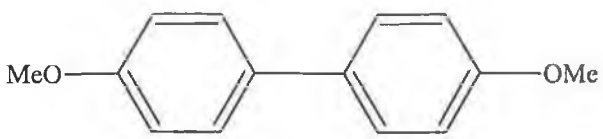
IR : ν_{max} (KBr) 3088, 1670, 1480, 1370, 1092, 730, 700 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.55–7.59 (m, 4H), 7.39–7.44 (m, 4H), 7.29–7.35 (m, 2H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 141.6, 129.2, 127.6, 127.5 ppm.

4,4'-dimethoxybiphenyl **139**

Into a three-neck 250ml round-bottom flask, $(PPh_3)_2NiCl_2$ (3.625g, 5mmol), PPh_3 (2.62g, 10mmol), Zn (0.66g, 10mmol) and 25ml dry, O_2-free [BMIM]PF_6 were placed. The flask was evacuated and filled with N_2, placed in an oil bath at 80°C while the reactants were stirred rapidly for 24h, during which time the colour changed from the initial dark blue to dark green then light green-yellow. After 24h, 4-bromoanisole **131** (1.87g, 10mmol) was added and the mixture was stirred under N_2 at 80°C for 48h. When cooled down to the room temperature, the mixture was extracted with diethyl ether 5×20ml, which were combined together and then removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **139** (0.59g, 55%).



139

m.p. : 179 – 180°C, Lit. : 179°C [112]

R_f : 0.53 (hexane : ethyl acetate = 15 : 1)

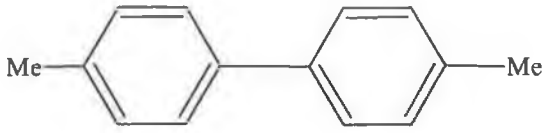
IR : ν_{max} (KBr) 2920, 2890, 1590, 1490, 1250, 1050, 810, 790 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.41 (d, J = 8.0Hz, 4H), 6.89 (d, J = 8.0Hz, 4H) 3.80 (s, 6H, $2CH_3$) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 159.1, 133.9, 128.1, 114.5, 55.8 ppm.

4,4'-dimethylbiphenyl **140**

Into a three-neck 250ml round-bottom flask, $(PPh_3)_2NiCl_2$ (3.625g, 5mmol), PPh_3 (2.62g, 10mmol), Zn (0.66g, 10mmol) and 25ml dry, O_2-free [BMIM]PF_6 were placed. The flask was evacuated and filled with N_2, placed in an oil bath at 80°C while the reactants were stirred rapidly for 24h, during which time the colour changed from the initial dark blue to dark green and then to light green-yellow. After 24h, 4-bromotoluene **132** (1.71g, 10mmol) was added and the mixture was stirred under N_2 at 80°C for 48h. When cooled down to room temperature, the mixture was extracted with diethyl ether (5×20ml), which were combined together and then removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **140** (0.69g, 76%).



140

m. p.: 118°C, Lit. : 121°C [113]

R_f : 0. 57 (hexane : ethyl acetate = 15 : 1)

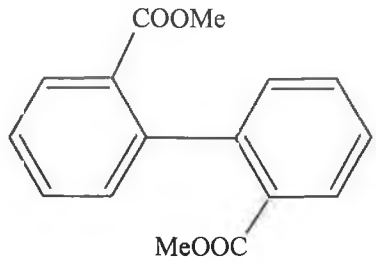
IR : ν_{max} (KBr) 3020, 2933, 1610, 1510, 1180, 1005, 725 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.51 (d, *J* = 8.12Hz, 4H), 7.26 (d, *J* = 8.12Hz, 4H), 2.44 (s, 6H, $2CH_3$) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 138.7, 137.1, 129.8, 127.2, 21.5 ppm.

Dimethyl biphenyl-2,2'-dicarboxylate **141**

Into a three-neck 250ml round-bottom flask, $(PPh_3)_2NiCl_2$ (3.625g, 5mmol), PPh_3 (2.62g, 10mmol), Zn (0.66g, 10mmol) and 25ml dry, O_2-free [BMIM]PF_6 were placed. The flask was evacuated and filled with N_2, placed in an oil bath at 80°C while the reactants were stirred rapidly for 24h, during which time the colour changed from the initial dark blue to dark green and then to light green-yellow. After 24h, methyl-2-iodobenzoate **133** (2.62g, 10mmol) was added and the mixture was stirred under N_2 at 80°C for 48h. When cooled down to room temperature, the mixture was extracted with diethyl ether (5×20ml), which were combined together and then removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **141** (0.54g, 40%).



141

m.p. : 70 – 72°C, Lit. : 73 – 74°C [114]

R_f : 0.42 (hexane : ethyl acetate = 15 : 1)

IR : ν_{max} (KBr) 3054, 2850, 1726, 1436, 1257, 1078, 822, 758 cm^{-1}.

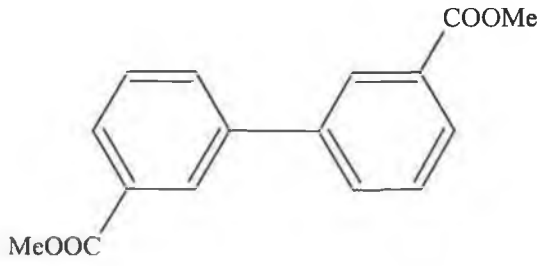
^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.94 (dd, *J* = 8.0Hz, *J* = 1.60Hz, 2H), 7.46 (tt, *J* = 9.20Hz, *J* = 1.60Hz, 2H), 7.36 (tt, *J* = 9.20Hz, *J* = 1.60Hz, 2H), 7.13 (dd, *J* = 8.0Hz, 2H), 3.55 (s, 6H, $2CH_3$) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 167.8, 143.7, 131.9, 130.6, 130.2, 129.7, 127.6, 52.2 ppm.

Dimethyl biphenyl-3,3'-dicarboxylate **142**

Into a three-neck 250ml round-bottom flask, $(PPh_3)_2NiCl_2$ (3.625g, 5mmol), PPh_3 (2.62g, 10mmol), Zn (0.66g, 10mmol) and 25ml dry, O_2-free [BMIM]PF_6 were placed. The flask was evacuated and filled with N_2, placed in an oil bath at 80°C while the reactants were stirred rapidly for 24h, during which time the colour changed from the initial dark blue to dark green and then to light green-yellow. After 24h, methyl-3-bromobenzoate **134** (2.15g, 10mmol) was added and the mixture was stirred under N_2 at 80°C for 48h. When cooled down to room temperature, the mixture was extracted with diethyl ether (5×20ml), which were combined together and then

removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **142** (0.96g, 71%).



142

m.p. : 102 –103°C, Lit. : 103°C [115]

R_f : 0.45 (hexane : ethyl acetate = 15 : 1)

IR : ν_{max} (KBr) 2960, 2840, 1726, 1436, 1235, 1112, 737, 686 cm^{-1}.

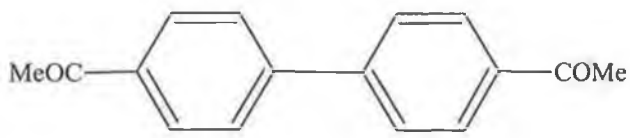
^{1}H-NMR (400MHz) ($CDCl_3$): δ 8.25 (s, 2H), 8.02 (d, J = 8.0Hz, 2H), 7.76 (d, J = 8.0Hz, 2H), 7.48 (t, J = 8.40Hz, 2H), 3.90 (s, 6H, $2CH_3$) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 167.3, 140.8, 131.9, 131.2, 129.4, 129.2, 128.7, 52.7 ppm.

4,4'-diacetylbiphenyl **143**

Into a three-neck 250ml round-bottom flask, $(PPh_3)_2NiCl_2$ (3.625g, 5mmol), PPh_3 (2.62g, 10mmol), Zn (0.66g, 10mmol) and 25ml dry, O_2-free [BMIM]PF_6 were placed. The flask was evacuated and filled with N_2, placed in an oil bath at 80°C while the reactants were stirred rapidly for 24h, during which time the colour changed from the initial dark blue to dark green and then to light green-yellow. After 24h, 4-bromoacetophenone **135** (1.99g, 10mmol) was added and the mixture was stirred under N_2 at 80°C for 48h. When cooled down to room temperature, the mixture was

extracted with diethyl ether (5×20ml), which were combined together and then removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 10 : 1) to give **143** (0.71g, 60%).



143

m.p. : 193°C, Lit. : 191°C [116]

R_f : 0.33 (hexane : ethyl acetate = 10 : 1)

IR : ν_{max} (KBr) 3170, 2980, 1680, 1600, 1220, 810 cm^{-1}.

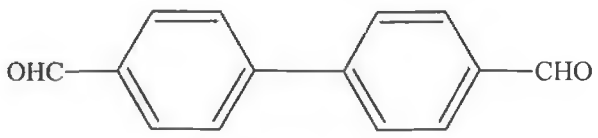
^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.88 (d, J = 8.12Hz, 4H), 7.54 (d, J = 8.12Hz, 4H), 2.48 (s, 6H, $2CH_3$) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 198.0, 144.7, 136.9, 129.4, 127.9, 27.1 ppm.

Biphenyl-4,4'-dibenzaldehyde **144**

Into a three-neck 250ml round-bottom flask, $(PPh_3)_2NiCl_2$ (3.625g, 5mmol), PPh_3 (2.62g, 10mmol), Zn (0.66g, 10mmol) and 25ml dry, O_2-free [BMIM]PF_6 were placed. The flask was evacuated and filled with N_2, placed in an oil bath at 80°C while the reactants were stirred rapidly for 24h, during which time the colour changed from the initial dark blue to dark green and then to light green-yellow. After 24h, 4-bromobenzaldehyde **136** (1.85g, 10mmol) was added and the mixture was stirred under N_2 at 80°C for 48h. When cooled down to room temperature, the mixture was extracted with diethyl ether (5×20ml), which were combined together and then

removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 10 : 1) to give **144** (0.46g, 44%)



144

m.p. : 141 –143°C, Lit. : 145°C [117]

R_f : 0.26 (hexane : ethyl acetate = 10 : 1)

IR : ν_{max} (KBr) 3226, 3153, 1692, 1602, 1385, 1210, 814, 660 cm^{-1}.

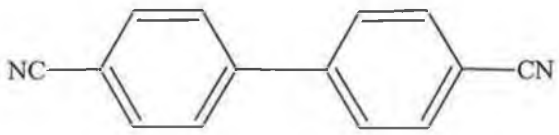
^{1}H-NMR (400MHz) ($CDCl_3$) : δ 10.02 (s, 2H), 7.94 (d, *J* = 8.0Hz, 4H), 7.74 (d, *J* = 8.0Hz, 4H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$) : δ 192.2, 145.9, 136.4, 130.8, 128.4 ppm.

4,4'-dicyanobiphenyl **145**

Into a three-neck 250ml round-bottom flask, $(PPh_3)_2NiCl_2$ (3.625g, 5mmol), PPh_3 (2.62g, 10mmol), Zn (0.66g, 10mmol) and 25ml dry, O_2-free [BMIM]PF_6 were placed. The flask was evacuated and filled with N_2, placed in an oil bath at 80°C while the reactants were stirred rapidly for 24h, during which time the colour changed from the initial dark blue to dark green and then to light green-yellow. After 24h, 4-bromobenzonitrile **137** (1.82g, 10mmol) was added and the mixture was stirred under N_2 at 80°C for 48h. When cooled down to room temperature, the mixture was extracted with diethyl ether (5×20ml), which were combined together and then removed under vacuum to afford the crude product. It was purified by flash column

chromatography on silica gel (hexane : ethyl acetate = 10 : 1) to give **145** (1.53g, 75%).



145

m.p.: 230 – 231°C, Lit.: 229 – 230°C [107]

R_f : 0.28 (hexane : ethyl acetae = 10 : 1)

IR : ν_{max} (KBr) 3080, 2210, 1422, 1480, 588 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.81 (d, *J* = 8.80Hz, 4H), 7.72 (d, *J* = 8.80Hz, 4H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 143.9, 133.3, 128.3, 118.8, 112.8 ppm.

2.5.3 Nickel complex catalyst recycling

The used nickel complex catalyst can be isolated from the ionic liquid by filtering. The main useful compound left in filtered cake is $(PPh_3)_2NiCl_2$, and it can be used again. Into a three-neck round flask, the filtered cake, Zn dust (0.66g 10mmol) and 20ml dry, O_2-free ionic liquid [BMIM]PF_6 were placed. The method and conditions are the same as in the previous reaction, and then bromobenzene **130** (1.57g, 10mmol) was injected into the flask, kept heated at 80°C for further 48h. After reaction the mixture was extracted with diethyl ether (6×25ml), which was combined and removed under vacuum to give the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **138** (0.62g, 80%).

2.5.4 The ionic liquid [BMIM]PF_6 recycling

The ionic liquid was isolated by filtering and extracted with diethyl ether thoroughly (making sure no reactant and product was left) and then placed under high vacuum for 24 h at 60°C to remove the diethyl ether and O_2. The recycled liquid can be reused to perform the same reaction. Bromobenzene **130** (1.57g, 10mmol) was injected into the flask after 48h at 80°C to afford crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **138** (0.63g, 82%).

Chapter 3.

3. The reaction of biotransformation in ionic liquid

3.1 Baker's yeast as a biotransformation catalyst

Baker's yeast is often used as a general biocatalyst in organic synthesis. Recently the study of baker's yeast becomes a more active area for the demand of high stereoselective compounds [118]. The advantages of using baker's yeast are as follows: (1) The active cell mass is extremely cheap and is available in unlimited quantities. More than 500,000 tons/year of baker's yeast are produced globally. (2) Handling of baker's yeast is simple, most of the transformations can be carried out in conventional laboratory or pilot plant equipment using inexpensive additives such as water, saccharose, ethanol, inorganic salts, and other nutrients. (3) Baker's yeast is neither toxic nor pathogenic and does not require sterile conditions. (4) Yeast cells contain lots of enzymes. More than a hundred enzymes have been isolated in a purified form from baker's yeast, several of which are commercially available. This facilitates the execution of many different transformations, including those requiring more than one enzyme.

On the other hand, there are a number of less attractive features to baker's yeast catalysed transformation: (1) In reactions performed with living cells, the ratio of cell mass to substrate is usually high (3~20:1, calculated for the dry cell mass) and the permissible limit of substrate concentration is low. (2) Reproducibility of the process may often be capricious. It was observed repeatedly that different strains of *S. cerevisiae* performed the transformation of the same substrate with varying selectivities [119a–b]. (3) Baker's yeast cannot be used when either the substrate or the product will be decomposed in water, since the living cells only work in an aqueous medium. Even when using an organic solvent, the cells themselves are in an aqueous micro-environment.

Generally, for the transformation of non-natural substrates, not growing but resting cell cultures are used, preferably under the following conditions: (1) Transformations are generally accomplished with vigorously fermenting yeast in a medium containing a substantial amount of sugar [120]. Under such conditions the non-buffered medium turns rapidly acidic with pH dropping to 4-5 or even lower. (2) Occasionally non-natural substrates are transformed in a non-fermenting medium using a high cell mass/substrate ratio [121]. In this case, an aqueous suspension of baker's yeast is used without any additive whereby the medium stays approximately neutral. (3) Both fermenting and non-fermenting processes can be carried out with immobilized cells of baker's yeast. Immobilization has the advantages of the simplicity of product isolation and ultimately increased selectivity. This however, must be balanced against lower productivity due to the diminished activity of immobilized cells and/or higher degree of product retention. (4) Biocatalysis by baker's yeast can be carried out in organic solvents with cells encapsulated into reverse micelles [122] or by using polymer entrapped yeast cells [123]. When compared to conventional methods proceeding in the presence of sugar, there have been occasional reports of enhanced selectivity using this technique.

3.2 Immobilised baker's yeast reduction of ketones in [BMIM]PF_6

Baker's yeast has been widely used in preparation of chiral compounds, however, it use sometimes is limited by the application of aqueous or aqueous-solvent systems. To become more widely applicable in synthetic chemistry for such a biocatalyst, they need to operate and retain their selectivity in solvents more compatible with organic compounds. There have been several reports discussing that alternative organic solvent can be employed for the biotransformation using baker's yeast, such as petroleum ether [124], hexane [125], benzene [126], toluene [127], carbon tetrachloride [127], and liquefied petroleum gas [128]. The main advantage of using such organic solvent is that the product can be separated easily, but the solvents are usually toxic to the biocatalyst and remain the problems of disposal to the environment.

Recently, the reactions of using purified enzyme as biocatalyst in ionic liquid have been reported [28, 94–98]. We speculated that it may have the possibility of carrying out whole-cell biotransformations such as yeast mediated reductions of ketones in an ionic liquid. This would combine the advantages of whole-cell bioreagents and the advantages of ionic liquids, such as being recyclable and not hazardous to the environment.

For this purpose, we chose some readily available ketones (Table 9.) for the study. Since yeast is a living material in an aqueous solution, every enzyme and coenzyme is recycled by a series of complex sequences of metabolising reaction pathways, it would not survive in an organic solvent, and its metabolic pathways thus no longer operate in an organic solvent. Consequently, NADPH, which is the necessary coenzyme for the reduction of ketones, is not regenerated automatically in yeast in an organic solvent and the amount of a substrate that can be reduced is quiet limited to the level of NADPH which exists in the yeast subjected to the reduction in an organic solvent.

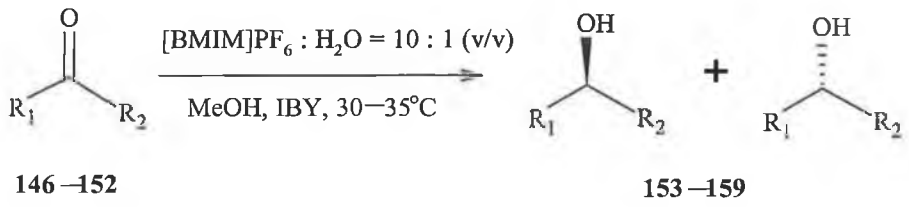
The use of organic solvent may also cause a serious damage of the cell membrane resulting in a scattering of cell contents towards the outside. However, immobilization of a biocatalyst has been known to enhance the stability of the catalyst against denaturation by organic solvents [129]. The immobilised baker's yeast (IBY) also can simplify the work-up procedure whereby the IBY could be easily removed by filtration.

It was shown that the inactivation of enzymes in organic solvents can be avoided if the enzyme is surrounded by a layer of water [130]. Thus, we decided to add a small quantity of water to the ionic liquid (The ratio of water : [BMIM]PF_6 by volume is 1:10) to keep the baker's yeast more active and we also added a small quantity of methanol as energy source [131] to the reaction system. The methods of immobilisation of baker's yeast include entrapment of the yeast cells in gel or

membrane, usually using alginate or polyurethane. The method we chose is the encapsulation in calcium alginate beads [132], which is efficient and facile.

3.2.1 Results and discussions

The reduction of ketones was carried out in [BMIM]PF_6 with immobilised baker's yeast in presence of water ([BMIM]PF_6 : water, v/v = 10 : 1) at 30–35°C for 72h (Scheme 40).



146–152 **153–159**

Scheme 40. The reduction of ketones in [BMIM]PF_6.

The results are given in Table 9. It was found that the yields of product varied over the range of substrates, some gave poor yields whilst others gave good yields. When we attempted to reduce the two aromatic ketones, 4-bromoacetophenone and 4-methoxyacetophenone, no corresponding alcohol was found after reaction and only the starting materials were observed. The reason may be that the substrates are highly toxic to the yeast cells, most cells lost their activity and could not carry out the conversion under such conditions.

The literature values for enantiomeric excesses (ee) given in Table 9 for yeast reduction were carried out in alternative media. In general the enantiomeric excesses obtained in an ionic liquid medium were comparable to those obtained in other media, although entry 6 and entry 7 were relatively lower.

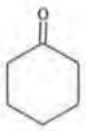
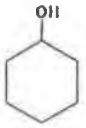
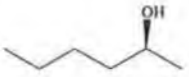
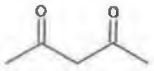
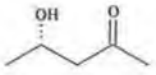
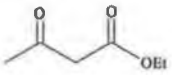
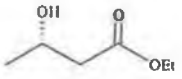
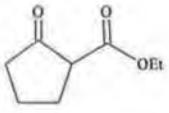
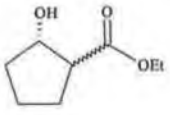
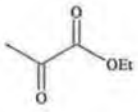
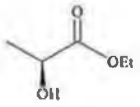
Entry	Substrate (ketone)	Product (alcohol)	Yield (%)	Ee (%) Lit( )	$[\alpha]^{20}_D$ Lit ( )
1	146 	153 	35	—	—
2	147 	154 	20	—	—
3	148 	155 	40	79 (82) [133]	+9.3 (+11.7) [134]
4	149 	156 	22	70 (74) [135]	+38.2 (+40.0) [135]
5	150 	157 	70	95 (97) [124]	+41.0 (+43.0) [136]
6	151 	158 	75	84 (99) [137]	+12.3 (+14.7) [137]
7	152 	159 	60	76 (91) [118]	-7.1 (-9.4) [138]

Table 9. The yields and ee for the reduction of ketones in ionic liquid [BMIM]PF_6.

The ionic liquid can be recycled after reaction and the immobilised baker's yeast can be used at least one more time. We also tried the reactions in the absence of water, finding the enantiomeric excesses were extremely poor, probably the inactivation of the enzyme lowered the level of the metabolising reaction in the baker's yeast.

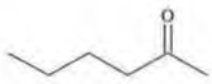
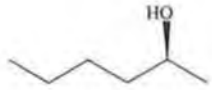
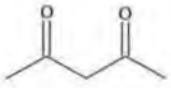
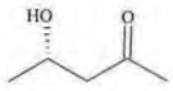
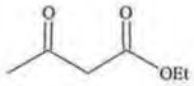
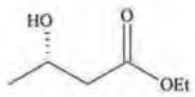
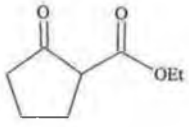
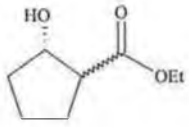
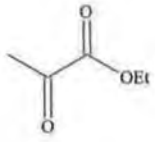
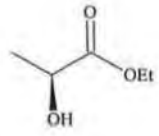
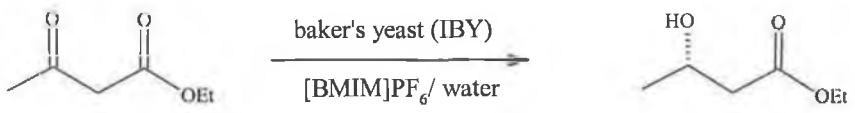
Entry	Substrate (ketone)	Product (alcohol)	Pure water		[BMIM]PF_6/water (v/v = 10 : 1)	
			Yield (%)	ee (%)	Yield (%)	ee (%)
1			55	81	40	79
2			35	98	22	70
3			77	90	70	95
4			83	80	75	84
5			86	70	60	76

Table 10. The reduction of ketones in pure water and water-ionic liquid system.

It was noteworthy that when the reduction of ketones by baker's yeast was carried out in pure water and [BMIM]PF_6/water respectively (Table 10), it was found that water/[BMIM]PF_6 system could enhance the ee value to different degree (entry 3, entry 4, entry 5) although the yields are lower than those were carried out in pure water. It showed that the ionic liquid would not deactivate the immobilised baker's yeast.

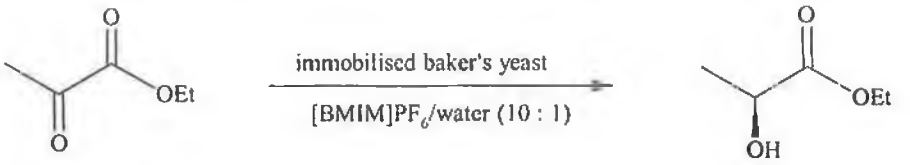
In order to investigate other factors which could influence the reduction on ee value, a substrate ethyl acetoacetate **150** was used as a model to be reduced by baker's yeast in different media (Table 11). It was found that the ionic liquid [BMIM]PF_6/water system is the most suitable solvent for the reduction of ketones by baker's yeast (entry 2). Normal solvents such as hexane, petrol ether, benzene and toluene gave lower ee values and yields (entry 3, 4, 7, 8, 9), because of the damage caused by solvents to the baker's yeast cells. It also found the [BMIM]BF_4/ water system gave similar results with [BMIM]PF_6 /water system.



Entry	Solvent	Yield (%)	Ee (%)
1	$[BMIM]PF_6$	0	0
2	$[BMIM]PF_6$ / water(10:1)	70	95
3	hexane/ water(10:1)	64	92
4	hexane	32	86
5	$[BMIM]BF_4$	0	0
6	$[BMIM]BF_4$ / water(10:1)	72	93
7	petrol ether	40	77
8	bezene	29	60
9	toluene	37	67

Table 11. The influences of various solvents on ee value.

Surprisingly, immobilisation of baker's yeast could effect on ee value as well. It was found that the immobilised yeast gave more *R*-hydroxy esters relative to the regular yeast, that is the ee of the *S*-hydroxy ester decreased (Table 12, entry 1 and 2), because the immobilisation could change the environment of the living cells resulting the change of metabolic pathway to give different product [118]. The additive could influence the ee value, it was found that the ee value would decrease when methanol was added in large portion, too much methanol is harmful to the cells. It also is noteworthy that the recycled ionic liquid and immobilised baker's yeast could be used again without any decrease on yield and ee value.



Entry	Solvent ([BMIM]PF_6 /water)	Yeast	Additive (methanol)	Yield(%)	Ec value(%) (s)
1	10:1	immobilised	2ml	60	76
2	10:1	free	2ml	62	85
3	10:1 (recycled)	immobilised (recycled)	2ml	61	76
4	10:1	immobilised	no	55	71
5	10:1	immobilised	5ml	60	72
6	1:1	immobilised	2ml	80	74

Table 12. The influences of reduction on ee in different conditions.

In conclusion, the reduction of ketones has been demonstrated in [BMIM]PF_6/water (v/v = 10 : 1) with immobilised baker's yeast. The ee values were comparable with those obtained in alternative media. The ionic liquid showed potential of enhancement to the enantioselectivity and stability together with their advantage of reusable. Further work will widen the range of biocatalysts and examine if the ee values would have some improvements in ionic liquids.

3.2.2 Experimental section

All infra-red spectra were recorded on a Perkin Elmer System 2000 FTIR spectrometer. $[\alpha]^{20}_{D}$ were recorded using Perkin Elmer Polarimeter 343 at 589nm sodium line measurement at 20°C temperature.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance NMR spectrometer, operating at 400 MHz and 100 MHz in Aldrich deuterated chloroform with tetramethylsiline as an internal standard respectively at the Dublin City University. (d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet).

Riedel-de Haën silica gel 60 F254 TLC plates (0.2mm layer thickness) were used for thin layer, and were examined with UV illumination at λ 254 nm. Riedel-de Haën silica gel S were used for flash chromatography according to the method of Still *et al.*[110].

All reagents and chemicals were obtained from Aldrich Chemical Company (UK) or Lancaster Synthesis Ltd.(UK) and were used without further purification, unless otherwise noted.

3.2.2.1 Immobilisation of baker's yeast

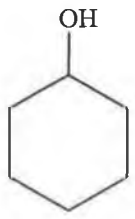
1) To a solution of 200ml water in 500ml conical flask, 5g sodium alginate was added and the mixture was stirred until the sodium alginate dissolved completely.
2) Into 80ml water in a 200ml beaker, 20g baker's yeast was added. The solution was stirred for 2h to give a homogenous suspension, and then was transferred into the solution of sodium alginate, stirred for further 2h.
3) The mixture of baker's yeast and alginate was transferred to a 500ml separating funnel with an outlet 2mm diameter. The mixture was added dropwise into aqueous calcium chloride (3%, solution, 800ml).
4) The beads were filtered, and then washed completely with water to give yeast beads 1.5–2mm diameter. The beads can be stored at 0°C for several weeks.

3.2.2.2 The reduction of ketones in ionic liquid [BMIM]PF_6

<u>The reduction of cyclohexanone **146**</u>

To a mixture of 100ml [BMIM]PF_6 and 10ml water in a 250ml three-neck round-bottomed flask, 130ml immobilised baker's yeast (includes 10g yeast) and 2ml methanol was added. The mixture was stirred vigorously in an oil-bath at 30–35°C. After 1h, cyclohexanone **146** (1.96g, 20mmol) was added, the mixture was stirred at 30–35°C for 72h. After reaction, the beads were filtered and the remaining filtrate was extracted with diethyl ether (5×30ml). The extracts were combined together, dried with anhydrous $MgSO_4$, and then filtered. The solvent was removed under vacuum to afford a pale yellow oil. It was purified by flash column chromatography on silica (hexane : ethyl acetate = 6 : 1) to give product **153** (0.71g, 35%).

Cyclohexanol



153

R_f : 0.57 (hexane : ethyl acetate = 6 : 1)

IR : ν_{max} (neat) 3420, 2910, 1460, 1365, 1070, 980 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 3.55–3.60 (m, 1H, CH), 2.76 (s, 1H, OH), 1.81–1.88 (m, 2H, CH_2), 1.66–1.71 (m, 2H, CH_2), 1.15–1.50 (m, 6H, $3CH_2$) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 70.5, 35.8, 26.0, 24.6 ppm.

The reduction of cyclopentanone **147**

To a mixture of 100ml [BMIM]PF_6 and 10ml water in a 250ml three-neck round-bottomed flask, 130ml immobilised baker's yeast (includes 10g yeast) and 2ml methanol was added. The mixture was stirred vigorously in an oil-bath at 30–35°C. After 1h, cyclopentanone **147** (1.68g, 20mmol) was added, the mixture was stirred at 30–35°C for 72h. After reaction, the beads were filtered and the remaining filtrate was extracted with diethyl ether (5×30ml). The extracts were combined together, dried with anhydrous $MgSO_4$, and then filtered. The solvent was removed under vacuum to afford a pale yellow oil. It was purified by flash column chromatography on silica (hexane : ethyl acetate = 6 : 1) to give product **154** (0.34g, 20%).

Cyclopentanol

154

R_f : 0.54 (hexane : ethyl acetate = 6 : 1)

IR : ν_{max} (neat) 3335, 2965, 1440, 1340, 1075, 990, 665 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 4.25–4.31 (m, 1H, CH), 2.65 (s, 1H, OH), 1.67–1.80 (m, 4H, $2CH_2$), 1.45–1.61 (m, 4H, $2CH_2$) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 74.2, 35.9, 23.8 ppm.

Reduction of 2-hexanone **148**

To a mixture of 100ml [BMIM]PF_6 and 10ml water in a 250ml three-neck round-bottomed flask, 130ml immobilised baker's yeast (includes 10g yeast) and 2ml methanol was added. The mixture was stirred vigorously in an oil-bath at 30–35°C. After 1h, 2-hexanone **148** (1.00g, 10mmol) was added, the mixture was stirred at 30–35°C for 72h. After reaction, the beads were filtered and the remaining filtrate was extracted with diethyl ether (5×30ml). The extracts were combined together, dried with anhydrous $MgSO_4$, and then filtered. The solvent was removed under vacuum to afford a pale yellow oil. It was purified by flash column chromatography on silica (hexane : ethyl acetate = 9 : 1) to give product **155** (0.41g, 40%).

(S)-(+)-2-hexanol

155

R_f : 0.42 (hexane : ethyl acetate = 9 : 1)

$[\alpha]^{20}_D$ = +9.3° (c = 0.01, $CHCl_3$) lit. +11.7° [134]

IR : ν_{max} (neat) 3350, 2960, 1460, 1052 cm^{-1}.

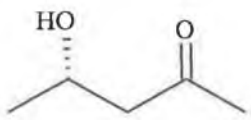
^{1}H-NMR (400MHz) ($CDCl_3$): δ 3.71–3.82 (m, 1H, CH), 2.01 (s, 1H, OH), 1.31–1.48 (m, 6H, $3CH_2$), 1.17 (d, J = 8.4Hz, 3H, CH_3), 0.89 (t, J = 8.4Hz, 3H, CH_3) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 68.4, 39.4, 28.1, 23.8, 23.1, 14.4 ppm.

Reduction of 2,4-pentadione **149**

To a mixture of 100ml [BMIM]PF_6 and 10ml water in a 250ml three-neck round-bottomed flask, 130ml immobilised baker's yeast (includes 10g yeast) and 2ml methanol was added. The mixture was stirred vigorously in an oil-bath at 30–35°C. After 1h, 2,4-pentadione **149** (1.00g, 10mmol) was added, the mixture was stirred at 30–35°C for 72h. After reaction, the beads were filtered and the remaining filtrate was extracted with diethyl ether (5×30ml). The extracts were combined together, dried with anhydrous $MgSO_4$, and then filtered. The solvent was removed under vacuum to afford a pale yellow oil. It was purified by flash column chromatography on silica (petrol ether : ethyl acetate = 6 : 1) to give product **156** (0.22g, 22%).

4-(S)-(+)-hydroxypentan-2-one



156

R_f : 0.42 (petrol ether : ethyl acetate = 6 :1)

$[\alpha]^{20}_D$ = +38.2° (c = 0.04, $CHCl_3$) lit. +40.0° [135]

IR : ν_{max} (neat) 3440, 2922, 1736 cm^{-1}

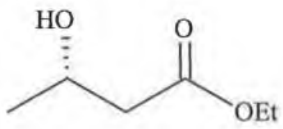
^{1}H-NMR (400MHz) ($CDCl_3$): δ 3.90–4.50 (m, 1H, CH), 3.80 (s, 1H, OH), 2.55 (d, *J* = 6.0Hz, 2H, CH_2), 2.10 (s, 3H, CH_3), 1.13 (d, *J* = 6.0Hz, 3H, CH_3) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 210.3, 64.1, 51.8, 31.1, 22.8 ppm

Reduction of ethyl acetoacetate **150**

To a mixture of 100ml [BMIM]PF_6 and 10ml water in a 250ml three-neck round-bottomed flask, 130ml immobilised baker's yeast (includes 10g yeast) and 2ml methanol was added. The mixture was stirred vigorously in an oil-bath at 30–35°C. After 1h, ethyl acetoacetate **150** (1.00g, 10mmol) was added, the mixture was stirred at 30–35°C for 72h. After reaction, the beads were filtered and the remaining filtrate was extracted with diethyl ether (5×30ml). The extracts were combined together, dried with anhydrous $MgSO_4$, and then filtered. The solvent was removed under vacuum to afford a pale yellow oil. It was purified by flash column chromatography on silica (petrol ether : ethyl acetate = 4 : 1) to give product **157** (0.91g, 70%).

Ethyl (S)-(+)-3-hydroxybutyrate



157

R_f : 0.35 (petrol ether : ethyl acetate = 4 : 1)

$[\alpha]^{20}_D$ = +41.0° (c = 0.01, $CHCl_3$) lit. +43.0° [136]

IR : ν_{max} (neat) 3445, 2980, 1730, 1300, 1200 cm^{-1}.

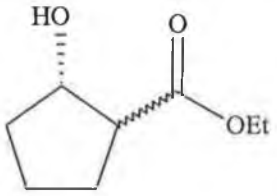
^{1}H-NMR (400MHz) ($CDCl_3$): δ 4.13–4.22 (m, 2H, CH_2), 4.10–4.13 (m, 1H, CH), 2.40–2.50 (m, 2H, CH_2), 2.01 (s, 1H, OH), 1.22 (t, J = 6.0Hz, 3H, CH_3), 1.15 (d, J = 6.0Hz, 3H, CH_3) ppm.

^{13}C-NMR (100MHZ) ($CDCl_3$): δ 173.3, 64.6, 61.0, 43.2, 22.8, 14.5 ppm.

Reduction of ethyl 2-oxocyclopentanecarboxylate **151**

To a mixture of 100ml [BMIM]PF_6 and 10ml water in a 250ml three-neck round-bottomed flask, 130ml immobilised baker's yeast (includes 10g yeast) and 2ml methanol was added. The mixture was stirred vigorously in an oil-bath at 30–35°C. After 1 h, ethyl 2-oxocyclopentanecarboxylate **151** (1.56g, 10mmol) was added, the mixture was stirred at 30–35°C for 72h. After reaction, the beads were filtered and the remaining filtrate was extracted with diethyl ether (5×30ml). The extracts were combined together, dried with anhydrous $MgSO_4$, and then filtered. The solvent was removed under vacuum to afford a pale yellow oil. It was purified by flash column chromatography on silica (petrol ether : ethyl acetate = 3 : 1) to give product **158** (1.17g, 75%).

Ethyl (S)-(+)-2-hydroxycyclopentanecarboxylate (75%)



158

R_f : 0.5 (petrol ether : diethyl ether = 3 : 1)

$[\alpha]^{20}_D$ = + 12.3° (c = 0.01, $CHCl_3$) lit. +14.7° [137]

IR : ν_{max} (neat) 3470, 2985, 1724, 1099, 857 cm^{-1}.

^1H NMR (400MHz) ($CDCl_3$): δ 4.31–4.42 (m, 1H, CH), 4.15 (q, J = 8.15Hz, 2H, CH_2), 3.02 (s, 1H, OH), 2.61–2.67 (m, 1H, CH), 1.82–2.10 (m, 2H, CH_2), 1.71–1.76 (m, 2H, CH_2), 1.55–1.63 (m, 2H, CH_2), 1.23 (t, J = 8.40Hz, 3H, CH_3) ppm.

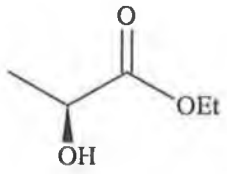
^{13}C NMR (100MHz) ($CDCl_3$): δ 175.2, 74.1, 60.9, 49.9, 34.3, 26.6, 22.4, 14.5 ppm.

Reduction of ethyl pyruvate **152**

To a mixture of 100ml [BMIM]PF_6 and 10ml water in a 250ml three-neck round-bottomed flask, 130ml immobilised baker's yeast (includes 10g yeast) and 2ml methanol was added. The mixture was stirred vigorously in an oil-bath at 30–35°C. After 1h, ethyl pyruvate **152** (1.16g, 10mmol) was added, the mixture was stirred at 30–35°C for 72h. After reaction, the beads were filtered and the remaining filtrate was extracted with diethyl ether (5×30ml). The extracts were combined together, dried with anhydrous $MgSO_4$, and then filtered. The solvent was removed under

vacuum to afford a pale yellow oil. It was purified by flash column chromatography on silica (petrol ether : ethyl acetate = 4 : 1) to give product **159** (0.70g, 60%).

Ethyl (S)-(-)-lactate (60%),



159

R_f : 0.44 (petrol ether : ethyl acetate = 4 : 1)

$[\alpha]^{20}_D$ = −7.1° (c = 0.01, EtOH) lit. −9.4° [138]

IR : ν_{max} (neat) 3450, 2995, 1735, 1220, 1140 cm^{-1}

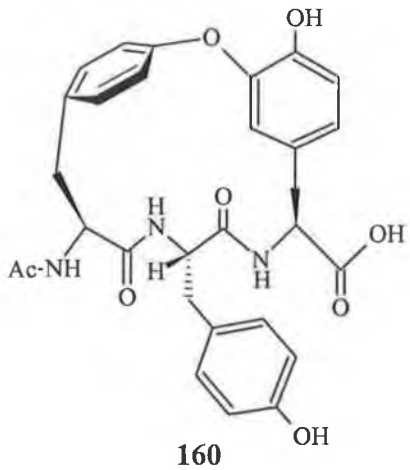
^1H NMR (400MHz) ($CDCl_3$): δ 4.22 (q, *J* = 6.0Hz, 2H, CH_2), 4.18 (q, *J* = 6.0Hz, 1H, CH), 3.28 (s, 1H, OH), 1.36 (d, *J* = 6.0Hz, 3H, CH_3), 1.24 (t, *J* = 6.0Hz, 3H, CH_3) ppm.

^{13}C NMR (100MHz) ($CDCl_3$): δ 176.1, 67.1, 61.9, 20.7, 14.5 ppm.

Chapter 4.

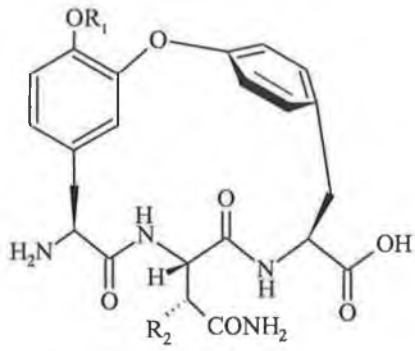
4. Palladium-catalysed preparation of diaryl ethers

Aryl ethers are useful intermediates in organic synthesis [139] and are found in many naturally occurring and medicinally important compounds [140a–d]. For example, **K-13** and **OF4949-I-IV** are natural inhibitors of the **metalloproteases ACE** and **aminopeptidase B** [141]; **combretastatin D-2** and **piperazinomycin** are natural antifungal agents [142a–b] (Figure 13, **160 – 166**).



160

K-13

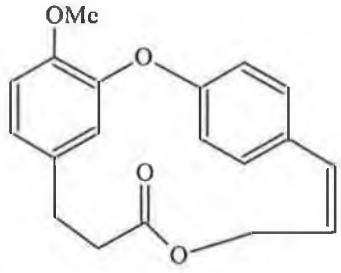


161 **OF49490-I**, R_1 = Me, R_2 = OH

162 **OF4949-II**, R_1 = H, R_2 = OH

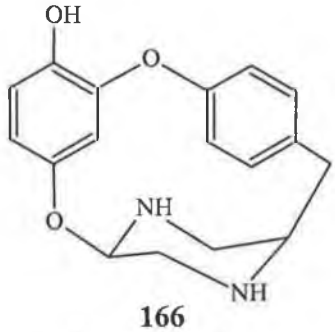
163 **OF4949-III**, R_1 = Me, R_2 = H

164 **OF4949-IV**, R_1 = H, R_2 = H



165

combretastatin D-2

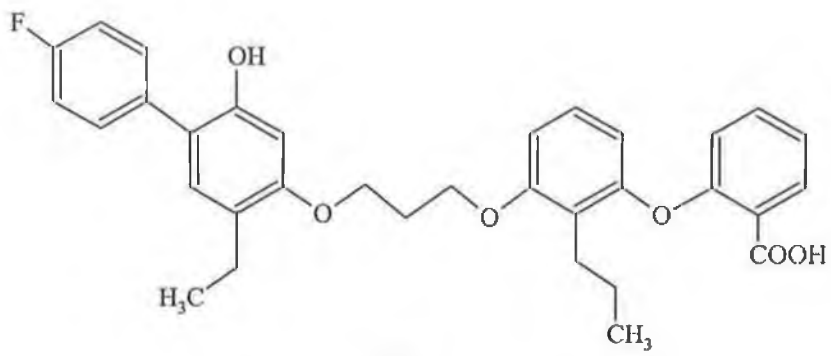


166

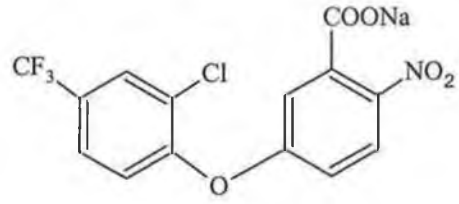
piperazinomycin

Figure 13. Naturally occurring protease inhibitors and antifungal agents.

Diaryl ethers are also present in purely synthetic bioactive agents such as **LY293111**(LTB_4 receptor anagonist) [143a–b] and **RH6201**(herbicidal) [144] (Figure 14, **167 – 168**).



167



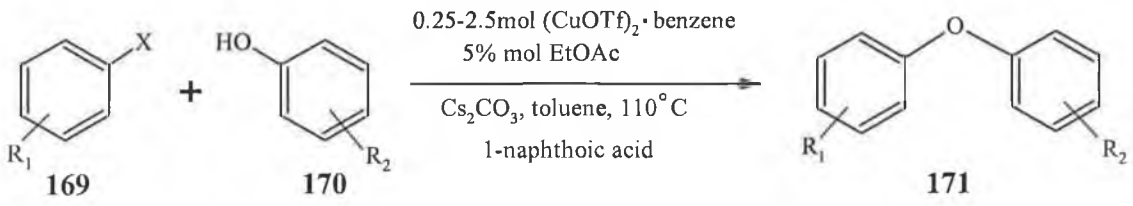
168

Figure 14. Structures of the synthetic bioactive agents.

4.1 The methods of synthesis of diaryl ethers

Of the methods used for preparation of diaryl ethers, the classical Ullmann ether synthesis is one of the most important, but it is often limited by the need to employ harsh reaction conditions and stoichiometric quantities of the copper complex. In fact unactivated aryl halides usually react in low yields.

Recently, a number of interesting and useful techniques for diaryl ether formation have been reported. Buchwald *et al.* have reported a new promoted Ullmann reaction for the formation of diaryl ethers using Cu complex (Scheme 41) [145]. The new procedure for the reaction of aryl bromides and iodides with a variety of phenols is characterized by the following features (1) its use of a catalytic amount of a copper complex (0.25 to 2.5 mol%), (2) its use of cesium carbonate as a base, which eliminates the need to form the phenoxide anion prior to the reaction, (3) its ability to employ a non-polar solvent (toluene) and lower reaction temperatures than previous reactions, and (4) its use of a stoichiometric amount of a carboxylic acid in the reactions of unactivated aryl halides with less soluble phenols and phenols containing electron-withdrawing groups.



X = Br, I

R_1 = CH_3, COOH, OMe, CN, *t*-Bu, MeCO R_2 = Me, *i*-Pr, Cl

Scheme 41. Cu complex catalysed synthesis of diaryl ethers.

It is noteworthy that this method achieved success for the coupling of unactivated aryl halides and less reactive phenols, such as phenol and chlorophenol. The mechanism proposed that the methoxylation of aryl bromides involves the formation of an active cuprate-like intermediate of the general structure $[(RO)_2Cu]^-M^+$ [146]. The authors believe that the nature of the cation plays an important role during the formation or the solubilization of such an intermediate. Cesium phenoxides and carboxylates are relatively soluble in organic solvents. Their use could enhance the solubility of the possible key reaction intermediates **A** and **B**, as compared to their potassium and sodium counterparts (Figure 15). In addition, the use of 1-naphthoic acid as an additive for the efficient coupling of less soluble phenoxides is important in that it

extends the generality of the reaction, rendering it more useful in organic synthesis [145].

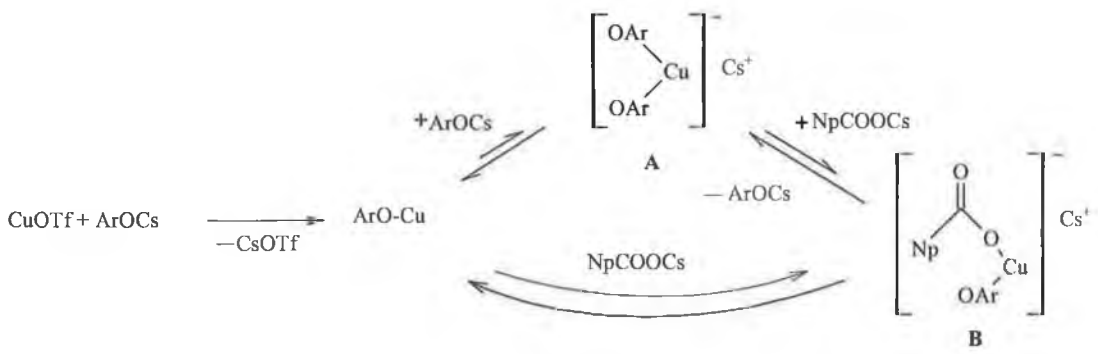


Figure 15. The mechanism of Cu complex catalysed synthesis of diaryl ethers.

The Ullmann reaction of diaryl ether synthesis promoted by P_4-*t*-Bu and CuBr is also reported recently [147]. They found the P_4-*t*-Bu base could form highly nucleophilic 'naked' anions and made the CuBr dissolve completely to form a homogeneous solution. The author suggested the phosphazene base was critical for performing the coupling reaction.

4.2 Palladium complexes in organic synthesis

Recently, the use of palladium catalysis for the combination of phenols or alcohols and aryl halides has been reported extensively [148a–c]. Before we introduce these reactions, let us have a short review on palladium complexes.

Palladium complexes have been used to catalyse organic reactions for several decades, and a number of important chemical reactions were involved, including Stille coupling [149a–b], Heck reaction [62a–b], Suzuki coupling reaction [150], Wacker oxidation [151a–c], and allylic substitution reactions [152]. It is considered one of the most commonly used versatile metals in organic synthesis.

Palladium complexes have a very rich organic chemistry and are among the most readily available, easily prepared and easily handled of transition metal complexes. Their real synthetic utility lies in the very wide range of organic transformations promoted by palladium catalysts, and in the specificity and functional group tolerance of most of these processes. They permit unconventional transformations and give the synthetic chemist wide latitude in their choice of starting materials.

Palladium enjoys two stable oxidation states, the +2 state and the zerovalent state, and it is the facile redox interchange between these two oxidation states which is responsible for the rich reaction chemistry that palladium complexes display. Each oxidation state has its own unique chemistry.

4.2.1 Palladium(II) complexes

Palladium(II) complexes are electrophilic, and tend to react with electron-rich organic compounds, particularly olefins and arenes. The most common starting material for the palladium complexes is palladium(II) chloride $[PdCl_2]_n$ (Figure 16).

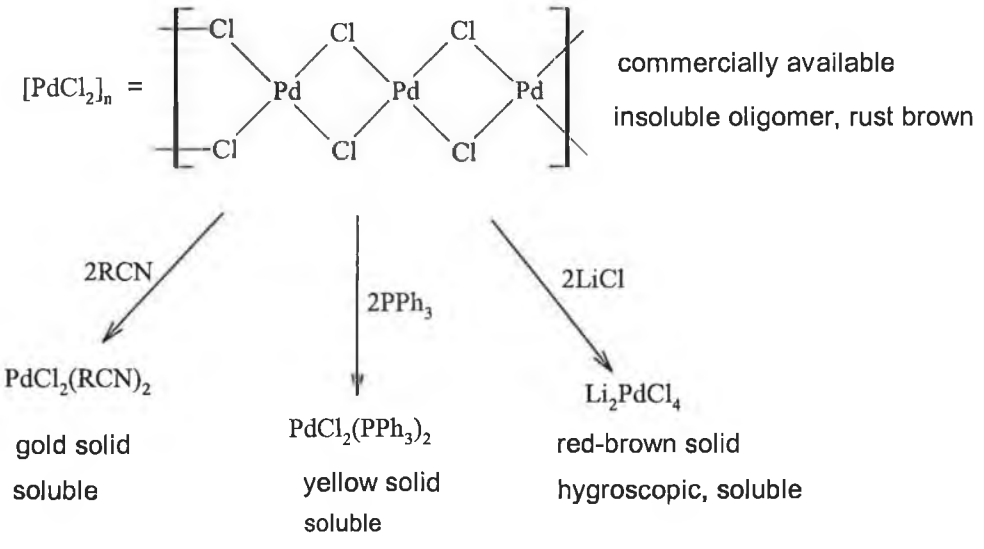


Figure 16. The preparation of some palladium(II) complex.

The polymeric structure is easily broken down by donor ligands, resulting in monomeric $PdCl_2L_2$ complexes stable to air and soluble in most common organic solvents.

Among the most useful are the nitrile complexes, $PdCl_2(RCN)_2$, prepared by stirring a suspension of $[PdCl_2]_n$ in the nitrile as solvent [153]. These solids are fairly soluble in organic solvents and stable to storage. The benzonitrile complex is most commonly used, but the elimination of non-volatile benzonitrile is inconvenient. Although slightly less soluble, the acetonitrile complex is more convenient to work with since acetonitrile is odourless, water soluble and volatile. Both nitriles are sufficiently labile to vacate coordination sites easily during reaction, making them excellent choices for catalysis.

Treatment of $[PdCl_2]_n$ with triphenylphosphine produces $PdCl_2(PPh_3)_2$ complex, which is stable and easily handled [154]. In contrast to the nitrile ligand, the phosphines are much less labile and, as a consequence, $PdCl_2(PPh_3)_2$ is infrequently used in systems requiring palladium(II) catalysis, although it is frequently the catalyst precursor of choice for palladium(0)-catalysed processes.

Even chloride ion is able to break the $[PdCl_2]_n$, oligomer, treatment of which with two equivalents of LiCl in methanol produces Li_2PdCl_4, a red-brown hygroscopic solid that is relatively soluble in organic solvents [155].

The final commonly used palladium(II) complex is palladium(II) acetate $Pd(OAc)_2$, which is commercially available and soluble in common organic solvents. It is most commonly used as a catalyst precursor for Pd(0)-catalysed processes.

4.2.2 Palladium(0) complexes

Palladium(0) complexes are strong nucleophiles and strong bases, and most commonly are used to catalyse reactions involving organic halides, acetates and

triflates. By far the most commonly used palladium(0) complex is $Pd(PPh_3)_4$, tetrakis(triphenylphosphine)palladium(0). With four triphenylphosphines contributing 1048 to its molecular weight, 1g of $Pd(PPh_3)_4$ contains very little expensive palladium and much of the inexpensive phosphine, it is easy to prepare, by reducing almost any palladium(II) complex in the presence of excess phosphine (Figure 17) [156].

In fact, in many instances palladium(0)-phosphine complexes are generated by reduction *in situ* and used without isolation, both saving time and permitting the use of phosphine ligands rather than triphenylphosphine.

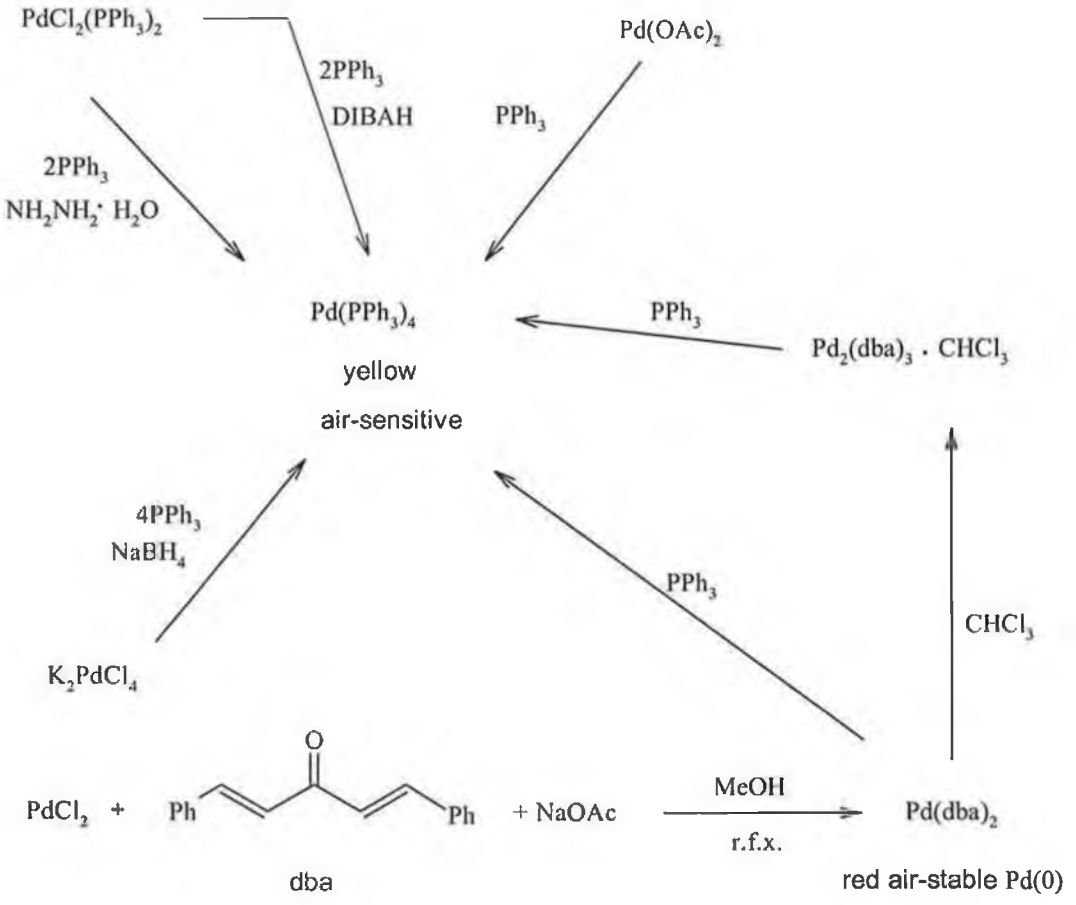


Figure 17. The preparation of some palladium(0) complex.

Another exceptionally useful palladium(0) complex is $Pd(dba)_2$, the bis(dibenzylidene acetone) complex. This is prepared by simple boiling palladium(II) chloride and dba together in methanol, a cherry-red precipitate $Pd(dba)_2$, forms and is easily separated by filtration [157]. It is air-stable, but the fact that it is a palladium(0) complex. Purification by recrystallisation from chloroform produces crystals of $Pd_2(dba)_3 \cdot CHCl_3$ which has the same activity as $Pd(dba)_2$.

These are very useful Pd(0) catalyst precursors because they are very easily handled, can be stored without precaution for years, yet when dissolved and treated with a wide variety of phosphines, produce yellow solution of the catalytically active PdL_n species *in situ*.

Perhaps the most widely used catalyst precursor for Pd(0)-catalysed processes is palladium(II) acetate $Pd(OAc)_2$, which is very easily reduced to palladium(0) complexes *in situ* by carbon monoxide, alcohols, tertiary amines, alkenes, main group organometallics, and phosphines.

Recently, a new catalyst precursor was reported by Herrmann *et al.* [158]. Treatment of palladium acetate with one equivalent of tri-*o*-tolylphosphine produces a cyclometallated species which is quite stable and handled. This catalyst can easily generate Pd(0) complexes when it is treated with NaO-*t*-Bu in the presence of P(*o*-tolyl)$_3$ ligand. It gave extremely high turnover numbers in Suzuki and Heck reactions [159].

Hence the synthetic chemist has a large number of palladium catalysts to choose from, and the best choice is not always obvious. As is the case with traditional organic synthetic methodology, the starting point is to find as close an analogy to the desired transformations as possible, and to start with that catalyst and those conditions.

4.2.3 Palladium(0) complexes in oxidative addition-transmetallation

The palladium(0)-catalyst coupling of aryl and vinyl halides and triflates with main group organometallics *via* oxidative addition-transmetallation-reductive elimination sequences has been broadly developed and has an overwhelming amount of literature associated with it [160].

A very wide range of palladium catalyst precursors can be used in this system, and the choice is best made analogy, although almost all will work reasonably well. Most often $Pd(PPh_3)_4$ or $Pd(dba)_2$ plus PPh_3 is used, although even palladium(II) catalyst precursors such as $(PPh_3)_2PdCl_2$, $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$ are efficient since they are readily reduced to the catalytically active Pd(0) state by most main group organometallics as well as phosphines and many other reagents [161]. Recall that palladium(0) complexes are electron-rich nucleophilic species prone to oxidation. The single most important reaction of palladium(0) complexes is their reaction with organic halides or triflates to form σ-alkylpalladium(II) complexes. This commonly known as 'oxidative addition' because the metal is formally oxidised from Pd(0) to Pd(II) and the 'oxidizing agent', RX, adds to the metal, hence the term oxidative addition.

The oxidative addition process has a number of general features. The order of reactivity is I >> OTf > Br >> Cl [162], such that chlorides are rarely useful in this reaction. With aryl halides, added phosphines are required for the reaction of aryl bromides, but suppress the reaction of aryl iodides, permitting easy discrimination. With most substrates, the oxidative addition step proceeds readily at 25°C. When higher temperatures are used, this is usually because some step other than the oxidative addition is sluggish at this temperature. From the standpoint of the substrate, the metal becomes oxidised, but the substrate becomes reduced. In general, electron-deficient halides are more reactive than electron-rich halides. Because β-hydrogen elimination is rapid above *ca* –20°C, the halide or triflate substrate usually cannot have β-hydrogens, restricting this process to aryl and vinyl substrates.

A very wide range of main group organometallics 'transmetallate' to palladium(II), they transfer their R group to palladium in exchange for the halide or triflate, generating a dialkylpalladium(II) complex and the main group metal halide or triflate. Transmetallations from Li, Mg, Zn, Zr, B, Al, Sn, Si, Ge, Hg, Tl, Cu, Ni have been known, but some (*e.g.* Mg, Sn, B and Zn) are much more useful than others.

Transmetallation is favoured from more electropositive to more electronegative metals, but this is of little use in assessing reactivity since eletronegativities are only crudely known and are sensitive to spectator ligands. If the next step in the process is irreversible, only a small equilibrium constant for transmetallation is required for the process to proceed.

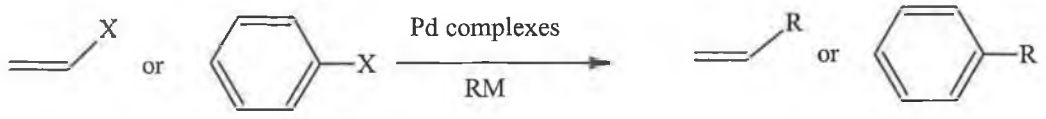
Transmetallation is almost invariably the rate-limiting step, and when oxidative addition-transmetallation sequences fail, it is this step which warrants attention. It is important that both metals involved in transmetallation benefit from the process energetically and the needs of the main group partner cannot be ignored. Thus, coupling of organotriflates with organotin reagents sometimes fails, since the product tin triflate is not stable, but often proceeds well with the addition of lithium chloride, permitting the production of the more stable organotin chloride rather than triflate.

Similarly, organosilanes only transmetallate in the presence of added fluoride to give the very stable Si-F compounds and organoboranes react only in the presence of added alkoxides to produce stable B-O compounds. Transmetallation occurs with retention of any stereochemistry in the organic group.

Once transmetallation has occurred, the remaining steps, rearrangement of the *trans*-dialkylpalladium(II) complex to the *cis*-complex and reductive elimination, producing the couple products and regenerating the Pd(0) catalyst are rapid. Therefore, β-hydrogens can be present in the R group transferred from main group organometallics, since reductive elimination is faster than β-hydride elimination from the dialkylpalladium(II) intermediate.

4.3 Palladium-catalysed preparation of diaryl ethers

Palladium-catalysed nucleophilic aromatic substitution for C-C bond-forming coupling reactions have been invaluable in organic synthesis (Scheme 42). These methods have been developed by a number of different research groups. Negishi developed palladium compounds as catalysts and number of main group alternatives to Grignard reagents [163]. Kosugi discovered the use of tin reagents as a stable and mild source of carbon-nucleophile in metal-catalysed coupling reactions with acid chlorides [164a–b]. Stille developed general coupling methodology using tin reagents and created a well-understood and synthetically convenient method for C-C bond-forming coupling chemistry [149]. Finally, Suzuki found that the addition of base to organoborane reagents allowed for their use in the coupling chemistry that is typically catalysed by palladium complexes [150].



172 **173** **174** **175**

X = Cl, Br, I, OSO_2CH_3 M = Mg, Al, Sn, B

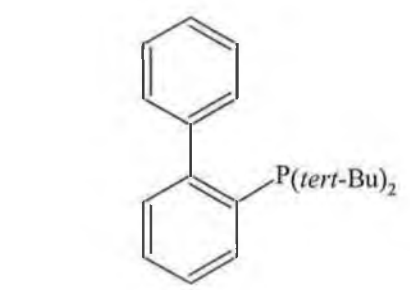
Scheme 42. Palladium-catalysed C-C bond-forming reaction.

Recently, the use of palladium catalysis for the combination of phenols and aryl halides or sulfonates is a desirable extension of other recently reported carbon-heteroatom bond-forming techniques [165a–d]. This procedure has been demonstrated, but the scope of the reported process was limited to the reaction of electron-deficient aryl bromides [166]. Moreover, the procedures usually required the use of the sodium salt of the phenol and in most cases the yields were only moderate.

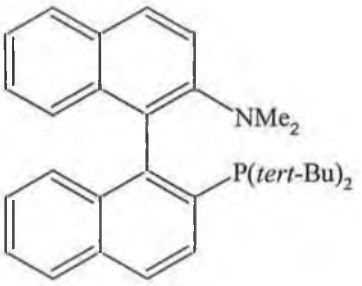
More recently, the Buchwald's group reported that a wide range of electron-deficient, electronically neutral and electron-rich aryl halides and sulfonates can be combined with a variety of phenols by using palladium catalysis, representing a substantial improvement in generality and utility of these coupling [167]. This method is a extension of their previously reported copper-catalysed preparation of diaryl ethers. Critical to the success of the method is the use of electron-rich, sterically bulky aryldialkylphosphines as ligands [168a–c]. Specifically, only the use of catalyst systems with ligands containing a phosphorus centre substituted with two *tert*-butyl groups effects efficiently the desired transformation.

They found that the new ligands (Figure 18) they made could enhance the yields significantly. In their examination of the use of **176** for the combination of electron-poor aryl halides with a variety of phenols, they found that aryl halides or triflates substituted in the *para* position with electron-withdrawing groups can be coupled with a wide variety of phenols to give the desired product in good to excellent yields. For example, 4-bromoacetophenone combined with phenol, use of as little as 0.1 mol % Pd was effective; the diaryl ether product was obtained in 95% yield. The combination of 4-bromobenzonitrile with 3-isopropylphenol afforded a 91% yield of the desired product. The 4-chlorobromobenzene combined with 2-isopropylphenol to give the corresponding diaryl ether in 88% yield.

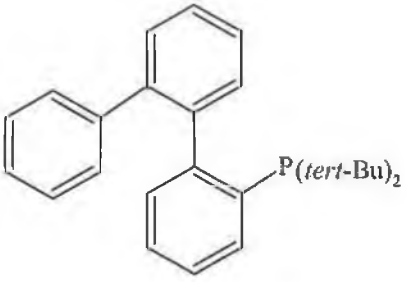
They also examined the reactions of electronically neutral and electron-rich aryl halides in the palladium catalysed diaryl ether-forming reaction employing **176** ligand and found in some cases **176** was unsatisfactory. Therefore, they prepared **177** and **178** ligand instead of **176** and found binaphthyl ligand **177** was quite effective for the processing of electronically neutral *ortho*-substituted aryl halides with phenols of several different substitution patterns. For example, 2-bromo-*p*-xylene combined with *o*-cresol to afford the corresponding diaryl in 94% yield. The **178** ligand was effective for the combination of an aryl halide lacking an *ortho* substituent with phenol. For example, 5-bromo-*m*-xylene and phenol afforded the corresponding diaryl in 83% yield.



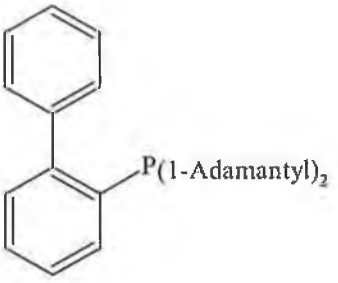
176



177



178



179

Figure 18. New ligands for the palladium catalysed preparation of diaryl ether.

However, ligands **176**, **177** and **178** are not effective in the reactions of highly electron-rich aryl chlorides (*e.g.* 4-chloroanisole). For these transformations, only ligand **179** has been shown to give synthetically useful yields. The 1-adamantyl group was chosen since it occupies a great volume of space and hence is bulkier than a *tert*-butyl group. For example, 4-chloroanisole and *o*-cresol are converted to the corresponding ether in 73% yield using **179**, a significantly high yield than when **176**, **177** and **178** were employed.

4.3.1 The mechanism of palladium-catalysed preparation of diaryl ethers

The catalytic cycle for diaryl ether formation is similar to that proposed for other palladium-catalysed carbon-carbon and carbon-heteroatom bond-forming processes (Figure 19) [167].

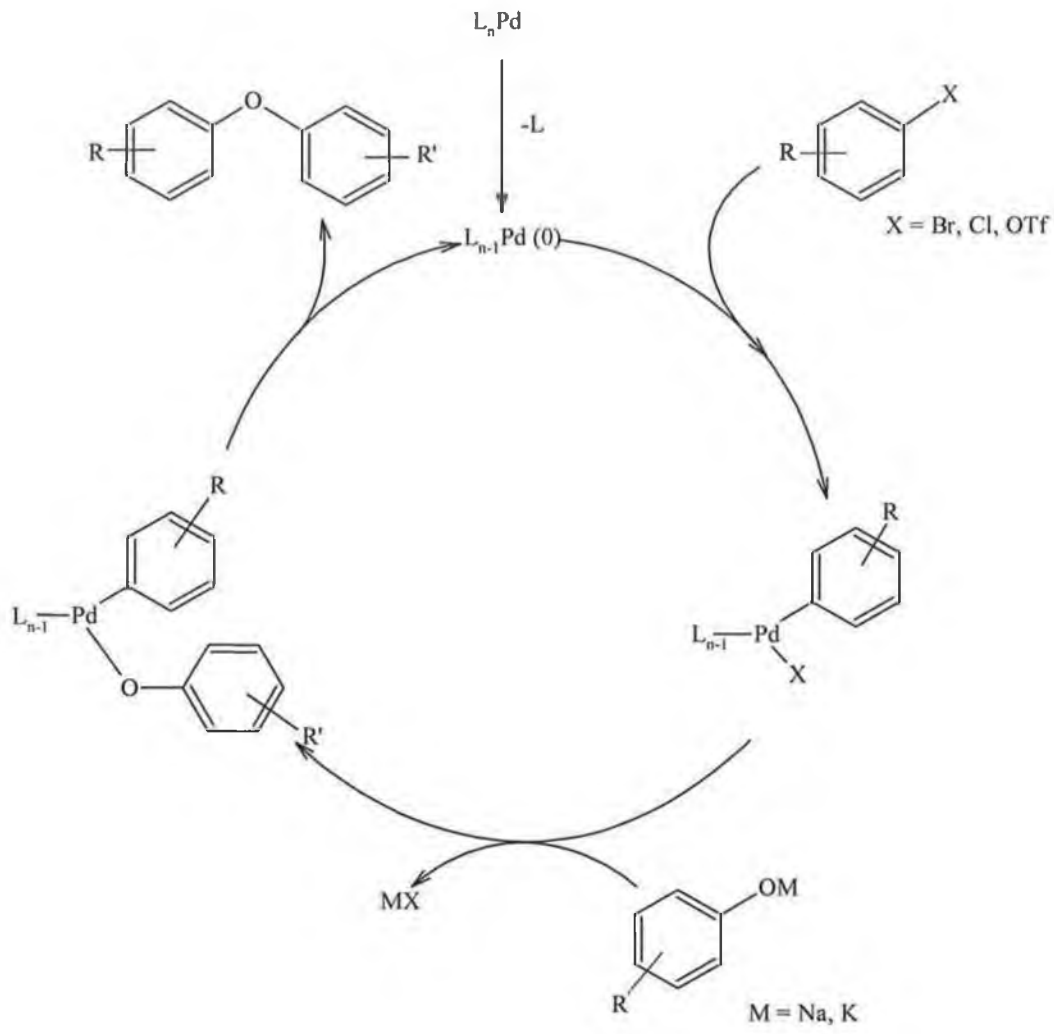


Figure 19. The catalytic cycle for the diaryl-forming reaction.

The catalytic cycle consists of three distinct stages: (1) oxidative addition of the aryl halide to $L_nPd(0)$, (2) formation of the Pd-aryloxide complex from the Pd-halide

adduct *via* transmetallation of a metal phenolate, and (3) reductive elimination of the diaryl ether product with concomitant regeneration of the active $L_nPd(0)$ species. While the oxidative addition and transmetallation may be expected to be relatively facile, the reductive elimination to form the C-O bond is disfavoured due to the Pd-C (LUMO) and Pd-O (HOMO) energy gap [169].

The palladium-catalyst diaryl ether-forming reaction require only a slight excess of ligand to palladium, and reactions in which the ratio of L/Pd was varied from 1/1 to 1.5/1 to 2/1 gave similar results. This provides circumstantial evidence that the key intermediates in the catalytic cycle are monophosphine palladium complexes [167]. Mechanistic studies by Hartwig of C-N bond-forming reactions catalysed by palladium complexes with bulky triarylphosphine ligands demonstrated that the key intermediates in the catalytic cycle were monophosphine palladium complexes [170a–d].

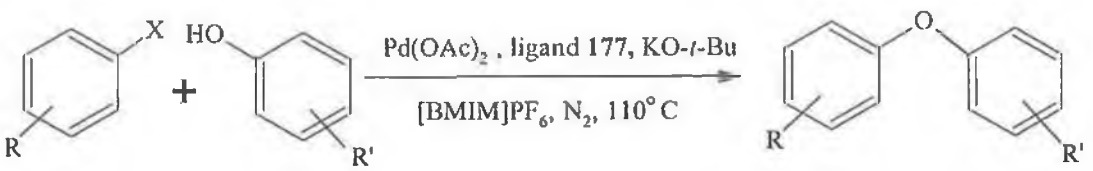
While the exact mechanism for the key reductive elimination step remains unknown, Buchwald *et al.* have previously developed several mechanistic hypotheses for related processes which can be used to account for the mechanism. For electro-deficient aryl halides, it might be involving transfer of the phenolate from palladium to the *ipso* carbon of the aryl halide to form a zwitterionic intermediate which converts to the diaryl ether and a palladium(0) complex [171]. For electronically neutral and electron-rich aryl halides, however, they suggest that a different mechanism for reductive elimination to form the carbon-oxygen bond most likely involves a three-centred transition state [172]. In these cases the bulkier ligands are necessary to destabilise the ground state of the $L_nPd(OAr)$-Ar′ complex, forcing the palladium-bond aryl and aryloxy groups closer together. In this way, the complex is distorted toward the three-centred transition state.

4.4 Palladium –catalysed formation of diaryl ether in ionic liquid

Recently, many reactions catalysed by palladium complexes have been achieved successfully in ionic liquid. Heck reaction is one of the most useful reaction which is extensively investigated in ionic liquid by many groups, Kaufmann *et al.* using palladium (II) chloride/acetate with PPh_3 in [BMIM]BF_4 [63], Hermann *et al.* using bis(1,3-dimethylimidazolin-2-ylidene)diiodopalladium(II) in [NBu_4]Br [64], Seddon's group using [$(BMIM)_2PdCl_4$] in [BMIM]PF_6 [65], and Xu *et al.* using palladium-carbene complexes in [BMIM]Br/ [BMIM]BF_4 [66]. Other reactions, such as, Suzuki cross-coupling reaction [69], allylation reaction [74], alkoxy carbonylation [81] and Stille reaction [87] were also carried out successfully in ionic liquid using palladium complexes.

We noticed that palladium-catalysed formation of diaryl ether has been demonstrated successfully in non-polar solvent (toluene) recently [167], but in ionic liquid, it is still unknown. Therefore we suggested such a kind of reaction could be done in ionic liquid as well. In order to verify our idea, the reaction of a wide range of electron-deficient, electronically neutral and electron-rich aryl halides combination with a variety of phenols was carried out in ionic liquid by using palladium complex catalyst. The ligand is a critical factor to the ether-formation [167].

The reagents 2-bromobiphenyl and di-*tert*-butylchlorophosphine can be commercially purchased from Aldrich, we only prepared 2-(di-*tert*-butylphosphino)biphenyl **176** as the electron-rich, sterically bulky ligand for our reaction. Therefore, we carried out the diaryl ether-forming reaction using $Pd(OAc)_2$ with ligand **176** and KO-*t*-Bu as base instead of K_3PO_4 in ionic liquid [BMIM]PF_6 under N_2 at 110°C for 24h (Scheme 43).



130—137 **180—183** **184—192**

X = Br R = Me, CN, COOMe, MeO, MeCO R' = Me

Scheme 43. Palladium-catalysed diaryl ether-forming reaction in $[BMIM]PF_6$.

4.5 Results and discussion

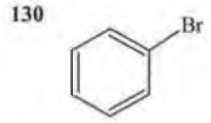
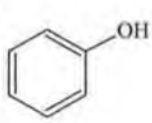
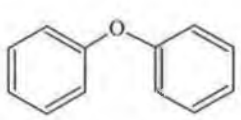
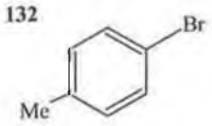
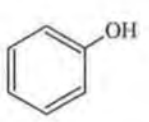
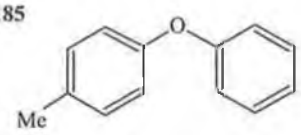
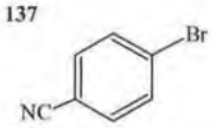
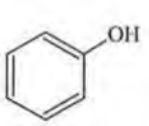
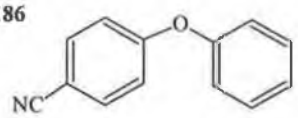
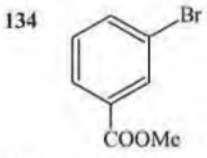
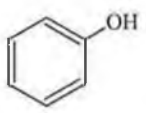
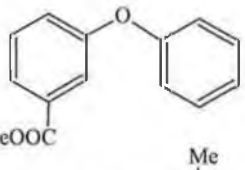
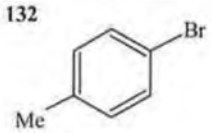
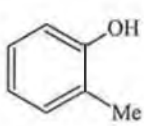
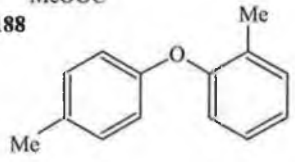
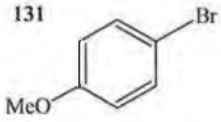
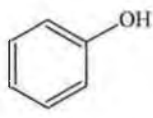
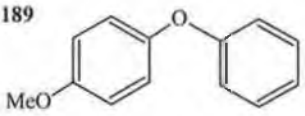
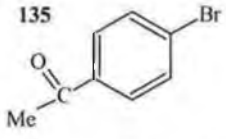
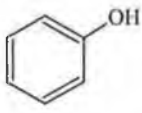
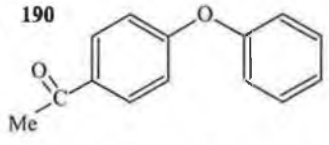
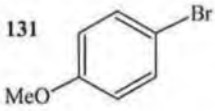
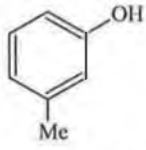
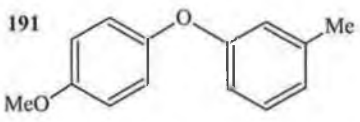
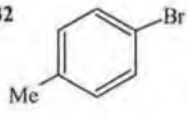
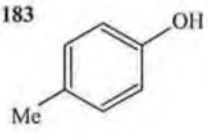
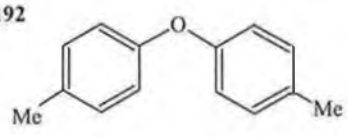
Entry	Halide	Phenol	Product	Yield(%)
1	**130** 	**180** 	**184** 	64
2	**132** 		**185** 	78
3	**137** 		**186** 	57
4	**134** 		**187** 	74
5	**132** 	**181** 	**188** 	82
6	**131** 		**189** 	83
7	**135** 		**190** 	53
8	**131** 	**182** 	**191** 	85
9	**132** 	**183** 	**192** 	88

Table 13. The yields of Pd-catalysed reaction of diaryl ethers in [BMIM]PF_6

The yields for diaryl ethers obtained by extraction of products with diethyl ether from ionic liquid are shown in Table 13. It was found that aryl halide with moderate electron-withdrawing groups coupled with phenol to give the desired product in good yields (Table 13, **187**, yield 74%). The aryl halide with strong electron-withdrawing group coupled with phenol to give lower yield (**186,** yield 57%; **190,** yield 53%), but if the phenol has *ortho* alkyl substituent (*e.g*, *o*-cresol) to give the increased yield (**188**, yield 82%). The electron-rich aryl halide reacted with phenol to afford the desired product in moderate to good yield (**185**, yield 78%; **189**, yield 83%; **191**, yield 85%; **192**, yield 88%). The electronically neutral aryl halide couple with phenol to give the product in moderate yield (**184**, yield 64%). These results showed that the ligand **176** was so effective for the aryl halide with electron-rich substituent, but not too effective for the aryl halide with electron-withdrawing substituent group.

It was surprisingly found that the lower yields obtained for diaryl ether forming reaction when the aryl halides with electron-withdrawing substituents coupled with phenols comparing with high yields in toluene [167]. One possible explanation for the lower yields could be the polarity of solvents. The less polar solvents could be better for diaryl ether forming in this case otherwise the electron-poor phosphine ligand could be employed [173].

In general, the aryl halides with moderate electron-withdrawing, electronically neutral and electron-donating groups reacting with phenols gave good yields in ionic liquids, which were comparable with those in toluene. The reason could be that the ionic liquid could improve the formation of ligand-palladium complex.

It is interesting to note that ionic liquid could increase the yields of the diaryl ether-forming reaction obviously. A comparison of the yields of the coupling reaction carried out in both DMF and ionic liquid [BMIM]PF_6 (Table 14) showed that ionic liquid could enhance the yields in most cases, except the entry 3. It might be that the ionic liquid could promote the electron-rich, sterically bulky ligand **176** both in

oxidative formation of the Pd-aryloxide complex and in reductive elimination for the formation of C-O bond easily.

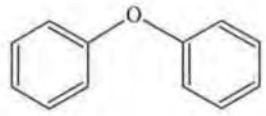
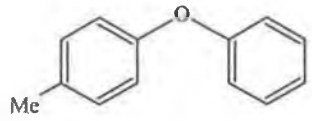
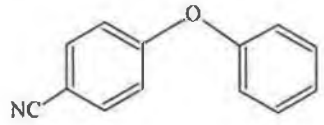
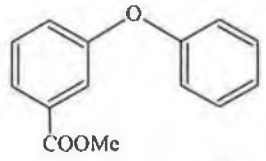
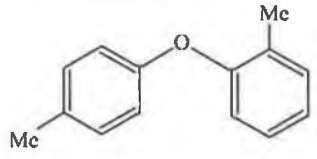
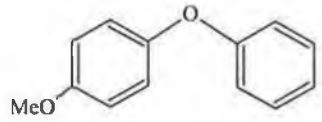
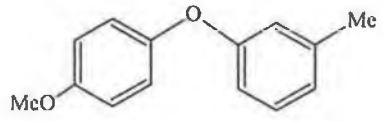
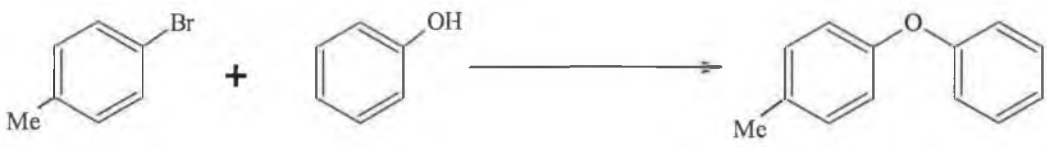
Entry	Product	yield (%)	
		DMF	$[BMIM]PF_6$
1		62	64
2		70	78
3		60	57
4		68	74
5		74	82
6		70	83
7		77	85

Table 14. The yields of diaryl ether-forming reaction in different solvents.



Entry	Base	Yield(%)
1	$CsCO_3$	80
2	K_2CO_3	71
3	K_3PO_4	75
4	CsF	68
5	KF	65
6	KO-*t*-Bu	78

Table 15. The influence of base for the formation of diaryl ether.

The base could influence the yields as well. It was found that the KO-*t*-Bu, Cs_2CO_3 and K_3PO_4 were more effective (Table 15, entry 1, 3 and 6). Among these bases the Cs_2CO_3 was the most effective, but it was more expensive than KO-*t*-Bu and we did not see too much better in yield than KO-*t*-Bu, so we preferred KO-*t*-Bu as base in our reaction. Other bases, such as CsF, K_2CO_3, KF and were less effective than KO-*t*-Bu (entry 4, 2 and 5).

In order to investigate other factors which influence on yields, a reaction of 4-bromotoluene with *p*-cresol was carried out under various conditions. It was found that the yields varied from different solvents, the toluene was more efficient than other normal solvents, but the ionic liquid was the best one (Table 16, entry 1, 2, 3, 4, 5 and 7). It also found that PPh_3 as ligand in the reaction gave the lowest yield (entry 6, 45%). The recycle ionic liquid and catalyst could reduce the yield in small degree

(entry 8 and 9). It could be the impure materials were still remained in ionic liquid and it influenced the solubility of ionic liquid. It should note that in ionic liquid the 3% amount of catalyst was efficient for the reaction of diaryl ether formation. The reaction would not happen if there no ligand was employed in the reaction.

Entry	Solvent	Catalyst	Ligand	Yield(%)
1	THF	4% $Pd(OAc)_2$	6% **176**	67
2	DME	4% $Pd(OAc)_2$	6% **176**	70
3	DMF	4% $Pd(OAc)_2$	6% **176**	72
4	NMP	4% $Pd(OAc)_2$	6% **176**	74
5	toluene	3% $Pd(OAc)_2$	5% **176**	86
6	$[BMIM]PF_6$	4% $Pd(OAc)_2$	6% **PPh_3**	45
7	$[BMIM]PF_6$	4% $Pd(OAc)_2$	6% **176**	88
8	$[BMIM]PF_6$ (recycled)	4% $Pd(OAc)_2$	6% **176**	84
9	$[BMIM]PF_6$ (recycled)	4% $Pd(OAc)_2$ (recycled)	6% **176** (recycled)	80
10	$[BMIM]PF_6$	4% $Pd(OAc)_2$	no	0

Table 16. The reaction of diaryl ether formation in different conditions.

Copper-catalysed synthesis of diaryl ethers has been investigated in ionic liquid $[BMIM]PF_6$ as well. The reactions were carried out in $[BMIM]PF_6$ using 4.0mol% CuBr as catalyst and 1.5 equiv Cs_2CO_3 as base in the presence of 5.0mol% ethyl acetate at 140°C for 24h. Comparing with the palladium-catalysed reaction of diaryl ethers formation, the yields were lower but the temperature was higher. It revealed that the copper catalyst was not as effective as palladium catalyst in ionic liquid. It

probably because of the palladium was more soluble in ionic liquid in the presence of ligand **176** than Cu complex.

The results were given in Table 17. It was found that the yields obtained using copper as catalyst were lower 6 % –16 % than the yields obtained using palladium/ligand as catalyst. The aryl iodide gave higher yield than aryl bromide, which is similar to the reaction catalysed by palladium (Table 17, entry 2).

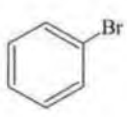
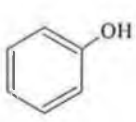
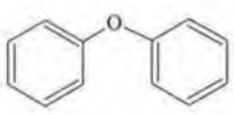
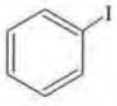
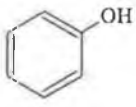
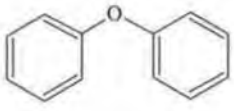
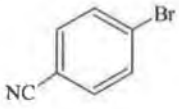
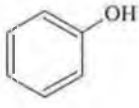
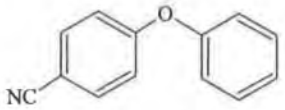
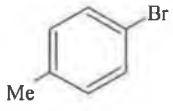
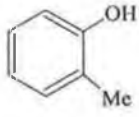
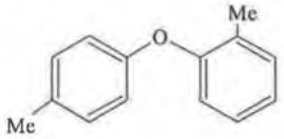
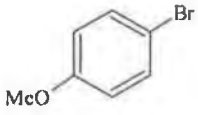
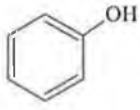
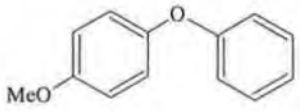
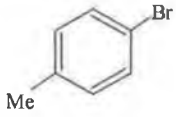
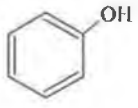
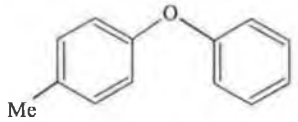
Entry	Halide	Phenol	Product	Yield (%)	
				$Pd(OAc)_2$/ligand	CuBr
1				64	50
2				71	55
3				57	42
4				74	68
5				82	73
6				78	65

Table 17. The copper-catalysed synthesis of diaryl ethers in $[BMIM]PF_6$.

It was also found that the reaction of *ortho*-substituted phenol with bromotoluene could give higher yield (entry 4), and the reaction of electron-withdrawing substituted aryl bromide with phenol gave lower yield (entry 3).

In conclusion, the palladium and ligand **176** catalysed diaryl ether forming reaction was successfully carried out in ionic liquid [BMIM]PF_6, a wide range of different substituted aryl halides coupling with phenols have been investigated. Although it was not effective for those aryl halides with electron-withdrawing substituents, the recyclable expensive catalyst and recyclable ionic liquid were advantages. Further work will carry out the reaction of electron-withdrawing substituted aryl halides coupling with phenols using electron-poor ligands.

4.6 Experimental section

All infra-red spectra were recorded on a Perkin Elmer System 2000 FTIR spectrometer.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance NMR spectrometer, operating at 400MHz and 100MHz in Aldrich deuterated chloroform with tetramethylsiline as an internal standard respectively at the Dublin City University. (d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet).

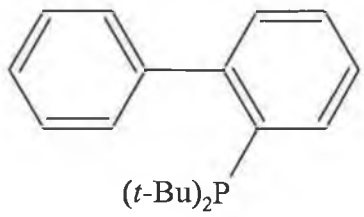
Riedel-de Haën silica gel 60 F254 TLC plates (0.2 mm layer thickness) were used for thin layer, and were examined with UV illumination at λ 254 nm. Riedel-de H aën silica gel S were used for flash chromatography according to the method of Still *et al.*[110].

THF was distilled from sodium metal in the presence of benzophenone before use. All reagents and chemicals were obtained from Aldrich Chemical Company (UK) or Lancaster Synthesis Ltd.(UK) and were used without further purification, unless otherwise noted.

4.6.1 The synthesis of ligand

Synthesis of 2-(di-tert-butylphosphino)biphenyl **176** [167]

An oven dried round-bottomed flask with a magnetic stirring-bar and rubber septum was allowed to cool to room temperature and purged with argon. The flask was charged with magnesium turnings (0.617g, 25.4mmol) and small crystal of iodine. The flask was purged with argon and a solution of 2-bromobiphenyl (5.38g, 23.1 mmol) in THF (40ml, sodium dried) was added. The mixture was heated to reflux with stirring for 2h and then allowed to cool to room temperature. The septum was removed, and anhydrous copper (I) chloride (2.40g, 24.2mmol) was added. The flask was capped with the septum and purged with argon for 2min. Di-*tert*-butylchlorophosphine (5.0g, 27.7mmol) was added *via* syringe, and the mixture was heated to reflux with stirring for 8h. The mixture was cooled down to room temperature and diluted with 1:1 hexane/ether (200ml). The resulting suspension was filtered, and the solids were washed with hexane (60ml). The solid material was transferred to a flask containing 1:1 hexane/ethyl acetate (150ml), and water (100ml) and 30% aqueous ammonium hydroxide (60ml) were added. The resulting slurry was stirred at room temperature for 5min and then transferred to a separatory funnel. The layers were separated, and the organic phase was washed with brine (100ml), dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The resulting solid was recrystallised from methanol to give **176** (3.01g, 45%).



176

IR : ν_{max} (KBr) 2950, 1460, 1365, 1175 cm^{-1}.

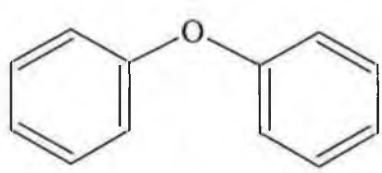
^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.82 (d, J = 8.50Hz, 1H), 7.15-7.36 (m, 8H), 1.15 (d, J = 11.50Hz, 18H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 151.8, 151.5, 144.2, 144.1, 136.1, 135.8, 135.7, 131.0, 130.9, 129.6, 128.7, 127.8, 127.5, 126.9, 126.8, 126.3, 126.1, 33.3, 33.0, 31.2, 31.1 ppm.

4.6.2 The synthesis of diaryl ethers

Biphenyl ether **184**

Into a three-neck 50ml round-bottom flask with 5ml dry, O_2-free [BMIM]PF_6, palladium acetate (0.09g, 0.4mmol, 4.0mol%), ligand **176** (0.18g, 0.6mmol, 6.0 mol%), potassium *tert*-butoxide (2.25g, 20.0mmol) were placed. The flask was purged with argon for half an hour and then bromobenzene **130** (1.57g, 10mmol) and phenol **180** (1.88g, 20mmol) were added. The mixture was stirred at 110°C for 24h under argon. The reaction mixture was then allowed to cool to room temperature and extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **184** (1.08g, 64%).



184

R_f : 0.44 (hexane : ethyl acetate = 15 :1)

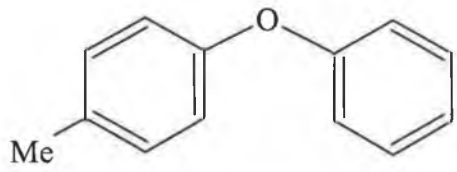
IR : ν_{max} (neat) 3060, 3044, 1585, 1487, 1240, 1072, 868, 745 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.40 (dd, *J* = 7.20Hz, 4H), 7.17 (tt, *J* = 6.80Hz, *J* = 1.2Hz, 2H), 7.09 (dd, *J* = 7.60Hz, *J* =1.2Hz, 4H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 157.7, 130.2, 123.7, 119.3 ppm.

4-methyldiphenyl ether **185**

Into a three-neck 50ml round-bottom flask with 5ml dry, O_2-free [BMIM]PF_6, palladium acetate (0.09g, 0.4mmol, 4.0mol%), ligand **176** (0.18g, 0.6mmol, 6.0 mol%), potassium *tert*-butoxide (2.25g, 20.0mmol) were placed. The flask was purged with argon for half an hour and then 4-bromotoluene **132** (1.71g, 10mmol), phenol **180** (1.88g, 20mmol) were added. The mixture was stirred at 110°C for 24h under argon. The reaction mixture was then allowed to cool to room temperature and extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **185** (1.43g, 78%).



185

R_f : 0.52 (haxene : ethyl acetate = 15 : 1)

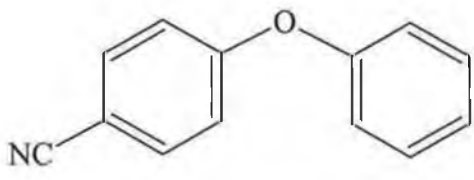
IR : ν_{max} (neat) 3034, 2928, 1589, 1491, 1240, 835, 754 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.36 (dd, *J* = 9.60Hz, *J* = 8.80Hz, 2H), 7.18 (d, *J* = 8.0Hz, 2H), 7.10 (tt, *J* = 7.20Hz, *J* = 1.20Hz, 1H), 7.04 (dd, *J* = 7.60Hz, *J* = 1.20Hz, 2H), 6.98 (d, *J* = 8.80Hz, 2H), 2.40 (s, CH_3, 3H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 158.2, 155.1, 133.3, 130.6, 130.1, 123.2, 119.5, 118.7, 21.1 ppm.

4-cyanodiphenyl ether **186**

Into a three-neck 50ml round-bottom flask with 5ml dry, O_2-free [BMIM]PF_6, palladium acetate (0.09g, 0.4mmol, 4.0mol%), ligand **176** (0.18g, 0.6mmol, 6.0 mol%), potassium *tert*-butoxide (2.25g, 20.0mmol) were placed. The flask was purged with argon for half an hour and then 4-bromobenzonitrile **137** (1.82g, 10mmol), phenol **180** (1.88g, 20mmol) were added. The mixture was stirred at 110°C for 24h under argon. The reaction mixture was then allowed to cool to room temperature and extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **186** (1.12g, 57%).



186

R_f : 0.29 (hexane : ethyl acetate = 15 : 1)

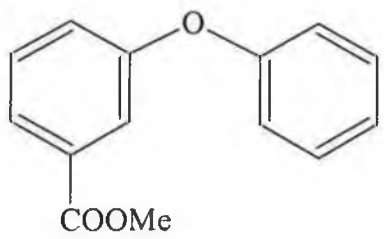
IR : ν_{max} (neat) 3098, 3064, 2229, 1589, 1487, 1244, 873, 771 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.61 (d, J = 9.20Hz, 2H), 7.45 (dd, J = 7.60Hz, J = 7.60Hz, 2H), 7.27 (tt, J = 7.60Hz, J = 0.80Hz, 1H), 6.91 (dd, J = 7.60Hz, J = 1.20Hz, 2H), 7.03 (d, J = 8.80Hz, 2H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 162.1, 155.2, 134.5, 130.7, 125.6, 120.8, 118.3, 106.2 ppm.

Methyl-3-phenoxybenzoate **187**

Into a three-neck 50ml round-bottom flask with 5ml dry, O_2-free [BMIM]PF_6, palladium acetate (0.09g, 0.4mmol, 4.0mol%), ligand **176** (0.18g, 0.6mmol, 6.0 mol%), potassium *tert*-butoxide (2.25g, 20.0mmol) were placed. The flask was purged with argon for half an hour and then methyl-3-bromobenzoate **134** (2.15g, 10 mmol), phenol **180** (1.88g, 20mmol) were added. The mixture was stirred at 110°C for 24h under argon. The reaction mixture was then allowed to cool to room temperature and extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **187** (1.75g, 74%).



187

R_f : 0.63 (hexane : ethyl acetate = 15 : 1)

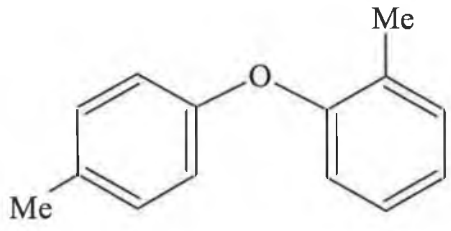
IR : ν_{max} (neat) 3073, 2952, 1726, 1581, 1487, 1278, 992, 899, 749 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.82 (tt, *J* = 8.0Hz, *J* = 1.2Hz, 1H), 7.70 (dd, *J* = 1.60Hz, *J* = 1.60Hz, 1H), 7.42 (t, *J* = 8.00Hz, 1H), 7.37 (dd, *J* = 8.40Hz, *J* = 0.80Hz, 2H), 7.24 (ddd, *J* = 8.0Hz, *J* =2.40Hz, *J* = 1.20Hz, 1H), 7.05 (dd, *J* = 7.60Hz, *J* = 0.80Hz, 2H), 3.92 (s, CH_3 3H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 166.9, 157.9, 157.1, 132.3, 130.4, 130.2, 124.7, 124.4, 123.8, 119.9, 119.5, 52.7 ppm.

2,4'-dimethyldiphenyl ether **188**

Into a three-neck 50ml round-bottom flask with 5ml dry, O_2-free [BMIM]PF_6, palladium acetate (0.09g, 0.4mmol, 4.0mol%), ligand **176** (0.18g, 0.6mmol, 6.0 mol%), potassium *tert*-butoxide (2.25g, 20.0mmol) were placed. The flask was purged with argon for half an hour and then 4-bromotoluene **132** (1.71g, 10mmol), *o*-cresol **181** (2.16g, 20mmol) were added. The mixture was stirred at 110°C for 24h under argon. The reaction mixture was then allowed to cool to room temperature and extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **188** (1.87g, 82%).



188

R_f : 0.57 (hexane : ethyl acetate = 15 : 1)

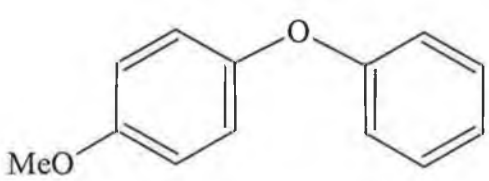
IR : ν_{max} (neat) 3034, 2928, 1585, 1504, 1236, 1107, 1039, 873, 775 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.36 (dd, *J* = 8.00Hz, *J* = 0.80Hz, 1H), 7.26 (tt, *J* = 8.0Hz, *J* = 1.60Hz, 1H), 7.21 (d, *J* = 8.0Hz, 2H), 7.15 (tt, *J* = 7.60Hz, *J* = 1.20Hz, 1H), 7.01 (dd, *J* = 8.0Hz, *J* = 0.80Hz, 1H), 6.95 (d, *J* = 8.0Hz, 2H), 2.45 (s, CH_3, 3H), 2.40 (s, CH_3, 3H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 156.0, 155.5, 132.4, 131.9, 130.6, 130.2, 127.5, 124.1, 119.6, 118.3, 21.3, 21.1 ppm.

4-phenoxyanisole **189**

Into a three-neck 50ml round-bottom flask with 5ml dry, O_2-free [BMIM]PF_6, palladium acetate (0.09g, 0.4mmol, 4.0mol%), ligand **176** (0.18g, 0.6mmol, 6.0 mol%), potassium *tert*-butoxide (2.25g, 20.0mmol) were placed. The flask was purged with argon for half an hour and then 4-bromoanisole **131** (1.87g, 10mmol), phenol **180** (1.88g, 20mmol) were added. The mixture was stirred at 110°C for 24h under argon. The reaction mixture was then allowed to cool to room temperature and extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **189** (1.66g, 83%).



189

R_f : 0.54 (hexane : ethyl acetate = 15 : 1)

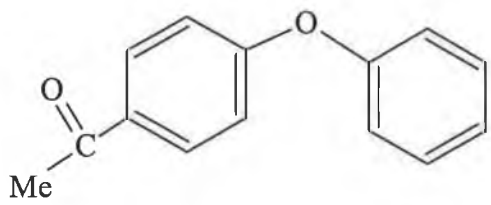
IR : ν_{max} (neat) 3043, 2958, 2834, 1589, 1500, 1231, 1035, 839, 754 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.35 (dd, *J* = 7.60Hz, *J* = 1.0Hz, 2H), 7.10 (t, *J* = 7.60Hz, 1H), 7.05 (d, *J* = 9.60Hz, 2H), 7.01 (dd, *J* = 8.0Hz, *J* = 0.80Hz, 2H), 6.94 (d, *J* = 9.20Hz, 2H), 3.86 (s, CH_3, 3H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 158.9, 156.3, 150.5, 129.9, 122.9, 121.3, 115.7, 115.3, 56.1 ppm.

4-phenoxyacetophenone **190**

Into a three-neck 50ml round-bottom flask with 5ml dry, O_2-free [BMIM]PF_6, palladium acetate (0.09g, 0.4mmol, 4.0mol%), ligand **176** (0.18g, 0.6mmol, 6.0 mol%), potassium *tert*-butoxide (2.25g, 20.0mmol) were placed. The flask was purged with argon for half an hour and then 4-bromoacetophone **135** (1.99g, 10mmol), phenol **180** (1.88g, 20mmol) were added. The mixture was stirred at 110°C for 24h under argon. The reaction mixture was then allowed to cool to room temperature and extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **190** (1.12g, 53%).



190

R_f : 0.33 (hexane : ethyl acetate = 15 : 1)

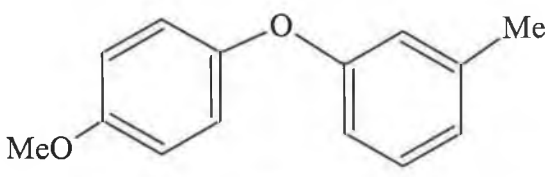
IR : ν_{max} (neat) 3064, 2970, 1679, 1585, 1491, 1240, 873, 761 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.97 (d, *J* = 8.80Hz, 2H), 7.42 (dd, *J* = 8.40Hz, *J* = 1.6Hz, 2H), 7.23 (tt, *J* = 6.80Hz, *J* = 0.80Hz, 1H), 7.10 (dd, *J* = 9.60Hz, *J* = 1.20Hz, 2H), 7.02 (d, *J* = 8.80Hz, 2H), 2.57 (s, CH_3, 3H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 191.2, 162.4, 155.8, 132.2, 131.0, 130.5, 125.0, 120.6, 117.7, 26.9 ppm.

4-(3'-methylphenoxy)anisole **191**

Into a three-neck 50ml round-bottom flask with 5ml dry, O_2-free [BMIM]PF_6, palladium acetate (0.09g, 0.4mmol, 4.0mol%), ligand **176** (0.18g, 0.6mmol, 6.0 mol%), potassium *tert*-butoxide (2.25g, 20.0mmol) were placed. The flask was purged with argon for half an hour and then 4-bromoanisole **131** (1.87g, 10mmol), *m*-cresol **182** (2.16g, 20mmol) were added. The mixture was stirred at 110°C for 24h under argon. The reaction mixture was then allowed to cool to room temperature and extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **191** (1.81g, 85%)



191

R_f : 0.45 (hexane : ethyl acetate = 15 : 1)

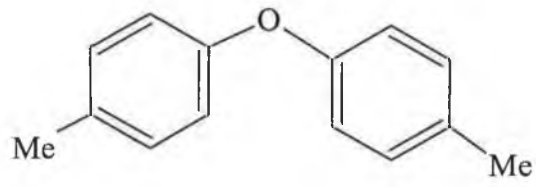
IR : ν_{max} (neat) 3047, 2958, 2834, 1585, 1504, 1244, 1035, 937, 826, 779 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.25 (t, *J* = 8.0Hz, 1H), 7.06 (d, *J* = 9.20Hz, 2H), 6.95 (d, *J* = 9.20Hz, 2H), 6.92-6.97 (m, 1H), 6.83 (dd, *J* = 12.80Hz, *J* = 4.40Hz, 2H), 3.87 (s, CH_3O, 3H), 2.40 (s, CH_3, 3H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 158.9, 156.3, 150.6, 140.2, 129.9, 123.7, 121.3, 118.7, 115.2, 115.1, 56.0, 21.8 ppm.

Di(p-tolyl) ether **192**

Into a three-neck 50ml round-bottom flask with 5ml dry, O_2-free [BMIM]PF_6, palladium acetate (0.09g, 0.4mmol, 4.0mol%), ligand **176** (0.18g, 0.6mmol, 6.0 mol%), potassium *tert*-butoxide (2.25g, 20.0mmol) were placed. The flask was purged with argon for half an hour and then 4-bromotoluene **132** (1.71g, 10mmol), *p*-cresol **183** (2.16g, 20mmol) were added. The mixture was stirred at 110°C for 24h under argon. The reaction mixture was then allowed to cool to room temperature and extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **192** (1.74g, 88%).



192

R_f : 0.60 (haxene : ethyl acetate = 15 : 1)

IR : ν_{max} (KBr) 3039, 2937, 1567, 1234, 1071, 873 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.20 (d, J = 8.0Hz, 4H), 6.97 (d, J = 8.80Hz, 4H), 2.40 (s, $2CH_3$, 6H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 155.7, 132.9, 130.6, 119.0, 21.0, 20.9 ppm.

4.6.3 The procedure for copper-catalysed synthesis of diaryl ethers

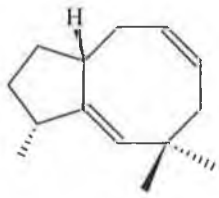
Into a three-neck 50ml round-bottom flask with 10ml dry, O_2-free [BMIM]PF_6, CuBr (0.057g, 0.4mmol, 4.0mol%), Cs_2CO_3 (4.0g, 15mmol), ethyl acetate (0.018g, 5.0 %mol) were placed. The flask was purged with argon for half an hour and then bromobenzene **130** (1.57g, 10mmol), phenol **180** (1.88g, 20mmol) were added. The mixture was stirred at 140°C for 24h under argon. The reaction mixture was then allowed to cool to room temperature and extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **184** (0.85g, 50%).

Chapter 5.

5. The catalytic Sakurai reaction in ionic liquids

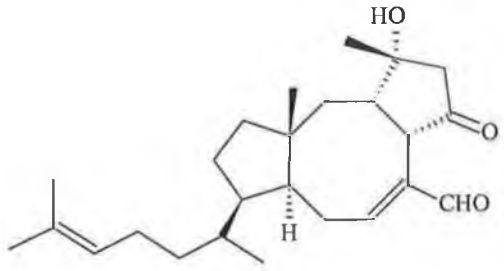
5.1 Introduction to Sakurai reaction

Many natural occurring compounds containing fused ring, which are very important for biological study (Figure 20). They have a potential for the synthesis of drugs. For example, Taxusin **196** is an intermediate for the synthesis of anti-breast cancer drug Taxol [174].



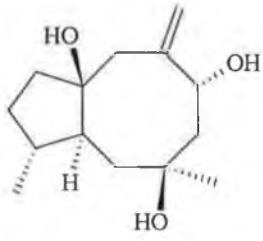
Precapnelladiene **193**

Isolated from soft coral *Capnella imbricata*



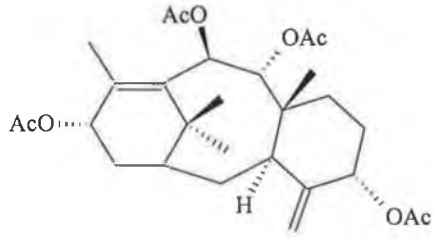
Ophiobolin **194**

Isolated from fungus *Ophiobolus miyabeanus*



Poitediol **195**

Isolated from red seaweed *Laurencia poitei*



Taxusin **196**

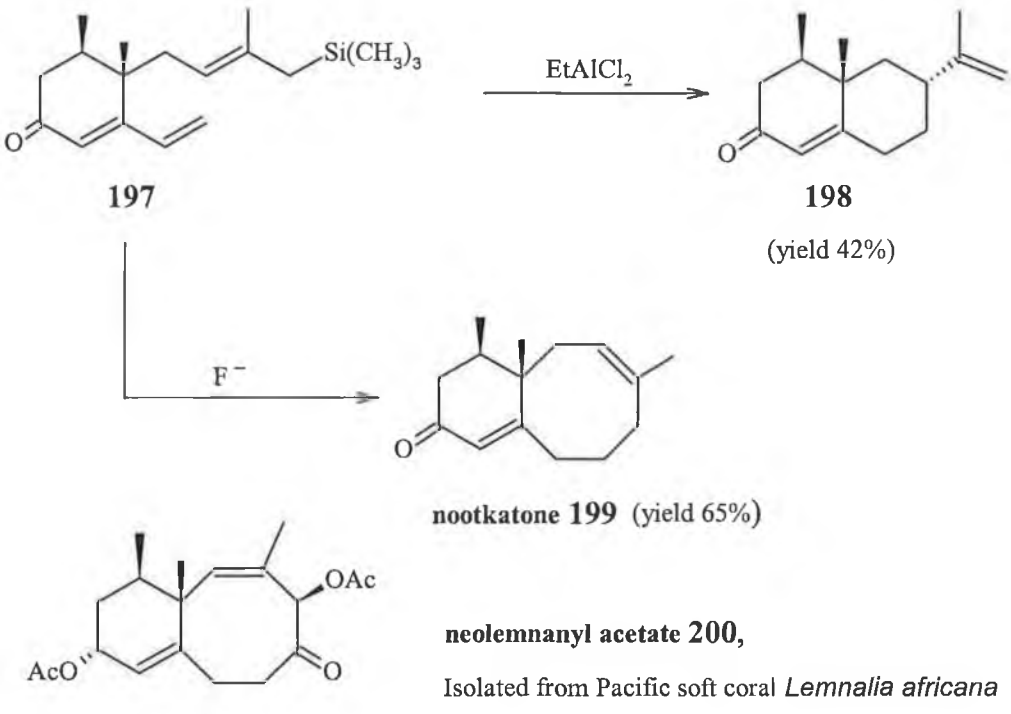
Isolated from the bark of Pacific yew tree

Figure 20 the natural occurring biologically active compounds.

Synthesis of these rare natural compounds is becoming more and more urgent for the increase demands. Recently, a lot of methods have been achieved for the synthesis of

these natural products [175a–d]. Among these methodologies, Sakurai reaction is considered to be one of the most efficient means of C-C bond formation for both inter- and intramolecular reaction in synthesis of natural compounds [176a–i].

Sakurai reaction, Lewis acid additions of allyltrimethylsilane with conjugated α, β-enones to form δ, ϵ-enones, was first reported by Sakurai in 1977 [177]. It has been extensively applied in organic synthesis, especially in natural product synthesis [178a–e]. For example, cyclisation of trienone **197** using ethylaluminum dichloride directly afforded **nootkatone 198**, which is a flavour component of grapefruit. If treatment of the same trienone **197** with fluoride ion gave fused cyclooctane **199**, which is an intermediate for **neolemnanyl acetate 200**. This compound is biologically active compound, potentially applied for synthesis of drugs (Scheme 44).



Scheme 44. The application of Sakurai reaction in synthesis of natural products.

The mechanistic explanation for Sakurai reaction is shown in Figure 21. The equivalent Lewis acid attacks the enone **202** to form enone-Lewis acid complex **I** and

then added to carbonyl group to form **II**. The nucleophilic attack in $C(4)^+$ by the allylsilane double bond electrons to produce **III** containing a silicon-stabilized carbocation $C(5)^+$. Loss of the trimethylsilane group generates methylene and trimethylsilane chloride **IV**. Aqueous work-up affords product **219** [179]

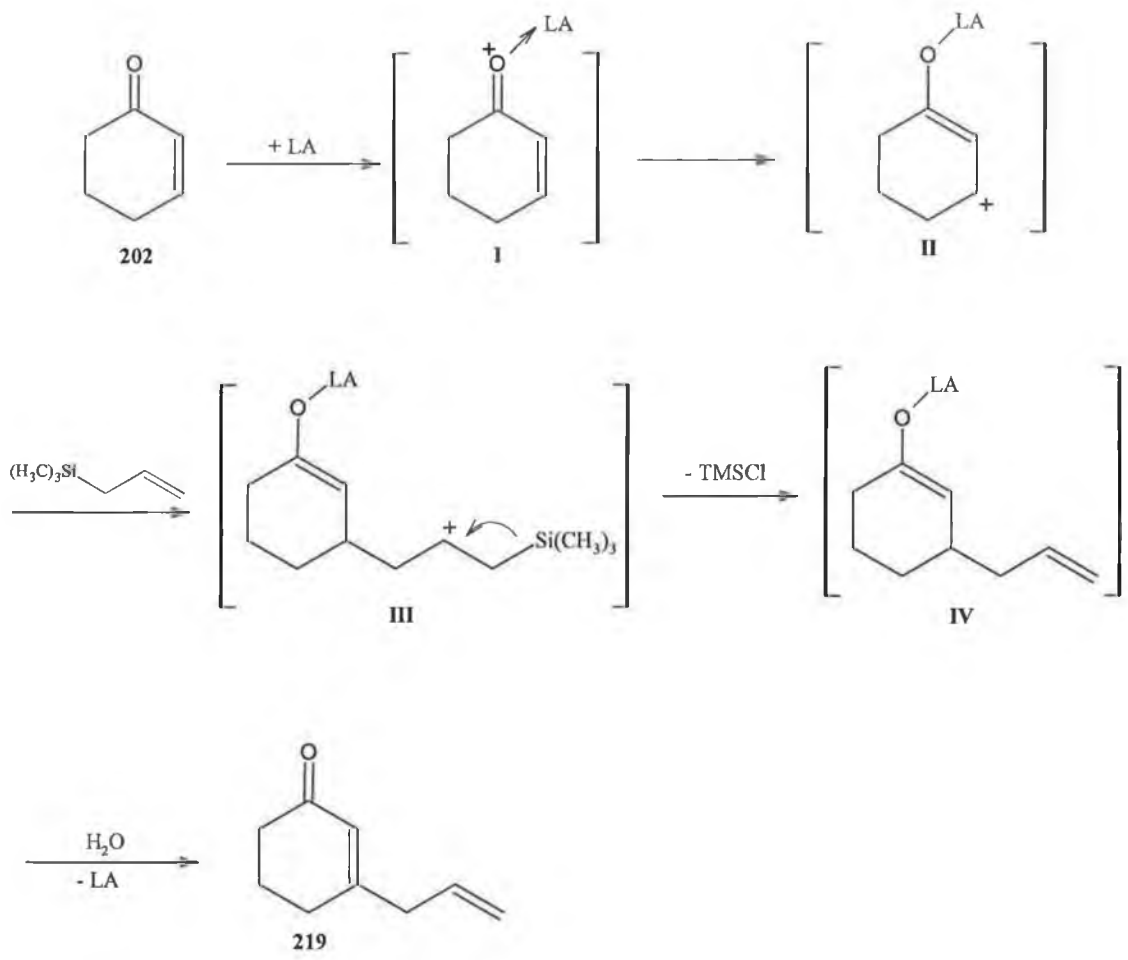


Figure 21. The mechanistic explanation for Sakurai reaction.

The range of Lewis acids employed in Sakurai reaction is extensive, among which $TiCl_4$, $AlCl_3$, $EtAlCl_2$ and $BF_3{\cdot}OEt_2$ are general the most effective for the allylations. In all cases, however, the procedures require a stoichiometric amount or even an excess of the Lewis acid to obtain reasonable reaction rates and acceptable yields of

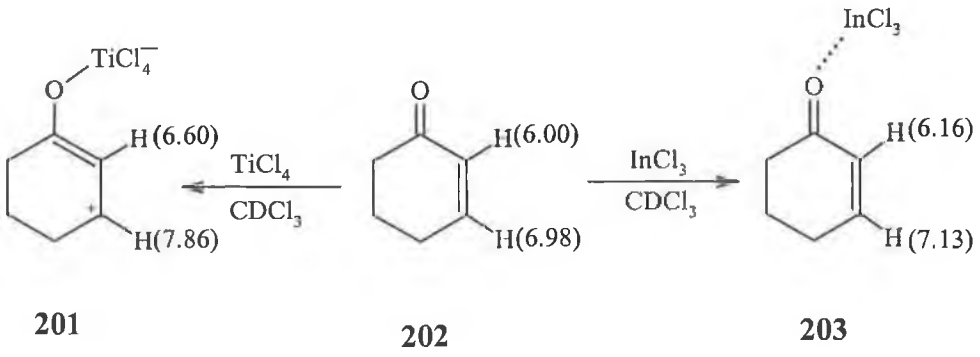
products and some reactions also need low temperature (-78°C). The suitable solvents for Sakurai reaction are CH_2Cl_2, $CHCl_3$ and benzene.

5.2 Indium complex catalysed Sakurai reaction

The studies of $InCl_3$-mediated organic transformation have become more active area for chemists recently [180a–d], it is because the advantages such as easy handling, high reactivity and selectivity, and low toxicity [181]. It has been shown to be effective in the allylation of carbonyl compound [182a–b] and aldimines [183a–c], in ring expansion reaction [184a–c], in Prins type cyclisation [185a–b], and in intramolecular carbocyclisations [186].

Recently, the Sakurai reaction catalysed by a Lewis acid $InCl_3$ has been achieved successfully with high reactivity and selectivity [187].

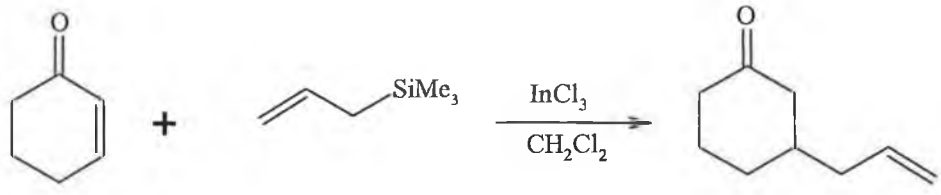
An investigation of $InCl_3$ in stoichiometric amount to a solution of 2-cyclohexen-1-one **202** in $CDCl_3$ showed that the ^1H NMR spectrum of the resulting solution exhibited two peaks at δ 6.16 and δ 7.13 ppm, which correspond to the α- and β-protons, respectively (Figure 22). Although chemical shifts of the α- and β-protons were shifted downfield relative to those of **202**, the enone moiety of **202** was maintained. In contrast, the enone moiety of **202** was entirely consumed to produce allylic carbocation species **201** in the presence of stoichiometric amounts of $TiCl_4$ indicating that the Ti complex coordinates to the enone irreversibly. These results strongly imply that although $InCl_3$ activates 2-cyclohexen-1-one, the extent of the activation is weak enough to have a reversible coordination; thus $InCl_3$ may act as a catalyst in Sakurai reaction [187].



201 **202** **203**

Figure 22. The difference between $TiCl_4$ and $InCl_3$ in Sakurai reaction.

The $InCl_3$-catalysed Sakurai reaction was carried out in dichloromethane as a solvent and at room temperature [187]. It was found that when 2-cyclohexen-1-one was treated with allyltrimethylsilane in the presence of a stoichiometric amount of $InCl_3$, 1,4-addition product **219** was obtained in a 62% yield (Scheme 45). When the reaction was carried out using 0.5 equiv of $InCl_3$ to give product in 52% yield. If the amount of catalyst is less than 0.25 equiv, there is no product to be found.



202 **205** **219**

Scheme 45. Indium-catalysed Sakurai reaction in CH_2Cl_2.

It was interesting that the additive of trimethylsilylchloride (TMSCl) could effect the reaction as well [187]. For example, when 0.1 equiv $InCl_3$ and 5 equiv TMSCl was added into the reaction, the yield of product **219** was the best (73%). However, the additive TMSCl was not effective to the catalysts $TiCl_4$ and $AlCl_3$. Otherwise, when

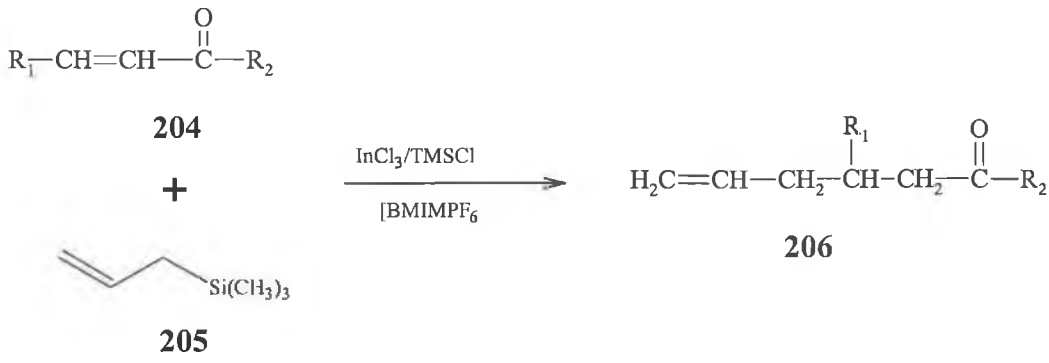
the stronger Lewis acid, such as InF_3 and $In(OTf)_3$ were used, the desired product was obtained in low yield.

Unlike $TiCl_4$, when mesityl oxide, isophorone, pulegone, or 3-methyl-2-cyclohexen-1-one was treated with allyltrimethylsilane and a catalytic or stoichiometric amount of $InCl_3$ under the same reaction conditions, the desired products were not obtained. These results revealed that the $InCl_3$ is a weaker acid and less oxophilic than $TiCl_4$. Unsaturated esters such as acrylate and methyl methacrylate did not provide the addition product, which is similar with $TiCl_4$.

5.3 Sakurai reaction in ionic liquid [BMIM]PF_6

Recently, some allylation reactions have been performed in ionic liquid successfully. For example, the allylation of aldehydes to produce homoallylic alcohols has been carried out in [BMIM]BF_4 and [BMIM]PF_6 using tetraallylstannane [71]. Indium mediated allylation of aldehydes and ketones have also been reported [72, 73]. Another example is palladium catalysed allylic alkylation. The reaction of 3-acetoxy-1,3-diphenylprop-1-ene with dimethylmalonate was carried out using $Pd(OAc)_2/PPh_3$ as catalyst in the presence of K_2CO_3 in [BMIM]BF_4 [74]. But for Sakurai reaction which was performed in ionic liquid has not been reported yet.

Ionic liquid as environmentally friendly solvent might be the suitable candidate for such reaction and the catalyst $InCl_3$ is also low toxic to environment. Therefore, in order to investigate the Sakurai reaction, a variety of α, β-enones with allyltrimethylsilane catalysed by $InCl_3$ in the presence of TMSCl were carried out in ionic liquid [BMIM]PF_6 (Scheme 46).



Scheme 46. Indium-catalysed Sakurai reaction in ionic liquid [BMIM]PF_6.

5.4 Results and discussions

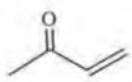
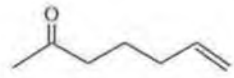
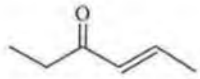
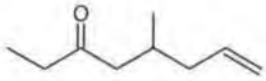
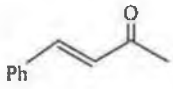
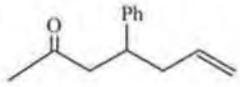
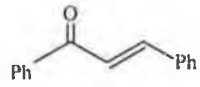
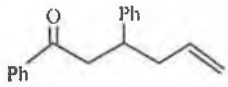
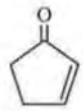
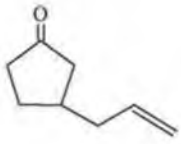
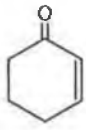
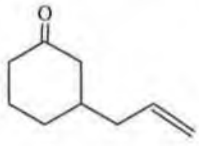
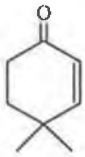
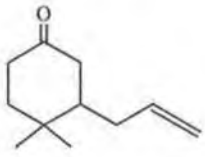
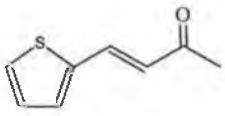
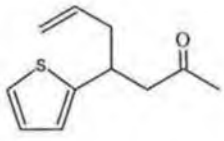
Entry	Substrate	Product	Yield (%)	
			CH_2Cl_2 [187]	$[BMIM]PF_6$
1	**207** 	**214** 	62	54
2	**208** 	**215** 	77	71
3	**209** 	**216** 	81	85
4	**210** 	**217** 	89	82
5	**211** 	**218** 	64	68
6	**202** 	**219** 	73	75
7	**212** 	**220** 	84	77
8	**213** 	**221** 	89	91

Table 18. Indium-catalysed Sakurai reaction in $[BMIM]PF_6$

The indium mediated allylation of α,β-enones with allyltrimethylsilane was carried out in [BMIM]PF_6 at room temperature in the presence of 4 equivalent TMSCl. Followed by extraction of products with diethyl ether. The results are shown in Table 18. In general, aliphatic enones gave products in lower yields than aromatic one, the yields were totally comparable with those carried out in CH_2Cl_2 and some reactions even gave better yields than in CH_2Cl_2.

It was found that ionic liquid could enhance the yield in some cases (Table 18, entry 3, 5, 6, 8). The reaction of methyl vinyl ketone **207** with allyltrimethylsilane gave lowest yield among these reactions in ionic liquid than in CH_2Cl_2. The yield was decreased 8% (entry 1). For the reaction of 4-hexen-3-one **208** with allyltrimethylsilane and the reaction of *trans*-chalcone **210** with allyltrimethylsilane, the yields of both were lower than in CH_2Cl_2, it might be that the steric hindrances were increased in ionic liquid than in CH_2Cl_2 (entry 2 and entry 4). It was also found that cyclic α, β-enone with substituent in *ortho* position could decrease in yield (entry 7).

It is worth noting that α, β-unsaturated ester such as methyl acrylate and methyl methacrylate had no Sakurai reaction in ionic liquid, which is similar to the reaction in CH_2Cl_2.

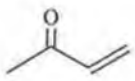
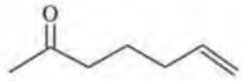
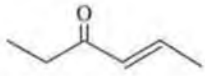
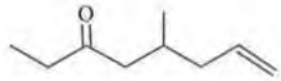
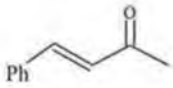
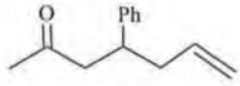
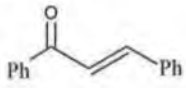
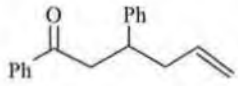
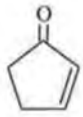
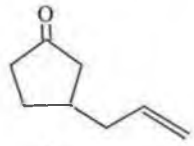
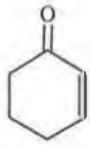
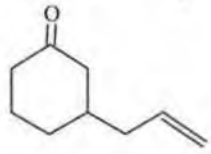
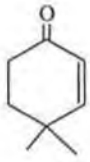
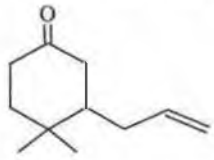
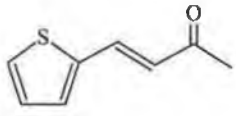
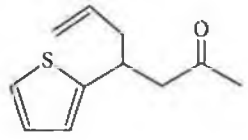
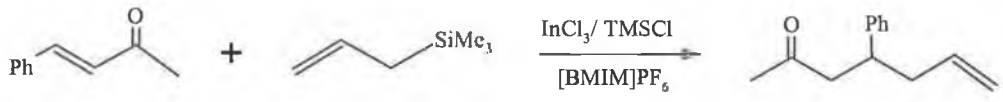
Entry	Substrate	Product	Yield(%)	
			$[BMIM]PF_6$	$[BMIM]BF_4$
1			54	56
2			71	68
3			85	82
4			82	83
5			68	74
6			75	76
7			77	77
8			91	88

Table 19. The Sakurai reaction in different ionic liquids

It was found that little difference occurred when the Sakurai reaction was carried out in different types of ionic liquids $[BMIM]PF_6$ and $[BMIM]BF_4$ (Table 19). It showed that the different anions of ionic liquids could hardly influence on yields in indium mediated Sakurai reaction.

Other factors could influence on yields were also investigated. The reaction of 4-phenyl-3-buten-2-one with allyltrimethylsilane to afford 4-phenyl-6-hepten-2-one was carried out in ionic liquid as a model for the investigation. It was found that Sakurai reaction could not happen either in DMF or in THF (Table 20, entry 1and entry 2) and CH_2Cl_2 was the suitable solvent among the normal solvents. But catalyst $InCl_3$ was more effective with TMSCl in ionic liquid than in CH_2Cl_2, product **216** was obtained in 85% yield (entry 4) with 0.20 equiv of $InCl_3$ in ionic liquid other than in 81% yield (entry 3) with 0.5 equiv of $InCl_3$ in CH_2Cl_2.



Entry	Solvent	Catalyst (equiv)	Additive (equiv)	Yield (%)
1	THF	$InCl_3$ (1.0)	TMSCl (4.0)	0
2	DMF	$InCl_3$ (1.0)	TMSCl (4.0)	0
3	CH_2Cl_2	$InCl_3$ (0.5)	TMSCl (4.0)	81
4	$[BMIM]PF_6$	$InCl_3$ (0.2)	TMSCl (4.0)	85
5	$[BMIM]PF_6$	$InCl_3$ (0.5)	TMSCl (4.0)	71
6	$[BMIM]PF_6$	$InCl_3$ (1.0)		59
7	CH_2Cl_2	$TiCl_4$ (1.0)		78
8	CH_2Cl_2	$TiCl_4$ (1.0)	TMSCl (4.0)	78
9	$[BMIM]PF_6$	$AlCl_3$ (1.0)		0
10	$[BMIM]PF_6$	$AlCl_3$ (1.0)	TMSCl (4.0)	0

Table 20. The Sakurai reaction in different conditions.

It noticed that the reaction could happen without the presence of additive TMSCl, but the yield was lower even more $InCl_3$ was added (entry 5 and entry 6). The equivalent amount of $InCl_3$ could be reduced when additive TMSCl was introduced to the reaction. It was found that the ratio (substrate : TMSCl = 1 : 4) could give best yields. Surprisingly, the additive TMSCl was not effective to $TiCl_4$ and $AlCl_3$ (entry 8 and entry10).

In conclusion, the indium mediated Sakurai reaction of α,β-enones with allyltrimethylsilane in presence of trimethylchloride has been successfully demonstrated in ionic liquids [BMIM]PF_6 and [BMIM]BF_4 at room temperature. The yields were comparable with those carried out in conventional solvent CH_2Cl_2. Further work will examine the steoroselectivity of Sakurai reaction in ionic liquids.

5.5 Experimental section

All infra-red spectra were recorded on a Perkin Elmer System 2000 FTIR spectrometer.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance NMR spectrometer, operating at 400MHz and 100MHz in Aldrich deuterated chloroform with tetramethylsiline as an internal standard respectively at the Dublin City University. (d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet).

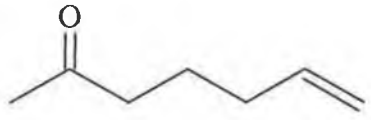
Riedel-de Haën silica gel 60 F254 TLC plates (0.2 mm layer thickness) were used for thin layer, and were examined with UV illumination at λ 254 nm. Riedel-de Haën silica gel S were used for flash chromatography according to the method of Still *et al.*[110].

All reagents and chemicals were obtained from Aldrich Chemical Company (UK) or Lancaster Synthesis Ltd.(UK) and were used without further purification, unless otherwise noted.

5.5.1 The synthesis of enones in ionic liquid

6-hepten-2-one **214**

An oven-dried 50ml round-bottom flask with a stir-bar was charged with indium chloride (0.22g, 1mmol) in 5ml [BMIM]PF_6. The flask was purged with argon for 10 minutes and then methyl vinyl ketone (0.35g, 5mmol), chlorotrimethylsilane (2.17g, 20mmol), and allyltrimethylsilane (0.63g, 5mmol) were added. The mixture was stirred at room temperature for 3h under argon. The reaction mixture was then extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **214** (0.31g, 54%).



214

R_f : 0.38 (hexane : ethyl acetate = 15 : 1)

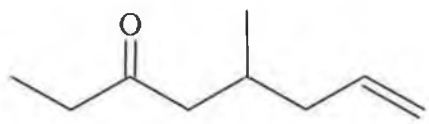
IR : ν_{max} (neat) 3070, 2950, 1710, 1640, 1470, 1420 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 5.65–5.75 (ddt, J = 17.20Hz, J = 10.00Hz, J = 7.20Hz, CH, 1H), 4.90–4.97(dd, J = 16.00Hz, J = 9.20Hz, CH_2, 2H), 2.40 (t, J = 7.50, CH_2, 2H), 2.10 (s, CH_3, 3H), 2.01(q, J = 7.50, CH_2, 2H), 1.64 (qn, J =7.60, CH_2, 2H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 207.0, 136.0, 113.3, 40.9, 31.1, 28.4, 21.0 ppm.

5-methyl-7-octen-3-one **215**

An oven-dried 50ml round-bottom flask with a stir-bar was charged with indium chloride (0.22g, 1mmol) in 5ml [BMIM]PF_6. The flask was purged with argon for 10 minutes and then 4-hexen-3-one (0.49g, 5mmol), chlorotrimethylsilane (2.17g, 20mmol), and allyltrimethylsilane (0.63g, 5mmol) were added. The mixture was stirred at room temperature for 3h under argon. The reaction mixture was then extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **215** (0.45g, 71%).



215

R_f : 0.32 (hexane : ethyl acetate = 15 : 1)

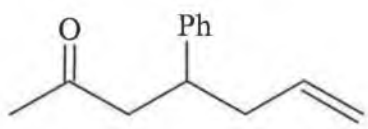
IR : ν_{max} (neat) 3077, 2953, 1710, 1640, 1457, 1375 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 5.73–5.84 (m, CH, 1H), 5.04–5.10 (dd, J = 16.40Hz, J = 10.04Hz, CH_2, 2H), 2.41–2.50 (m, CH_2CH, 3H), 2.10–2.27 (m, CH_2, 2H), 2.00–2.09 (m, CH_2, 2H), 1.10 (t, J = 6.40Hz, CH_3, 3H), 0.95 (d, J = 6.40Hz, CH_3, 3H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 211.8, 137.1, 116.8, 49.3, 41.6, 36.9, 29.3, 20.2, 8.2 ppm.

4-phenyl-6-hepten-2-one **216**

An oven-dried 50ml round-bottom flask with a stir-bar was charged with indium chloride (0.22g, 1mmol) in 5ml [BMIM]PF_6. The flask was purged with argon for 10 minutes and then *trans*-4-phenyl-buten-2-one (0.73g, 5mmol), chlorotrimethylsilane (2.17g, 20mmol), and allyltrimethylsilane (0.63g, 5mmol) were added. The mixture was stirred at room temperature for 3h under argon. The reaction mixture was then extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **216** (0.80g, 85%).



216

R_f : 0.57 (hexane : ethyl acetate = 15 : 1)

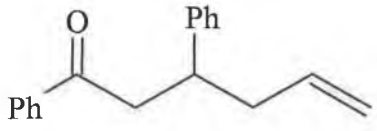
IR : ν_{max} (neat) 3077, 3000, 2919, 1717, 1641, 1453, 1358, 1163, 911 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.18–7.32 (m, C_6H_5, 5H), 5.60–5.70 (ddt, J = 16.00Hz, J = 10.04Hz, J = 7.20Hz, CH, 1H), 4.95–5.02 (dd, J = 17.80Hz, J = 10.50Hz, CH_2, 2H), 3.28 (qn, J = 7.25Hz, CH, 1H), 2.75 (m, CH_2, 2H), 2.35 (m, CH_2, 2H), 2.00 (s, CH_3, 3H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 208.1, 144.5, 136.6, 129.2, 127.6, 126.8, 117.2, 49.9, 41.5, 41.2, 31.1 ppm.

1,3-diphenyl-1-oxo-5-hexene **217**

An oven-dried 50ml round-bottom flask with a stir-bar was charged with indium chloride (0.22g, 1mmol) in 5ml [BMIM]PF_6. The flask was purged with argon for 10 minutes and then *trans*-chalcone (1.04g, 5mmol), chlorotrimethylsilane (2.17g, 20mmol), and allyltrimethylsilane (0.63g, 5mmol) were added. The mixture was stirred at room temperature for 3h under argon. The reaction mixture was then extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **217** (1.02g, 82%).



217

R_f : 0.61 (hexane : ethyl acetate = 15 : 1)

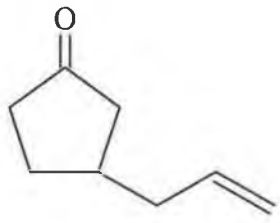
IR : ν_{max} (neat) 3069, 3026, 2919, 1679, 1491, 1449, 1265 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.90 (d, *J* = 7.20Hz, 2H), 7.50 (t, *J* = 7.60Hz, 1H), 7.40 (t, *J* = 7.60Hz, 2H), 7.20–7.30 (m, 4H), 7.10 (t, *J* = 7.60Hz, 1H), 5.60–5.70 (ddt, *J* =17.20Hz, *J* = 10.04Hz, *J* = 7.20Hz, CH, 1H), 4.97–4.90 (m, CH_2, 2H), 3.40 (qn, *J* = 7.20Hz, CH, 1H), 3.30 (d, *J* = 6.80Hz, CH_2, 2H), 2.40 (m, CH_2, 2H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 199.4, 144.8, 137.6, 136.7, 133.4, 128.9, 128.8, 128.4, 127.9, 126.8, 117.2, 44.9, 41.1, 41.2 ppm.

3-allylcyclopentanone **218**

An oven-dried 50ml round-bottom flask with a stir-bar was charged with indium chloride (0.22g, 1mmol) in 5ml [BMIM]PF_6. The flask was purged with argon for 10 minutes and then cyclopenten-2-one (0.41g, 5mmol), chlorotrimethylsilane (2.17g, 20mmol), and allyltrimethylsilane (0.63g, 5mmol) were added. The mixture was stirred at room temperature for 3h under argon. The reaction mixture was then extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **218** (0.42g, 68%).



218

R_f : 0.45 (hexane : ethyl acetate = 15 : 1)

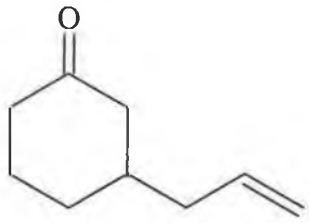
IR : ν_{max} (neat) 3062, 2955, 2910, 1680, 1432, 1410 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 5.78–5.88 (ddt, J = 17.20Hz, J = 10.00Hz, J = 7.20Hz, CH, 1H), 5.05–5.12 (dd, J = 16.00Hz, J = 9.20Hz, CH_2, 2H), 2.15–2.45 (m, $CH_2CH_2CH_2CH$, 7H), 1.85–1.95 (dd, J = 9.2Hz, 1H), 1.55–1.65 (m, 1H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 220.0, 136.8, 116.9, 45.2, 40.1, 38.9, 37.2, 29.5 ppm.

3-allylcyclohexanone **219**

An oven-dried 50ml round-bottom flask with a stir-bar was charged with indium chloride (0.22g, 1mmol) in 5ml [BMIM]PF_6. The flask was purged with argon for 10 minutes and then cyclohexen-2-one (0.48g, 5mmol), chlorotrimethylsilane (2.17g, 20mmol), and allyltrimethylsilane (0.63g, 5mmol) were added. The mixture was stirred at room temperature for 3h under argon. The reaction mixture was then extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **219** (0.51g, 75%).



219

R_f : 0.54 (hexane : ethyl acetate = 15 : 1)

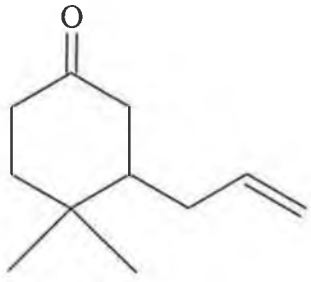
IR : ν_{max} (neat) 3081, 2932, 2860, 1709, 1670, 1444, 1423 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 5.78 (m, CH, 1H), 5.05–5.10 (m, CH_2, 2H), 2.38–2.50 (m, CH_2, 2H), 2.25–2.32 (m, CH, 1H), 2.00–2.19 (m, $2CH_2$, 4H), 1.82–2.00 (m, CH_2, 2H), 1.60–1.73 (m, CH, 1H), 1.30–1.45 (m, CH, 1H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 212.4, 136.2, 117.4, 48.3, 41.9, 41.4, 39.3, 31.4, 25.7 ppm.

3-allyl-4,4-dimethylcyclohexanone **220**

An oven-dried 50ml round-bottom flask with a stir-bar was charged with indium chloride (0.22g, 1mmol) in 5ml [BMIM]PF_6. The flask was purged with argon for 10 minutes and then 4,4-dimethylcyclohexen-2-one (0.625g, 5mmol), chlorotrimethylsilane (2.17g, 20mmol), and allyltrimethylsilane (0.63g, 5mmol) were added. The mixture was stirred at room temperature for 3h under argon. The reaction mixture was then extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **220** (0.64g, 77%).



220

R_f : 0.50 (hexane : ethyl acetate = 15 : 1)

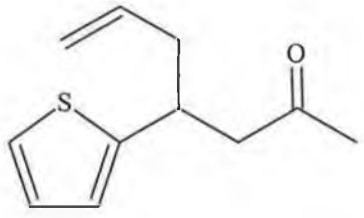
IR : ν_{max} (neat) 3077, 2975, 2936, 2864, 1717, 1640, 1474, 1291,1146, 916 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 5.70–5.60 (m, CH, 1H), 5.02–4.95 (m, CH_2, 2H), 2.40–2.22 (m, $2CH_2$, 4H), 2.02 (dd, J = 16.40Hz, J = 10.08Hz, CH, 1H), 1.75–1.52 (m, $2CH_2$, 4H), 1.05 (s, CH_3, 3H), 1.00 (s, CH_3, 3H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 212.4, 137.2, 117.0, 46.8, 42.9, 40.7, 38.7, 35.8, 33.1, 29.1, 19.9 ppm.

4-(2-thienyl-)6-hepten-2-one **221**

An oven-dried 50ml round-bottom flask with a stir-bar was charged with indium chloride (0.22g, 1mmol) in 5ml [BMIM]PF_6. The flask was purged with argon for 10 minutes and then *trans*-4-(2-thienyl)-3-buten-2-one (0.76g, 5mmol), chlorotrimethylsilane (2.17g, 20mmol), and allyltrimethylsilane (0.63g, 5mmol) were added. The mixture was stirred at room temperature for 3h under argon. The reaction mixture was then extracted with diethyl ether (5×10ml). The diethyl ether fractions were combined together and removed under vacuum to afford the crude product. It was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 15 : 1) to give **221** (0.90g, 91%).



221

R_f : 0.63 (hexane : ethyl acetate = 15 : 1)

IR : ν_{max} (neat) 3073, 2919, 1716, 1640, 1436, 1359, 1159, 916 cm^{-1}.

^{1}H-NMR (400MHz) ($CDCl_3$): δ 7.13 (dd, J = 6.0Hz, J = 1.2Hz, CH, 1H), 6.91 (dd, J = 6.0Hz, J =3.6Hz, CH, 1H), 6.81 (d, J = 3.6Hz, CH, 1H), 5.65–5.75 (ddt, J = 17.20Hz, J = 10.04Hz, J = 7.20Hz, CH, 1H), 5.07–5.00 (m, CH_2, 2H), 3.51 (qn, J =

7.20Hz, CH, 1H), 2.80–2.78 (dd, J = 1.2Hz, J = 2.4Hz, CH_2, 2H), 2.45–2.40 (m, CH_2, 2H), 2.10 (s, CH_3, 3H) ppm.

^{13}C-NMR (100MHz) ($CDCl_3$): δ 207.5, 148.3, 136.04, 126.9, 124.3, 123.5, 117.7, 50.6, 41.9, 36.3, 31.1 ppm.

References

[1] (a) Freemantle, M. *Chem. Eng.* **1999**, *77*, 23.
(b) Freemantle, M. *Chem. Eng.* **2000**, *78*, 37.
(c) Bradly, D. *Chem. Ind.* **1999**, 86.

[2] Walden, P. *Bull. Acad. Imper. Sci. (St. Petersburg)* **1914**, 1800.

[3] Hurly, F. H., Wier, T. P. *J. Electrochem. Soc.* **1951**, *98*, 207.

[4] Chum, H. L., Koch, V. R., Miller, L. L., Osteryoung, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 3264.

[5] Wilkes, J. S., Levisky, J. A., Wilson R. A., Hussey, C. L. *Inorg. Chem.* **1982**, *21*, 1263.

[6] (a) Scheffler, T. B., Hussey, C. L., Seddon, K. R., Kear, C. M., Armitage, P. D. *Inorg. Chem.* **1983**, *22*, 2099.
(b) Laher, T. M., Hussey, C. L. *Inorg. Chem.* **1983**, *22*, 3247.
(c) Scheffler, T. B., Hussey, C. L. *Inorg. Chem.* **1984**, *23*, 1926.
(d) Hitchcock, P. B., Mohammed, T. J., Seddon, K. R., Zora, J. A., Hussey, C. L., Ward, E. H. *Inorg. Chim. Acta* **1986**, *113*, 25.

[7] Boon, J. A., Levisky, J. A., Pflug, J. L., Wilkes, J. S. *J. Org. Chem.* **1986**, *51*, 480.

[8] Fry, S. E., Pienta, N. J. *J. Am. Chem. Soc.* **1985**, *107*, 6399.

[9] Chauvin, Y., Gilbert, B., Guilbard, I. *J. Chem. Soc., Chem. Commun.* **1990**, 1715.

[10] Carlin, R. T., Wilkes, J. S. *J. Mol. Catal.* **1990**, *63*, 125.

[11] Wilkes, J. S., Zaworotko, M. J . *J. Chem. Soc., Chem. Commun.* **1992**, 965.

[12] (a) Gordon, C. M. *Appl. Catal. A* **2001**, *222*, 101
(b) Olivier-Bourbigou, H., Magna, L. *J. Mol. Catal. A* **2002**, *182*, 419.
(c) Zhao, D., Wu, M., Kou, Y., Min, E. *Catalysis Today* **2002**, *74*, 157.

[13] (a) Hussey, C. L. *Adv. Molten Salt Chem.* **1983**, *5*, 185.
(b) Ford, W. T., Hauri, R. J., Hart, D. J. *J. Org. Chem.* **1973**, *38*, 3916.

[14] Fuller, J., Carlin, R. T., De Long, H. C., Haworth, D. *J. Chem. Soc., Chem. Commun.* **1994**, 299.

[15] Poole, C. F., Kersten, B.R., Ho, S. S., Coddens, M. E., Furton, K.G. *J. Chromatogr.* **1986**, *352*, 407.

[16] Poole, S. K., Shetty, P. H., Poole, C. F. *Anal. Chim. Acta* **1989**, *218*, 241.

[17] Bonhôte, P., Dias, A. P., Papageorgiou, N., Kalyanasundaram, K., Grätzel, M. *Inorg. Chem.* **1996**, *35*, 1168.

[18] Namboodiri, V. V., Varma, R. S. *Chem. Commun.* **2002**, 342.

[19] (a) Seddon, K. R. *J. Chem. Tech. Biotechol.* **1997**, *68*, 351.
(b) Seddon, K. R. *Kinet. Catal. Engl. Transl.* **1996**, *37*, 693.
(c) Stegemann, H., Rhode, A., Reiche, A., Schnittke, A., Füllbier, H. *Electrochim. Acta* **1992**, *37*, 379.

[20] Fannin, A. A., Floreani, Jr. D. A., King, L. A., Landers, J. S., Piersma, B. J., Stech, D. J., Vaughn, R. L., Wilkes, J. S., Williames, J. L. *J. Phys. Chem.* **1984**, *88*, 2614.

[21] Holbrey, J. D., Seddon, K. R. *J. Chem. Soc., Dalton Trans.* **1999**, 2133.

[22] (a) Hitchcock, P.B., Seddon, K.R., Welton, T. *J. Chem. Soc., Dalton Trans.* **1993**, 2639.
(b) Elaiwi, A., Hitchcock, P. B., Seddon. K. R., Srinivasan, N., Tan, Y-M., Welton T., Zora, J. A. *J. Chem. Soc., Dalton Trans.* **1995**, 3467.

[23] Huddleston, J. G., Willauer, H. D., Swatloski, R. P., Visser, A. E., Rogers, R. D. *Chem. Commun.* **1998**, 1765.

[24] Blanchard, L. A., Hancu, D., Beckman, E. J., Brennecke, J. F. *Nature* **1999**, *399*, 28.

[25] Blanchard, L. A., Gu, Z., Brennecke, J. F. *J. Phys. Chem. B* **2001**, *105*, 2437.

[26] (a) Brown, R. A., Pollet, P., McKoon, E., Eckert, C. A. Liotta, C. A., Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254.
(b) Liu, F., Abrams, M. B., Baker, R.T., Tumas, W. *Chem. Commun.* **2001**, 433.

[27] Sellin, M. F., Webb, P.B., Cole-Hamilton, D. J. *Chem. Commun.* **2001**, 781.

[28] Reetz, M. T., Wiesenhöfer, W., Franciò, G., Leitner, W. *Chem. Commun.* **2002**, 992.

[29] Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319.

[30] Shetty, P. H, Youngberg, P. J., Kersten, B. R., Poole, C. F. *J. Chromatogr.* **1987**, *411*, 61.

[31] Muldoon, M. J., Gordon, C., M., Dunkin, I. R. *J. Chem. Soc., Perkin Trans.2* **2001**, 433.

[32] Carmichael, A. J., Seddon, K. R., *J. Phys. Org. Chem.* **2000**, 13, 591.

[33] Armstrong, D. W., He, L., Liu, Y.-S. *Anal. Chem.* **1999**, *71*, 3873.

[34] Jaeger, D. A., Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785.

[35] Fischer, T., Sethi, A., Welton, T. *Tetrahedron Lett.* **1999**, *40*, 793.

[36] Howarth, J., Hanlon, K., Fayne, D., McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097.

[37] Song, C, E., Shim, W. H., Roh, E. J., Lee, S., Choi, J. H. *Chem. Commun.* **2001**, 1122.

[38] Stark, A., Maclean, B. L., Singer, R. D. *J. Chem. Soc., Dalton Trans.* **1999**, 63.

[39] (a) Kobayashi, S., *Synlett.* **1994**, 689.
(b) Marshman, R. W., *Aldrichimica Acta* **1995**, *28*, 77.
(c) Kobayashi, S. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 370.

[40] Song, C. E., Shim, W. H., Roh, E. J., Choi, J. H. *Chem. Commun.* **2000**, 1695.

[41] Adams, C. J., Earle, M. J., Roberts, G., Seddon, K. R. *Chem. Commun.* **1998**, 2245.

[42] Chauvin, Y., Hirschauer, A., Oliver, H. *J. Mol. Catal.* **1994**, *92*, 155.

[43] Keim, W. *World Patent* WO 00/16902 (**2000**).

[44] Suarez, P. A. Z., Dullius, J. E. L., Einloft, S., De Souza, R. F., Dupont, J. *Polyhedron.* **1996**, *15*, 1217.

[45] Simon, L. C., Dupont, J., De Souza, R. F. *Applied Catalysis A*: *General* **1998**, *175*, 215.

[46] Chauvin, Y., Mussmann, L., Oliver, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2698.

[47] Monteiro, A. L., Zinn, F. K. de Souza, R. F., Dupont, J. *Tetrahedron Asymmetry* **1997**, *2*, 177.

[48] Adams, C. J., Earle, M. J., Seddon, K. R. *Chem. Commun.* **1999**, 1043.

[49] Suarez, P. A. Z., Dullius, J. E. L., Einloft, S., De Souza, R. F., Dupont, J. *Inorg. Chim. Acta* **1997**, *255*, 207.

[50] Dyson, P. J., Ellis, D. J., Parker, D.G., Welton, T. *Chem. Commun.* **1999**, 25.

[51] Müller, L. A., Dupont, J., de Souza, R. F. *Makromol. Chem. Rapid Commun.* **1998**, *19*, 409.

[52] Brown, R. A., Pollet, P., McKoon, E., Eckert, C. A., Liotta, C. L., Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254.

[53] Carmichael, A. J., Haddleton, D, M., Bon, S. A. F., Seddon, R. K. *Chem. Commun.* **2000**, 1237.

[54] Brassat, I., Englert, U., Keim, W., Keitel, D. P., Killat, S., Suranna, G. P., Wang, R. *Inorg. Chim. Acta* **1998**, *280*, 150.

[55] Chauvin, Y., Mussmann, L., Oliver, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2698.

[56] Silva, S. M., Suarezz, P. A. Z., De Souza, R. F., Dupont, J. *Polymer Bull.* **1998**, *40*, 401.

[57] Freemantle, M. *Chem. Eng. News* **1998**, *76*, 32.

[58] Karodia, N.,Guise, S., Newlands, C., Anderson, J. A. *Chem. Commun.* **1998**, 2341.

[59] Keim, W., Vogt, D., Waffenschmidt, H., Wasserscheid, P. *J. Catal.* **1999**, *186*, 481.

[60] Crofts, D., Dyson, P. J., Sanderson, K. M., Srinivasan, N., Welton, T., *J. Organomet. Chem.* **1999**, *573*, 292.

[61] Dyson, P. J., Grossed, M. C., Srinivasan, N., Vien, T., Welton, T. Williams, D. J., White, A. J-P., Zigras, T. *J. Chem. Soc., Dalton Trans.* **1997**, 3465.

[62] (a) Heck, R. F. *J. Am. Chem. Soc.* **1986**, *90*, 4546.
(b) Mizoriki, T. Mori, K., Ozaki, A. *Bull. Soc. Jpn.* **1971**, *44*, 581.

[63] Kaufmann, D. E., Nouroozian, M., Henze, H. *Synlett.* **1996**, 1091.

[64] Herrmann, W. A., Böhm, V. P. W. *J. Organomet. Chem.* **1999**, 572, 141.

[65] Carmichael, A. J., Earle, M. J., Holbrey, J. D., McCormac, P. B. Seddon, K. R. *Org. Lett.* **1999**, *1*, 997.

[66] Xu, L., Chen, W., Xiao, J. *Organometallics* **2000**, *19*, 1123.

[67] Xu, L. J., Chen, W. P., Ross, J., Xiao, J. L. *Org. Lett.* **2001**, *3*, 295.

[68] Howarth, J. Dallas, A. *Molecules* **2000**, *5*, 851.

[69] Mathews, C. J., Smith, P. J., Welton, T. *Chem. Commun.* **2000**, 1249.

[70] Le Boulaire, V., Gree, R. *Chem. Commun.* **2000**, 2195.

[71] Gordon, C. M., McCluskey, A. *Chem. Commun.* **1999**, 1431.

[72] Gordon, C. M., Ritchie, C. *Green Chem.* **2002**, *4*, 124.

[73] Law, M. C., Wong, K. Y., Chan, T. H. *Green Chem.* **2002**, *4*, 161.

[74] Chen, W., Xu, L., Chatterton, C., Xiao, J. *Chem. Commun.* **1999**, 1247.

[75] Bar. G., Parson, A. F., Thomas, C. B., *Chem. Commun.* **2001**, 1350.

[76] Song, C. E., Roh, E. J. *Chem. Commun.* **2000**, 837.

[77] Song, C. E., Oh, C. R., Roh, E. J., Choo, D. J. *Chem. Commun.* **2000**, 1743.

[78] Martinez, L. E., Leighton, J. L., Carsten, D. H., Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.

[79] Howarth, J. *Tetrahedron Lett.* **2000**, *41*, 6627.

[80] Owens, G. S., Abu-Omar, M. M. *Chem. Commun.* **2000**, 1165.

[81] Mizushima, E., Hayashi, T., Tanaka, M. *Green Chem.* **2001**, *3*, 76.

[82] Zim, D., de Souza, R. F., Dupont, J., Monteiro, A. L. *Tetrahedron Lett.* **1998**, *39*, 7071.

[83] Wheeler, C., West, K. N., Liotta, C. L., Eckert, C. A. *Chem. Commun.* **2001**, 887.

[84] Earle, M. J., McCormack, P. B., Seddon, K. R. *Green Chem.* **2000**, *2*, 261.

[85] Zulfiquar, F., Kitazume, T. *Green Chem.* **2000**, *2*, 296.

[86] Kitazume, T., Zulfiquar, F., Tanaka, G. *Green Chem.* **2000**, *2*, 133.

[87] Handy, S. T., Zhang, X. L. *Org. Lett.* **2001**, *3*, 233.

[88] Kabalka, G. W., Malladi, R. R. *Chem. Commun.* **2000**, 2191.

[89] Laali, K. K., Gettwert, V. *J. Org. Chem.* **2001**, *66*, 35.

[90] Kitazume, T., Kasai, K. *Green Chem.* **2001**, *3*, 30.

[91] Green, L., Hemeon, I., Singer, R. D. *Tetrahedron Lett.* **2000**, *41*, 1343.

[92] Brown, R. J. C., Dyson, P. J., Ellis, D. J., Welton, T. *Chem. Commun.* **2001**, 1862.

[93] Scot, J. L., MacFarlane, D. R., Raston, C. L., Teoh, C. M. *Green Chem.* **2000**, *2*, 123.

[94] Carrea, G., Riva, S. *Angew. Chem. Int. Ed.* **2000**, *112*, 2312.

[95] Erbeldinger, M., Mesiano, A. J., Russell, A. J. *Biotechnol. Prog.* **2000**, *16*, 1129.

[96] Schöfer, S. H., Kaftzik, N., Wasserscheid, P., Kragl, U. *Chem. Commun.* **2001**, 425.

[97] Kim, K. W., Song, B., Choi, M. Y., Kim, M. J. *Org. Lett.* **2001**, *3*, 1507.

[98] Cull, S. G., Holbrey, J. D., Vargas-Mora, V., Seddon, K. R., Lye, G. J. *Biotechnol. Bioeng.* **2000**, *69*, 227.

[99] (a) Normant, J. F. *Synthesis* **1972**, 63.
(b) Jukes, A. E. *Adv. Organomet. Chem.* **1974**, *12*, 215.

[100] (a) McKillop, A., Elsom, L. F., Taylor, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 2423.
(b) Pallaud, R., Pleau, J. M. *C. R. Acad. Sci., Ser. C.* **1968**, *266*, 35.

[101] Semmelhack, M. F., Helquist, P. M., Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*, 5908.

[102] (a) Semmelhack, M. F. *Org. Reacts.* **1972**, *19*, 179.
(b) Schunn, R. A. *Inorg. Synth.* **1973**, *13*, 124.

[103] Kende, A. S., Liebeskind, L. S., Braitsch, D. M. *Tetrahedron Lett.* **1975**, 3375.

[104] Tsou T. T., Kochi J. K., *J. Am. Chem. Soc.* **1979**, *101*, 6319.

[105] Amatore, C., Jutand, A. *Organometallics* **1988**, *7*, 2203.

[106] Colon, I., Kelsey, D. R. *J. Org. Chem.* **1986**, *51*, 2627.

[107] Percec, V., Bae, J.-Y., Zhao, M., Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176.

[108] Jutand, A., Mosleh, A. *J. Org. Chem.* **1997**, *62*, 261.

[109] Tsou T. T., Kochi J. K., *J. Am. Chem. Soc.* **1979**, *101*, 7547.

[110] Still, W. C., Kahn, M., Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[111] Forrest, J. *J. Chem. Soc.* **1960**, 574.

[112] Jutand, A., Mosleh, A. *J. Am. Chem. Soc.* **1997**, *62*, 261.

[113] Zincke, T. *Ber.* **1871**, *4*, 396.

[114] Lindstead, R. P., Doering, W. E. *J. Am. Chem. Soc.* **1942**, *64*, 1991.

[115] Kondo, H., Ikeda, T. *Ber.* **1940**, *73*, 867.

[116] Silver, S. L., Lowy, A. *J. Am. Chem. Soc.* **1934**, *56*, 2429.

[117] Hinkel, A. B. *J. Chem. Soc.* **1936**. 339.

[118] Nakamura, K., Inoue, K., Ushio, K., Oka, S. *J. Org. Chem.* **1988**, *53*, 2589.

[119] (a)Takaishi, Y., Yang, Y. L., Di Tullio, D., Sih, C. J. *Tetrahedron Lett.* **1982**, *23*, 5489.

(b) Deol, B. S., Ridley, D. D., Simpson, G. W. *Aust. J. Chem.* **1976**, *29*, 2459.

[120] Seebach, D., Sutter, M. A., Weber, R. M., Züger, M. F. *Org. Synth.* **1985**, *63*, 1.

[121] Bucciarelli, M., Forni, A., Morreti, I., Torre, G. *Synthesis* **1983**, 897.

[122] Fadnavis, N. W., Reddy, N. P., Bhalerao, U. T. *J. Org. Chem.* **1989**, *54*, 3281.

[123] Naoshima, Y., Nishiyama, T., Munakata, Y. *Chem. Lett.* **1989**, 1517.

[124] Jayasinghe, L. Y., Smallridge, A. J., Trewhella, M. A. *Tetrahedron Lett.* **1993**, *34*, 3949.

[125] Naoshima, Y., Maeda, J., Munakata, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 659.

[126] Nakamura, K., Kondo, S., Kawai, Y., Ohno, A. *Tetrahedron Lett.* **1991**, *32*, 7075.

[127] Jayasinghe, L. Y., Kodituwakku, D., Smallbidge, A. J., Trewhella, M. A. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2528.

[128] Johns, M. K., Smallbridge, A. J., Trewhella, M. A. *Tetrahedron Lett.* **2001**, *42*,4261.

[129] Klivanov, A. M. *Anal. Biochem.* **1979**, *93*, 1.

[130] Katyar, S. S., De Tapas, K. *Biochem. Ind.* **1990**, *20*, 1127.

[131] Naoshima, Y., Maeda, J., Munakata, Y., Nashiyama, T., Kamezawa, M., Tachibana, H. *J. Chem. Soc., Chem. Commun.* **1990**, 964.

[132] Takeda, A., Sakai, T., Nakamura, T., Fukuda, K., Amano, E., Utaka, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3185.

[133] McLeod, R., Prosser, H., Frskentscher, L., Lanyi, J., Mosher, H., S. *Biochemistry* **1964**, *3*, 838.

[134] Rickard, R. H., Kenyon, J. *J. Chem. Soc.* **1914**, *105*, 1120.

[135] Fauve, A., Verchambre, H. *J. Org. Chem.* **1988**, *53*, 5215.

[136] Wipt, B., Kupfer, E., Berlazzi, R., Leuenberger, H.G.W. *Helv. Chim. Acta* **1983**, *66*, 485.

[137] Seebach, D., Roggo, S., Maetzke, T., Braunshweiger, H. *Helv. Chim. Acta* **1987**, *70*, 1605.

[138] Beckett, A. H., Happer, N. J. Clitherrow, J. W. *J. Pharm. Pharmaco.* **1963**, *15*, 349.

[139] Pellón, R. F., Carrasco, R., Millián, V., Rodes, L. *Synth. Commun.* **1995**, *25*, 1077.

[140] (a) Evans, D. A., DeVries, K. M. *Glycopeptide Antibiotics, Drugs and the Pharmaceutical Sciences* Nagarajan, R., Ed.; Marcel, Decker, Inc.: New York 1994, *Vol.63*, 63.

(b) Deshpende, V. E., Gohkhale, N. J. *Tetrahedron Lett.* **1992**, *33*, 4213.

(c) Singh, S. B., Pettit, G. R. *J. Org. Chem.* **1990**, *55*, 2797.

(d) Seldon, R. A. *Chirotechnology* Marcel Dekker Inc., New York, **1998**, 62.

[141] Janetka, J. W., Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 6488.

[142] (a) Boger, D.L., Sakaya, S. M., Yohannes, D. *J. Org. Chem.* **1991**, *56*, 4204.

(b) Jung, M. E., Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909.

[143] (a) Sawyer, J. S. *Drugs Future* **1996**, *21*, 610.

(b) Sawyer, J. S. *Expert Opin. Invest. Drugs* **1996**, *5*, 73.

[144] Johnson, W. O., Kollman, G. E., Swithenbank, C., Yih, R. Y. *J. Agric. Food Chem.* **1978**, *26*, 285.

[145] Marcoux, J-F. Dooye, S., Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539.

[146] Aalten, H. L., van Koten, G., Grove, D. M., Kuilman, T., Piekstra, O. G., Hulshof, L. A., Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565.

[147] Palomo, C., Oiarbide, M., López, R., Gómez-Bengoa, E. *Chem. Commun.* **1998**, 2091.

[148] (a) Hartwig, J. F. *Synlett* **1997**, 329.

(b) Palucki, M., Wolfe, J. P., Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395.

(c) Palucki, M., Wolfe, J. P., Buchwald, S. L *J. Am. Chem. Soc.***1996**, *118*, 10333.

[149] (a) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

(b) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.

[150] Miyaura, N., Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[151] (a) Januszkiewicz, K., Alper, H. *Tetrahedron Lett.* **1983**, *24*, 5159.

(b) Kishi, A., Higashino, T., Sakaguchi, S., Ishii, Y. *Tetrahedron Lett.* **2000**, *41*, 99.

(c) Karakhanov, E., Maximov, A. Kirillov, A. *J. Mol. Catal. A.* **2000**, *157*, 23.

[152] Consiglio, G., Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.

[153] Kharasch, M. S., Seyler, R. C., Mayo, F. R. *J. Am. Chem. Soc.* **1938**, *60*, 882. Doyle, J. R., Slade, P. E., Jonassen, H. B. *Inorg. Synth.* **1960**, *6*, 218.

[154] Jenkins, J. M., Shaw, B. L. *J. Chem. Soc.* **1966**, 770.

[155] Henry, P. M., Marks, B. W. *Inorg. Chem.* **1971**, *10*, 373.

[156] Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 21.

[157] Ukai, T., Kawazura, H., Ishii, Y., Bonnet, J. J., Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253.

[158] Herrmann, W. A., Brossmer, C., Ofele, K., Reisinger, C.-P., Priermeier, T., Beller, M., Fischer, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844.

[159] Beller, M., Riermeier, T. H. *Tetrahedron Lett.* **1996**, *37*, 6535.

[160] Fariana, V. in *Comprehensive Organometallic Chemistry II*, Vol. 12, (Abel, E. W., Stone, F. G., Wilkinson, G. Eds.), Pergamon, Oxford, UK, **1995**, 161.

[161] Amatore, G., Carre, E., Jutland, A., M'Barke, M. A. *Organometalics* **1995**, *14*, 1818.

[162] Jutland, A., Mosleh, A. *Organometallics* **1995**, *14*, 1810.

[163] Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

[164] (a) Kosugi, M., Shimizu, Y., Migita, T. *Chem. Lett.* **1977**, 1423.

(b) Kosugi, M., Shimizu, Y., Migita, T. *J. Organomet. Chem.* **1977**, *129*, C36.

[165] (a) Wolfe, J. P., Wagaw, S., Marcoux, J.-F., Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

(b) Hartwig, J. F. *Angew. Chem. Int. Ed. Engl.* **1998**. *37*, 2046.

(c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

(d) Mann, G., Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109.

[166] Mann, G., Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005.

[167] Aranyos, A., Old, D. W., Kiyomori, A., Wolfe, J. P., Sadighi, J. P., Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

[168] (a) Nishiyama, M., Yamamoto, T., Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367.

(b) Reddy, N. P., Tanaka, M. *Tetrahedron Lett.* **1998**, *39*, 617.

(c) Hamann, B. C., Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.

[169] Bäckvall, J. E., Björkman, E. E., Petterson, L., Siegbahn, P. *J. Am. Chem. Soc.* **1984**, *106*, 4369.

[170] (a) Hartwig, J. F. Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373.

(b) Paul, F., Patt, J., Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.

(c) Louie, J., Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598.

(d) Louie, J., Paul, F., Hartwig, J. F. *Oganometallics* **1996**, *15*, 2794.

[171] Baranano, D., Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937.

[172] Widenhoefer, R. A., Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504.

[173] Mann, G., Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005.

[174] Holton, R. A., Juo, R. R., Kim, H. B., Williams, A. D., Harusawa, S., Lowenthal, R. E., Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

[175] (a) Kinney, W. A., Coghlan, M. J., Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868.

(b) Kishi, Y., Rowley, M., Tsukamoto, M. *J. Am. Chem. Soc.* **1989**, *111*, 2735.

(c) Gadwood, R. C., Lett, R. M., Wissinger, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 3869.

(d) Harusawa, S., Holton, R. A., Juo, R. R., Kim, H. B., Lowental, R.E., Williams, A. D., Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

[176] (a) Schinzer, D. S., *Synthesis* **1988**, 263.

(b) Schinzer, D. S., Allagiannis, C., Wichmann, S. *Tetrahedron* **1988**, *44*, 3851.

(c) Majetich, G., Desmond, R., Casares, A. M. *Tetrahedron Lett.* **1983**, *24*, 1913.

(d) Wilson, S. R., Price, M. F. *J. Am. Chem. Soc.* **1982**, *104*, 1124.

(e) Tokoroyama, T., Tsukamoto, M., Iio, H. *Tetrahedron Lett.* **1984**, *25*, 5067.

(f) Schinzer, D. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 308.

(g) Majetich, G., Defauw, J., Hull, K., Shawe, T. *Tetrahedron Lett.* **1985**, *26*, 4711.

(h) Schinzer, D., Ringe, K. *Synlett* **1994**, 463.

(i) Kuhnert, N, Peverley, J., Robertson, J. *Tetrahedron Lett.* **1998**, *39*, 3215.

[177] Hosomi, A., Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1675.

[178] (a) Tokoroyama, T., Tsukamoto, M., Asada, T., Iio, H. *Tetrahedron Lett.* **1987**, *28*, 6645.

(b) Nakamura, H., Oya, T., Murai, A. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 929.

(c) Majetich, G., Song, J-S., Ringold, C., Nemeth, G. A. *Tetrahedron Lett.* **1990**, *31*, 2239.

(d) Yamamoto, Y., Furuta, T. *J. Org. Chem.* **1990**, *55*, 3971.

(e) Majetich, G., Ringold, C. *Heterocycles* **1987**, *25*, 271.

[179] Majetich, G., Song, J.-S., Leigh, A. J., Condon, S. M. *J. Org. Chem.* **1993**, *58*, 1030.

[180] (a) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643.

(b) Li, C.-J., Chan, T.-H. *Organic Reactions in Aqueous Media* Willey: New York, **1997**.

(c) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023.

(d) Li, C.-J, Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149.

[181] King, R.B., Ed., *Encyclopedia of Inorganic Chemistry*, John Wiley & Sons, New York, **1994**, Vol *3*, p 1514.

[182] (a) Li, C.-J., Chan, T.-H. *Tetrahedron Lett.* **1991**, *32*, 7017.
(b) Isaac, M. B., Chan, T.-H. *Tetrahedron Lett.* **1995**, *36*, 8957.
[183] (a) Beuchet, P., Marrec, N., Mosset, P. *Tetrahedron Lett.* **1992**, *33*, 5959.
(b) Loh, T.-P., Ho, D. S., Xu, K.-C., Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865.
(c) Chan, T.-H., Lu., W. *Tetrahedron Lett.* **1998**, *39*, 8605.
[184] (a) Li, C.-J., Chen, D.-L., Lu, Y.-Q., Haberman, J. X., Mague, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 4216.
(b) Haberman, J. X., Li, C.-J. *Tetrahedron Lett.* **1997**, *38*, 4735.
(c) Li, C.-J., Chen, D.-L., Lu, Y.-Q., Haberman, J. X., Mague, J. T. *Tetrahedron* **1998**, *54*, 2347.
[185] (a) Yang, J., Viswanathan, G. S. *Tetrahedron Lett.* **1999**, *40*, 1627.
(b) Viswanathan, G. S., Yang, J., Li, C.-J. *Org. Lett.* **1999**, *1*, 993.
[186] Bryan, V. J., Chan, T.-H. *Tetrahedron Lett.* **1996**, *37*, 5341.
[187] Lee, P. H., Lee, K., Sung, S-Y., Chang, S. *J. Org. Chem.* **2001**, *66*, 8646.

Appendix

Publications :

1) *The coupling of aryl halides in the ionic liquid [BMIM]PF_6*. Joshua Howarth, Paraic James and Jifeng Dai, *Tetrahedron Letters* **2000**, *41*, 10319-10321.

2) *Immobilized baker's yeast reduction of ketones in an ionic liquid, [BMIM]PF_6 and water mix*. Joshua Howarth, Paraic James and Jifeng Dai, *Tetrahedron Letters* **2001**, *42*, 7517-7519.

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TETRAHEDRON LETTERS

The coupling of aryl halides in the ionic liquid [bmim]PF_6

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Abstract

Several aryl halides have been coupled using the zero valent nickel catalyst [$(PPh_3)_nNi(0)$], to give the biaryl in moderate to good yield, employing the ionic liquid [bmim]PF_6. The ionic liquid and catalyst were recycled after extraction of the biaryl.

Keywords: ionic liquid; [bmim]PF_6; coupling; catalyst.

The ionic liquids [emim]PF_6 and [emim]BF_4, where $[emim]^+$ is the 1-ethyl-3-methylimidazolium cation, were first discovered in 1994 and 1992, respectively.[1] The analogous [bmim]PF_6 **1** and [bmim]BF_4 ionic liquids, where $[bmim]^+$ is the 1-butyl-3-methylimidazolium cation, followed shortly after.[2] These liquids have several very interesting properties; they can solvate a wide range of organic and inorganic materials, they are highly polar yet non-coordinating, they are immiscible with a wide range of organic solvents, and they have a nonvolatile nature. The search for clean technologies to minimise industrial waste requires the redesign and rethinking of many important industrial processes. One area of obvious interest is the replacement of environmentally damaging solvents used on a large scale, especially those that are volatile and difficult to contain. Moisture stable ionic liquids may provide an alternative, and unlike the moisture sensitive imidazolium based chloroaluminate ionic liquids, they do not require specialist facilities. As such a rapid growth in the investigation of the [bmim]PF_6 and [bmim]BF_4 type ionic liquids as substitutes for classical solvents is underway. Several important reactions have already been carried out and investigated in [bmim]PF_6 and [bmim]BF_4, such as a simple Diels–Alder reaction between cyclopentadiene and methyl methacrylate,[3] *N*-alkylation of indole and *O*-alkylation of 2-naphthol,[4] hydrogenations,[5] hydroformylation,[6] dimerisation of olefins,[7] oxidation of aromatic aldehydes,[8] and the Heck reaction.[9]

Herein we report, as far as we are aware, the results of the first low valent metal catalysed coupling of aryl halides **2a–g** using [$(PPh_3)_nNi(0)$] as the catalyst **3**, to be carried out in the new and versatile solvent [bmim]PF_6, a further, and industrially important example of the general

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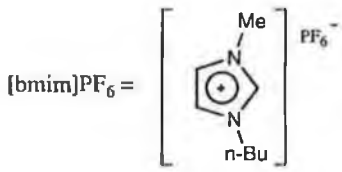


1

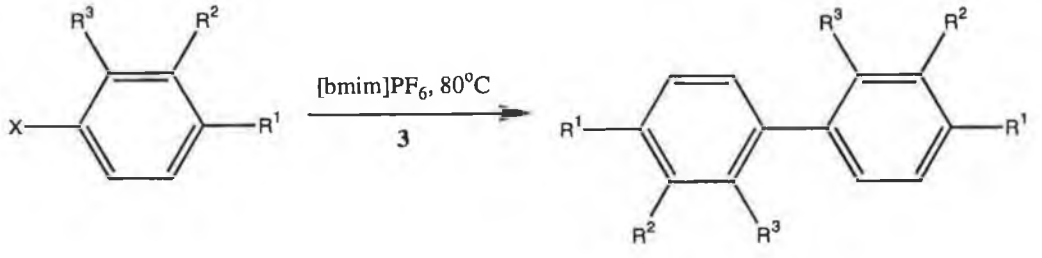
$$(PPh_3)_2NiX_2 + Zn \xrightarrow{PPh_3} (PPh_3)_nNi(0) + ZnX_2$$

$$(PPh_3)_nNi(0) + 2ArX \longrightarrow (PPh_3)_2NiX_2 + Ar\text{-}Ar$$

4

Scheme 1.

application of this type of solvent. Zero valent nickel complexes are excellent catalysts for the coupling of aryl halides,[10] and it is easy to reduce nickel from its divalent to zero valent state using zinc. In our study of aryl halide coupling reactions in the ionic liquid [bmim]PF_6 we used zinc powder to reduce bis(triphenylphosphine)nickel(II) dichloride in the presence of triphenylphosphine to generate [$(PPh_3)_nNi(0)$], to which the aryl halide was added, subsequently producing the biaryl **4** (Scheme 1). The results for seven aromatic halides are given in Scheme 2.



	X	R^1	R^2	R^3		R^1	R^2	R^3	Yield%
2a	Br	H	H	H	4a	H	H	H	87
2b	Br	OMe	H	H	4b	OMe	H	H	55
2c	Br	Me	H	H	4c	Me	H	H	76
2d	I	H	H	CO_2Me	4d	H	H	CO_2Me	40
2e	Br	H	CO_2Me	H	4e	H	CO_2Me	H	71
2f	Br	COMe	H	H	4f	COMe	H	H	60
2g	Br	CHO	H	H	4g	CHO	H	H	44

Scheme 2.

General procedure for the [$(PPh_3)_nNi(0)$] catalysed coupling of aryl halides **2a–g** in the ionic liquid [bmim]PF_6, using bromobenzene **2a** as an example: [$(PPh_3)_2Ni(II)Cl_2$] (3.63 g, 5 mmol), PPh_3 (2.62 g, 10 mmol) and Zn powder (0.66 g, 10 mmol) were added to a Schlenk tube containing dry (heat at 60°C under vacuum for 48 h), O_2-free [bmim]PF_6 (25 mL).[11] The flask

was evacuated, filled with dry N_2, and heated to 80°C with rapid stirring for 24 h. During this time the colour changed from the initial dark blue to dark green and then to light green/yellow. After 24 h bromobenzene (1.57 g, 10 mmol) was added and the reaction was stirred for a further 48 h at 80°C under dry N_2. After cooling the [bmim]PF_6 was extracted with diethyl ether (3×20 mL) and after drying the combined extractions ($MgSO_4$) removal of solvent and recrystallisation gave the biphenyl[12] (1.34 g, 87% yield).

It is interesting to note that in general the aryl bromides substituted at the *ortho* or *para* position by an electron withdrawing substituent give lower yields of the biaryl than the simple bromobenzene **2a**, compound **2d** giving the lowest yield of all. In the case of **2d** it is unlikely that this low yield is because we have employed an aryl iodide instead of an aryl bromide, as aromatic iodides consistently give high yields for this reaction in DMF, except when there is acyl substitution at the *para* or *ortho* position. The low yield is therefore consistent with these earlier findings and is due to the influence of the ester group in the *ortho* position. It is also known that aryl bromides show dramatic variations in yields of the biaryl as a result of substitution in the aromatic ring.[13]

The yields obtained using the ionic liquid [bmim]PF_6 as the solvent for the reaction were comparable to those yields obtained in the usual solvent for this reaction, DMF.[10] However, we were able to recycle the ionic liquid and the nickel catalyst. The used [bmim]PF_6 containing the spent catalyst was dried under vacuum at 60°C for 48 h and then deoxygenated. The $[(PPh_3)_nNi(0)]$ could be reformed and used once more in the above procedure without requiring the addition of further $[(PPh_3)_2Ni(II)Cl_2]$. There was however a small decrease in the yield of biaryls, for example the second run for bromobenzene only produced an 81% yield of the biphenyl.

References

1. Wilkes, J. S.; Zaworotko, M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 965; Fuller, J.; Carlin, R. T.; De Long, H. C.; Haworth, D. *J. Chem. Soc., Chem. Commun.* **1994**, 299.
2. Wilkes, J. S.; Levisky, J. A.; Wilson, R. A.; Hussey, C. L. *Inorg. Chem.* **1982**, *21*, 1263; Huddleston, J. G.; Willauer, H. D.; Swatloski, R. P.; Visser, A. E.; Rogers, R. D. *J. Chem. Soc., Chem. Commun.* **1998**, 1765.
3. Fischer, T.; Sethi, A.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793.
4. Earle, M. J.; McCormac, P. B.; Seddon, K. R. *J. Chem. Soc., Chem. Commun.* **1998**, 2245.
5. Chauvin, Y.; Olivier, H. CHEMTECH **1995**, 26; Chauvin, Y.; Einloft, S.; Olivier, H. *Ind. Eng. Chem. Res.* **1995**, *34*, 1149; Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; De Souza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 1217; Simon, L. C.; Dupont, J.; De Souza, R. F. *Appl. Catal. A: Gen.* **1998**, *175*, 215.
6. Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2698.
7. Kobryanskii, V. M.; Arnautov, S. A. *J. Chem. Soc., Chem. Commun.* **1992**, 727; Arnautov, S. A. *Synth. Metals* **1997**, *84*, 295; Goldenberg, L. M.; Osteryoung, R. A. *Synth. Metals* **1994**, *64*, 63.
8. Howarth, J. *Tetrahedron Lett.* **2000**, *41*, 6627.
9. Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 997; Howarth, J.; Dallas, A. *Molecules* **2000**, *5*, 851.
10. Kende, A. S.; Liebeskind, L. S.; Braitsch, D. M. *Tetrahedron Lett.* **1975**, 3375.
11. The solvent [bmim]PF_6 is commercially available from Solvent Inovation, see http://www.solvent-innovation.com for a catalogue. For a method of synthesis see Reference 8 and references cited therein.
12. The ^1H and ^{13}C NMR spectra for compounds **4a–g** corresponded exactly to those cited in the literature, or obtained from the commercially available biaryl, as did their melting points.
13. Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319.

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TETRAHEDRON LETTERS

Immobilized baker's yeast reduction of ketones in an ionic liquid, [bmim]PF_6 and water mix

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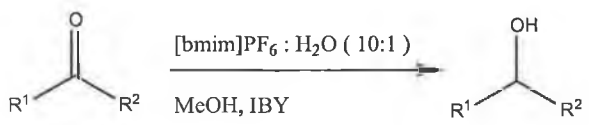
Abstract—The bioreduction with immobilized baker's yeast of several ketones was carried out in a 10:1 [bmim]PF_6 ionic liquid/water mix. The reductions produced alcohols with comparable enantioselectivities to baker's yeast reductions in alternative media.

Baker's yeast has been used to carry out a variety of transformations in synthetic organic chemistry. However, its use in this area has been limited by the necessity to employ aqueous solvent systems. For such bioreagents/catalysts to become more widely applicable in synthetic chemistry they need to operate and retain their selectivity in solvents more compatible with organic compounds. There have been several reports discussing alternative organic solvents such as liquefied petroleum gas,[1] hexane,[2] benzene,[3] toluene,[4] carbon tetrachloride,[4] and petroleum ether.[5] The main advantage of employing such solvents is the ease with which the product can be isolated. The drawbacks associated with the use of organic solvents are their potential toxicity to the bioreagent/catalyst, and problems associated with their disposal.

Concurrent research on ionic liquids has shown that they support a large and diverse range of organic reactions, these include amongst many others oxidations,[6] coupling reactions,[7] nucleophilic displacements,[8] reductions,[9] and alkylations.[10] There have also been reports of purified enzyme reactions in ionic liquids.[11] We speculated that it may be possible to carry out whole-cell biotransformations such as yeast mediated reductions of ketones in an ionic liquid. This would combine the advantages of whole cell bioreagents with the advantages of ionic liquids, principally their recyclable nature. For the purposes of the investigation we chose the readily available ketones **1–7** for reduction. It has been shown that the inactivation of enzymes in organic solvents can be avoided if the enzyme is surrounded by a layer of water.[12] Thus, we decided to add a quantity of water to the ionic liquid. The ionic liquid we chose to use was the moisture stable 1-butyl-3-methylimidazolium phosphorous pentafluoride, [bmim]PF_6, because like previous organic solvents explored[1–5] it is essentially immiscible with water. We also decided to employ immobilized baker's yeast (IBY) in order to simplify the work-up procedure whereby the IBY could be removed by filtration. The method of yeast immobilization that we chose was encapsulation in calcium alginate beads,[13] as this is a cost effective and facile method of immobilization. We also added a quantity of methanol as an energy source[2] to the reaction system, Scheme 1, (see Ref. 14 for details of reaction procedure).



Scheme 1.

It should be noted that, whilst in an aqueous system the coenzyme, NADPH, necessary for reduction is, through various metabolic pathways within the yeast, continuously recycled, this does not occur in non aqueous systems. Thus, the extent of the reaction is limited by the initial concentration of the coenzyme within the yeast.[5]

The results from our investigation are given in Table 1. We found that the yield of product varied over the range of substrates, some giving poor yields whilst

Keywords: baker's yeast; ionic liquid; reduction.

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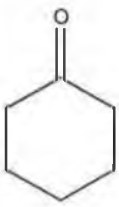
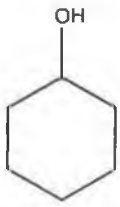
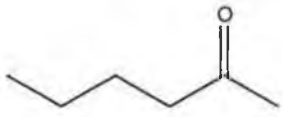
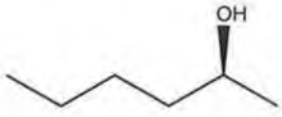
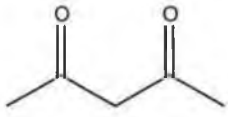
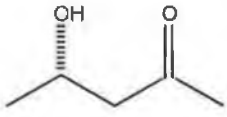
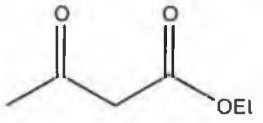
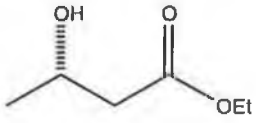
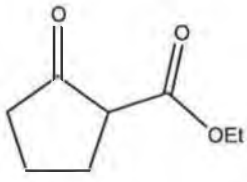
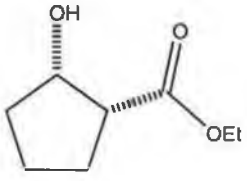
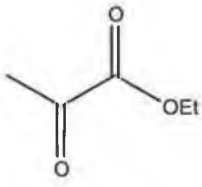
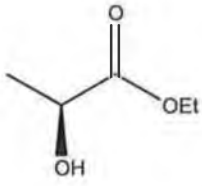
Table 1.

Entry	Ketone substrate	Entry	Alcohol product	Yield % Lit. ( )	Ee % Lit. ( )	$[\alpha]_D^{20}$ Lit. ( )
1		1a		35	–	–
2		2a		20	–	–
3		3a		40 (18)[15]	79 (82)[15]	+9.3 (+11.7)[16]
4		4a		22 (90)[17]	95 (74)[17]	+38.2 (+40.0)[17]
5		5a		70 (78)[5]	95 (97)[5]	+41.0 (+43.0)[18]
6		6a		75 (66)[19]	84 (99)[19]	+12.3 (+14.7)[19]
7		7a		60 (43)[20]	76 (91)[20]	−7.1 (−9.4)[21]

others gave good yields. When we attempted to reduce the two aromatic ketones, 4-bromoacetophenone and 4-methoxyacetophenone, we observed no reduction and only starting material was recovered. The literature values for enantiomeric excesses given in Table 1 are for yeast reductions carried out in alternative media. In general the enantiomeric excesses obtained in an ionic liquid medium were comparable to those obtained in other media, although entry **4a** was significantly higher and entry **7a** significantly lower.

We also found that under high vacuum that it was possible to distil the alcohols **1a** and **2a** directly from the [bmim]PF_6. This negated the extraction with organic solvents. The ionic liquid [bmim]PF_6 was recycled after use in the reactions. We also noted that whilst these reactions may be carried out in the absence of water the yields and enantiomeric excesses were extremely poor, probably because of the inactivation of the enzyme within the yeast responsible for the reduction as stated above.

As far as we are aware this is first example of the use of a whole-cell biotransformation in a moisture stable ionic liquid, in this case [bmim]PF_6, and it clearly expands the potential and possibilities for moisture stable ionic liquids as environmentally sound solvents to support a broad range of synthetic organic transformations. Furthermore it points to further development for the role of bioreagents, in particular yeast, in this field of synthetic chemistry.

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References

1. Johns, M. K.; Smallridge, A. J.; Trewhella, M. A. *Tetrahedron Lett.* **2001**, *42*, 4261.
2. (a) Naoshima, Y.; Maeda, J.; Munakata, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 659; (b) Naoshima, Y.; Maeda, J.; Munakata, Y.; Nishiyama, T.; Kamezawa, M.; Tacibana, H. *J. Chem. Soc., Chem. Commun.* **1990**, 964.
3. Nakamura, K.; Kondo, S.; Kawai, Y.; Ohno, A. *Tetrahedron Lett.* **1991**, *32*, 7075.
4. Jayasinghe, L. Y.; Kodituwakku, D.; Smallridge, A. J.; Trewhella, M. A. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2528.
5. Jayasinghe, L. Y.; Smallridge, A. J.; Trewhella, M. A. *Tetrahedron Lett.* **1993**, *34*, 3949.
6. Howarth, J. *Tetrahedron Lett.* **2000**, *41*, 6627.
7. (a) Howarth, J.; Dallas, A. *Molecules* **2000**, *5*, 851; (b) Howarth, J.; James, P.; Dai, J. *Tetrahedron Lett.* **2000**, *41*, 10319; (c) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 997.
8. Wheeler, C.; West, K. N.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* **2001**, 887.
9. Howarth, J.; James, P.; Ryan, R. *Synth. Commun.* **2001**, *31*, 51.
10. Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Chem. Commun.* **1998**, 2245.
11. (a) Cull, S. G.; Holbrey, J. D.; Vargas-Mora, V.; Seddon, K. R.; Lye, G. J. *Biotechnol. Bioeng.* **2000**, *69*, 226; (b) Madeira Lau, R.; Van Rantwijk, F.; Seddon, K. R.; Sheldon, R. A. *Org. Lett.* **2000**, *2*, 4189; (c) Erbeldinger, M.; Mesiano, A. J.; Russell, A. J. *Biotechnol. Prog.* **2000**, *16*, 1129.
12. Katyar, S. S.; De Tapas, K. *Biochem. Ind.* **1990**, *20*, 1127.
13. Takeda, A.; Sakai, T.; Nakamura, T.; Fukuda, K.; Amano, E.; Utaka, M. *Bull. Chem. Soc. Jpn.* **1986**, 59, 3185
Preparation of immobilized baker's yeast: Sodium alginate (5 g) was added to water (200 mL) and the mixture was stirred until the sodium alginate was completely dissolved. Baker's yeast (20 g) was added to water (80 mL) and the mixture was stirred for 2 h to produce a homogenous suspension. This suspension was then transferred to the sodium alginate solution. The combined mixture was stirred for a further 2 h. After this time the mixture was transferred to a dropping funnel with a 2 mm outlet. The sodium alginate and yeast mixture was added dropwise to aqueous calcium chloride (3% solution, 800 mL). The resultant beads that were formed were filtered and washed several times with water. They were then stored in a refrigerator until required.
14. **Bioreduction reaction procedure**: The ionic liquid [bmim]PF_6 (100 mL) and water (10 mL) were mixed together and warmed to a temperature of 33°C. Subsequently calcium alginate beads containing yeast (10 g) were added to the solution that was then stirred. After 10 min methanol (2 mL) was added and the whole system was stirred for a further 1 h. The ketone (10 mmol) was then added and the reaction was stirred at 33°C for 72 h. The beads were then filtered and the remaining filtrate was extracted with diethyl ether (5×100 mL). The extracts were combined and dried (anhyd. Na_2SO_4), filtered and the solvent was removed in vacuo. The resulting oil was purified by flash chromatography or short path distillation. All products **1a** to **7a** were characterized by ^1H, ^{13}C and IR spectroscopy.
15. McLeod, R.; Prosser, H.; Fiskentscher, L.; Lanyi, J.; Mosher, H. S. *Biochemistry* **1964**, *3*, 838.
16. (a) Rickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1911**, *99*, 58; (b) Rickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1914**, *105*, 1120.
17. Fauve, A.; Verchambre, H. *J. Org. Chem.* **1988**, *53*, 5215.
18. Wipt, B.; Kupfer, E.; Berlazzi, R.; Leuenberger, H. G. W. *Helv. Chim. Acta* **1983**, *66*, 485.
19. Seebach, D.; Roggo, S.; Maetzke, T.; Braunshweiger, H. *Helv. Chim. Acta.* **1987**, *70*, 1605.
20. Nakamura, K.; Inoue, K.; Ushio, K.; Oka, S.; Ohno, A. *J. Org. Chem.* **1988**, *53*, 2589.
21. Beckett, A. H.; Happer, N. J.; Clitherrow, J. W. J. *Pharm. Pharmaco.* **1963**, *15*, 349.